An Open-Label, Phase 2 Trial of Nanatinostat in Combination with Valganciclovir in Patients with Epstein-Barr Virus-Positive (EBV$^+$) Relapsed/Refractory Lymphomas (NAVAL-1)

Protocol Number:	VT3996-202 (NCT05011058)
Sponsor Name and Legal Registered Address:	Viracta Therapeutics, Inc. 2533 S. Coast Hwy 101 Suite 210 Cardiff, CA 92007 (858) 400-8470
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Investigational Drugs:	Nanatinostat (Nstat), VRx-3996 Valganciclovir (VGCV)
Short Title:	Nanatinostat and Valganciclovir in R/R EBV$^+$ Lymphoma ("NAVAL-1")
Regulatory Agency Identifying Number(s):	IND Number 132679 EUDRA CT Number: 2020-005197-10
Original Protocol:	Version 1.0, 05 February 2021
Amendment 1:	Version 2.0, 03 April 2021
Amendment 2:	Version 3.0, 22 April 2021
Amendment 3:	Version 4.0, 16 March 2022
Amendment 3.1:	Version 4.1, 23 June 2022
Amendment 4.1:	Version 5.1, 27 March 2023
Amendment 5.1:	Version 6.1, 26 October 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.

Confidentiality Statement

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:

Darrel P. Cohen, MD, PhD
Chief Medical Officer

26 OCTOBER 2023
Date

Susan Spruill, MS, PStat®
Statistician

26 October 2023
Date

Cheryl A. Madsen, RAC
SVP, Regulatory Affairs

26 OCT 2023
Date

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 me 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	VT3996-202
Study Title	An Open-Label, Phase 2 Trial of **Na**natinostat in Combination with **Val**ganciclovir in Patients with Epstein-Barr Virus-Positive (EBV$^+$) Relapsed/Refractory Lymphomas (NAVAL-1)
Sponsor	Viracta Therapeutics, Inc.
Investigational Drugs	Nanatinostat (Nstat, VRx-3996) Valganciclovir (VGCV)
Study Phase	Phase 2
Objectives (Primary and Secondary)	**Primary:** To evaluate the anti-tumor activity of the combination treatment of nanatinostat (Nstat) with valganciclovir (VGCV) based on objective tumor response rates. **Secondary:** • To determine the duration of tumor control. • To determine survival outcomes. • To describe the safety profile of the combination treatment of Nstat with VGCV. • To generate pharmacokinetic (PK) data with the intended commercial dose and administration of Nstat.
Endpoints (Primary and Secondary)	**Primary:** Objective response rate (ORR) as assessed by an Independent Review Committee (IRC) – defined as the proportion of patients who achieve a complete response (CR) or partial response (PR) using the 2007 International Working Group (IWG) criteria (Cheson 2007). **Secondary:** • Duration of response (DOR) – defined as the interval from date of first observed CR or PR to the date of disease progression, death due to any cause, or last adequate (radiographic) response assessment. • Time to next anti-lymphoma treatment (TTNLT) – defined as the interval from the start of study drug treatment to date of next anti-lymphoma 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. • Time to progression (TTP) – defined as the interval from the start of study drug treatment to date of disease progression. • Overall survival (OS) – defined as the interval from the start of study drug treatment to date of death, for any reason. • Incidence and severity of treatment-emergent adverse events (TEAEs). Adverse events (AEs) will be graded according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 5.0. • Pharmacokinetic parameters (eg, time to maximum plasma concentration [t_{max}], maximum plasma concentration [C_{max}], area under the plasma concentration-time curve [AUC]).
Study Design	This is an open-label, multicenter, multinational single-arm, Phase 2 basket design study, utilizing Simon's 2-stage design options for discontinuing enrollment into each cohort where treatment appears to be futile (Simon 1989). The study will include 7 cohorts of patients with the following EBV$^+$ relapsed/refractory lymphomas:

- **Cohort 1**: EBV$^+$ diffuse large B-cell lymphoma, not otherwise specified (DLBCL, NOS)
- **Cohort 2**: Extranodal NK/T-cell lymphoma (ENKTL)
- **Cohort 3**: Peripheral T-cell lymphoma (PTCL), including PTCL-NOS and angioimmunoblastic T-cell lymphoma (AITL):
  - **Cohort 3a**: Nanatinostat monotherapy
  - **Cohort 3b**: Nanatinostat + valganciclovir
- **Cohort 4**: Hodgkin lymphoma (HL)
- **Cohort 5**: Post-transplant lymphoproliferative disorder (PTLD)
- **Cohort 6**: Lymphomas associated with human immunodeficiency virus (HIV) infection (HIV-L): Plasmablastic, Burkitt, Hodgkin, and DLBCL
- **Cohort 7**: EBV$^+$ lymphomas other than Cohorts 1, 3, 4, 5, and 6 above (Cohort 7 will **not** enroll patients in France)

In Stage 1, 6 cohorts (Cohorts 1, 2, 3b, 4, 5, and 6) will enroll up to 10 patients each. Any cohort that fails to enroll any patients within 1 year from the date the first patient is enrolled in the study will be considered for termination of enrollment. Enrollment in Cohorts 2, 4, and 6 has been closed as of 17 October 2023, 24 August 2023, and 24 August 2023, respectively. Patients currently enrolled in these cohorts may continue to receive study treatment per protocol until which time treatment discontinuation is required as defined in Section 7.2.3.

All cohorts that have a response in 2 or more patients in Stage 1 will continue to enroll patients in Stage 2, for a total of 21 patients in each cohort. If ≥7 responses are observed in the initial 21 patients in any cohort, then enrollment will be expanded to include up to 120 additional patients in that cohort (N=141), with the possibility of performing an interim efficacy analysis in that cohort to be described in the statistical analysis plan. Cohort 3a will not enroll beyond the initial 10 patients, regardless of the number of responders in Stage 1.

To evaluate the activity of single-agent nanatinostat, the first 20 patients enrolled with PTCL will be randomized 1:1 to either nanatinostat monotherapy (20 mg PO once daily on Days 1 to 4 per week in Cohort 3a) or nanatinostat plus valganciclovir (in Cohort 3b). Following a disease response assessment at 6 weeks, patients in Cohort 3a with a CR or PR will continue nanatinostat monotherapy. Those in Cohort 3a with stable disease at 6 weeks or disease progression at any time (confirmed by CT or MRI) will have the option to cross over to combination therapy for the remainder of the study. Patients must complete the End of Monotherapy Disease assessment and qualify (labs, no sign of CNS disease progression, Eastern Cooperative Oncology Group [ECOG]) prior to beginning Cycle 1 Day 1 of the nanatinostat plus valganciclovir combination therapy.

Cohort 7 will be closed to enrollment when all other cohorts are closed, regardless of the number of patients recruited at that time and will not be subject to the decision criteria of the Simon's 2-stage design.

It is thus estimated that up to 486 patients in Cohorts 1 to 6 may be enrolled for combination therapy, of which approximately 60 would be enrolled in Stage 1 and 66 would be enrolled in Stage 2, and up to 360 would be enrolled into the post-Stage 2 expansion cohorts. Additional patients (n=10) with PTCL will be enrolled in Cohort 3a for nanatinostat monotherapy, and patients with lymphoma subtypes other than those assigned to Cohorts 1, 3, 4, 5, and 6 may be enrolled into Cohort 7 (with the exception of France; see above).

If 10 patients of a given lymphoma subtype are enrolled into Cohort 7, then the Simon's decision criteria will be applied to determine whether or not to add patients in Stage 2 for that subtype. If none of the subtypes represented in Cohort 7 enrolls at least 10 patients,

	efficacy data collected on those patients will be listed, but not summarized by group. All patients will be summarized for safety, regardless of decision to discontinue enrollment into any cohort. Patients enrolled in Cohorts 1 to 7 (with the exception of Cohort 3a), and patients crossed over from Cohort 3a will receive intermittent dosing of nanatinostat and continuous valganciclovir in 28-day cycles as follows: 1. Nanatinostat 20 mg orally once daily on Days 1 to 4 per week (ie, 4 days on, 3 days off) 2. Valganciclovir 900 mg orally once daily. Patients with a CrCl 50-59 mL/min at study entry will receive valganciclovir 450 mg orally once daily as per Table 4. Patients who develop disease progression but, in the opinion of the Investigator, would still benefit from continuing study drug may continue treatment with nanatinostat and valganciclovir after agreement with the Sponsor, provided that they are i) asymptomatic from or have no overt signs of disease progression and ii) have a performance status of 0-1. It is recommended to perform an interval follow-up radiologic disease assessment before the next scheduled time point. Such patients will be recorded as having had a PFS event. All patients will be monitored at weekly intervals through the first cycle of treatment, and then at 2-week intervals thereafter. Tumor response will be evaluated after every 2 cycles × 3, and after every 3 cycles thereafter. The responses will be assessed by both the Investigator and an IRC. The PK parameters of nanatinostat and its metabolites and ganciclovir (primary active hydrolytic product of valganciclovir) will be evaluated for patients enrolled in Stage 1 and sparse sampling will be collected during the Stage 2 part of the study at selected sites. Enrolled patients will receive treatment until disease progression (per Investigator assessment), unacceptable toxicity, withdrawal of consent, Investigator's discretion, death, initiation of new antineoplastic therapy, discontinuation from the study for any reason, or study termination by the Sponsor. Patients receiving nanatinostat monotherapy who have disease progression will be offered the option to receive combination therapy with valganciclovir. All antineoplastic therapies given after the last dose of study drug (and time to next therapy) will be recorded in the electronic case report form (eCRF) (unless the patient withdraws consent or is lost to follow-up). Patients will be followed for survival regardless of treatment discontinuation reason (except if consent is withdrawn or patient is lost to follow-up).
Population	Patients with EBV$^+$ relapsed/refractory lymphoma following prior systemic therapy(ies) with no available standard therapies as per the eligibility criteria.
Inclusion Criteria	1. Adult patients age ≥18 years or as permitted by applicable local regulations at the time of providing informed consent. Patients must be able to swallow whole tablets. a. **For patients with PTLD:** Age ≥12 years and weighing ≥40 kg. 2. Histologically confirmed (by 2016 WHO classification (Swerdlow 2016)) EBV$^+$ lymphoma* per local laboratory by EBER-ISH (or for PTLD only, by LMP-1 immunohistochemistry) on a representative disease specimen. Any degree of EBER-ISH or LMP-1 positivity is considered to be eligible (ie, there is no cut-off value for % positive cells). * Tumor cells are EBV+, with the exception of AITL, which is characterized by EBV-negative neoplastic T cells and EBV+ associated B-lineage cells (of immunoblastic/plasmablastic immunophenotype) a. A recent formalin-fixed paraffin-embedded (FFPE) specimen must be available for retrospective central review of diagnosis. FFPE tissue blocks are preferred; if a tissue block is not available, at least 15 unstained slides or freshly cut serial

	sections (3−5 μm in thickness), preferably with an accompanying block punch will be accepted. The specifications for the age of the tumor samples are: • **For patients with ENKTL, AITL, PTLD and HIV-L:** preferably ≤1 year old. For tumor specimens >1 year old, please consult the Medical Monitor to discuss eligibility. • **For patients with all other lymphoma subtypes:** preferably ≤6 months old. For tumor specimens >6 months old, please consult the Medical Monitor to discuss eligibility. 3. **For patients with EBV$^+$ DLBCL, NOS:** Relapsed or refractory disease following 1 or more prior systemic therapy(ies) with curative intent. Patients must have received at least one course of an anti-CD20 immunotherapy such as rituximab, and at least one course of anthracycline-based chemotherapy (unless contraindicated, in which case, an accepted anthracycline-free alternative for DLBCL was given). 4. **For patients with ENKTL:** Relapsed or refractory disease following 1 or more prior systemic therapy(ies) with a curative intent. Patients must have failed an asparaginase-containing regimen. 5. **For patients with PTCL (PTCL, NOS and AITL):** Relapsed or refractory disease following 2 or more prior systemic therapy(ies) with a curative intent. 6. **For patients with HL:** Patients must have received at least one course of anthracycline-based chemotherapy (unless contraindicated, in which case, an accepted anthracycline-free alternative for HL was given). Patients with relapsed/refractory classical Hodgkin lymphoma(cHL) should have failed or be ineligible for an anti-PD-1 agent (eg, pembrolizumab, nivolumab) and CD30-directed therapy (ie, brentuximab vedotin). 7. **For patients with PTLD:** Patients with relapsed or refractory EBV$^+$ PTLD who have received at least one prior therapy must have received at least one course of an anti-CD20 immunotherapy such as rituximab. For solid-organ transplant (SOT) patients, prior therapy also includes chemotherapy, administered concurrently or sequentially, unless chemotherapy is inappropriate. 8. For patients with the following lymphomas associated with HIV infection: plasmablastic, Burkitt, Hodgkin, and DLBCL. a. Prior therapy requirements for DLBCL and HL are specified in inclusion criteria 3 and 6. b. **France only:** For Burkitt and plasmablastic lymphoma - Patients must have received a regimen such as EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, hydroxydaunorubicin), CODOX-M (original or modified; cyclophosphamide, vincristine, doxorubicin, and high-dose methotrexate) or Hyper-CVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone), including CNS prophylaxis or therapy. 9. Patients with HIV-L should meet the following criteria for inclusion: a. Currently on a stable regimen of anti-retroviral therapy (ART) b. Compliant with ART and follow-up according to the investigator c. No evidence of a worsening HIV viral load (as assessed by HIV quantitative polymerase chain reaction [qPCR]) d. CD4 count >50 cells/mm^3 10. No available standard therapies in the opinion of the Investigator. 11. Not eligible for high-dose chemotherapy with allogeneic/autologous stem cell transplantation or CAR-T therapy at the time of study entry. 12. Presence of at least one bi-dimensionally measurable lesion by computed tomography (CT) or magnetic resonance imaging (MRI): longest diameter (LDi) >1.5 cm for a nodal lesion; LDi >1.0 cm for an extranodal lesion within 28 days prior to start of treatment.

13. Able to provide a prior core or excisional biopsy for biomarker analysis at screening. If no tissue is available, then a new biopsy must be performed.
14. Eastern Cooperative Oncology Group (ECOG) performance status 0, 1, or 2.
15. All acute toxic effects of any prior anti-tumor therapy resolved to Grade ≤1 before initiation of study treatment (excluding alopecia and stable Grade 2 sensory neuropathy).
16. Required baseline laboratory data (within 2 weeks prior to start of study drug administration) as shown in the table below:

System	Laboratory Value
Hematology	
Absolute neutrophil count (ANC)	≥1000/mm^3 (no growth factor support within 14 days)
Platelets	≥50,000/mm^3 (no platelet transfusion within 14 days)
Hemoglobin	≥8.0 g/dL (no red cell transfusion within 21 days)
Renal	
Creatinine clearance	≥50 mL/min (Cockcroft-Gault)
Hepatic	
Total bilirubin	≤2.0 × upper limit of normal (ULN) (except patients with documented Gilbert's syndrome [<3.5 × ULN])
Aspartate aminotransferase (AST [SGOT]) and alanine aminotransferase (ALT [SGPT])	≤3.0 × ULN (or ≤5.0 × ULN if liver involvement by primary disease)
Coagulation	
International normalized ratio (INR) Activated partial thromboplastin time (aPTT)	≤1.5 × ULN unless participant is receiving anticoagulant therapy (as long as INR or aPTT are within the therapeutic range of intended use of anticoagulants)

17. Life expectancy >3 months.
18. Women of childbearing potential (ie, reached menarche, and not premenarchal or 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 true abstinence from heterosexual intercourse: When this is in line with the preferred and usual lifestyle of the patient (Periodic abstinence [eg, calendar, ovulation, symptothermal, post-ovulation methods], declaration of abstinence for the duration of exposure to the investigational medicinal product [IMP], or the withdrawal method are not acceptable forms of contraception). Otherwise, begin a highly effective method of birth control with a Pearl-Index <1%, without interruption, throughout the study dosing period and for 6 months after the last dose of nanatinostat. 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 (oral, intravaginal, transdermal). Note: Although the potential for drug interactions and risk of venous thromboembolism is low (see Section 5.5.2.3), 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. 19. Male patients must agree to use condoms during intercourse throughout the study dosing period and for 90 days after the last dose of nanatinostat. Female partners of male patients participating in the study are to consider the use of effective methods of contraception while their partner is treated on study and for 90 days after the last administration of nanatinostat. 20. The patient is willing and able to provide informed consent and comply with the protocol. Assent must be obtained for adolescent patients <18 years old, or as permitted by applicable local regulations, and a parent/guardian must provide written consent.
Exclusion Criteria	1. Presence or history of central nervous system (CNS) involvement by lymphoma. 2. Systemic anticancer therapy within 21 days prior to Cycle 1 Day 1 dosing. 3. Antibody (anticancer) agents within 28 days of Cycle 1 Day 1 dosing. 4. Less than 14 days from prior local site radiation therapy. 5. Less than 60 days from prior autologous hematopoietic stem cell or solid organ transplant. 6. Less than 21 days from prior CAR-T therapy (any AEs must be Grade 1 or less to be eligible for enrollment) 7. Less than 90 days from prior allogeneic transplant. 8. Receiving systemic corticosteroids during the last week prior to Cycle 1 Day 1, unless administered at a dose equivalent to ≤20 mg/day of prednisone. 9. For recipients of prior allogeneic HSCT: Receiving systemic immunosuppressants as either prophylaxis or treatment for graft-versus-host disease (GvHD). 10. Major surgery within 28 days within the first dose of study drug. In the case of recent major surgery, the patient must have recovered adequately from the procedure and/or any complications prior to starting study treatment. • Note: Minor surgery (eg, minor biopsy of extracranial site, central venous catheter placement, shunt revision) is permitted within 3 weeks prior to enrollment. 11. 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. 12. History of other malignancy that could affect compliance with the protocol or interpretation of results. Patients with any malignancy appropriately treated with curative intent and the malignancy has been in remission without treatment for ≥2 years prior to enrollment are eligible. Also eligible are the following: • Curatively treated: i. Basal cell, squamous cell carcinoma, or melanoma of the skin (at any time prior to the study). ii. Cervical carcinoma in situ (at any time prior to the study). • Low-grade early-stage prostate cancer (Gleason score 6 or below, stage 1 or 2) with no requirement for therapy at any time prior to study, or previously fully resected.

