Protocol Number ALRN-6924-1-01

IND Number 122,392

A Phase 1/2a Open-Label Study to Determine the Safety and Tolerability of ALRN-6924 Alone or in Combination in Patients with Advanced Solid Tumors or Lymphomas Expressing Wild-Type p53 Protein

Protocol Version Amendment 7 – 25 September 2018

Previous versions:
Amendment 6 – 20 October 2017
Amendment 5 – 27 March 2017
Amendment 4 – 08 July 2016
Amendment 3 – 31 December 2015
Amendment 2 – 18 February 2015
Amendment 1 – 23 September 2014 - Submitted to FDA only
Version 1.1 – 22 July 2014 - Submitted to IRBs for approval
Original – 16 June 2014 – Submitted in IND

9/25/2018

Manuel Aivado, MD, PhD
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Aileron Therapeutics, Inc.
490 Arsenal Way
Watertown, MA 02472

Date

INVESTIGATOR'S SIGNATURE PAGE

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Protocol Amendment 7 – 25 September 2018

I have reviewed this protocol and agree that it contains all the information necessary to conduct the study as required. I am aware of my responsibilities as an Investigator under the guidelines of the International Council on Harmonization (ICH) Good Clinical Practice (GCP), the Declaration of Helsinki, and the Code of Federal Regulations (CFR) Title 21. I will conduct the trial in accordance with the principles of ICH GCP, the Declaration of Helsinki and the CFR.

I will maintain as confidential all written and verbal information provided to me by the Sponsor, including but not limited to, the protocol, case report forms, Investigator's Brochure, material supplied at Investigator meetings, minutes of teleconferences, etc. Such material will only be provided as necessary to site personnel involved in the conduct of the trial, involved IRBs or local regulatory authorities.

I will obtain written informed consent from each prospective trial patient or each prospective trial patient's legal representative prior to conducting any protocol-specified procedures. The ICF used will have the approval of the IRB appropriate for each institution.

I will maintain adequate source documents and record all observations, treatments and procedures pertinent to trial patients in their medical records. I will accurately complete the case report forms supplied by the Sponsor in a timely manner. I will ensure that my facilities and records will be available for inspection by representatives of the Sponsor, the IRB, or relevant regulatory authorities. I will ensure that my staff and I are available to meet with Sponsor representatives during regularly scheduled monitoring visits.

I will notify the Sponsor or its designee within 24 hours of any serious adverse events. Following this notification, a written report describing the serious adverse event will be provided to the Sponsor or its designee as soon as possible, but no later than four working days following the initial notification.

_____

Investigator's Name (print)

_____ _____

INVESTIGATOR'S SIGNATURE DATE

ALRN-6924-1-01 SYNOPSIS

<table>
<tr><td>Protocol Number
ALRN-6924-1-01</td><td colspan="2">Protocol Title
A Phase 1/2a Open-Label Study to Determine the Safety and Tolerability of ALRN-6924 Alone or in Combination in Patients with Advanced Solid Tumors or Lymphomas Expressing Wild-Type p53 Protein</td></tr>
<tr><td>Name of Study Drug
ALRN-6924 for IV infusion</td><td>Sponsor
Aileron Therapeutics, Inc.</td><td>Phase of Development
Phase 1/2a</td></tr>
<tr><td></td><td>Research Facilities
Multi Center</td><td>Location
USA</td></tr>
<tr><td>Name of Active Ingredient
ALRN-6924

Palbociclib (IBRANCE®)</td><td colspan="2">Study Drug Description
ALRN-6924 is a Stapled Peptide clinical candidate designed to disrupt the interaction between the p53 tumor suppressor protein and its predominant endogenous inhibitors, murine double minute 2 (MDM2) and murine double minute X (MDMX). ALRN-6924 drug product is a frozen or refrigerated liquid product supplied in single use glass vials in single dose strength of 75 mg in 5.0 mL, dissolved in 20 mM sodium phosphate, 240 mM trehalose, 300 ppm Polysorbate 20, and pH 7.5. Each vial contains recoverable 5.0 mL and is filled with formulated ALRN-6924 to 5.5 ± 0.2 mL.

Palbociclib is a cyclin-dependent kinase-4 and -6 inhibitor indicated for the treatment of hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer in combination with an aromatase inhibitor as initial endocrine based therapy in postmenopausal women; or in combination with fulvestrant in women with disease progression following endocrine therapy. Palbociclib is available as 125 mg capsules, 100 mg capsules, or 75 mg capsules for oral use.</td></tr>
<tr><td colspan="3">Study Objectives – Phase 1 Dose Escalation (ALRN-6924 administered as single agent therapy)
The primary objectives of the Phase 1 dose escalation are to:
• Evaluate the safety and tolerability of ALRN-6924 in adult patients with advanced solid tumors or lymphomas with wild-type (WT) TP53 who are refractory to or intolerant of standard therapy, or for whom no standard therapy exists
• Determine the dose limiting toxicities (DLT) and the maximum tolerated dose (MTD) or the optimal biological dose (OBD) of ALRN-6924 in adult patients with advanced solid tumors or lymphomas
The secondary objectives of the Phase 1 dose escalation are to:
• Describe the pharmacokinetics (PK) of ALRN-6924 and its metabolites in blood following single and multiple intravenous (IV) infusions
• Assess potential patient biomarkers (e.g., p53 status, MDM2 and MDMX expression levels), the effect of ALRN-6924 treatment on these biomarkers, and possible correlation between these biomarkers and clinical response
• Assess the effect of ALRN-6924 treatment on potential pharmacodynamic (PD) biomarkers in tumor biopsy</td></tr>
</table>

samples (including bone marrow aspirates) (e.g., p21, caspase, MDM2) and blood samples (e.g., macrophage inhibitory cytokine-1 [MIC-1]), and assess possible correlation between these biomarkers and clinical response