	13. Inability to take oral medication, malabsorption syndrome or any other gastrointestinal condition (nausea, diarrhea, vomiting) that may impact the absorption of nanatinostat and valganciclovir. 14. Active GvHD. 15. Positive hepatitis B core antibody or surface antigen unless DNA qPCR is negative, and patient will be receiving prophylaxis for reactivation. 16. Positive hepatitis C virus on RNA polymerase chain reaction (PCR). 17. Known SARS-CoV-2 positivity by any testing method at time of screening. Patients with a positive PCR test should only be enrolled if ≥10 days have passed since COVID symptoms first appeared and they have recovered from symptoms or have mild symptoms. 18. History of allergic reactions attributed to compounds of similar chemical or biologic composition to valganciclovir or nanatinostat. 19. Active infection requiring systemic therapy (excluding viral upper respiratory tract infections). Patients may be receiving prophylactic antiviral, antifungal or antibacterial therapies at the discretion of the Investigator. 20. 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). 21. Receiving concomitant drugs that are inhibitors of P-glycoprotein (P-gp) and/or 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). 22. Psychiatric illness/social situations/substance abuse disorder that would interfere with compliance with study requirements. 23. Has a prior or ongoing clinically significant illness such as New York Heart Association Class III or IV cardiac disease, myocardial infarction within the last 6 months, unstable arrhythmias, or unstable angina, or pulmonary disease), 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 compliance with the protocol, or is not in the best interest of the patient to participate. 24. Is pregnant or breastfeeding or expecting to conceive or father children within the projected duration of the study, starting with the Screening visit through 6 months after the last dose of nanatinostat.
Sample Size Calculations and Hypothesis Testing	This multinational, multicenter study will employ a Simon's 2-stage design to allow termination of enrollment into cohorts where treatment appears futile (Simon 1989). The decision to transition from Stage 1 to Stage 2 is dependent on the assumption of ORR: ORR ≤10% (poor response); ORR ≥35% (good response). The sample size estimation uses 1-sided alpha = 0.05 and targets statistical power = 85%. Using the Simon's 2-stage design approach, the null hypothesis that the true response rate is 10% will be tested against a one-sided alternative. In the first stage, up to 10 patients will be accrued in each cohort. If there are 1 or fewer responses, the cohort will be discontinued. If the cohort fails to enroll any patients within 1 year from the enrollment of the first patient, the cohort will be considered for termination of enrollment. Otherwise, if at least 2 patients in a cohort respond, additional patients will be accrued for a total of 21 in the cohort. The null hypothesis that the true response rate is 10% will be rejected in each cohort where 5 or more responses are observed in 21 patients. This design yields a type I error rate of 0.0440 and power of 86.2% within each cohort where the true response rate is 35%. If 10 patients of a given lymphoma subtype are enrolled into Cohort 7, then the Simon's decision criteria will be applied to determine whether or not to add patients in Stage 2 for

	that subtype. If none of the subtypes represented in Cohort 7 enrolls at least 10 patients, efficacy data collected on those patients will be listed, but not summarized by group. All patients will be summarized for safety, regardless of the decision to discontinue enrollment into any cohort. If at the end of Stage 2 there are at least 7 responders observed in the initial 21 patients in any cohort (ORR≥33.3%), enrollment will be expanded to include up to 120 additional patients in that cohort (N=141), with the possibility of performing an interim analysis in that cohort to be described in the statistical analysis plan. The maximum sample size estimated for the expanded cohort is dependent on the assumption of ORR ≥35% with the lower bound of its 95% CI excluding ORR 25%.
Study Treatments, Dose, Route of Administration, Treatment Regimen	Patients enrolled in Cohorts 1 to 7 (with the exception of Cohort 3a), and patients crossed over from Cohort 3a will receive intermittent dosing of nanatinostat and continuous valganciclovir in 28-day cycles as follows: 1. Nanatinostat 20 mg orally once daily on Days 1 to 4 per week (ie, 4 days on, 3 days off). 2. Valganciclovir 900 mg orally once daily for patients ≥17 years of age. Patients with a CrCl 50-59 mL/min at study entry will receive valganciclovir 450 mg orally once daily as per Table 4. The daily dose of valganciclovir for patients <17 years of age is based on body surface area (BSA) and CrCl derived from a modified Schwartz formula (see Section 5.2.2). Nanatinostat and valganciclovir should be taken at the same time following a light meal. On days with pre- and post-dose PK assessments, patients will be asked to consume one can of Ensure® or equivalent, prior to the dose of study drugs (within 30 minutes). Alternatively, patients may consume a light breakfast in place of consuming an Ensure equivalent and should start the meal 30 minutes before administration study drugs. For Cohorts 1, 2, 3b, 4, 5, 6, and 7, patients will receive nanatinostat/valganciclovir (nanatinostat 20 mg orally once daily on Days 1 to 4 per week and valganciclovir 900 mg orally once daily) continuously for 28-day treatment cycles. Patients with a CrCl 50-59 mL/min at study entry will receive valganciclovir 450 mg orally once daily as per Table 4. During treatment Cycle 1, visits will occur on Days 1, 8, 15, and 22. Starting at Cycle 2, visits will occur on Days 1 and 15. Each scheduled clinic visit has an allowable ±3-day window. For Cohort 3a, the PTCL patients randomized to monotherapy will begin with 6 weeks of nanatinostat monotherapy (20 mg orally once daily on Days 1 to 4 per week) with visits on Days 1, 15, 29, and 43. Each scheduled clinic visit has an allowable ±3-day window. If a patient has stable or progressive disease at the Day 43 visit (or progressive disease prior to Day 43), the patient will be offered the option to switch to nanatinostat/valganciclovir combination and follow the 28-day treatment cycles as described above. Patients must complete the End of Monotherapy Disease assessment and qualify (labs, no sign of CNS disease progression, ECOG) prior to beginning Cycle 1 Day 1 of the nanatinostat/valganciclovir combination therapy. If a patient has a response (complete or partial response) to nanatinostat monotherapy at the Day 43 visit, the patient will continue monotherapy treatment.
Efficacy Assessment(s)	Disease response assessments will be made every 8 weeks until 24 weeks, and then every 12 weeks for the remainder of the study, according to the revised response criteria for malignant lymphoma based on the IWG-NHL guidelines (Cheson 2007). A scan to confirm an unconfirmed PR or unconfirmed CR ≥4 weeks later may also be performed. ^{18}FDG-PET/CT and a diagnostic contrast-enhanced CT scan (or MRI if a CT with contrast is contraindicated) will be performed at baseline, and for the 8-week and 16-week tumor assessments. Subsequent evaluations will be by CT with contrast (without PET) or MRI only. Patients with FDG-avid lymphoma at baseline may have an ^{18}FDG-PET/CT performed to evaluate a possible CR or PR after Week 16 (unless prohibited by local practice) and may use a diagnostic contrast-enhanced CT for follow-up once a complete

	metabolic response is obtained. ^{18}FDG-PET/CT scans may also be obtained per investigator discretion (eg, in instances where extranodal disease may be inadequately imaged by contrast-enhanced CT). Efficacy will be evaluated in terms of ORR, DOR, PFS, OS, TTP, and TTNLT. ORR will be used to move from Stage 1 to Stage 2.
Special Safety Assessment(s)	The safety and tolerability of study drug treatments will be evaluated by means of AE reports (incidence, causality, and severity), ECOG performance status, physical examinations, 12-lead ECGs, and laboratory safety evaluations. Laboratory abnormalities and AE severity will be graded according to NCI Common Terminology Criteria for Adverse Events (CTCAE), version 5.0.
Pharmacokinetics	• PK sampling for nanatinostat and its metabolites • PK sampling for ganciclovir
Biomarker Assessments	The biomarker analyses outlined in this study are intended to foster an understanding of how baseline expression of certain biomarkers may impact efficacy, as well as to evaluate the effect of combination therapy with nanatinostat and valganciclovir on pharmacodynamic markers of activity, such as plasma EBV DNA levels, and correlation with clinical efficacy. Potential predictive markers will be studied to identify patients with optimal responses to nanatinostat plus valganciclovir. The impact of study drug administration on B-cell/T-cell/NK cell/myeloid cell populations will be evaluated over time. Cells and plasma from peripheral blood, or tumor tissue (lymph nodes), will be sent to a central laboratory selected by the study sponsor for analysis of viral DNA levels, and gene expression, phenotypic alterations in B-cells/T-cells/NK cells/myeloid cells and mutation profile.
Independent Review Committee	An IRC will be established to provide an independent review of radiographic and pertinent clinical data to provide expert interpretation of changes in tumor status and response assessment
Statistical Methods and Data Analysis	**Efficacy Analysis:** The number and percentage of patients with EBV$^+$ lymphoma with a CR or PR after initiation of treatment will be summarized overall and by cohort. Ninety-five percent (95%) confidence intervals (CIs) around the ORR: CR + PR will be calculated using the ClopperPearson method. For patients who achieve CR/PR, the DOR, defined as the start of the response to documented disease progression, death due to any cause, or last adequate (radiographic) response assessment will be estimated using the KaplanMeier method. Any patient who does not need anti-lymphoma treatment, experiences disease progression, or death will be censored at the last non-missing assessment. Patients initiating anti-cancer therapy will be censored at the last adequate disease assessment prior to the start of therapy. Overall survival will be estimated using the Kaplan-Meier method and will include all enrolled patients. Patients still alive will be censored at the last non-missing assessment. The 95% CI around the OS rate at 12 months will be presented. Analyses of other time-to-event efficacy endpoints (DOR, TTP, PFS, and TTNLT) will be analyzed in a similar manner. All efficacy summaries will be presented by cohort and overall. **Safety Analysis:** AEs will be summarized by cohort and overall, by System Organ Class, and Preferred Term. Tabulations and listings of values for ECGs, vital signs, and laboratory safety evaluations will be presented. Any abnormal or out-of-range values from laboratory safety evaluations or physical examinations will be presented in data listings.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
Ab	antibody
ABVD	doxorubicin, bleomycin, vinblastine, and dacarbazine
AE	adverse event
Ag	antigen
AIDS	acquired immunodeficiency syndrome
AITL	angioimmunoblastic T-cell lymphoma
ALCL	anaplastic large cell lymphoma
allo-SCT	allogeneic stem cell transplant
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
ART	antiretroviral therapy
ASCO	American Society of Clinical Oncology
ASCT	autologous stem cell transplant
ASH	American Society of Hematology
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
β-hCG	beta human-chorionic gonadotropin
BCRP	breast cancer resistance protein
BEACOPP	bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone
BID	*bis in die* (twice daily)
CAR	chimeric antigen receptor
cART	combination antiretroviral therapy
CBC	complete blood count
CI	confidence interval
CFR	Code of Federal Regulations
cHL	classical Hodgkin Lymphoma
C_{max}	maximum plasma concentration
CMV	Cytomegalovirus
CNS	central nervous system

Abbreviation	Definition
CR	complete response
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DHAP	dexamethasone, cytarabine, and cisplatin
DLBCL	diffuse large B-cell lymphoma
DLT	dose-limiting toxicity
DOR	duration of response
EBER-ISH	Epstein-Barr virus encoded RNA – in situ hybridization
EBV	Epstein-Barr virus
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EEA	European Economic Area
ENKTL	extranodal NK/T-cell lymphoma
EOT	End of Treatment
EPOCH	Etoposide, prednisone, vincristine, cyclophosphamide, hydroxydaunorubicin
ESHAP	etoposide, solumedrol, high-dose cytarabine, cisplatin
FDA	Food and Drug Administration
FDG	fluorodeoxyglucose
FFPE	formalin-fixed paraffin-embedded
GCP	Good Clinical Practice
GCV	Ganciclovir
GvHD	graft-versus-host disease
HBV	hepatitis B virus
HCT	hematopoietic cell transplantation
HCV	hepatitis C virus
HDAC	histone deacetylase
HDACi	histone deacetylase inhibitor
HHV-6/HHV-8	human herpesvirus-6/human herpesvirus-8
HIV	human immunodeficiency virus
HIV-L	HIV-associated lymphoma

Abbreviation	Definition
HL	Hodgkin lymphoma
IARC	International Agency for Research on Cancer
IB	Investigator's Brochure
IC_{50}	half-maximal inhibitory concentration
ICE	ifosfamide, carboplatin, and etoposide
ICF	informed consent form
ICH	International Council for Harmonisation
ICMJE	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
Ig	immunoglobulin
IHC	immunohistochemistry
IND	Investigational New Drug
INR	international normalized ratio
IRB	Institutional Review Board
IRC	Independent Review Committee
ITT	Intent-to-Treat
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenous(ly)
IWG	International Working Group
JAK	Janus kinase
LDH	lactate dehydrogenase
LDi	longest diameter
LMP-1	latent membrane protein-1
MedDRA	Medical Dictionary for Regulatory Activities
MMF	mycophenolate mofetil
mITT	modified Intent-to-Treat
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
mTOR	mammalian target of rapamycin
N	number of patients
n	number of patients in the category

Abbreviation	Definition
NCI	National Cancer Institute
NF-κB	nuclear factor-kappa B
NHL	non-Hodgkin lymphoma
NK/T	natural killer/T-cell
Nstat	Nanatinostat
NOS	not otherwise specified
ORR	objective response rate
OS	overall survival
P-gp	P-glycoprotein
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PD	progressive disease
PD-1	programmed cell death-1
PD-L1	programmed cell death-ligand 1
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetic
PO	*per os* (orally)
PR	partial response
PT	prothrombin time
PTCL	peripheral T-cell lymphoma
PTLD	post-transplant lymphoproliferative disorder
QD	*quaque die* (once daily)
qPCR	quantitative polymerase chain reaction
QTcF	corrected QT interval using Fridericia's method
R-CHOP	rituximab with cyclophosphamide, doxorubicin, vincristine, and prednisone
RBC	red blood cell
REB	Research Ethics Board
RNA	ribonucleic acid
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SAHA	suberoylanilide hydroxamic acid (vorinostat, Zolinza®)

Abbreviation	Definition
SD	stable disease
SGOT	serum glutamic-oxaloacetic transaminase
SGPT	serum glutamic-pyruvic transaminase
SMILE	dexamethasone, methotrexate, ifosfamide, L-asparaginase, and etoposide
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SOT	solid organ transplant
SRC	Safety Review Committee
SSC	Study Steering Committee
SUSAR	suspected unexpected serious adverse reaction
TdP	Torsades de Pointes
TEAE	treatment-emergent adverse event
TIL	tumor-infiltrating lymphocyte
TK	thymidine kinase
$t_{½}$	terminal elimination half-life
t_{max}	time to maximum plasma concentration
T-NHL	T-cell non-Hodgkin lymphoma
TTNLT	time to next anti-lymphoma treatment
TTP	time to progression
ULN	upper limit of normal
US	United States
USPI	United States Prescribing Information
VGCV	Valganciclovir
WBC	white blood cell
WHO	World Health Organization

1. INTRODUCTION

Epstein-Barr virus-positive (EBV$^+$) lymphomas are a heterogeneous group of malignancies that harbor latent EBV within the lymphoma cells, and are associated with variable clinical features, treatments, and prognoses. EBV positivity in lymphomas has been shown to be a poor prognostic indicator in some subtypes, and no established therapies for the treatment of EBV$^+$ lymphomas. In a meta-analysis evaluating survival outcomes across several lymphoma types (Hodgkin lymphoma [HL], diffuse large B-cell lymphoma [DLBCL], natural killer/T-cell [NK/T] lymphoma, peripheral T-cell lymphoma [PTCL]), EBV$^+$ disease was associated with significantly worse overall survival (OS) (Ding 2016). Irrespective of the lymphoma subtype, EBV positivity is associated with significantly reduced OS with standard therapy compared to patients who are EBV negative (EBV$^-$).

Nanatinostat (VRx-3996) is an orally administered hydroxamic acid-based, selective and potent inhibitor of histone deacetylase (HDAC) Class I enzymes HDAC1, HDAC2, and HDAC3, and a potent inducer of EBV kinases (thymidine kinase [TK] and protein kinase [EBV-PK]). These EBV kinases activate the antiviral nucleoside analog ganciclovir via mono-phosphorylation (Gustafson 1998, Meng 2010), resulting in sensitization of tumor cells to ganciclovir (Ghosh 2012), leading 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. This dual or combination approach is predicted to have high tumor specificity based on targeting of EBV-containing cells, while sparing EBV$^-$ cells.

Valganciclovir (VALCYTE® United States Prescribing Information (Genentech 2021) and Summary of Product Characteristics (Roche 2018)), an oral prodrug of ganciclovir, is approved internationally for the treatment of cytomegalovirus (CMV) retinitis in adult patients with acquired immunodeficiency syndrome (AIDS) and prevention of CMV disease in adult and pediatric kidney and heart transplant patients at high risk. Outside of its approved indication, valganciclovir has been shown to be effective in mitigating EBV viral load in EBV$^+$ pediatric liver transplant patients at risk for development of a post-transplant proliferative disorder (Venturi 2009).

EBV-associated lymphomas are often very aggressive and respond poorly to conventional treatments. Clinical support for combining an HDAC inhibitor (HDACi) with an antiviral drug was initially provided by a Phase 1/2 proof-of-concept study conducted with the pan-HDACi, arginine butyrate, in combination with ganciclovir in patients with recurrent EBV$^+$ lymphomas, which demonstrated significant anti-tumor activity (4 complete responses and 6 partial responses) among 15 patients treated (Perrine 2007). In a Burkitt lymphoma cell line, P3HR1, induction of EBV-TK was observed at concentrations of nanatinostat approaching 1 μM, demonstrating approximately 1,000-fold greater potency compared to sodium butyrate. This unique combination approach thus allows nanatinostat to be used as an activator of specific EBV-associated genes present in malignant cells, which confers targeted susceptibility of the cell to the antiviral valganciclovir (an oral prodrug for ganciclovir), causing apoptosis.

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 November 2019. In an ongoing Phase 1b/2 trial (VT3996-201), nanatinostat given in combination with

valganciclovir has been shown to have promising safety, tolerability, and anti-tumor activity in patients with EBV$^+$ lymphomas (see Section 1.2.4).

Based on these findings, as well as the urgent need for new therapies for EBV$^+$ lymphoma, particularly for patients with relapsed or refractory T-cell non-Hodgkin lymphoma (T-NHL), this global Phase 2 study has been developed to continue the evaluation of nanatinostat with valganciclovir in patients with relapsed/refractory EBV$^+$ lymphomas.

1.1. Overview of EBV$^+$ Lymphomas and Current Treatment(s)

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 recognized as a carcinogenic agent by the World Health Organization (WHO) (Swerdlow 2016) and the International Agency for Research on Cancer (IARC) (Chen 2021). Primary infection with EBV typically occurs in childhood and is generally asymptomatic; however, infection later in life may manifest as infectious mononucleosis. 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, and specific expression patterns (Types I to III) of these genes are associated with specific EBV-driven malignancies (Saha 2011). Epigenetic mechanisms play a major role in generating and maintaining the diverse patterns of viral gene expression that can expand tissue tropism, enable evasion of immune detection, and drive oncogenesis (Tempera 2014).

The American Cancer Society estimates 77,240 new cases of non-Hodgkin lymphoma (NHL) and 8,480 new cases of HL in 2020, with 8,480 and 970 deaths, respectively (Siegel 2020). The proportion of EBV positivity varies with the lymphoma subtype. For example, within North America, 30% of HL, 70–80% of angioimmunoblastic T-cell lymphoma (AITL), 30–40% of peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS), and ≥80% of post-transplant lymphoproliferative disorders (PTLDs) are EBV$^+$ (Roschewski 2012, Dojcinov 2018). The incidence of EBV$^+$ disease varies with geographic location; Burkitt lymphomas are almost always EBV$^+$ in tropical regions but less than 30% are positive in the US. EBV is associated with 5–10% of DLBCL in western countries (Tracy 2018) and 10–15% in Asia (Lu 2015).

Outcomes in EBV$^+$ lymphoma patients are typically inferior compared to EBV$^-$ lymphomas of the same subtype. EBV$^+$ DLBCL patients have worse outcomes and share similar poor prognostic indicators, irrespective of age (Lu 2015). For PTCL, EBV$^+$ patients have been reported to have a shorter OS than EBV$^-$ patients (13 vs 72 months respectively, $p = 0.04$) (Haverkos 2017). For HL patients, those who were EBV$^+$ had inferior failure-free survival outcomes compared to EBV$^-$ patients (Kanakry 2013).

As there is no established targeted treatment specific for EBV$^+$ lymphoid malignancies, the standard of care therapy for each lymphoma subtype is utilized. Cytotoxic chemotherapy is the mainstay for front-line treatment of lymphomas with ancillary anti-CD20 antibodies and/or radiotherapy etc., depending on the diagnosis and stage of disease. Treatment options for recurrent lymphomas depend upon the subtype, but generally include "salvage" chemotherapy regimens, stem cell transplantation, brentuximab, chimeric antigen receptor (CAR) T-cell therapy, checkpoint inhibitors, and HDAC inhibitors, among others. However, the prognosis

in relapsed/refractory lymphoma is generally poor. Treatment of relapsed/refractory EBV$^+$ lymphoma is therefore an unmet medical need.

1.1.1. EBV$^+$ Diffuse Large B-cell Lymphoma (EBV$^+$ DLBCL, NOS)

EBV$^+$ diffuse large B-cell lymphoma, not otherwise specified (EBV$^+$ DLBCL, NOS) per the WHO classification (Swerdlow 2016)) is the most common subtype of EBV$^+$ NHL, and approximately 10% of DLBCL is EBV$^+$. Originally considered to be a disorder of elderly patients and included as a provisional entity in the WHO classification in 2008 as "EBV$^+$ DLBCL of the elderly", the category was updated in 2016 to "not otherwise specified" as cases were increasingly noted in younger individuals. Patients with EBV$^+$ DLBCL, NOS tend to be older when diagnosed, with a more advanced disease stage and higher rates of extranodal involvement (particularly with respect to the gastrointestinal tract, skin, and bone marrow) (Castillo 2018).

There is no uniformly accepted treatment for EBV$^+$ DLBCL beyond the current standard of care, the combination of the anti-CD20 monoclonal antibody rituximab with cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP). Limited data have been published comparing the outcomes of rituximab-based regimens in patients with EBV$^+$ DLBCL and patients with EBV$^-$ DLBCL. One study reported that OS and progression-free survival (PFS) were significantly worse in EBV$^+$ patients compared to EBV$^-$ patients who received CHOP/CHOP-like regimens ($p = 0.0002$ and $p < 0.0001$, respectively) (Sato 2014). In contrast, another retrospective analysis reported similar survival outcomes for EBV$^+$ and EBV$^-$ patients in the post-rituximab era, although complete response (CR) rates were lower in EBV$^+$ patients (59% vs 73%) (Beltran 2018). The largest retrospective study reported the outcomes of 250 DLBCL patients, 35 (14%) were EBV$^+$ (Lu 2015). EBV$^+$ patients, irrespective of age (> or ≤50) had a significantly worse PFS ($p < 0001$) and OS ($p < 0001$) compared to the EBV$^-$ patients. However, given its aggressive nature, and the poor outcomes of EBV$^+$ DLBCL (Lu 2015, Sato 2014, Oyama 2007, Park 2007), other novel therapies are needed, particularly for patients who have relapsed or are refractory to therapy. Treatment options for patients with relapsed/refractory DLBCL are based upon the intention to proceed to autologous stem cell transplant (ASCT) or not, and initially may include various cisplatin-containing chemotherapy regimens such as DHAP (dexamethasone, cytarabine, and cisplatin), ESHAP (etoposide, solumedrol, high-dose cytarabine, cisplatin), ICE (ifosfamide, carboplatin, and etoposide), gemcitabine-containing regimens, or anti-CD19 CAR-T-cell therapy. More recently approved options for patients having received ≥2 prior therapies include Selinexor (US only) and polatuzumab vedotin + bendamustine/rituximab, and for those who are not eligible for ASCT, tafacitamab with lenalidomide (US only).

1.1.2. Peripheral T-Cell Lymphoma (PTCL)

Peripheral T-cell lymphomas comprise a heterogeneous group of aggressive malignancies, classified into nodal and extranodal subtypes. Nodal PTCLs are the most common and include PTCL, PTCL-NOS, AITL, and anaplastic large cell lymphoma (ALCL). Around 70% of patients with PTCL are refractory to first-line therapy or relapse of their disease (Dreyling 2013). Clinical practice guidelines (Dreyling 2013, NCCN 2022) and data from a recent prospective multicenter cohort study (Carson 2017) support use of an anthracycline-containing regimen (CHOP) +/- etoposide for initial therapy. Monotherapy options for recurrent disease in some

countries include the HDAC inhibitor, belinostat, and pralatrexate and bendamustine, with 26% to 47% overall response rates (11% to 29% CR rates) reported (reviewed in (Dreyling 2013, O'Connor 2015), or brentuximab vedotin (for CD30+ PTCL). While romidepsin was previously approved in the US for recurrent PTCL, a recent Phase 3 study evaluating romidepsin plus CHOP (Ro-CHOP) versus CHOP in first-line PTCL patients did not meet the primary efficacy endpoint of PFS, and the PTCL indication was withdrawn from the US market (Bachy 2022). Combination platinum-based regimens such as DHAP, ESHAP, ICE, or with gemcitabine-containing regimens, followed by ASCT for consolidation are recommended with chemosensitive disease (Dreyling 2013, NCCN 2022). Allogeneic stem cell transplant (allo-SCT) has so far offered the only curative treatment in relapsed/refractory PTCL.
Single-agent therapies (eg, lenalidomide, belinostat, brentuximab vedotin) are recommended for palliative intent. Clinical trials are currently recommended for all lines of therapy for PTCL (Dreyling 2013, NCCN 2022). Most patients with relapsed or refractory PTCL have poor outcomes, with median PFS and median OS reported to be 3.7 and 6.5 months, respectively, for those who receive chemotherapy at relapse (Mak 2013).

1.1.3. Extranodal NK/T-Cell Lymphoma (ENKTL)

Extranodal NK/T-cell lymphoma (ENKTL) is a subtype of mature T- and NK-cell lymphoma included in the WHO classification (Swerdlow 2016), and while less prevalent than nodal PTCL, has a higher incidence in Asian and South American populations and is uncommon in other countries (Tse 2017). A defining feature of ENKTL is the infection of lymphoma cells with EBV, and the involvement of the nasal and upper pharyngeal regions. This is an aggressive malignancy that is resistant to anthracycline-containing regimens because of its expression of P-glycoprotein (P-gp), and no standard treatment has been established based on the results of randomized clinical trials. Following greatly improved outcomes (objective response rate [ORR] 79%) with L-asparaginase-based regimens for patients with recurrent disease (Yamaguchi 2011), it is currently recommended that first-line treatment of ENKTL should include L-asparaginase (eg, SMILE: dexamethasone, methotrexate, ifosfamide, L-asparaginase, and etoposide) and local (nasopharyngeal) radiotherapy (Dreyling 2013, NCCN 2022), with hematopoietic stem cell transplantation recommended as front-line consolidation therapy for patients with advanced disease. However due to the aggressive nature of this disease, the 3-year OS of high-risk patients (per the PINK-E prognostic index for ENKTL) is less than 30% (Kim 2016).

Nearly 50% of patients with newly diagnosed ENKTL develop disease progression, and for patients who have previously received regimens not containing L-asparaginase, salvage therapy with SMILE or similar regimens is effective. However, patients who have relapsed following or are refractory to L-asparaginase-based therapy have a very poor outcome with salvage chemotherapy, even after allogeneic stem cell transplantation, with a reported median PFS and OS of 2.3 and 4.9 months, respectively (Ahn 2013, Jeong 2018).

NK/T-cell lymphoma cells express programmed death-ligand 1 (PD-L1), which is upregulated by the EBV latent membrane protein 1. Some preliminary responses in patients receiving anti-PD-L1 and anti-programmed cell death-1 (PD-1) inhibitors have been reported in early phase clinical trials with a limited number of patients (Li 2018, Kim 2020). Therefore, new treatment options are urgently needed for ENKTL patients with recurrent/persistent disease following first-line therapy due to a lack of available treatment options and very poor outcomes with salvage therapy.

1.1.4. Hodgkin Lymphoma (HL)

EBV is associated with approximately one-third of HL cases, and in a contemporary retrospective population-based study, EBV positivity was demonstrated to be an independent adverse prognostic factor in patients >50 years of age with classic HL (Diepstra 2009). The standard treatment of EBV^+ HL is not different from that for EBV^- HL of the same stage, histology, and prognosis (Ansell 2018) and is guided by clinical stage and risk stratification. Systemic chemotherapy with doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD), followed by involved-field radiotherapy when indicated, is considered the standard of care. Brentuximab vedotin in combination with doxorubicin, vinblastine, and dacarbazine (AVD) is also recommend as an alternative regimen for patients with advanced HL; 5-year PFS compared with ABVD was 82.2% versus 75.3% (HR 0.68 [95% CI 0.53-0.87]; p=0.0017) in a recently-reported Phase 3 randomized controlled clinical trial (Straus 2021, NCCN 2022). The regimen of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP) is an alternative option for patients with high-risk, advanced-stage disease. Patients who are refractory to or have relapsed following these therapies have been treated with novel agents targeting CD30, PD-1, HDAC, nuclear factor-kappa B (NF-κB), Janus Kinase (JAK) 2, and mammalian target of rapamycin (mTOR), with varying degrees of success; ASCT remains the standard of care for curative therapy (Karantanos 2017).

1.1.5. Post-Transplant Lymphoproliferative Disorders (PTLD)

Post-transplant lymphoproliferative disorders (PTLD) occur in the setting of prolonged immunosuppression following hematopoietic stem cell or solid organ transplantation, with the majority associated with EBV. PTLD is classified into 4 general groups: monomorphic PTLD, B-cell type; polymorphic PTLD; monomorphic PTLD, T-cell type; and classical HL PTLD; about 85% are of B-cell origin. The evaluation of EBV status is an essential part of the diagnostic work-up, commonly performed by available lab-developed assays such as latent membrane protein 1 (LMP-1) or Epstein-Barr encoded region *in situ* hybridization (EBER-ISH). Given that recipient EBV seronegativity is considered a risk factor for the development of PTLD and given that the seroprevalence of EBV increases with age, younger patients post-transplant are particularly at risk.

Treatment is largely dependent on the PTLD subtype. Due to a deficiency of randomized controlled trials and the heterogeneity of PTLD, the standard of care therapy has not been defined. The initial management of monomorphic PTLD, B-cell, and polymorphic PTLD involves the reduction of immunosuppressive therapy (RI) if possible, or a risk-stratified sequential approach to therapy with either rituximab alone for patients who would not be eligible for chemotherapy due to underlying comorbidities or chemoimmunotherapy (eg with R-CHOP) (Dierickx 2018). Using such approaches has resulted in reported CR rate of 70% with a median OS rate of 6.6 years (Trappe 2017).

Responses to first-line therapy are not durable in most cases. In the hematopoietic cell transplantation (HCT) setting, approximately 50% of cases fail initial treatment. Patients whose disease is relapsed or refractory after treatment with first-line therapy have limited treatment options and rapidly decline with high mortality, often within 1 or 4 months, respectively (Sanz 2021, Dharnidharka 2021). In solid organ transplant (SOT) patients who failed rituximab plus chemotherapy or cannot receive a chemotherapy regimen, the median survival was

approximately 3 months. In a recent retrospective cohort study of 18 HCT subjects, the median survival from diagnosis of rituximab-refractory disease was 1.7 months (Socié 2020). Analysis of an expanded multinational population in 2021 confirmed these findings: patients with EBV^+ PTLD following HCT who failed rituximab have a median OS of 0.7 months (Sanz 2021), and patients with EBV^+ PTLD following SOT who failed rituximab plus chemotherapy, the median survival was 4.1 months (Dharnidharka 2021).

There are no established treatments for relapsed or refractory PTLD, although reduced-intensity chemotherapy, rituximab monotherapy, or other agents (interferon-α, anti-interleukin-6 antibodies) (Zimmermann 2011) have been used, with variable and often limited success. EMA recently approved an EBV-specific allogeneic T-cell immunotherapy for adult and pediatric patients with relapsed or refractory EBV^+ PTLD who have received at least one prior therapy. Treatment options for pediatric patients with PTLD follow the same treatment algorithms as adults with generally similar outcomes. Yet, new therapeutic options are urgently needed for PTLD, especially for patients with relapsed or refractory disease.

1.1.6. Lymphomas Associated with HIV infection (HIV-L)

In human immunodeficiency virus (HIV)-positive individuals, EBV-related lymphomas are more prevalent than in HIV-negative cases, despite effective control of viremia and improvement in CD4 counts with combination antiretroviral therapy (cART). The most common HIV-associated lymphomas according to the 2017 WHO classification of tumors of hematopoietic and lymphoid tissues include plasmablastic, Burkitt, DLBCL, and Hodgkin lymphoma (Swerdlow 2017). EBV is associated with DLBCL and HL in 30 to 90% and almost all cases respectively, as well as up to 50% of AIDS-related lymphomas (Carbone 1993, Shindiapina 2020). Classic HL in the setting of HIV is mostly the mixed cellularity subtype, although the prevalence of nodular sclerosing HL has increased with higher CD4 counts due to the impact of cART (Biggar 2006). The prevalence of EBV in HIV positive- cases of Burkitt lymphoma in a multicenter study in the US was reported to be 60% versus 20% in non-endemic HIV-negative cases (Mbulaiteye 2014). Clinically, these lymphomas tend to present with advanced stages of disease, and involve the gastrointestinal tract, central nervous system (although less frequently after the introduction of cART) and extranodal sites including the liver and bone marrow, and lymphoma remains the most frequent neoplastic cause of mortality in individuals with HIV (Grulich 2015).

Although initially outcomes for HIV-associated lymphomas were inferior to HIV-negative individuals, the advent of cART boosting immune function has had a major impact on the tolerability of chemotherapy regimens, and therapeutic approaches to disease management are largely similar to standard of care in HIV-negative individuals (eg, for HL) (Dunleavy 2012). For aggressive HIV-associated B-cell lymphomas, although rituximab (if CD20+) with EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, hydroxydaunorubicin) is the preferred regimen, R-CHOP is acceptable, with a risk-adapted approach to intrathecal therapy (NCCN 2022). For relapsed or refractory disease, salvage regimens include bortezomib-ICE or other regimens (see Section 1.1.1).

1.2. Overview of Investigational Treatment

1.2.1. Overview of Nanatinostat

Nanatinostat (VRx-3996) is a selective HDAC Class I inhibitor with activity against HDAC1, HDAC2, and HDAC3. In both 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).

1.2.1.1. Nonclinical Experience with Nanatinostat

1.2.1.1.1. Nonclinical PK and Metabolism of Nanatinostat

Preclinical studies have shown that nanatinostat, as a single agent, has good oral bioavailability in rats and dogs, on the order of 30–40%, and demonstrates good tissue penetration in rat models. Nanatinostat metabolism is not CYP-mediated, does not induce CYP459 isoforms, and appears to be a poor inhibitor of CYP450 isoforms, using model substrates and inhibitors across all studies.

1.2.1.1.2. 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 suggested both a dose relationship and plateau in biologic response, with increased acetylation apparent at the 20 mg per day dose level and plateauing at levels ≥40 mg/day.

1.2.1.2. Clinical Experience with Nanatinostat Monotherapy in Advanced Cancers

A Phase 1 study evaluating nanatinostat as a single agent was performed in 39 patients with refractory solid tumors (Banerji 2012). Nanatinostat was administered once daily (QD) orally (PO) at doses ranging from 5 to 160 mg on a 28-day cycle. Dose-limiting toxicities (DLTs) were thrombocytopenia (160 mg), fatigue (80 and 120 mg), elevations in serum creatinine (80 and 120 mg), and atrial fibrillation (40 mg). The maximum tolerated dose (MTD) was established as 80 mg. Most adverse events (AEs) were low grade (Grade 1 or 2), most commonly fatigue and nausea. Regarding efficacy, there was 1 partial response (PR) (160 mg dose group) and 9 had stable disease (SD).

The pharmacokinetics (PK) of nanatinostat showed rapid absorption with peak plasma concentrations occurring at approximately 1 hour. Although there was pronounced variability in exposure across the dose levels, areas under the plasma concentration-time curve (AUCs) were broadly proportional over the administered dose range. The median terminal elimination half-life ($t_{½}$) was approximately 2 hours. There were no apparent differences between Day 1 and Day 28 PK parameters, suggestive of no apparent accumulation.

For further details on clinical and nonclinical experience, please refer to the latest version of the nanatinostat (VRx-3996) Investigator's Brochure (IB).

1.2.2. Overview of Valganciclovir

Valganciclovir (VALCYTE®), an oral prodrug of ganciclovir, is approved internationally for treatment of CMV retinitis in adult patients with AIDS and prevention of CMV disease in adult and pediatric kidney and heart transplant patients at high risk. The antiviral activity of valganciclovir is based on the generation of ganciclovir-triphosphate, which is a competitive substrate for the CMV DNA polymerase.

The recommended adult dosing for treatment of CMV retinitis is 900 mg orally twice daily (BID) for 21 days followed by a maintenance dose of 900 mg QD. 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. Dosage reductions based on creatinine clearance are recommended for patients with renal impairment. Notable AEs include cytopenias and acute renal failure. Elderly patients, patients receiving nephrotoxic drugs, and inadequately hydrated patients are at higher risk for renal dysfunction.

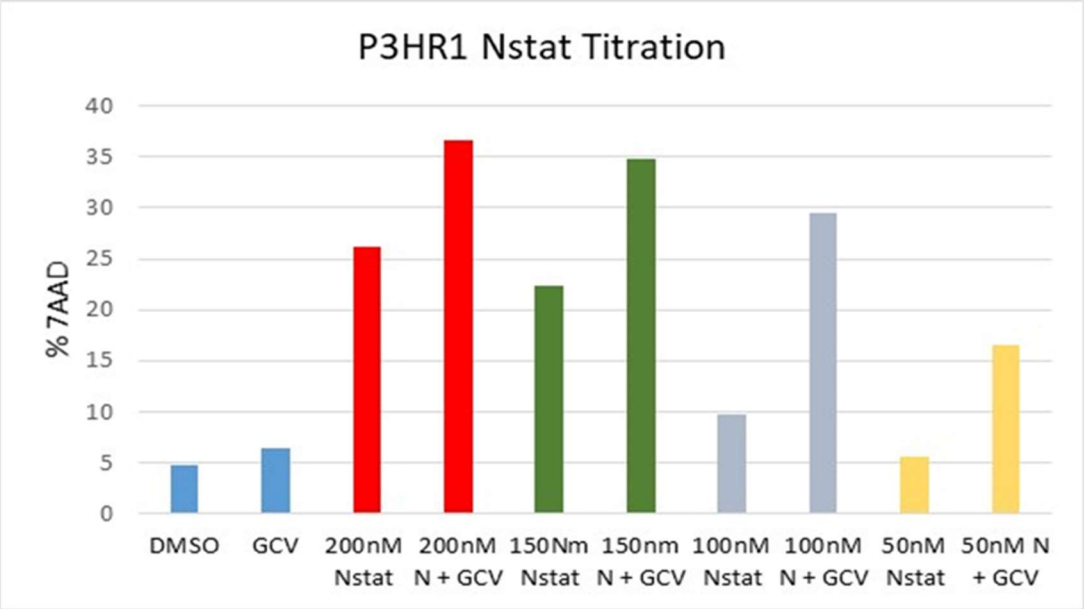
1.2.3. Rationale for the Combination of Nanatinostat (VRx-3996) and Valganciclovir

1.2.3.1. Nonclinical Experience with Nanatinostat and Valganciclovir

The mechanism of action underlying the combination therapy approach to EBV^+ lymphomas depends upon both drug components – nanatinostat as a virus gene-inducing agent, and ganciclovir as the prodrug that is activated by viral gene products induced by nanatinostat to cause tumor cytotoxicity. In published time-course experiments, discontinuous exposure to the HDACi 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). Exposure of P3HR1 cells to the HDACi butyrate in vitro induced measurable EBV-TK and protein kinase gene expression at 6 hours. Subsequently, 6-hour pulses daily for 1, 2, or 3 days were shown to sensitize P3HR1 cells in vitro to ganciclovir, with significantly greater cytotoxicity observed with the combination compared to either butyrate or ganciclovir alone.

The cytotoxic activity of the combination of nanatinostat plus ganciclovir has been demonstrated in in vivo models of EBV^+ Burkitt lymphoma, substantially inhibiting tumor growth compared to the administration of either agent alone. In vitro, the combination of increasing concentrations of nanatinostat with a fixed dose of ganciclovir in P3HR1 cells increased cytotoxicity compared to either nanatinostat or ganciclovir alone (Figure 1).

Figure 1: Cytotoxicity in P3HR1 Cells



Abbreviations: DMSO = dimethyl sulfoxide; GCV = ganciclovir; N = nanatinostat; Nstat = nanatinostat.
7AAD is a cell viability assay. % 7AAD indicates the fraction of tumor cells that take up the dye 7AAD, resulting in fluorescence, and are therefore dead.

In an in vivo murine lymphoma model, 5 Balb/C nude mice per treatment group were injected with 1×10^7 P3HR1 cells in Matrigel® in the right flank and once tumors reached 100–150mm^3, received 5 mg/kg nanatinostat on a 4 day/week intermittent dosing cycle as a monotherapy or in combination with daily ganciclovir (5 mg/kg nanatinostat + 100 mg/kg ganciclovir). Tumor volumes were reduced by approximately 32% by Day 30 for nanatinostat plus ganciclovir but were not significantly affected by either nanatinostat or ganciclovir alone (data on file).

Similar effects have been demonstrated in xenograft models of EBV$^+$ solid tumors. The combination of romidepsin and ganciclovir was reported to induce enhanced killing of EBV$^+$ tumor cells in xenograft models of nasopharyngeal carcinoma (HA cell line) and gastric cancer (SNU-719 cell line) compared to either drug alone (Hui 2016). Similarly, the combination of nanatinostat plus ganciclovir induced significant cytotoxicity in murine xenograft models of EBV$^+$ gastric cancer (SNU-719 cell line) compared to either drug alone. SNU-719 tumor cells were injected subcutaneously into immunocompromised B-NDG mice. Once tumors reached a volume of 100–150 mm^3, treatment was initiated according to the following dosing groups (n = 8 mice/group): Control (saline), ganciclovir 50 mg/kg, nanatinostat 5 mg/kg, nanatinostat 15 mg/kg, nanatinostat 5 mg/kg + ganciclovir 50 mg/kg, nanatinostat 15 mg/kg + ganciclovir 50 mg/kg. Nanatinostat was administered 4 days/week and ganciclovir 7 days/week. The combination of nanatinostat 15 mg/kg + ganciclovir 50 mg/kg showed a significant reduction in tumor burden for SNU719 tumors at 32 days, compared to ganciclovir or nanatinostat alone. This anti-tumor effect of the combination was dose-dependent as the nanatinostat dose was increased (in combination with the fixed ganciclovir dose).

The relative potency of nanatinostat compared to other clinically approved and experimental HDACi for inhibition of Class I HDAC is presented in Table 1.

Table 1: IC_{50} Values (nM) for Various HDAC Inhibitors

Agent	Nstat*	Vorinostat*	Panobinostat	Belinostat	Entinostat	Mocetinostat	Givinostat
HeLa extract	9	60	-	-	11,000	1,850	-
HDAC1 (I)	3	90	3	41	181	34	28
HDAC2 (I)	4	25	-	-	-	-	-
HDAC3 (I)	7	150	4	30	2311	998	21

Abbreviations: HDAC = histone deacetylase; IC_{50} = half-maximal inhibitory concentration; Nstat = nanatinostat.
*Data on file. Other data from literature (Beckers 2007, Moffat 2010). Nanatinostat was assayed using vorinostat (suberoylanilide hydroxamic acid [SAHA], Zolinza®) as a positive control; (-) indicates not determined.

It is well established that selective inhibition of HDAC-1, -2, and -3 by small interfering RNA or specific HDACi (eg, romidepsin, MS-275, and apicidin) can induce the latently infected EBV^+ lymphoma cells into the EBV lytic cycle. This in turn mediates enhanced killing with ganciclovir in vitro and in vivo (Hui 2016).

The observation that nanatinostat is a highly potent inhibitor of Class I HDAC supports the rationale for the combination of nanatinostat with ganciclovir at concentrations of nanatinostat below the level required to induce direct cytotoxicity to maximize cell killing through activation of EBV-PK and subsequent activation of ganciclovir.

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, PK data from the VT3996-201 study has demonstrated that nanatinostat does not reach these concentrations at the doses tested in human plasma and it is rapidly eliminated from the circulation. These data suggest that while nanatinostat could be capable of inducing tumor cell death as a single agent, the concentrations of nanatinostat required would be much higher that observed or potentially achievable with the current dosing regimen. In addition, the nanatinostat dose for this study (20 mg daily, Days 1 to 4 per week) is <20% of the MTD (80 mg daily), as determined in a single agent Phase 1 study in patients with advanced solid tumors (Banerji 2012).

Regarding valganciclovir as a monotherapy, during active EBV infections, EBV lytic phase protein kinases are required to convert the prodrug valganciclovir to an active antiviral drug. However, since EBV exists in its latent form in tumor cells, valganciclovir has no activity against EBV in the absence of EBV lytic phase protein kinases. Taken together, these data support the conclusion that the activity of nanatinostat and ganciclovir is dependent on their coadministration and is superior to that of either compound alone.

1.2.4. Clinical Experience with Nanatinostat Plus Valganciclovir in EBV^+ Lymphoma

A single arm Phase 1b/2 dose escalation/expansion study of nanatinostat in combination with valganciclovir (Study VT3996-201) is being conducted in patients with relapsed/refractory EBV^+ lymphoma. Key eligibility criteria for enrollment included age ≥18 with histologically confirmed EBV^+ lymphomas, ≥1 prior lines of therapy and no curative treatment options per investigator. In Phase 1b (n=25), the RP2D of nanatinostat (20 mg daily, Days 1 to 4 per week) and valganciclovir (900 mg daily) was selected based on evaluation of the following dose levels:

- Cohort 1 (n = 7): nanatinostat 10 mg oral twice daily + valganciclovir 900 mg oral twice daily (20+1800)

- Cohort 2a (n = 5): nanatinostat 5 mg oral twice daily + valganciclovir 450 mg oral twice daily (10+900)
- Cohort 2b (n = 4): nanatinostat 10 mg oral once daily + valganciclovir 450 mg oral once daily (10+900)
- Cohort 2c (n = 4): nanatinostat 10 mg oral once daily + valganciclovir 900 mg oral once daily (10+900)
- Cohort 3 (n = 5): nanatinostat 20 mg oral once daily, Days 1 to 4/week + valganciclovir 900 mg oral once daily (20+900)

In Cohort 1, 3 of the first 4 patients enrolled developed DLTs (Grade 4 neutropenia × 29 days, Grade 3 thrombocytopenia × 6 days, Grade 4 thrombocytopenia × 8 days), and 3/4 patients developed Grade 1 and 2 creatinine elevations. The picture of 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 this, 1 patient developed a DLT (uncomplicated Grade 3 thrombocytopenia × 7 days), therefore, Cohort 1 was considered to have exceeded the MTD. In Cohort 2, across the 3 cohorts (2a, 2b, 2c; n = 13), there were no DLTs reported. The Safety Review Committee (SRC) made the recommendation to proceed in Cohort 3 with nanatinostat 20 mg daily using an intermittent schedule for administration (ie, 4 days on, 3 days off) with valganciclovir 900 mg once daily. The dosing regimen for Cohort 3 was subsequently declared to be the RP2D, as no DLTs were reported.

As of the data cutoff date (04 May 2023), 64 patients (14 B-NHL, 25 T-NHL, 12 HL, 13 other) were enrolled; 25 in Phase 1b, and 39 patients received the RP2D (nanatinostat 20 mg daily, Days 1 to 4 per week plus valganciclovir 900 mg daily) in a Phase 2 expansion cohort; all patients had been followed for DoR for almost 12 months from first dose of study drug. Ten additional patients were planned to receive the nanatinostat tablet formulation in a PK cohort.

Lymphoma subtypes were DLBCL (n=10), ENKTL (n=10), PTCL-NOS (n=5), AITL (n=8), cutaneous T-cell lymphoma (n=2), HL (n=12), other B-cell (n=4), and immunodeficiency-associated lymphoproliferative disorders (IA-LPD; n=13), including PTLD (n=4), HIV associated (n=5), and other (n=4: systemic lupus erythematosus [n=2], common variable and primary immunodeficiency [n=1 each]). Patients had a median of 2 prior therapies (range 1 to 13); 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. For all evaluable patients (n=50), the ORR/CR rate was 36% (18/50) / 16% (8/50), and the median duration of response (DOR) was 6.5 months.

Responses were observed across multiple lymphoma subtypes, including AITL, DLBCL, IA-LPD, PTCL, and PTLD. The lead lymphoma subtype of (8 evaluable) PTCL patients, the ORR, CRR, and median and mean DOR were 50%, 37.5%, and 17.1 months and 22.2 months, respectively. Of the 9 evaluable patients with DLBCL, 3 had a CR (both primary refractory DLBCL), and 3 had a PR; prior therapies and response durations in these patients are shown in Table 6. In most patients, responses were seen by the time of the first disease response assessment. Several durable responses were observed, as the median and mean DORs were 6.5 and 15 months, respectively. The median DOR was 38.3 months in the AITL subgroup and 20.8 months in the ENKTL subgroups, with the median not yet reached in the DLBCL cohort where a few patients continued on study treatment at the time of this analysis. Of note, one of the CRs

was achieved in an EBV+ PTCL patient whose disease never responded to second-line histone deacetylase inhibitor (HDACi) treatment, and one of the CRs was achieved in an EBV+ DLBCL patient whose disease never responded to first-line R-CHOP chemotherapy. Also notable, 2 patients with DLBCL and 1 patient with ENKTL continued on treatment approximately 39+ months. Three patients (PTCL, ENKTL, HL), who at the time of enrollment in this study were not eligible for SCT or CAR-T-cell therapy, achieved adequate disease control and were able to proceed to SCT (n=1 autologous and n=1 allogeneic) or CAR-T-cell therapy (n=1), which are notable outcomes for heavily pretreated patients with poor prognoses. Four patients remained on study treatment at the time of data cutoff.

As of the data cutoff date (04 May 2023), 64 patients overall were evaluable for safety (Phase 1b: 25 patients, Phase 2: 30 patients, nanatinostat tablet PK cohort: 9 patients). The most common (>20% of patients) treatment-emergent AEs (TEAEs) reported overall were platelet count decreased / thrombocytopenia (16 [25%] and 11 [17.2%]), nausea (25 [39.1%]), neutropenia / neutrophil count decreased (14 [21.9%] and 11 [17.2%]), anaemia (24 [37.5%]), fatigue (22 [34.4%]), constipation and diarrhea (19 patients each [29.7%]), increased blood creatinine (17 [26.6%]), and vomiting (15 [23.4%]). Most TEAEs were Grade 1 or 2 in severity. Most TEAEs were Grade 1 or 2 in severity.

Across all cohorts, the most frequently reported Grade 3/4 TEAEs (>10% of patients) were neutropenia / neutrophil count decreased (12 [18.8%] and 9 [14.1%]), platelet count decreased / thrombocytopenia (6 [9.4%] and 8 [12.5%]), and anaemia (13 [20.3%]). Specifically, among the events of increased creatinine, all were Grade 1 or 2 in severity.

No study drug-related deaths occurred. Serious adverse reactions (n=12) included febrile neutropenia and atrial fibrillation (each n=2, [3.1%]), and anemia, neutropenia, thrombocytopenia, pharyngitis, sepsis, myelodysplastic syndrome, tumor necrosis, and dyspnoea (each n=1 [1.6%]). Thirteen (20%) patients had adverse events resulting in drug withdrawal.

The combination of nanatinostat and valganciclovir was well-tolerated and showed preliminary efficacy in a population of heavily pretreated patients with a variety of EBV^+ lymphomas, the majority of whom were refractory to their last therapy prior to entering the study. Patients with relapsed/refractory T/NK-NHL and DLBCL showed the most promising response rates. Thus, the combination of nanatinostat and valganciclovir may be a potential therapy for patients with relapsed/refractory EBV^+ lymphomas for whom effective therapies are urgently needed.

1.3. Potential Benefits and Risks

1.3.1. Potential Benefits

As described in Section 1.2.4, preliminary data from the Phase 1b/2 VT3996-201 study indicate that at the RP2D, the combination of nanatinostat and valganciclovir was generally well-tolerated and demonstrated clinical activity in a population of heavily pretreated patients with a variety of recurrent EBV^+ lymphomas, the majority of whom were refractory to their last therapy prior to entering the study. Patients with relapsed/refractory DLBCL and ENKTL showed the most promising response rates, including CRs in 2 patients with primary refractory DLBCL. The combination appears to be highly active in patients with recurrent PTCL and ENKTL, including those who had failed stem cell transplantation. The oral administration of both

nanatinostat and valganciclovir is an added benefit to patients, as they can take their study treatment at home. The eligibility of adolescents (≥12 years of age) with PTLD in this study is supported by the guidance in which the histology and biologic behavior of the cancer under study is the same as adult patients, or when the molecular target of the investigational treatment is relevant to both adult and adolescent patients (*federalregister.gov/d/2019-04582*).

1.3.2. Potential Risks

HDAC inhibitors are potent inducers of the EBV lytic cycle; the production of infectious virus by virtue of HDACi-mediated induction of the tumor lytic cycle is a clinically documented AE described in a monotherapy clinical trial with the HDACi romidepsin, but this potential safety issue can be abrogated by the coadministration of ganciclovir (GCV). In the Phase 1b/2 VT3996-201 study, patients' EBV genome levels have been serially monitored. There have been no reported cases of EBV or CMV reactivation, and no significant elevations of plasma EBV DNA have been noted thus far in these patients receiving nanatinostat co-administered with valganciclovir, indicating that this combination is potentially preventing EBV viremia.

EBV reactivation has been reported in 3 ENKTL patients receiving romidepsin as a monotherapy (Kim 2016). Romidepsin-induced EBV reactivation was also reported in 2 patients with relapsed PTCL who were receiving romidepsin in a Phase 2 trial (Ritchie 2009). The romidepsin prescribing information describes a risk of reactivation of DNA viruses, including EBV (ISTODAX® USPI 2021 (Celgene 2021)). Due to the reported activity of HDACi's in PTCL, the potential anti-tumor activity of nanatinostat as a monotherapy will be evaluated in 10 patients with PTCL in this study. Because of the risk of EBV reactivation in patients with EBV^+ lymphomas receiving monotherapy with HDACi's, these patients will be monitored closely for clinical signs and lab evidence of EBV or other viral reactivation during their short course (6 weeks) of monotherapy.

Dosing for valganciclovir is consistent with the approved dose. Any necessary dose adjustments (eg, in the case of creatinine elevations) will be made according to the prescribing information. The safety profile for this dose of valganciclovir is well defined and appears acceptable as part of a treatment regimen for patients with relapsed/refractory lymphoma. Further information about valganciclovir can be found in the prescribing information (VALCYTE® USPI 2021 and SmPC 2018 (Genentech 2021, Roche 2018).

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, in prior clinical studies other toxicities reported for one or both agents include fatigue, atrial fibrillation, nausea/vomiting, anemia, leukopenia, and neutropenia.

As QTc prolongation has been reported with other HDAC inhibitors, (Gryder 2012), medications with a known risk of prolonging the QT interval should be avoided (Section 5.5.4).

As with any new combination, toxicities which have not been seen with either agent alone or with combinations of similar agents may become manifest.

Available clinical data indicates a 2- to 2.5-fold higher systemic exposure of nanatinostat with the co-administration of valganciclovir, which is expected, as valganciclovir/ganciclovir is the MDR1 and BCRP inhibitor, and nanatinostat is the substate of MDR1 and BCRP transporters.

The systemic exposure of ganciclovir from nanatinostat and valganciclovir co-administration is consistent with that from valganciclovir monotherapy reported in the literature.

Further information about the safety profile of nanatinostat as a single agent and in combination with valganciclovir can be found in the current IB.

1.3.3. Risks Related to Study Procedures

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

1.3.4. 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 5.4). Patients receiving nanatinostat monotherapy will be closely monitored for potential EBV reactivation and will have a disease response assessment 2 weeks earlier than patients in the combination arm.

The benefit-risk balance of the oral treatment regimen with nanatinostat and valganciclovir is anticipated to be positive for the target study population of relapsed/refractory EBV^+ lymphoma patients who have previously received 1 or more prior therapies and in the opinion of the Investigator have exhausted all standard therapies.

2. OBJECTIVES AND ENDPOINTS

The study objectives and related endpoints are presented in Table 2. Details of the statistical analysis are described in Section 9.

Table 2: Objectives and Endpoints

Objective(s)	Endpoint(s)
Primary	Refer to Section 9.6.1 for methods of analysis.
To evaluate the anti-tumor activity of the combination treatment of nanatinostat (Nstat) with valganciclovir (VGCV) based on objective tumor response rates	• Objective response rate (ORR) as assessed by an Independent Review Committee (IRC) – defined as the proportion of patients who achieve a complete response (CR) or partial response (PR) using the 2007 International Working Group (IWG) criteria (Cheson 2007); Table 13. The Investigator will also use the 2007 IWG criteria for assessment of progression/relapse and for any clinical decisions requiring assessment of disease progression/relapse.
Secondary	Refer to Section 9.6.2 for methods of analysis.
To determine the duration of tumor control	• Duration of response (DOR) – defined as the interval from the date of first observed CR or PR to the date of disease progression, death due to any cause, or last adequate (radiographic) response assessment. • Time to next anti-lymphoma treatment (TTNLT) – defined as the interval from the start of study drug treatment to date of next anti-lymphoma treatment.

Objective(s)	Endpoint(s)
	• 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. • Time to progression (TTP) – defined as the interval from the start of study drug treatment to date of disease progression.
To determine survival outcomes	• Overall survival (OS) – defined as the interval from the start of study drug treatment to date of death, for any reason.
To describe the safety profile of the combination treatment of Nstat with VGCV	• Incidence and severity of treatment-emergent adverse events (TEAEs). Adverse events will be graded according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 5.0.
To generate pharmacokinetic (PK) data with the intended commercial dose and administration of Nstat	• Pharmacokinetic (PK) parameters (eg, time to maximum plasma concentration [t_{max}], maximum plasma concentration [C_{max}], area under the plasma concentration-time curve [AUC]).
Exploratory	Refer to Section 9.6.3 for methods of analysis.
Explore correlation of baseline PD-L1 expression and other immune checkpoint molecules with outcome	• Expression of PD-L1 and other immune checkpoint molecules in tumor • Tumor-infiltrating lymphocyte (TIL) counts (eg, CD3, CD4, CD8) • EBV-associated genes/proteins (eg, EBER, BZLF-1/ZTA, LMP-1, BGLF-4/PK, BXLF-1/TK, BRLF-1Rta)
Evaluate potential biomarkers of activity of combination therapy	• Histone H3 acetylation • Plasma EBV DNA levels • RNA expression of selected immunological genes • Flow cytometry/IF/IHC for immune cell markers
Identify potential resistance markers to therapy	EBER, LMP-1, TIL counts, PD-L1 and other immune checkpoint molecules; markers related to resistance

3. STUDY DESIGN

The purpose of this study is to determine the efficacy of the combination treatment of nanatinostat with valganciclovir in patients with relapsed/refractory EBV^+ lymphomas.
No therapies are currently established for the treatment of EBV^+ lymphoma; with use of standard therapies for the lymphoma subtypes, outcomes such as PFS and OS are increasingly recognized to be inferior for EBV^+ lymphomas such as EBV^+ DLBCL (NOS), HL, and PTCL, creating an unmet need for these patients. Promising preliminary safety and efficacy of the combination of oral nanatinostat and oral valganciclovir has been demonstrated in the VT3996-201 Phase 1b/2 study in heavily previously treated (median of 2 prior therapies) patients with a variety of relapsed/refractory EBV^+ lymphomas, 75% of whom were refractory to their most recent therapy prior to enrolling in the study (Porcu 2020, Haverkos 2021).

Since there are no clinical monotherapy data with nanatinostat in lymphoma patients, and other HDAC inhibitors have demonstrated activity in patients with PTCL, nanatinostat will also be evaluated as monotherapy in patients with PTCL. The first 20 PTCL patients enrolled into the study will be randomized to receive nanatinostat monotherapy (n = 10) or nanatinostat plus valganciclovir combination therapy (n = 10). Patients receiving nanatinostat monotherapy may have the option to cross over to combination therapy (see Section 3.1).

An Independent Review Committee (IRC) will be established to determine the ORR. A Study Steering Committee (SSC) composed of study Investigators will be established to i) manage the overall stewardship of the study according to the protocol, and ii) to recommend and approve any modifications needed.

3.1. Description of Study Design

This is an open-label, multicenter, multinational single-arm, Phase 2 basket design study, utilizing Simon's 2-stage design options for discontinuing enrollment into each cohort where treatment appears to be futile (Simon 1989). The study will include 7 cohorts of patients with the following EBV^+ relapsed/refractory lymphomas:

- **Cohort 1**: EBV^+ DLBCL, NOS
- **Cohort 2**: ENKTL
- **Cohort 3**: PTCL, including PTCL-NOS and AITL
  - **Cohort 3a**: Nanatinostat monotherapy
  - **Cohort 3b**: Nanatinostat + valganciclovir
- **Cohort 4**: HL
- **Cohort 5**: PTLD
- **Cohort 6**: Lymphomas associated with HIV infection (HIV-L): Plasmablastic, Burkitt, Hodgkin, and DLBCL
- **Cohort 7**: EBV^+ lymphomas other than Cohorts 1, 3, 4, 5, and 6 above (Cohort 7 will **not** enroll patients in France)

In Stage 1, 6 cohorts (Cohorts 1, 2, 3b, 4, 5, and 6) will enroll up to 10 patients each. Any cohort that fails to enroll any patients within 1 year from the date the first patient is enrolled in the study will be considered for termination of enrollment. Enrollment in Cohorts 2, 4, and 6 has been closed as of 17 October 2023, 24 August 2023, and 24 August 2023, respectively. Patients currently enrolled in these cohorts may continue to receive study treatment per protocol until which time treatment discontinuation is required as defined in Section 7.2.3.

All cohorts that have a response in 2 or more patients in Stage 1 will continue to enroll patients in Stage 2, for a total of 21 patients in each cohort (Figure 2). If ≥7 responses are observed in the initial 21 patients in any cohort, then enrollment will be expanded to include up to 120 additional patients in that cohort (N=141), with the possibility of performing an interim efficacy analysis in that cohort to be described in the statistical analysis plan. Cohort 3a will not enroll beyond the initial 10 patients, regardless of the number of responders in Stage 1.

To evaluate the activity of single-agent nanatinostat, the first 20 patients enrolled with PTCL will be randomized 1:1 to either nanatinostat monotherapy (20 mg PO once daily on Days 1 to 4 per week in Cohort 3a) or nanatinostat plus valganciclovir (in Cohort 3b). Following a disease response assessment at 6 weeks, patients in Cohort 3a with a CR or PR will continue nanatinostat monotherapy. Those in Cohort 3a with stable disease at 6 weeks or disease progression at any time (confirmed by CT or MRI) will have the option to cross over to combination therapy for the remainder of the study. Patients must complete the End of Monotherapy Disease assessment and

qualify (labs, no sign of CNS disease progression and Eastern Cooperative Oncology Group [ECOG]) prior to beginning Cycle 1 Day 1 of the nanatinostat plus valganciclovir combination therapy.

Cohort 7 will be closed to enrollment when all other cohorts are closed, regardless of the number of patients recruited at that time and will not be subject to the decision criteria of the Simon's 2-stage design.

It is thus estimated that up to 486 patients in Cohorts 1 to 6 may be enrolled for combination therapy, of which approximately 60 would be enrolled in Stage 1, 66 would be enrolled in Stage 2, and up to 360 would be enrolled in the post-Stage 2 expansion cohorts. Additional patients (n=10) with PTCL will be enrolled in Cohort 3a for nanatinostat monotherapy, and patients with lymphoma subtypes other than those assigned to Cohorts 1, 3, 4, 5, and 6 may be enrolled into Cohort 7 (with the exception of France; see above).

If 10 patients of a given lymphoma subtype are enrolled into Cohort 7, then the Simon's decision criteria will be applied to determine whether or not to add patients in Stage 2 for that subtype. If none of the subtypes represented in Cohort 7 enrolls at least 10 patients, efficacy data collected on those patients will be listed, but not summarized by group. All patients will be summarized for safety, regardless of decision to discontinue enrollment into any cohort.

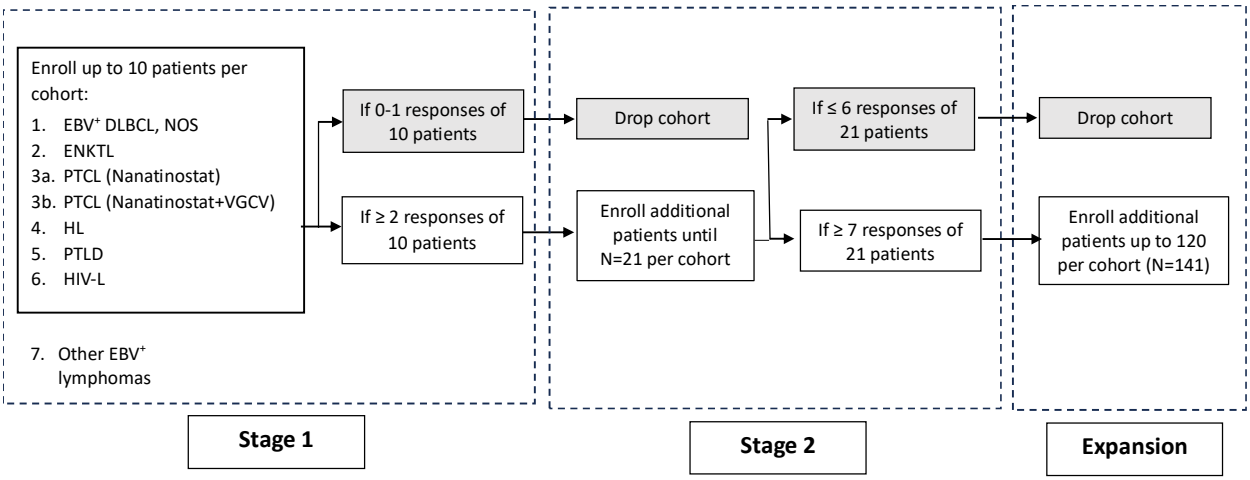
Patients enrolled in Cohorts 1 to 7 (with the exception of Cohort 3a), and patients crossed over from Cohort 3a will receive intermittent dosing of nanatinostat and continuous valganciclovir in 28-day cycles as follows:

a. Nanatinostat 20 mg orally once daily on Days 1 to 4 per week (ie, 4 days on, 3 days off)
b. Valganciclovir 900 mg orally once daily. Patients with a CrCl 50-59 mL/min at study entry will receive valganciclovir 450 mg orally once daily as per Table 4.

For adolescent patients, see Section 5.2.2 for appropriate dosing recommendations for valganciclovir. Patients who develop disease progression but, in the opinion of the Investigator, would still benefit from continuing study drug may continue treatment with nanatinostat and valganciclovir after agreement with the Sponsor, provided that they are i) asymptomatic from or have no overt signs of disease progression; and ii) have a performance status of 0-1. It is recommended to perform an interval follow-up radiologic disease assessment before the next scheduled time point. Such patients will be recorded as having had a PFS event.

All patients will be monitored at weekly intervals through the first cycle of treatment, and then at 2-week intervals thereafter. Tumor response will be evaluated after every 2 cycles × 3, and after every 3 cycles thereafter. The responses will be assessed by both the Investigator and an IRC.

Figure 2: Study Design



Note: Patients enrolled with PTCL will be randomized 1:1 to either nanatinostat monotherapy (in Cohort 3a) or nanatinostat plus valganciclovir (in Cohort 3b).

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 to the central pathology lab should occur as early as possible, and no later than 8 weeks following Cycle 1 Day 1 (see Section 4.1.1). The tumor sample will be used for central confirmation of EBV status and verification of lymphoma subtype. Additional screening evaluations must be performed within 28 days or 14 days before treatment start as defined in the Schedule of Events (Section 6.1). At the time of screening, patients should be advised around their options to store germ cells.

3.1.2. Treatment Period

Patient eligibility will be confirmed once all screening procedures are completed.

Enrolled patients will receive treatment until disease progression (per Investigator assessment), unacceptable toxicity, withdrawal of consent, Investigator's discretion, death, initiation of new antineoplastic therapy, discontinuation from the study for any reason, or study termination by the Sponsor. Patients receiving nanatinostat monotherapy who have disease progression will be offered the option to receive combination therapy with valganciclovir. All antineoplastic therapies given after the last dose of study drug (and time to next therapy) will be recorded in the electronic case report form (eCRF) (unless the patient withdraws consent or is lost to follow-up). Patients will be followed for survival regardless of treatment discontinuation reason (except if consent is withdrawn or patient is lost to follow-up).

3.1.3. Safety Follow-up Period

Upon discontinuation of the protocol-specified treatments, patients will enter the Follow-up period. All patients will be followed for AEs for 28 days after the last dose of study drug (permanent discontinuation) and complete the Safety Follow-up visit as described in Section 7.2.5, except if the patient is lost to follow-up or withdraws consent (see Section 8.1).

3.1.4. Long-term Follow-up Period

In the Long-term Follow-up period, patients will be followed-up as described in Section 7.2.6 (or more frequently if a survival update is required for safety or regulatory reasons) for disease progression, OS, subsequent anti-lymphoma therapies, and response (best overall responses and disease progression date) to subsequent lymphoma therapies. Survival information can be obtained by phone calls, clinic visits, or public records, such as government census or death records, until the patient is lost to follow-up, death, or withdraws consent.

3.1.5. Timing of Analyses

Because of the open-label single treatment regimen design elements, each cohort will be monitored individually for safety and efficacy. Therefore, each cohort may move from Stage 1 to Stage 2 and complete Stage 2 at different rates. The decision to expand enrollment will also occur independently for each cohort. However, a study-wide analysis of response and safety over all cohorts will be performed once all cohorts have either discontinued or completed assessments of response at the end of Stage 2 and those with responses have been followed for up to 3 years.

3.1.6. 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 SD 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 drugs on an individual basis (eg, by separate protocol or post-trial access plan) with Sponsor approval.

4. SELECTION OF STUDY POPULATION

Patients must have a histologically confirmed diagnosis of relapsed EBV^+ lymphoma, must have been previously treated for their lymphoma with systemic therapy, must be refractory to or have relapsed after their last treatment, must have at least one measurable lesion by computed tomography (CT) or magnetic resonance imaging (MRI) scan, and must have adequate bone marrow function, liver function, and renal function.

The eligibility criteria are designed to limit enrollment to patients who have relapsed/refractory EBV^+ lymphoma and who are sufficiently well to safely participate in study procedures and provide interpretable results. Prior therapy provisions are intended to define patient subgroups that have already received available/standard of care therapies with well-defined activities.

4.1. Patient Population

4.1.1. Inclusion Criteria

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

1. Adult patients age ≥18 years or as permitted by applicable local regulations at the time of providing informed consent. Patients must be able to swallow whole tablets.
   a. **For patients with PTLD:** Age ≥12 years and weighing ≥40 kg.
2. Histologically confirmed (by 2016 WHO classification (Swerdlow 2016)) EBV^+ lymphoma* per local laboratory by EBER-ISH (or for PTLD only, by LMP-1 immunohistochemistry) on a representative disease specimen. Any degree of EBER-ISH or LMP-1 positivity is considered to be eligible (ie, there is no cut-off value for % positive cells).
   * Tumor cells are EBV^+, with the exception of AITL, which is characterized by EBV-negative neoplastic T cells and EBV^+ associated B-lineage cells (of immunoblastic/plasmablastic immunophenotype)
   a. A recent FFPE specimen must be available for retrospective central review of diagnosis. FFPE tissue blocks are preferred; if a tissue block is not available, at least 15 unstained slides or freshly cut serial sections (3−5 µm in thickness), preferably with an accompanying block punch will be accepted. The specifications for the age of the tumor samples are:
      - **For patients with ENKTL, AITL, PTLD and HIV-L:** preferably ≤1 year old. For tumor specimens >1 year old, please consult the Medical Monitor to discuss eligibility.
      - **For patients with all other lymphoma subtypes:** preferably ≤6 months old. For tumor specimens >6 months old, please consult the Medical Monitor to discuss eligibility.
3. **For patients with EBV^+ DLBCL, NOS:** Relapsed or refractory disease following 1 or more prior systemic therapy(ies) with curative intent. Patients must have received at least one course of an anti-CD20 immunotherapy such as rituximab, and at least one course of anthracycline-based chemotherapy (unless contraindicated, in which case, an accepted anthracycline-free alternative for DLBCL was given).
4. **For patients with ENKTL:** Relapsed or refractory disease following 1 or more prior systemic therapy(ies) with a curative intent. Patients must have failed an asparaginase-containing regimen.
5. **For patients with PTCL (PTCL, NOS and AITL):** Relapsed or refractory disease following 2 or more prior systemic therapy(ies) with a curative intent.
6. **For patients with HL:** Patients must have received at least one course of anthracycline-based chemotherapy (unless contraindicated, in which case, an accepted anthracycline-free alternative for HL was given). Patients with relapsed/refractory classical Hodgkin lymphoma(cHL) should have failed or be ineligible for an anti-PD-1 agent (eg, pembrolizumab, nivolumab) and CD30-directed therapy (ie, brentuximab vedotin).

7. **For patients with PTLD:** Patients with relapsed or refractory EBV^+ PTLD who have received at least one prior therapy must have received at least one course of an anti-CD20 immunotherapy such as rituximab. For solid-organ transplant (SOT) patients, prior therapy also includes chemotherapy, administered concurrently or sequentially, unless chemotherapy is inappropriate.
8. For patients with the following lymphomas associated with HIV infection: plasmablastic, Burkitt, Hodgkin, and DLBCL.
    a. Prior therapy requirements for DLBCL and HL are specified in inclusion criteria 3 and 6.
    b. **France only:** For Burkitt and plasmablastic lymphoma – Patients must have received a regimen such as EPOCH, CODOX-M (original or modified; cyclophosphamide, vincristine, doxorubicin, and high-dose methotrexate) or Hyper-CVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone), including CNS prophylaxis or therapy.
9. Patients with HIV-L should meet the following criteria for inclusion:
    a. Currently on a stable regimen of anti-retroviral therapy (ART)
    b. Compliant with ART and follow-up according to the investigator
    c. No evidence of a worsening HIV viral load (as assessed by HIV quantitative polymerase chain reaction [qPCR])
    d. CD4 count >50 cells/mm^3
10. No available standard therapies in the opinion of the Investigator.
11. Not eligible for high-dose chemotherapy with allogeneic/autologous stem cell transplantation or CAR-T therapy at the time of study entry.
12. Presence of at least one bi-dimensionally measurable lesion by CT or MRI: longest diameter (Ldi) >1.5 cm for a nodal lesion; Ldi >1.0 cm for an extranodal lesion within 28 days prior to start of treatment.
13. Able to provide a prior core or excisional biopsy for biomarker analysis at screening. If no tissue is available, then a new biopsy must be performed.
14. Eastern Cooperative Oncology Group (ECOG) performance status 0, 1, or 2.
15. All acute toxic effects of any prior anti-tumor therapy resolved to Grade ≤1 before initiation of study treatment (excluding alopecia and stable Grade 2 sensory neuropathy).

16. Required baseline laboratory data (within 2 weeks prior to start of study drug administration) as shown in the table below:

System	Laboratory Value
Hematology	
Absolute neutrophil count (ANC)	≥1000/mm^3 (no growth factor support within 14 days)
Platelets	≥50,000/mm^3 (no platelet transfusion within 14 days)
Hemoglobin	≥8.0 g/dL (no red cell transfusion within 21 days)
Renal	
Creatinine clearance	≥50 mL/min (Cockcroft-Gault)
Hepatic	
Total bilirubin	≤2.0 × upper limit of normal (ULN) (except patients with documented Gilbert's syndrome [<3.5 × ULN])
Aspartate aminotransferase (AST [SGOT]) and alanine aminotransferase (ALT [SGPT])	≤3.0 × ULN (or ≤5.0 × ULN if liver involvement by primary disease)
Coagulation	
International normalized ratio (INR) Activated partial thromboplastin time (aPTT)	≤1.5 × ULN unless participant is receiving anticoagulant therapy (as long as INR or aPTT are within the therapeutic range of intended use of anticoagulants)

17. Life expectancy >3 months.
18. Women of childbearing potential (ie, reached menarche, and not premenarchal or 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 true abstinence from heterosexual intercourse: When this is in line with the preferred and usual lifestyle of the patient (Periodic abstinence [eg, calendar, ovulation, symptothermal, post-ovulation methods], declaration of abstinence for the duration of exposure to the investigational medicinal product [IMP], or the withdrawal method are not acceptable forms of contraception). Otherwise, begin a highly effective method of birth control with a Pearl-Index <1%, without interruption, throughout the study dosing period and for 6 months after the last dose of nanatinostat. Apart from abstinence, highly effective methods of birth control include the following:
        - Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal). Please note: Although the potential for drug interactions and risk of venous

thromboembolism is low (see Section 5.5.2.3), the use of an alternative method of contraception is recommended.

- Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable).
- Intrauterine device (IUD).
- Intrauterine hormone-releasing system (IUS).
- Bilateral tubal occlusion.
- Vasectomized partner.

19. Male patients must agree to use condoms during intercourse throughout the study dosing period and for 90 days after the last dose of nanatinostat. Female partners of male patients participating in the study are to consider the use of effective methods of contraception while their partner is treated on study and for 90 days after the last administration of nanatinostat.
20. The patient is willing and able to provide informed consent and comply with the protocol. Assent must be obtained for adolescent patients <18 years old, or as permitted by applicable local regulations, and a parent/guardian must provide written consent.

4.1.2. Exclusion Criteria

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

1. Presence or history of central nervous system (CNS) involvement by lymphoma.
2. Systemic anticancer therapy within 21 days prior to Cycle 1 Day 1 dosing.
3. Antibody (anticancer) agents within 28 days of Cycle 1 Day 1 dosing.
4. Less than 14 days from prior local site radiation therapy.
5. Less than 60 days from prior autologous hematopoietic stem cell or solid organ transplant.
6. Less than 21 days from prior CAR-T therapy (any AEs must be Grade 1 or less for enrollment).
7. Less than 90 days from prior allogeneic transplant.
8. Receiving systemic corticosteroids during the last week prior to Cycle 1 Day 1, unless administered at a dose equivalent to ≤20 mg/day of prednisone.
9. For recipients of prior allogeneic HSCT: Receiving systemic immunosuppressants as either prophylaxis or treatment for graft-versus-host disease (GvHD).
10. Major surgery within 28 days within the first dose of study drug. In the case of recent major surgery, the patient must have recovered adequately from the procedure and/or any complications prior to starting study treatment.
    - Note: Minor surgery (eg, minor biopsy of extracranial site, central venous catheter placement, shunt revision) is permitted within 3 weeks prior to enrollment.

11. 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.
12. History of other malignancy that could affect compliance with the protocol or interpretation of results. Patients with any malignancy appropriately treated with curative intent and the malignancy has been in remission without treatment for ≥2 years prior to enrollment are eligible. Also eligible are the following:
    - Curatively treated:
        i. Basal cell, squamous cell carcinoma, or melanoma of the skin (at any time prior to the study).
        ii. Cervical carcinoma in situ (at any time prior to the study).
    - Low-grade, early-stage prostate cancer (Gleason score 6 or below, Stage 1 or 2) with no requirement for therapy at any time prior to study, or previously fully resected.
13. Inability to take oral medication, malabsorption syndrome or any other gastrointestinal condition (nausea, diarrhea, vomiting) that may impact the absorption of nanatinostat and valganciclovir.
14. Active GvHD.
15. Positive hepatitis B core antibody or surface antigen unless DNA qPCR is negative, and patient will be receiving prophylaxis for reactivation.
16. Positive hepatitis C virus on RNA polymerase chain reaction (PCR).
17. Known SARS-CoV-2 positivity by any testing method at time of screening. Patients with a positive PCR test should only be enrolled if ≥10 days have passed since COVID symptoms first appeared and they have recovered from symptoms or have mild symptoms.
18. History of allergic reactions attributed to compounds of similar chemical or biologic composition to valganciclovir or nanatinostat.
19. Active infection requiring systemic therapy (excluding viral upper respiratory tract infections). Patients may be receiving prophylactic antiviral, antifungal or antibacterial therapies at the discretion of the Investigator.
20. 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).
21. Receiving concomitant drugs that are inhibitors of P-glycoprotein (P-gp) and/or 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).

22. Psychiatric illness/social situations/substance abuse disorder that would interfere with compliance with study requirements.
23. Has a prior or ongoing clinically significant illness such as New York Heart Association Class III or IV cardiac disease, myocardial infarction within the last 6 months, unstable arrhythmias, or unstable angina, or pulmonary disease, 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 compliance with the protocol, or is not in the best interest of the patient to participate.
24. Is pregnant or breastfeeding or expecting to conceive or father children within the projected duration of the study, starting with the Screening visit through 6 months after the last dose of nanatinostat.

5. STUDY TREATMENT PRODUCT INFORMATION

For this study, the term "study treatment" refers to the combination of nanatinostat and valganciclovir, except for those patients enrolled into Cohort 3a (nanatinostat monotherapy for the first 6 weeks).

5.1. Nanatinostat

5.1.1. Dosage Form and Composition

Nanatinostat is available as 10 mg tablets. Instructions for requesting and receiving nanatinostat from the Sponsor will be included in the Pharmacy Manual. Nanatinostat will be dosed on a flat scale of mg/day.

Nanatinostat film coated immediate-release (IR) 10 mg tablets consist of the active nanatinostat (VRx-3996), and inactive excipients (ie, mannitol, microcrystalline cellulose, croscarmellose sodium, sodium stearyl fumarate, and coating material).

All inactive ingredients in the drug product meet compendial requirements of the United States Pharmacopeia (USP) 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 15 to 30ºC (59 to 86ºF). Once the bottle seal is broken, bottles should be stored tightly capped.

5.1.3. Nanatinostat Administration

All patients will receive nanatinostat 20 mg orally once daily on Days 1 to 4 per week (ie, 4 days on, 3 days off). Patients will continue dosing in 28-day cycles until discontinuation as described in Section 7.2.3.

There are no special dietary restrictions or requirements associated with nanatinostat, however valganciclovir absorption is affected by food and it should be taken with food (see Section 5.2.2

for additional clarification). Valganciclovir and nanatinostat should be taken at the same time following a light meal.

On study visit days requiring PK trough levels, patients will be asked to consume one can of Ensure® or equivalent or consume a light breakfast in place of consuming an Ensure® equivalent prior to dosing in order to avoid taking study drugs on an empty stomach (see Section 5.3).

See Section 5.5.2 for medications to be used with caution with nanatinostat.

5.2. Valganciclovir

Valganciclovir is available as 450 mg tablets. Valganciclovir tablets will be provided to the investigational sites by Viracta. Instructions for requesting and receiving valganciclovir will be included in the Pharmacy Manual. Valganciclovir tablets must not be broken or crushed. Valganciclovir tablets consist of the active valganciclovir hydrochloride, and inactive excipients (ie, microcrystalline cellulose, povidone K-30, crospovidone, magnesium stearate or stearic acid and coating material).

5.2.1. Valganciclovir Study Drug Storage

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

5.2.2. Valganciclovir Administration

The daily dose of valganciclovir for patients ≥17 years of age is 900 mg orally (continuous treatment) in combination with nanatinostat. Patients with a CrCl 50-59 mL/min at study entry will receive valganciclovir 450 mg orally once daily as per Table 4. Patients will continue to receive nanatinostat plus valganciclovir in 28-day cycles until discontinuation as described in Section 7.2.3.

The daily dose of valganciclovir for patients ≤16 years of age is based on body surface area (BSA) and CrCl derived from a modified Schwartz formula, and is calculated using the equation below:

$$Adolescent\ dose\ (mg) = 7\ x\ BSA\ x\ Schwartz\ Creatinine\ Clearance$$

$$Mosteller\ BSA\ (m^2) = \sqrt{\frac{Height\ (cm)\ x\ Weight\ (kg)}{3600}}$$

$$Schwartz\ Creatinine\ Clearance\ (mL/\min/1.73m^2) = \frac{k\ x\ Height\ (cm)}{Serum\ Creatinine\ (mg/dL)}$$

Note: *k* value is 0.55 (boys <13 years and girls <16 years) or 0.7 (boys aged 13 to 16 years).

Patients should be monitored for serum creatinine levels regularly, consider changes in height and body weight, and adapt the valganciclovir dose as appropriate. Valganciclovir tablet dose is

determined based on the calculated valganciclovir dose in mg and available tablet strength (450 mg) ±10% range of the tablet strength. For example, if the calculated dose exceeds 900 mg, a maximum dose of 900 mg should be administered. If the calculated dose is between 900 mg and 810 mg, a 900 mg dose (two 450 mg tablets) should be taken. If the calculated dose is between 809 mg and 405 mg, 450 mg dose (one 450 mg tablet) should be taken.

Adequate hydration should be maintained for all patients. For patients who develop an elevated creatinine while on study, their dose of valganciclovir should be adjusted (see Section 5.4.1).

In patients who are unable to tolerate oral dosing of valganciclovir, the Investigator will have the option of administering ganciclovir intravenously (IV) at 5 mg/kg QD. In patients who are receiving a dose of valganciclovir less than 900 mg orally once daily, the dose of ganciclovir will be reduced accordingly using the ratio of 900 mg valganciclovir to 5 mg/kg ganciclovir.

Valganciclovir absorption is affected by food. Therefore, 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 during the study must be accurately recorded in the eCRFs.

5.3. 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® or equivalent, prior to the dose of study drugs (within 30 minutes) on days with pre- and post-dose PK assessments as outlined in Section 7.3.3. Note that valganciclovir and nanatinostat should be taken at the same time, including on Cycle 1 Day 1. 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® equivalent and should start the meal 30 minutes before administration of valganciclovir and nanatinostat.

See Section 5.5.3 for medications to be used with caution with valganciclovir.

5.4. Dose Modifications of Nanatinostat and Valganciclovir

For patients who do not tolerate the protocol-specified dosing schedule, or develop toxicities, dose adjustments are permitted to allow the patient to continue study treatment. Dose adjustments, except for valganciclovir adjustments based on renal function (Section 5.4.1) 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. Requirements for dose modifications and criteria for resumption of dosing are presented in Table 3.

Table 3: Dose Modification Guidelines for Study Treatment-Related Toxicity

NCI CTCAE v5.0 Toxicity Grade	Action to be Taken with Study Drugs
Grade 4 neutropenia (ANC $<0.5 \times 10^9$/L)	• Interrupt nanatinostat/valganciclovir dosing. • Resume nanatinostat/valganciclovir at the same doses when ANC $\geq 1.0 \times 10^9$/L.

NCI CTCAE v5.0 Toxicity Grade	Action to be Taken with Study Drugs
	• If the grade 4 neutropenia lasts more than 7 days or recurs, then reduce valganciclovir to 450 mg orally daily. If the reduced dose is tolerated for ≥4 weeks, then the valganciclovir dose may be increased to 900 mg daily. • Use of growth factors (G-CSF, GM-CSF) is permitted as per the ASCO 2015 clinical practice guidelines (Smith 2015).
Grade 3 neutropenia (ANC 0.5 – <1.0 × 10^9/L)	• If persistent (>7 days) then interrupt nanatinostat/valganciclovir dosing. Resume nanatinostat/valganciclovir at the same doses when ANC ≥1.0 × 10^9/L. If recurs and persists >7 days, then consider reducing valganciclovir to 450 mg orally daily. • Use of growth factors (G-CSF, GM-CSF) is permitted as per the ASCO 2015 clinical practice guidelines (Smith 2015).
Grade 4 thrombocytopenia (Platelet count <25 × 10^9/L)	• Interrupt nanatinostat/valganciclovir dosing. • If thrombocytopenia resolves to ≤Grade 2 (>50 × 10^9/L), then restart both drugs. • If recurs, then consider reducing valganciclovir to 450 mg orally daily.
Grade 3 anemia (Hemoglobin <8.0 g/dL)	• Interrupt nanatinostat/valganciclovir dosing. • If anemia resolves to ≤Grade 2 (≥8.0 g/dL), then restart both drugs. • If recurs, then consider reducing valganciclovir to 450 mg orally daily.
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)	• Interrupt nanatinostat/valganciclovir dosing. • Resume nanatinostat/valganciclovir at the same doses when ANC ≥1.0 × 10^9/L. • Use of growth factors (G-CSF, GM-CSF) is permitted as per the ASCO 2015 clinical practice guidelines (Smith 2015).
QTc prolongation	**For QTc interval >450 msec and ≤480 msec**: Check magnesium and potassium levels and correct any abnormalities. If possible, stop any medications that may prolong the QTc interval. Continue nanatinostat/valganciclovir at the same dose. **For QTc interval >480 msec and <500 msec**: Check magnesium and potassium levels and correct any abnormalities. If possible, stop any medications that may prolong the QTc interval. Decrease nanatinostat to 10 mg once daily, days 1 to 4/7 for the remainder of the cycle. 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 10 mg once daily, days 1–4/7. **For QTc interval >500 msec**: Check magnesium and potassium levels and correct any abnormalities. Interrupt nanatinostat/valganciclovir dosing and stop any medications that may prolong the QTc interval. If the QTc interval improves to ≤470 msec just prior to the start of the next cycle, resume nanatinostat/valganciclovir at the initial dose. If no other cause of QTc prolongation is identified, reduce dose of nanatinostat to 10 mg once daily, days 1-4/7. 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 or clinically significant laboratory abnormalities: Discontinue nanatinostat/valganciclovir dosing. 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 Viracta.

NCI CTCAE v5.0 Toxicity Grade	Action to be Taken with Study Drugs
	Grade 3 non-hematologic AE or clinically significant laboratory abnormalities: withhold dose until toxicity resolves to ≤Grade 1 and resume nanatinostat/valganciclovir at the same dose.

Abbreviations: ANC = absolute neutrophil count; 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.

Patients should be monitored approximately twice weekly for 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 6.1). If the dose interruption extends beyond the end of the cycle, the subsequent cycle will not begin until dosing has resumed. If the dose is held for more than 14 days, the Investigator should consult with the 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 should be considered. Re-escalation of study drug dose may only be performed after approval by Medical Monitor.

5.4.1. Dose Modifications for Patients with Renal Impairment

Patients ≥17 years of age who develop an elevated creatinine while on study should have their creatinine clearance (CrCl) recalculated and dose of valganciclovir adjusted per Table 4.

An estimated CrCl 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 4, the Investigator should discuss the amount of dose reduction with the Medical Monitor.

Table 4: Valganciclovir Dosing for Patients with Renal Impairment

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

Source: Valcyte USPI 2021(Genentech 2021) and SmPC 2018 (Roche 2018)
Note: Patients ≥17 years of age receiving hemodialysis (CrCl less than 10 mL/min) cannot use valganciclovir tablets because the daily dose of valganciclovir tablets required for these patients is less than 450 mg. In this case the Investigator will have the option of administering ganciclovir IV at 5 mg/kg QD, after discussion with the Study Medical Monitor.

Patients 12 to 16 years of age who develop an elevated creatinine while on study should have their CrCl recalculated (by a modified Schwartz formula per Section 5.2.2) and dose of valganciclovir adjusted based on body surface area (BSA).

5.4.2. Missed or Vomited Doses

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, but within 8 hours of the missed dose. If more than 8 hours or an entire day has passed, the normal dosing schedule will be resumed the following day without a change in the daily dose or schedule.

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 the Medical Monitor.

5.5. Prior and Concomitant Medications

Prior and concomitant medications include all vitamins, vaccinations, herbal remedies and 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 and valganciclovir. Patients are not allowed to participate concurrently in any other therapeutic study.

5.5.1. Permitted Concomitant Medications

During the time on study treatment, 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 (see Section 5.5.4). 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.

5.5.1.1. 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 3). The American Society of Clinical Oncology (ASCO) clinical practice guidelines should be followed (Smith 2015). Hematopoietic growth factors may not be used to allow for patient eligibility at screening.

5.5.2. Concomitant Therapy Requiring Caution and/or Action

5.5.2.1. 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-lymphoma 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.

5.5.2.2. Proton-Pump Inhibitors

The effect of gastric pH on nanatinostat absorption is not known. Proton-pump inhibitors and H_2 antagonists should be excluded from patient use if possible. If they must be given, then do not administer proton-pump inhibitors, H_2 antagonists, or antacids within 2 hours prior or within 4 hours post-nanatinostat administration.

5.5.2.3. Concomitant Therapies to be Used with Caution with Nanatinostat

A study with recombinant human cytochrome P450 isoforms (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 11). Please refer to the IB for a detailed description.

Select antiretroviral therapies (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 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 12).

5.5.3. Concomitant Therapies to be Used with Caution with Valganciclovir

Drug-drug interaction studies with ganciclovir/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.

5.5.4. Prohibited Medications

The following medications/therapies are prohibited during the study

- Other investigational and antineoplastic therapies, including anti-CD20 agents
- Prednisone >10 mg per day (or equivalent)
- Live vaccines
- 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.

5.6. Patient Numbering & Treatment Assignment

5.6.1. 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.).

5.6.2. Treatment Assignment (Including Randomization)

Patients will be enrolled into each cohort based on their primary lymphoma diagnosis to receive the combination nanatinostat plus valganciclovir with exception of Cohort 3a.

The first 20 patients enrolled with PTCL in Cohort 3 will be randomized 1:1 to either Cohort 3a (nanatinostat monotherapy) or Cohort 3b (nanatinostat plus valganciclovir). Randomization will occur at the time of drug dispensation for Cycle 1 Day 1. Following a disease response

assessment at 6 weeks, patients in Cohort 3a with a CR or PR will continue nanatinostat monotherapy. Those in Cohort 3a with stable disease at 6 weeks or disease progression at any time will be offered the option to cross over to combination therapy for the remainder of the study, provided they qualify per hematology, chemistry, no sign of CNS disease progression, and ECOG parameters (see Section 4.1.1).

5.6.3. Treatment Blinding

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

5.7. Study Drug Preparation and Dispensation

5.7.1. Study Drug Packaging and Labelling

The study drugs 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) and Section 5.2 (valganciclovir).

5.7.2. Drug Supply and Storage

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

5.7.3. Study Drug Compliance and Accountability

5.7.3.1. Study Drug Compliance

Patient compliance with 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 document at each patient visit. Paper diaries will be utilized to record doses and collect tablet counts.

5.7.3.2. 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.

5.7.4. Study Drug Handling and Disposal

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

6. SCHEDULE OF EVENTS

The Schedule of Events provided in Section 6.1 lists all the on-study assessments and the visit dates when they are to be performed. Every effort should be made to follow the schedule outlined in the Schedule of Events. Allowed visit windows are specified as follows:

a. Screening assessments per the Schedule of Events must occur within 28 days (14 days for laboratory assessments, urinalysis, and pregnancy test) of Cycle 1 Day 1.

b. Vital signs, ECOG performance status, and physical exam should be performed within 28 days of start of study drug (Cycle 1 Day 1). Required laboratory assessments should be performed within 14 days of the start of study drug (Cycle 1 Day 1).

c. Radiologic assessments must be performed as indicated in Section 6.1. A visit window of ±7 days is allowed. Radiological assessments should stay on schedule even if there are dose holds.

d. For all other visits, a general ±3-day window is permitted on assessments; the disease assessments window is ±7 days.

6.1. Schedule of Events Tables

Table 5: Visit/Evaluation Schedule

	Screening[a]		Cycle 1 (±3 days)				Cycle 2 (±3 days)		Cycles 3+ (±3 days)		EOT	Safety Follow-up[b] (±3 days)	Long-Term Follow-up (±7 days)	
Day(s) of Cycle[c]	**-28 to -1**	**-14 to -1**	**1**	**8**	**15**	**22**	**4**	**15**	**1 (or 4 in Cycle 6)**	**15**	**+14 Days After Last Dose**	**+28 Days After Last Dose**	**Without PD (q12 weeks)**	**With PD (q6 months)**
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		
FFPE tumor specimen[d]	X													
Physical examination	X		X				X		X		X			
Weight	X		X				X		X		X			
Height	X		X[w]				X[w]		X[w]					
ECOG performance status	X		X				X		X		X			
Vital signs[e]	X		X				X		X		X			
Laboratory assessments														
Hematology[f]		X	X	X	X	X	X	X	X	X	X			
Chemistry[g]		X	X	X	X	X	X	X	X	X	X			
Creatinine clearance (Cockcroft-Gault estimation)[h]		X												

	Screening[a]		Cycle 1 (±3 days)				Cycle 2 (±3 days)		Cycles 3+ (±3 days)		EOT	Safety Follow-up[b] (±3 days)	Long-Term Follow-up (±7 days)	
Day(s) of Cycle[c]	**-28 to -1**	**-14 to -1**	**1**	**8**	**15**	**22**	**4**	**15**	**1 (or 4 in Cycle 6)**	**15**	**+14 Days After Last Dose**	**+28 Days After Last Dose**	**Without PD (q12 weeks)**	**With PD (q6 months)**
Serum immunoglobulins[i]			X						X		X			
Coagulation[f]		X									X			
Urinalysis		X												
Hepatitis serology[j]	X													
Serum pregnancy test[k]		X												
Serum or urine pregnancy test[k]			X				X		X		X	X	X[q12wks for 6 mos]	X[q12wks for 6 mos]
Disease assessments														
CT with contrast (or MRI) of brain	X													
^{18}FDG-PET/CT[l]	X								X[Wks 8, 16]					
CT with contrast (or MRI) of neck, chest, abdomen, and pelvis[m]	X								X[Wks 8, 16, 24 + q12wks]		X		X[q12wks]	
Bone marrow biopsy[n]	X													
Safety assessments														
12-lead ECG[o]	X		[X]								X			
Adverse events	X		X	X	X	X	X	X	X	X	X	X		
CMV, HHV-6, HHV-8, HIV levels[p]			X		X		X		X		X	X		
EBV DNA levels[p]	X		X		X		X		X		X	X	X	
Pharmacokinetics														
PK sampling (Stage 1)[q]							[X][q]		[X][q]					

	Screening[a]		Cycle 1 (±3 days)				Cycle 2 (±3 days)		Cycles 3+ (±3 days)		EOT	Safety Follow-up[b] (±3 days)	Long-Term Follow-up (±7 days)	
Day(s) of Cycle[c]	**-28 to -1**	**-14 to -1**	**1**	**8**	**15**	**22**	**4**	**15**	**1 (or 4 in Cycle 6)**	**15**	**+14 Days After Last Dose**	**+28 Days After Last Dose**	**Without PD (q12 weeks)**	**With PD (q6 months)**
PK sampling (Stage 2)[q]							X[q]							
Biomarkers[r]														
Immunophenotype and function, and mutation analysis[s]			X						X		X			
Histone acetylation[t]			X											
On-study biopsy/fine needle aspirate (optional with disease progression or relapse)[u]							X							
Nanatinostat/valganciclovir dispensing/return			X				X		X		X			
Anti-lymphoma therapies since discontinuation of study treatment and response[v]											X	X	X	X
Survival assessment[v]													X	X

Abbreviations: 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; HHV = human herpesvirus; HIV = human immunodeficiency virus; mo = month; MRI = magnetic resonance imaging; PD = progressive disease; ^{18}FDG-PET = fluorodeoxyglucose positron emission tomography; PK = pharmacokinetic; q = once; wk = week.

Note: Brackets ("[X]") indicate procedures performed in Stage 1 only.

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 14 days of Cycle 1 Day 1.

b. **Safety Follow-up** – Visit must be conducted in-person.

c. **Visit windows** – There is a ±3-day window allowable for each clinic visit. The End of Treatment visit must be completed within 14 days after the last dose. The Safety Follow-up visit has a +3-day allowable window, and Long-term Follow-up has a ±7-day allowable window. For disease assessments, a ±7-day window is allowable (not applicable during Screening).

d. **Formalin-Fixed Paraffin-Embedded (FFPE) tumor specimen** – 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 15 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.

A recent biopsy is ideal, but if not available, an archival biopsy may be submitted, provided the tumor specimen meets the criteria described in Section 7.1.5. The specimen must be representative of the current disease (eg, for patients who have relapsed, the biopsy specimen should have been taken after the most recent relapse). Details will be discussed in the separate Pathology Manual. 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.

e. **Vital signs** – Vital signs include heart rate, blood pressure, and temperature. For patients requiring serial PK draws and ECGs, vital signs should be collected following ECGs and prior to the PK blood draw at pre-dose and 1, 2, and 4 hours post-dose on Cycle 2 Day4 (ECG and vital signs are not performed at the 6-hour post-dose PK draw). At time points requiring ECGs, vital signs, and PK blood draws, assessments should be performed in as short of a timeframe as possible and in this order: ECG, vital signs, then blood draw.

f. **Hematology and coagulation** – Hematology includes complete blood count to include white blood cells (WBCs) with differential, red blood cells (RBCs), hemoglobin (Hgb), hematocrit, platelets, mean corpuscular volume (MCV), and mean corpuscular hemoglobin (MCH). Coagulation includes prothrombin time (PT) or International Normalized Ratio (INR) and activated partial thromboplastin time (aPTT).

g. **Chemistry** – Chemistry includes sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, glucose, calcium, phosphate, magnesium, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, alkaline phosphatase, total protein, albumin, uric acid, lactate dehydrogenase (LDH), and serum amylase.

h. **Creatinine clearance (Cockcroft-Gault estimation)** – The Cockcroft-Gault formula will be used to calculate estimated creatinine clearance (CrCl):

- 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 5.4.1 for patients who develop creatinine elevations/impaired renal function while on study.

i. **Serum immunoglobulins** – Samples will be collected to evaluate serum immunoglobulins including quantitative levels of IgA, IgE, IgG and IgM. Samples 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 the EOT visit.

j. **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 patient positive for HCV Ab will be evaluated by qPCR).

k. **Pregnancy testing** – Pregnancy testing is only required for females of childbearing potential. Serum test must be performed during screening. Serum or urine tests are to be performed at the beginning of each cycle, the EOT visit, the 28-day Safety Follow-up visit, and every 12 weeks for 6 months following the last dose of study drug.

l. **^{18}FDG-PET/CT** – Scans will be performed at Screening, Week 8, Week 16 (±7 days), and subsequently for evaluation of a possible CR or PR. *Diagnostic contrast-enhanced CT scans obtained as part of a PET/CT scan may be used in lieu of dedicated CT scans.*

m. **CT with contrast (or MRI) of neck, chest, abdomen, and pelvis** – A diagnostic contrast-enhanced CT (or MRI, if CT contraindicated) will be conducted at Screening, Week 8, and Week 16, Week 24 then every 12 weeks until relapse or disease progression (Week 36, 48, 60, etc.), ±7 days. MRI may be performed only if CT with contrast is contraindicated in the opinion of the Investigator or if frequent CT scans are not allowed according to local IRB/IEC. The same imaging modality used at screening **must** be used for all response evaluations throughout the study to ensure consistency across the different time points for each patient. A scan to confirm an unconfirmed PR or unconfirmed CR ≥4 weeks later may also be performed.

For patients who discontinue due to relapse/progression, the EOT visit ^{18}FDG-PET/CT and/or CT with contrast is not needed if the last scan was within 4 weeks of the EOT visit.

n. **Bone marrow biopsy** – A recent bone marrow biopsy, conducted within 12 weeks of Cycle 1 Day 1, is acceptable as the screening biopsy (if the biopsy is available for review by central pathology). If no such recent bone marrow biopsy is available, then re-biopsy will be required prior to enrollment except as noted in Section 7.1.7.2. During the study, a repeat bone marrow biopsy is required only for patients who have attained a complete response (CR) and had bone marrow involvement at screening. The bone marrow biopsy should be performed within 28 days after the criteria for radiological CR have been met. For patients with Hodgkin lymphoma and DLBCL, a baseline bone marrow biopsy is not necessary if the PET/CT demonstrates bone disease.

o. **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. For patients enrolled in Stage 1, ECGs will be performed in triplicate as follows: 2 ECGs will be performed pre-dose within 1 hour of dosing at least 15 minutes apart. Post-dose ECGs will be performed prior to and as close as possible to PK blood draws at 1, 2, and 4 hours post-dose on Cycle 2 Day 4. An additional triplicate ECG will be obtained at screening, Day 46 (Cohort 3a only) visit, and EOT. Detailed instructions on ECGs are provided in Section 7.3.2.8 and in the separate ECG Manual.

p. **EBV, CMV, HHV-6, HHV-8, HIV levels** – Plasma samples will be collected to investigate circulating EBV, HHV-8, HHV-6, CMV, and HIV (HIV^+ patients only). EBV levels will be utilized for both safety and biomarker analyses, and will continue every 12 weeks during Long-term Follow-up until disease progression or the start of new lymphoma treatment. Only EBV levels will be measured at Screening.

q. **PK sample collection** – During Stage 1 of the study PK will be collected on Cycle 2 Day 4 and Cycle 6 Day 4 from Cohorts 1, 2, 3b, 4, 5, 6, and 7 at pre-dose and 1, 2, 4, and 6 hours post-dose (±15 minutes). For patients in Cohort 3a, PK will be conducted at Cycle 2 Day 4 of the monotherapy and repeated on Cycle 2 Day 4 and Cycle 6 Day 4 of the combination therapy for patients that cross over. 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. During Stage 2 of the study sparse PK sampling will be conducted at selected sites. Sparse sampling will occur at Cycle 2 Day 4. Patients will be assigned one of 3 sampling schedules:
    - Pre-dose and 4 hours post-dose (±15 minutes)
    - 0.5 and 2 hours post-dose (±15 minutes)
    - 1 and 6 hours post-dose (±15 minutes)

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

s. **Immunophenotype and immune function, and mutation analysis** – Peripheral blood mononuclear cells (PBMCs) and plasma 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 the EOT visit. Cycle 1 Day 1 pre-dose sample may be collected during screening within 14 days of Cycle 1 Day 1.

t. **Histone acetylation** – PBMCs for histone acetylation will be collect pre-dose and at 3 hours (±15 minutes) post-dose on Cycle 1 Day 1.

u. **On-study biopsy –** FFPE tumor specimens collected during the study as standard of care should be provided to the central pathology laboratory, along with a frozen tissue specimen, if available. For patients with disease progression on study, a frozen and an FFPE tumor specimen will be provided to the central pathology laboratory.

v. **Subsequent anti-lymphoma therapies and response** – Patients will be contacted by telephone or e-mail for assessment of additional therapy, response status, and survival following the Safety Follow-up assessment.

w. **Height** – Height measurements should be obtained for all patients at Screening. Post-baseline height measurements should be obtained for patients 12 to 17 years of age.

Table 6: Visit/Evaluation Schedule for Cohort 3a (Nanatinostat Monotherapy), Days 1-43

	Nanatinostat Monotherapy Cycle				
Day(s) of Cycle [c]	**1**	**15**	**29**	**43[1,2,3]**	
Enrollment/Randomization	X				Responders continue monotherapy (Table 5; Cycle 3, Day 1) Non-responders cross -over to combination treatment (Table 5; Cycle 1, Day 1)
Prior and concomitant medications	X	X	X	X	
Physical examination	X		X		
Weight	X		X		
ECOG performance status	X		X	X	
Vital signs[e]	X		X	X	
Laboratory assessments					
Hematology[f]	X	X	X	X	
Chemistry[g]	X	X	X	X	
Creatinine clearance (Cockcroft-Gault estimation)[h]				X	
Serum immunoglobulins[i]	X			X	
Coagulation[f]				X	
Urinalysis				X	
Serum or urine pregnancy test[k]	X		X	X	
Disease assessments					
^{18}FDG-PET/CT[4]				X	
CT with contrast (or MRI) of neck, chest, abdomen, and pelvis[4]				X	
Safety assessments					
12-lead ECG[o]	X			X	
Adverse events	X	X	X	X	
CMV, HHV-6, HHV-8, HIV levels[p]	X	X	X	X	
EBV DNA levels[p]	X	X	X	X	
Pharmacokinetics					
PK sampling[q]	X				
Biomarkers[r]					
Immunophenotype and function[s]	X				
Histone acetylation[t]	X				
On-study biopsy/fine needle aspirate (optional with disease progression or relapse)[u]			X		
Nanatinostat dispensing/return	X		X		

Abbreviations and lettered footnotes are defined in Table 5. Numbered footnotes are defined below.

1. If a patient has stable or progressive disease AND qualifies to continue (safety laboratory assessments, no sign of CNS disease progression, and ECOG status) at the Day 43 visit (or progressive disease prior to Day 43), the patient may switch to the combination therapy. Crossover to combination therapy must occur within 7 days of the disease assessment. The Day 43 visit (considered the end of monotherapy visit for these patients) and the Cycle 1 Day 1 visit for combination therapy may be combined into a single visit. Patients must complete the

Day 43 Monotherapy Disease Assessment and qualify prior to beginning the Cycle 1 Day 1 of the nanatinostat/valganciclovir combination therapy.

2. If a patient discontinues monotherapy prior to the Day 43 disease assessment for reasons other than disease progression the patient will follow the EOT, Safety Follow-up, and Long-term Follow-up procedures outlined in Table 5.
3. If patient has a response (complete or partial response) to nanatinostat monotherapy at the Day 43 disease response assessment, the patient will continue monotherapy treatment, restarting assessments at Day 57 (Cycle 3, Day 1). Visits will continue every 14 days as described in Table 5.
4. **^{18}FDG-PET/CT and CT with contrast (or MRI) of neck, chest, abdomen, and pelvis** – ^{18}FDG-PET/CT and CT with contrast (or MRI, if CT with contrast is contraindicated) will be conducted at Week 6 ± 7 days. Patients continuing on monotherapy will have ^{18}FDG-PET/CT and CT with contrast conducted at Week 14 and Week 22, ±7 days. Subsequent contrast-enhanced CTs (or MRI, if CT contraindicated) will be performed at Week 34 then every 12 weeks until relapse or disease progression (Week 46, 58, 70, etc.), ±7 days. MRI may be performed only if CT with contrast is contraindicated in the opinion of the Investigator or if frequent CT scans are not allowed according to local IRB/IEC. The same imaging modality used at screening **must** be used throughout the study for each patient.

7. Enrollment and Study Procedures

7.1. Screening Period

Selected screening procedures are highlighted below. For the additional screening assessments to be performed, please see the Schedule of Events provided in Section 6.1.

7.1.1. Informed Consent

Written informed consent in a language fully comprehensible to the prospective patient and/or designee will be obtained prior to performing any study-related procedures. A copy of the signed informed consent form (ICF) will be provided to the patient and/or designee. The Investigator will retain all original versions of signed ICFs.

After ICF signature, 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 (See Section 7.3.4.3).

Rescreening of patients is only allowed once per patient if the patient was not registered as entering the treatment phase before (ie, 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.

7.1.2. Demographic Information

Demographic information will be collected at the Screening visit. Standard demography parameters include age, gender, and race/ethnicity (recorded in accordance with local regulations).

7.1.3. Physical Examinations

Physical examinations will be performed as specified in the Schedule of Events (Section 6.1). 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.

7.1.4. Medical History

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

- Lymphoma diagnosis
- Prior lymphoma therapies and dates
- Responses to prior lymphoma therapies (including stem cell transplantation, radiotherapy, CAR-T cell or other adaptive T-cell therapies, surgery, etc.)
- Whether patient was refractory to their most recent prior therapy

The non-lymphoma-related medical history should include any ongoing medical conditions and symptoms and should also include the toxicity grade.

7.1.5. Tumor Specimen

A FFPE tumor block is preferred; if a tissue block is not available, at least 15 unstained slides or freshly cut serial sections (3−5 µm in thickness), preferably with an accompanying block punch will be accepted. A representative tumor specimen or lymph node meeting the following criteria must be available at the time of screening and submitted to the central pathology laboratory within 8 weeks after Cycle 1 Day 1:

- **For patients with ENKTL, AITL, PTLD, and HIV-L**: Tumor specimen is preferably ≤1 year old. For tumor specimens >1 year old, please consult the Medical Monitor to discuss eligibility.
- **For patients with all other lymphoma subtypes**: Tumor specimen is preferably ≤6 months old. For tumor specimens >6 months old, please consult the Medical Monitor to discuss eligibility.

The specimen must be representative of the current disease (eg, for patients who have relapsed, the biopsy specimen should have been taken after the most recent relapse).

The process for submitting archived tissue or fresh tissue biopsy as FFPE tissue specimens and procedures for central pathology review is provided in a separate Pathology Manual.

7.1.6. Central Review of EBV Status and Verification of Lymphoma Subtype

All enrolled patients will have tumor tissue from a representative biopsy reviewed centrally for confirmation of EBV-positive lymphoma. *In situ* hybridization for EBV encoded RNA (EBER-ISH) and/or immunohistochemistry for LMP-1 will be performed. The central pathology lab slides and local pathology report will be reviewed regarding morphology and ancillary test results to confirm the diagnosis. Appropriate pathology review and/or immunophenotyping will be conducted to confirm the diagnosis.

For clinical trial sites with capability, digital images of slides utilized in local diagnosis, subclassification, and EBV status with controls, will be submitted to the central pathology laboratory.

Patients enrolled based on local pathology results will not be removed from the study if the central pathology lab shows a different result (eg, patient is EBV^+ based on local pathology and EBV^- on central review).

7.1.7. Baseline Disease Assessments

7.1.7.1. ^{18}FDG-PET/CT and CT with Contrast

Any imaging assessments already completed during the regular work-up of the patient within 28 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.

An ^{18}FDG-PET/CT and a diagnostic contrast-enhanced CT (or MRI if a CT with contrast is contraindicated) of the neck, chest, abdomen, and pelvis is required to confirm measurable disease (one target lesion) greater than 1.5 cm in diameter or at least one extranodal lesion greater than 1.0 cm in both long and short diameter. All evaluable or measurable disease must be documented at baseline/screening and re-assessed at each subsequent tumor evaluation.

^{18}FDG-PET/CT scans in conjunction with diagnostic contrast-enhanced CT scans will be obtained in this study. Diagnostic contrast-enhanced CT scans obtained as part of a PET/CT scan may be used in lieu of a dedicated CT scan. Patients may have extranodal disease that is inadequately imaged by CT scan. MRI may be preferred in these cases. The same imaging modality used for lymphoma evaluation at screening must be used for all response evaluations throughout the study to ensure consistency across the different time points for each patient.

7.1.7.2. Bone Marrow Biopsy

For patients with HL and DLBCL, a baseline bone marrow biopsy is not necessary if the PET/CT demonstrates bone disease.

Patients with HL and DLBCL are only required to have a baseline bone marrow biopsy if clinically indicated (eg, cytopenias are present and the screening PET/CT scan does not indicate bone/bone marrow involvement).

For all other patients, a baseline bone marrow biopsy is required at screening.

If a bone marrow biopsy was performed within 12 weeks prior to Cycle 1 Day 1 and is available, it may be used as the screening biopsy. Bone marrow biopsy samples must be submitted to central pathology within 8 weeks after Cycle 1 Day 1.

The process for submitting tissue to the central pathology laboratory is provided in a separate Laboratory Manual.

7.1.8. Eligibility Determination and Patient Registration

Investigative sites will submit patient registration materials for 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 Medical Monitor for review. Eligibility will be reviewed and approved by the Sponsor Chief Medical Officer (CMO) or designee (eg, Medical Monitor) prior to patient enrollment.

7.1.8.1. Screen Failures

Patients who have provided informed consent or assent 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.

7.2. Treatment Period

Patients will be treated with nanatinostat and valganciclovir until discontinuation of study treatment as described in Section 7.2.3.

7.2.1. Treatment Cycles

For Cohorts 1, 2, 3b, 4, 5, 6, and 7, patients will receive nanatinostat/valganciclovir (nanatinostat 20 mg orally once daily on Days 1 to 4 per week and valganciclovir 900 mg orally once daily) continuously for 28-day treatment cycles. During treatment Cycle 1, visits will occur on Days 1, 8, 15, and 22. Starting at Cycle 2, visits will occur on Days 1 and 15. Each scheduled clinic visit has an allowable ±3-day window. Visit windows are not applicable to dosing. Should a visit occur during the ± 3-day window, patients will be instructed to continue following the 4 days on, 3 days off dosing cycle for nanatinostat.

For Cohort 3a, the PTCL patients randomized to monotherapy will begin with 6 weeks of nanatinostat monotherapy (20 mg orally once daily on Days 1 to 4 per week) with visits on Days 1, 15, 29, and 43. Each scheduled clinic visit has an allowable ±3-day window. If a patient has stable or progressive disease at the Day 43 visit, the patient will be offered the option to switch to nanatinostat/valganciclovir combination and follow the 28-day treatment cycles as described above. Patients must complete the End of Monotherapy Disease assessment and qualify (labs, no sign of CNS disease progression, ECOG) prior to beginning Cycle 1 Day 1 of the nanatinostat/valganciclovir combination therapy. If a patient has a response (complete or partial response) to nanatinostat monotherapy at the Day 43 visit, the patient will continue monotherapy treatment.

7.2.2. 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.

7.2.3. Discontinuation of Study Treatment

Patients will continue on study until disease progression, unacceptable toxicity, withdrawal of consent by the patient, patient is lost to follow-up, death, or discontinuation from the study due to any other reason (eg, Sponsor terminates the study).

Patients may voluntarily discontinue from study treatment at any time and for any reason. In this case, the Investigator must make every effort to determine the primary reason for the decision and record this information in the eCRF.

When 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 and yet agree to continued follow-up of associated clinical outcome information in which case this information would be collected and maintained in the clinical trial database.

The Investigator may discontinue study treatment for a given patient if he/she is of the opinion that continuation of therapy would be detrimental to the patient's well-being.

For patients that discontinue treatment without relapse/disease progression, follow the CT scan assessment schedule until disease progression, start of new anti-lymphoma therapy, or end of study (see Table 5).

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

- Adverse event
- Progressive disease or relapse
- Lost to follow-up
- Physician decision
- Pregnancy
- Withdrawal of consent
- Death
- Study terminated by Sponsor
- Any protocol deviation where continuing participation in the study would result in a significant risk to the patient's safety

7.2.4. 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 minimum, all patients who discontinue study treatment, including those who refuse to return for a final visit, will be contacted for safety evaluations during the 28 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 Section 6.1.

7.2.5. Safety Follow-up Visit

The Safety Follow-up visit will occur approximately 28 days following the final administration of nanatinostat/valganciclovir. The Safety Follow-up visit has an allowable ±3-day window.

If a patient withdraws consent after the EOT visit but prior to the 28-day safety evaluation, safety data should be collected on the patient up to the date of consent withdrawal.

Adverse events will be assessed (contact by phone is permitted) until 28 days following the last dose of study drug. In addition to AEs, all concomitant medications given to a patient as a result of an AE during this period will be recorded on the Prior and Concomitant medication eCRF page. All new anti-lymphoma therapies given to a patient within 28 days after the last dose of study drug must be recorded in the eCRF.

7.2.6. Long-term Follow-up Visits

Patients who discontinue treatment for reasons other than disease progression will start Long-term Follow-up visits every 12 weeks (±7 days) following the EOT visit. Scans performed during the Follow-up period should be performed on the same schedule with the same imaging modality as previously used. Tumor and EBV DNA level assessments will continue as part of the Long-term Follow-up visits until disease progression or start of new anti-lymphoma therapy.

At disease progression/relapse or the start of new anti-lymphoma therapy, patients will be contacted (eg, telephone, e-mail) at least every 6 months (±7 days) following the previous Long-term Follow-up assessment for a description of subsequent anti-lymphoma therapy given, response to subsequent therapies, and survival, unless they withdraw consent.

Long-term Follow-up visits will continue until all patients have either withdrawn consent, died, become lost to follow-up, completed 3 years of follow-up, or the trial is terminated by the Sponsor.

7.2.7. 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.

7.3. 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 Section 6.1. A central laboratory will be used for the analysis of hematology and chemistry. Clinical decisions and dose modifications during the study can be based on local laboratory results.

7.3.1. Efficacy Assessments

7.3.1.1. Baseline Evaluation

The following radiologic assessments are to be performed in the screening period (within 28 days prior to the start of treatment):

1. A brain CT or MRI to rule out CNS involvement with lymphoma.
2. ^{18}FDG-PET/CT and diagnostic CT with contrast or MRI from base of skull to mid-thigh (including other known sites of disease) to establish disease status at baseline. A diagnostic contrast enhanced CT scan obtained as part of a PET/CT scan may be used in lieu of dedicated CT scans.

7.3.1.2. Tumor Response Assessments

Disease response assessments will be made every 8 weeks until 24 weeks, and then every 12 weeks for the remainder of the study, according to the revised response criteria for malignant lymphoma based on the IWG-NHL guidelines (Cheson 2007). A scan to confirm an unconfirmed PR or unconfirmed CR ≥4 weeks later may also be performed.

^{18}FDG-PET/CT scans in conjunction with diagnostic contrast-enhanced CT scans (or MRI if a CT with contrast is contraindicated) will be obtained in this study at baseline, and for the 8-week and 16-week tumor assessments. Diagnostic contrast enhanced CT scans obtained as part of a PET/CT scan may be used in lieu of dedicated CT scans.

Subsequent evaluations will be by CT with contrast (without PET) or MRI only. Patients with FDG-avid lymphoma at baseline may have an ^{18}FDG-PET/CT performed to evaluate a possible CR or PR after Week 16 (unless prohibited by local practice) and may use a diagnostic contrast-enhanced CT for follow-up once a complete metabolic response is obtained. ^{18}FDG-PET/CT scans may also be obtained per investigator discretion (eg, in instances where extranodal disease may be inadequately imaged by contrast-enhanced CT), and responses recorded in the eCRF.

MRI may be substituted only if i) CT is contraindicated as assessed by the Investigator, ii) if frequent CT scanning is not permitted by the local Institutional Review Board (IRB)/Independent Ethics Committee (IEC), or iii) in the case of extranodal disease that is inadequately imaged by CT scan.

At all times during the study, suspected disease progression based on clinical findings must be confirmed by imaging as soon as possible (and before initiating non-protocol specified anti-lymphoma therapy).

Efficacy will be evaluated in terms of ORR, DOR, PFS, OS, TTP, and TTNLT. ORR will be used to move from Stage 1 to Stage 2. The responses will be assessed by both the Investigator (for management of the patient) and the IRC (for the primary and secondary endpoints).

Investigator-determined response assessments at each assessment time point will be entered onto the appropriate eCRF.

All CT or MRI 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 patient. The scans will be performed:

- Every 8 weeks (±1 week) until 24 weeks
- Every 12 weeks (±1 week) for the remainder of the study
- At the EOT visit (unless the previous scan was within 4 weeks of the EOT visit)
- A scan to confirm an unconfirmed PR or unconfirmed CR ≥4 weeks later may also be performed.

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

All patients will be followed for disease progression (ie, PD) or relapse using the schedule described in the Schedule of Events provided in Section 6.1. This includes patients who discontinue the protocol-specified treatments or the study early for any reason without documented evidence of PD or relapse.

Protocol-defined efficacy endpoints except OS and TTNLT will be assessed by an IRC. The IRC review includes central radiology and clinical review. Since the study endpoint is ORR based on PET/CT (first 2 disease response assessments) and thereafter CT with contrast, disease progression will typically be based on CT scans. In limited instances where disease progression is evident only by assessments other than CT, CT scans must still be provided along with the non-CT documentation of disease progression.

The radiologic assessments (^{18}FDG-PET/CT, CT with contrast, or MRI) are considered the primary method of response assessment. Any additional assessments – clinical assessments, bone marrow biopsy assessments, etc. are considered confirmatory.

Repeat bone marrow biopsies will be performed to confirm CR only for patients with bone marrow involvement reported at baseline.

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

Disease assessment data including actual scan data and radiology reports will be submitted to the Sponsor as it becomes available for evaluation by a central radiology reader.

7.3.2. Safety and Tolerability Assessments

Adverse events will be assessed, and concomitant medications, procedures, and hospitalizations will be recorded from the signing of the ICF until 28 days post-last dose of study treatment.

All 12-lead ECGs will be conducted in triplicate. Average corrected QT interval using Fridericia's method (QTcF) is to be calculated to confirm eligibility. For patients enrolled in any Stage 1 cohort, ECGs will be performed in triplicate, as described in Section 7.3.2.8. ECG tracings will be provided to a central laboratory, instructions are provided in the ECG Manual.

Viral levels [EBV, CMV, HHV-6, HHV-8, and HIV (for HIV$^+$ patients only)] will be monitored for viral reactivation.

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

7.3.2.1. Physical Examination

The physical examination including ECOG performance status (see Section 7.3.2.4) should be repeated at the beginning of each cycle, at treatment discontinuation, and any additional times deemed necessary by the Investigator.

7.3.2.2. Vital Signs

Vital signs (temperature, blood pressure, and heart rate) will be obtained at the Screening visit (Day -28 to Day -1), on Day 1 of each cycle (Day 4 of Cycles 2 and 6), and at the EOT visit. Vital signs should be collected just prior to the first dose of valganciclovir and nanatinostat, and in concert and just prior to PK blood draws. On other indicated visit days, collect vital signs once (prior to dosing of study drugs, if administered in clinic).

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

7.3.2.3. 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 (Day 4 of Cycles 2 and 6) and at the EOT visit. Height should additionally be measured in patients 12 to 17 years of age on Day 1 of each cycle (Day 4 of Cycles 2 and 6).

7.3.2.4. ECOG Performance Status

The ECOG performance status will be assessed according to Table 7 (Oken 1982).
ECOG performance status will be assessed at screening (Day -28 to Day -1), on Day 1 of each cycle (Day 4 of Cycles 2 and 6), and the EOT visit.

Table 7: ECOG Performance Status

Grade	ECOG Performance 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

7.3.2.5. Laboratory Evaluations

7.3.2.6. Clinical Laboratory (Safety) Testing

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

A central laboratory will be used for the analysis of hematology and chemistry. Clinical decisions and dose modifications during the study can be based on local laboratory results.

Hematology, serum chemistry, urinalysis, serology, and other parameters to be tested are listed in Table 8 and will be performed per the Schedule of Events provided in Section 6.1. In addition, the investigative sites will provide archived or newly obtained tumor samples at baseline and optionally at the time of relapse.

Table 8: Clinical Laboratory Tests

Laboratory Test Category	Specific Laboratory Tests	
Hematology	WBCs with differential (neutrophils, monocytes, eosinophils, lymphocytes, basophils), RBCs, Hgb, hematocrit, platelets, MCV, MCH	
Coagulation	PT or INR, activated partial thromboplastin time (aPTT)	
Serum Chemistry	Aspartate aminotransferase (AST [SGOT])	Lactate dehydrogenase (LDH)
	Alanine aminotransferase (ALT [SGPT])	Bicarbonate
	Alkaline phosphatase (ALP)	Blood urea nitrogen (BUN)
	Albumin	Creatinine
	Total bilirubin	Glucose
	Sodium	Chloride
	Potassium	Calcium
	Magnesium	Phosphate
	Total protein	Uric acid
	Amylase	
Urinalysis [a]	Macroscopic panel (dipstick)	
Serology	Hepatitis B virus (HBV) surface antigen (Ag)	HBV DNA PCR [a, b]
	HBV core and surface antibody (Ab)	Hepatitis C virus (HCV) Ab [a, c]
	EBV, CMV, HHV-6, HHV-8 levels	
Pregnancy [a]	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.	

Abbreviations: CMV = cytomegalovirus; Hgb = hemoglobin; HHV-6 = human herpesvirus-6; HHV-8 = human herpesvirus-8; INR = international normalized ratio; MCH = mean corpuscular hemoglobin; MCV = mean corpuscular volume; PCR = polymerase chain reaction; PT = prothrombin time; RBC = red blood cell; SGOT = serum glutamic-oxaloacetic transaminase; SGPT = serum glutamic-pyruvic transaminase; WBC = white blood cell.

a. Collected and analyzed in an accredited local/site laboratory in accordance with quality standards.

b. HBV DNA PCR only for patients with positive HBV core Ab or surface Ag.

c. Any patient positive for HCV Ab will be evaluated by quantitative polymerase chain reaction (qPCR).

7.3.2.7. Pregnancy Testing

Pregnancy testing is only required for females of childbearing potential. Serum test must be performed during screening. Serum or urine tests are to be performed at the beginning of each cycle (Day 4 of Cycles 2 and 6), the EOT visit, the 28-day Safety Follow-up visit, and every 12 weeks for up to 6 months post-last dose of study drugs.

7.3.2.8. Cardiac Assessments: Electrocardiograms (ECGs)

Triplicate ECGs should be obtained in close succession from the first ECG to the third ECG. For each sampling time point, 3 standard resting 12-lead ECGs will be obtained in close succession and no more than 2 minutes apart (4 minutes total for 3 ECGs). 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 on days that include PK sample collection (Stage 1), two triplicate 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 C_{max} (1 and 2 hours) and 4 hours. If possible, patients should not consume additional food between dosing and the last ECG time point.

For days with no scheduled PK sample collections, the ECG may be performed at any time during the clinic visit, or 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 ECG 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.

7.3.3. Pharmacokinetics

The PK parameters of nanatinostat and its metabolites and ganciclovir (primary active hydrolytic product of valganciclovir) will be evaluated for patients enrolled in Stage 1, and sparse sampling will be collected during the Stage 2 part of the study at selected sites. The scheduled time points are outlined in the Schedule of Events in Section 6.1. Pharmacokinetic parameters to be evaluated include time to maximum plasma concentration (t_{max}), maximum plasma concentration (C_{max}), area under the plasma concentration-time curve (AUC) for patients in the PK substudy. Details for collection, shipment, and storage are provided in the Laboratory Manual.

7.3.4. Biomarker Assessments

7.3.4.1. Rationale for Biomarker Assessments

The exploratory biomarker analyses outlined in this study are intended to foster an understanding of how baseline expression of certain biomarkers may impact efficacy, as well as to evaluate the effect of combination therapy with nanatinostat and valganciclovir on pharmacodynamic markers of activity, such as plasma EBV DNA levels, and correlation with clinical efficacy. Potential predictive markers will be studied to identify patients with optimal responses to nanatinostat plus valganciclovir. The impact of study drug administration on B-cell-/T-cell/NK cell/myeloid cell populations will be evaluated over time. The specific study procedures to be conducted for each patient enrolled in the study are presented in the Schedule of Events in Section 6.1. Cells and plasma from peripheral blood, or tumor tissue (lymph nodes), will be sent to a central laboratory selected by the study sponsor for analysis of viral DNA levels, and gene expression, phenotypic alterations in B-cells/T-cells/NK cells/myeloid cells and mutation profile and stored for up to 15 years after the study is completed for this purpose. After the duration of the storage, samples will be destroyed.

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

Table 9: Biomarker Sample Collection Plan

Sample Type	Visit/Time Point	Analyses	Purpose
Archival FFPE tumor sample	Screening	• IHC: PD-1, PD-L1 and other immune checkpoint molecules • Tumor-infiltrating lymphocyte (TIL) counts (CD3, CD4, CD8) • TP53, MYC, BCL2, etc. • EBV-associated genes/proteins: EBER, BZLF-1/ZTA, LMP-1, BGLF-4/PK, BXLF-1/TK, BRLF-1/Rta, etc. • RNA expression of selected immunological/cancer-related genes	Identify possible predictive markers
Tumor biopsy (optional)	At relapse or with disease progression	EBER, LMP-1, TIL counts, PD-L1 and other immune checkpoint molecules; markers related to resistance	Identify potential resistance markers
Plasma	• Screening • Cycle 1 Day 1, Cycle 1 Day 15, then monthly • Every 3 months in follow-up	• EBV DNA levels (EBV viral load by q-PCR) • Tumor-associated mutation profiling	Pharmacodynamic effect (on and off treatment)
PBMC (whole blood)	• Screening • Every 3 months	• Histone H3 acetylation (prior to and 3 hours post-nanatinostat administration, Cycle 1 Day 1 only) • RNA expression of selected immunological genes • Flow cytometry/IF for immune cell markers • Flow cytometry for identification of circulating lymphoma cells and RNAseq	Pharmacodynamic effect (on treatment)

Abbreviations: EBER = Epstein-Barr encoded RNA; EBV = Epstein-Barr virus; FFPE = formalin-fixed paraffin-embedded; IHC = immunohistochemistry; LMP-1 = latent membrane protein 1; PBMC = peripheral blood mononuclear cell; PD-1 = programmed cell death-1; PD-L1 = programmed death-ligand 1; qPCR = quantitative polymerase chain reaction.

7.3.4.2. Pharmacodynamic Assessments in Blood

For pharmacodynamic assessments in blood/plasma, collection of pre- and on-treatment samples as indicated in the Schedule of Events provided in Section 6.1 is mandatory for all patients.

7.3.4.3. Additional Biomarker Assessments

Once protocol defined exploratory testing (Section 7.3.4.1) is complete and the patient agrees, any remaining biomarker samples (tumor, blood) and residual PK samples may be further analyzed to address pertinent scientific questions related to EBV^+ lymphomas. 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.

An overdose, accidental or intentional, associated with an AE, or abuse, withdrawal, sensitivity, or toxicity to an investigational product should be reported as an AE. Overdoses with or without an associated AE will be recorded on the dosing eCRF. All patients will be monitored for AEs during the study and continue until 28 days after the last dose of study drugs or until a new anticancer treatment is started, whichever occurs first.

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.

Assessments may include monitoring any or all of the following parameters: the patient's clinical symptoms, laboratory, pathological, radiological, or surgical findings, physical examination findings, or other appropriate tests and procedures.

All AEs will be recorded by the Investigator from the time the patient signs the informed consent. Adverse events and serious adverse events (SAE) will be recorded on the Adverse Events eCRF and in the patient's source documents. All SAEs must be reported to ICON Drug Safety 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.

Pre-existing conditions are not considered AEs unless the condition worsens by at least one grade following the start of administration of the study drugs.

<u>Clarification in Reporting of Deaths</u>

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 and of itself. All reports of death should include an adverse event term for the cause of death (if known).

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 term for standard adverse event reporting, and if applicable, serious adverse event reporting. Death due to disease progression should only be reported in the clinical database on the designated eCRF.

8.1.1. Laboratory Test Abnormalities

An abnormal laboratory value is considered to be 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 (see 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 was 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:

- 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 SAEs

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 e-mail the report to:

ICON Pharmacovigilance e-mail at CHOSafety@iconplc.com (North/South America) or MHG Safety@iconplc.com (Europe, Asia, Pacific)

or

Fax to +888-772-6919 (North/South America) or +44 1792 525 720 (Europe, Asia, Pacific)

The Investigator should discuss with the Medical Monitor any SAEs for which the issue of seriousness is unclear or questioned. Contact information for the Medical Monitor is:

Table 10: ICON Medical Monitoring Support Center

Region	Phone	Fax	E-mail
North America (NA)	+1 866 326 5053 (toll-free) +1 434 951 4082 (direct)	+1 800 280 7035 (toll-free) +1 913 307 5751 (direct)	NAVAL1@iconplc.com
Europe, Asia Pacific & Africa (EAPA)	+ 49 621 878 2850	+ 44 203 365 6752	

Serious adverse events 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.

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 one or both study drugs.

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 the purpose of regulatory reporting, the Sponsor will determine the expectedness of events suspected of being related to the study drugs based on the IB.

For countries within the European Economic Area (EEA), 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, 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).

For the purpose of regulatory reporting in the EEA, the Sponsor will determine the expectedness of events suspected of being related to valganciclovir based on the Reference Safety Information (RSI) as included in the IB.

Disease progression or relapse, death related to disease progression or relapse (in the absence of serious study drug-related events), and serious events due to the relapse of the studied indication will not be subject to expedited reporting by the Sponsor to regulatory authorities.

8.6. Reporting Adverse Events

Any AEs which occur following signing of the informed consent up to and including 28 days after the last dose of study drugs or until the start of subsequent anticancer therapy, whichever occurs first, will be recorded.

Unanticipated problems that require reporting to IRB might include:

- 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. Positive urine pregnancy 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 ICON 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 ICON 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 was abnormal (eg, spontaneous or therapeutic abortion), the Investigator should report the abnormal outcome as an AE. If the abnormal outcome meets

any of the serious criteria, it must be reported as an SAE to ICON Drug Safety within 24 hours of the Investigator's knowledge of the event using the SAE Report Form.

All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 28 days that the Investigator suspects is related to the *in utero* exposure to the study treatment should also be reported to ICON 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 the IRB/IEC's requirements.

8.7.2. Male Patients

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.

Of note, valganciclovir may cause temporary or permanent inhibition of spermatogenesis. The Sponsor recommends that the Investigator provide advice to patients regarding the conservation of sperm prior to treatment with valganciclovir.

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.

All overdoses, whether accidental or intentional, should be recorded in the eCRF. All AEs associated with an overdose should be captured on the Adverse Events eCRF. If an overdose occurs 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 serious 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 trial.

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

All cases of emergency must immediately be reported to the medical expert 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 subjects and reported to the IRB/IEC, only if it was 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 the following criteria could be reported by the Investigator to the IRB/IEC as an unanticipated problem:

- Unexpected given:
  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 was 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 in patients with EBV^+ relapsed/refractory lymphoma following prior systemic therapy(ies) with no available standard therapies as per the eligibility criteria.

All data will be summarized by EBV^+ lymphoma subtype and overall subtypes. In addition, sub-cohorts of PTCL patients randomized to monotherapy versus those randomized to combination therapy will be summarized separately.

9.2. Statistical and Analytical Plans

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

9.3. Definition of Analysis Populations

The following 4 populations will be used in the analysis:

1. **Intent-to-Treat (ITT) population:** All patients who are enrolled into the trial, regardless of whether they received study treatment or not.

   The ITT population will be used for the primary efficacy analysis. Patients will be analyzed according to their disease/cohort. If a patient has no post-baseline tumor assessment for efficacy, they will be counted as a treatment failure in this population analysis.

2. **Modified ITT (mITT) population:** All enrolled patients who have received at least one dose of study medication, met all eligibility criteria, and have at least one post-baseline tumor assessment for efficacy.

   The efficacy analysis will also be performed on the mITT population as supportive evidence and/or sensitivity analyses. Patients will be analyzed according to their cohort and overall.

3. **Safety population:** All patients who have received at least one dose of study medication will be summarized for safety based on cohort and overall.

4. **PK population:** All patients with PK assessments.

9.4. Sample Size and Power Considerations

This multinational, multicenter study will employ a Simon's 2-stage design to allow termination of enrollment into cohorts where treatment appears futile (Simon 1989). The decision to transition from Stage 1 to Stage 2 is dependent on the assumption of ORR: ORR ≤10% (poor response); ORR ≥35% (good response). The sample size estimation uses 1-sided alpha = 0.05 and targets statistical power = 85%.

Using the Simon's 2-stage design approach, the null hypothesis that the true response rate is 10% will be tested against a one-sided alternative. In the first stage, up to 10 patients will be accrued in each cohort. If there are 1 or fewer responses, the cohort will be discontinued. If the cohort fails to enroll any patients within 1 year from the enrollment of the first patient, the cohort will

be considered for termination of enrollment. Otherwise, if at least 2 patients in a cohort respond, additional patients will be accrued for a total of 21 in the cohort. The null hypothesis that the true response rate is 10% will be rejected in each cohort where 5 or more responses are observed in 21 patients. This design yields a type I error rate of 0.0440 and power of 86.2% within each cohort where the true response rate is 35%.

If 10 patients of a given lymphoma subtype are enrolled into Cohort 7, then the Simon's decision criteria will be applied to determine whether or not to add patients in Stage 2 for that subtype. If none of the subtypes represented in Cohort 7 enrolls at least 10 patients, efficacy data collected on those patients will be listed, but not summarized by group. All patients will be summarized for safety, regardless of the decision to discontinue enrollment into any cohort.

If at the end of Stage 2 there are at least 7 responders observed in the initial 21 patients in any cohort (ORR ≥33.3%), enrollment will be expanded to include up to 120 additional patients in that cohort (N=141), with the possibility of performing an interim analysis in that cohort to be described in the statistical analysis plan. The maximum sample size estimated for the expanded cohort is dependent on the assumption of ORR ≥35% with the lower bound of its 95% CI excluding ORR 25%.

9.5. Baseline Characteristics and Patient Disposition

Demographic and baseline (last non-missing observation prior to treatment) disease characteristics will be summarized by treatment group for the ITT, mITT, and Safety populations. Patients' age, height, weight, and continuous baseline characteristics will be summarized using descriptive statistics (N, mean, standard deviation, median, minimum, maximum), while age group, gender, ethnicity, histology, and other categorical variables will be provided using frequency tabulations (count, percent) by treatment group. Medical history data (coded by Medical Dictionary for Regulatory Activities [MedDRA] dictionary) will be summarized using frequency tabulations by treatment group, System Organ Class and Preferred Term for the ITT, mITT, and Safety populations.

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 ITT population. Corresponding patient listings will be provided as well.

9.6. Efficacy Analysis

All efficacy analyses will be performed on the ITT population. Key efficacy analyses will be performed on the mITT population as supportive evidence and to assess robustness of efficacy findings.

9.6.1. Primary Efficacy Endpoint Analysis

The primary efficacy endpoint is ORR assessed by an IRC. Disease response assessments will be made every 8 weeks until 24 weeks, and then every 12 weeks for the remainder of the study, according to the revised response criteria for malignant lymphoma based on the IWG-NHL

guidelines (Cheson 2007). A scan to confirm an unconfirmed PR or unconfirmed CR ≥4 weeks later may also be performed.

^{18}FDG-PET/CT scans in conjunction with diagnostic contrast-enhanced CT scans (or MRI if a CT with contrast is contraindicated) will be performed at baseline, and for the 8-week and 16-week tumor assessments. Diagnostic contrast enhanced CT scans obtained as part of a PET/CT scan may be used in lieu of dedicated CT scans.

Subsequent evaluations will be by CT with contrast (without PET) or MRI only. Patients with FDG-avid lymphoma at baseline may have an ^{18}FDG-PET/CT performed to evaluate a possible CR or PR after Week 16 (unless prohibited by local practice) and may use a diagnostic contrast-enhanced CT for follow-up once a complete metabolic response is obtained. ^{18}FDG-PET/CT scans may also be obtained per investigator discretion (eg, in instances where extranodal disease may be inadequately imaged by contrast-enhanced CT). Efficacy will be evaluated in terms of ORR, DOR, PFS, OS, TTP, and TTNLT. ORR will be used to move from Stage 1 to Stage 2.

ORR is defined as the proportion of patients who achieve a confirmed CR or PR as determined by an IRC.

Patients will be analyzed according to their cohort/lymphoma subtype. The number and percentage of patients with a CR or PR after initiation of treatment will be summarized overall and by cohort. Ninety-five percent (95%) confidence intervals (Cis) around the ORR (CR + PR) will be calculated using the Clopper-Pearson method.

For patients who achieve CR/PR, the duration of response (DOR), defined as time from date of first observed complete or partial response to the date of disease progression, death due to any cause, or last adequate (radiographic) response assessment, will be estimated using the Kaplan-Meier method. Any patient who does not need new anti-lymphoma treatment, experiences disease progression, or death will be censored at the last non-missing assessment. Patients initiating new anti-cancer therapy will be censored at the last adequate disease assessment prior to the start of therapy.

Overall survival will be estimated using the Kaplan-Meier method and will include all enrolled patients. Patients still alive will be censored at the last non-missing assessment. The 95% CI around the OS rate at 12 months will be presented. Analyses of other time-to-event efficacy endpoints (DOR, TTP, PFS, and TTNLT) will be analyzed in a similar manner.

9.6.2. Secondary Efficacy Endpoints Analysis

Secondary efficacy endpoints will include OS, DOR, PFS, and TTNLT.

- **Duration of response** (DOR): defined as the interval from date of first observed CR or PR to the date of disease progression, death due to any cause, or last adequate (radiographic) response assessment.
- **Time to next anti-lymphoma treatment** (TTNLT): defined as the interval from the start of study drug treatment to date of next anti-lymphoma treatment (including chemotherapy, radiotherapy, radioimmunotherapy or immunotherapy).
- **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.

- **Overall survival** (OS): defined as the interval from the start of study drug treatment to date of death, for any reason.

For time-to-event type of endpoints (OS, DOR, PFS, TTNLT), Kaplan-Meier estimates will be provided.

9.6.3. Exploratory Endpoints

All exploratory endpoints will be summarized by cohort and overall. Future analysis of these endpoints will be described in a separate analysis plan.

9.7. Safety Analysis

Safety analysis will be based on all patients in the Safety population and will be summarized overall, by cohort, and by any other relevant subgroup, such as randomization to monotherapy.

Study medication exposure will be summarized for each patient and tabulated by cohort 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 cohort. Tabulations and listings of values for vital signs and laboratory safety evaluations will be presented.

Adverse events will be coded according to MedDRA and classified using the NCI CTCAE Version 5.0. The incidence rates of AEs will be tabulated by System Organ Class and Preferred Term. Subsets of AEs to be summarized include serious AEs (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 cohort, 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 selected 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 cohort.

9.8. Interim Analysis

Aside from the Stage 1 analysis specified by the Simon's decision criteria for proceeding to Stage 2, an interim analysis may be conducted during the Expansion phase. Further details will be provided in the statistical analysis plan.

10. STUDY COMMITTEES

10.1. Study Steering Committee

An SSC will be responsible for assisting the Sponsor with i) management of the overall stewardship of the study according to the protocol, and ii) to recommend and approve any modifications needed upon request of the Sponsor (eg, assisting the Sponsor with review of any study amendments, interpretation of data, presentation and publication of study results). The SSC will be composed of 4 to 5 Investigators and the Sponsor's medical expert for the study. Other specialists may be invited to participate as members of the SSC at any time if additional expertise is desired.

10.2. Independent Review Committee

An IRC will be established to provide an independent review of radiographic and pertinent clinical data to provide expert interpretation of changes in tumor status and response assessment. The IRC will include an independent board-certified radiologist and an independent board-certified hematologist/oncologist, and will be managed by the contracted imaging provider, Clario (Philadelphia, PA USA). The review of radiographic and clinical data by the IRC will be performed on an ongoing basis. The specifics of Clario's processes and reading methods will be described in an IRC charter developed by Clario in conjunction with the study Sponsor.

11. STUDY ADMINISTRATION

11.1. Regulatory and Ethical Consideration

11.1.1. 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:

- US Code of Federal Regulations (CFR) applicable to clinical studies: 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

11.1.2. Ethics Review

Each participating institution must provide for the review and approval of this protocol and the associated informed consent documents prior to the initiating the study and on an annual basis and approve any recruitment material by an appropriate IRB or IEC.

Protocol amendments require review and approval by the applicable IRB/IEC prior to implementation.

Changes to the ICF will be submitted to the appropriate IRB/IEC for review and approval.

At the time of any protocol amendment or change to the informed consent document, an assessment will be made regarding the need for re-consenting existing patients.

Additional materials may be provided to the appropriate IRB or IEC per local regulations.

11.1.3. 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. Assent must be obtained for adolescent patients <18 years old, and a parent/guardian must provide written consent.

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.

11.1.4. 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.

11.1.5. Use of Research Samples and Data

The Sponsor will be responsible for all stored samples generated during this study and the types of analyses to be done on the sample. 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. Samples will be stored via pseudonymization. Samples will be labeled with a code that only the study team can link to a patient. Patients' identities will not be revealed to the laboratory(ies) where samples will be stored or analyzed.

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 any biological specimens left over from study-specified assessments stored and used for future research. However, withdrawal of consent with regard to 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. 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.

11.2. Data Handling and Recordkeeping

11.2.1. 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 CRF Manual. Clinical data will be entered directly from the source documents.

11.2.2. Retention of Records

This study is conducted under an Investigational New Drug (IND) application with the FDA; therefore, ICH GCP guidelines apply. 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.

11.2.3. 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 with regard to 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.

11.2.4. 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 Good Clinical Practice (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.

11.2.5. Quality Control and Quality Assurance

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.

11.3. 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.

In the event that the Sponsor elects to terminate or suspend this study prior to completion, it will discuss the feasibility of continued administration of nanatinostat/valganciclovir with each participating Investigator for those patients that appear to be benefitting from nanatinostat/valganciclovir.

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.

11.4. Use of Study Information and Publication

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).

Upon study completion and finalization of the study report, the results of this study will be submitted for publication. Data derived from the study are the exclusive property of the Sponsor.

The results of the study may be published or presented by the Investigator(s) following review and agreement by the Sponsor.

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13. APPENDICES

APPENDIX 1. CONCOMITANT THERAPIES TO BE USED WITH CAUTION WITH NANATINOSTAT

Table 11: 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

Note: This list is not exhaustive of all substrates. For more information, discuss with your research pharmacist.

Table 12: 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

Note: This list is not exhaustive of all inhibitors. For more information, discuss with your research pharmacist.

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	Monitor 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

Abbreviation: CBC = complete blood count.
[a] Includes, but is not limited to, adefovir, adriamycin, dapsone, doxorubicin, flucytosine, hydroxyurea, pentamidine, tacrolimus, tenofovir, trimethoprim/sulfamethoxazole, vinblastine, vincristine, and zidovudine.
Adapted from VALCYTE® USPI 2021 (Genentech 2021).

APPENDIX 3. RESPONSE CRITERIA FOR MALIGNANT LYMPHOMA

Table 13: Response Definitions for Clinical Trials

Response	Definition	Nodal Masses	Spleen, Liver	Bone Marrow
CR	Disappearance of all evidence of disease	(a) FDG-avid or PET positive prior to therapy; mass of any size permitted if PET negative (b) Variably FDG-avid or PET negative; regression to normal size on CT	Not palpable, nodules disappeared	Infiltrate cleared on repeat biopsy; if indeterminate by morphology, immunohistochemistry should be negative
PR	Regression of measuable disease and no new sites	≥ 50% decrease in SPD of up to 6 largest dominant masses; no increase in size of other nodes (a) FDG-avid or PET positive prior to therapy; one or more PET positive at previously involved site (b) Variably FDG-avid or PET negative; regression on CT	≥ 50% decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of liver or spleen	Irrelevant if positive prior to therapy; cell type should be specified
SD	Failure to attain CR/PR or PD	(a) FDG-avid or PET positive prior to therapy; PET positive at prior sites of disease and no new sites on CT or PET (b) Variably FDG-avid or PET negative; no change in size of previous lesions on CT		
Relapsed disease or PD	Any new lesion or increase by ≥ 50% of previously involved sites from nadir	Appearance of a new lesion(s) > 1.5 cm in any axis, ≥ 50% increase in SPD of more than one node, or ≥ 50% increase in longest diameter of a previously identifed node > 1 cm in short axis Lesions PET positive if FDG-avid lymphoma or PET positive prior to therapy	> 50% increase from nadir in the SPD of any previous lesions	New or recurrent involvement

Abbreviations: CR, complete remission; FDG, [^{18}F]fluorodeoxyglucose; PET, positron emission tomography; CT, computed tomography; PR, partial remission; SPD, sum of the product of the diameters; SD, stable disease; PD, progressive disease.

Source: (Cheson 2007).