• Evaluate potential clinical activity of ALRN-6924

• Investigate the immunogenicity of ALRN-6924

The exploratory objectives are to:

• Starting at dose level 3: assess the effect of ALRN-6924 treatment on potential PD biomarkers (e.g., p21, p53, caspase) in circulating tumor cells (CTC), where detectable, or in mononuclear blood cells (MNC)

• Assess the effects of ALRN-6924 treatment on cell-free DNA from blood

Study Objectives – Phase 2a Dose Expansion in Peripheral T-cell Lymphoma (PTCL) (ALRN-6924 administered as single agent therapy)

The primary objectives of the Phase 2a dose expansion are to:

• Assess overall response rate (ORR)

• Further evaluate the safety and tolerability of ALRN-6924

The secondary objectives of the Phase 2a dose expansion are to:

• Describe the pharmacokinetics (PK) of ALRN-6924 and its metabolites in blood following single and multiple intravenous (IV) infusions in patient populations selected for dose expansion

• Assess duration of response (DOR)

• Assess progression free survival (PFS)

• Assess overall survival (OS)

• Assess PFS and OS at 1 year

• Assess time to response

• Assess the effect of ALRN-6924 treatment on potential pharmacodynamic (PD) biomarkers in tumor biopsy samples (including bone marrow aspirates, where clinically indicated) by measuring potential biomarkers such as e.g., p53, p21, caspase, MDM2, MDMX and in blood samples by measuring potential biomarkers such as MIC-1, and assessing possible correlation between these biomarkers and clinical outcomes

• Investigate the immunogenicity of ALRN-6924

The exploratory objectives of the Phase 2a dose expansion are to:

• Assess the effects of ALRN-6924 treatment on cell-free DNA from blood and on potential PD biomarkers (e.g., p21, p53, caspase) in circulating tumor cells (CTC), where detectable, or in mononuclear blood cells (MNC)

• Assess the effect of ALRN-6924 using alternative response criteria other than the IWG 2014 or RECIST 1.1 criteria

Study Objectives – Phase 2a Dose Expansion in MDM2 amplified or MDM2/CDK4 co-amplified solid tumors (ALRN-6924 plus palbociclib)

The primary objectives of this Phase 2a dose expansion cohort (added per Amendment 7) are to:

• Assess ORR

• Evaluate the safety and tolerability of ALRN-6924 and palbociclib when administered in combination

The secondary objectives are to:

• Describe the PK of ALRN-6924 (and its metabolites) and palbociclib when administered in combination

• Estimate DOR

• Estimate additional measures of efficacy, including time to response (TTR), PFS, OS, and PFS and OS at 1 year

The exploratory objective is to:

• Explore potential markers of response to treatment with ALRN-6924 and palbociclib

Study Endpoints – Phase 1 dose escalation (ALRN-6924 administered as single agent therapy)

• Safety and tolerability

• PK parameters (e.g., area-under-the-curve [AUC], maximum concentration [C_{max}], time of C_{max} [T_{max}], half-life [$t_{1/2}$]) of ALRN-6924 and its metabolites

• Patient biomarkers (e.g., p53 status, MDM2 and MDMX expression levels), PD biomarkers (e.g., p21, caspase, MDM2) in tumor biopsy samples, and PD biomarkers (e.g., MIC-1) in blood samples

• Anti-tumor effect

• Incidence of anti-ALRN-6924 antibodies

• Levels of biomarkers (e.g., p21, p53, caspase) in blood, CTCs, where detectable, or MNCs pre- and post-treatment with ALRN-6924.

Study Endpoints – Phase 2a dose expansion in PTCL (ALRN-6924 administered as single agent therapy)

• Anti-tumor effect

• Safety and tolerability

• PK parameters (e.g., AUC, C_{max}, T_{max}, and $t_{1/2}$]) of ALRN-6924 and its metabolites

• Levels of biomarkers (e.g., p53, MDM2, and MDMX gene sequence and copy number, as well as p21 RNA and/or protein expression) in tumor biopsy samples, and in blood, CTCs, where detectable, or MNC samples

• Incidence of anti-ALRN-6924 antibodies

Study Endpoints – Phase 2a dose expansion in MDM2 amplified or MDM2/CDK4 co-amplified solid tumors (ALRN-6924 plus palbociclib)

Primary endpoints:

• The proportion of efficacy-evaluable patients who achieve complete response (CR) or partial response (PR), per investigator assessment, in accordance with RECIST 1.1 or iRECIST (for solid tumor patients) or Response Assessment in Neuro-Oncology (RANO) criteria (for glioblastoma patients).

• Safety and tolerability including the occurrence of adverse events (AEs) and serious adverse events (SAEs), and changes from baseline in vital signs, laboratory analytes, and physical examination findings

Secondary endpoints:

• PK parameters, including AUC, C_{max}, T_{max}, and $t_{1/2}$ for ALRN-6924, its metabolites, and palbociclib

• The median time, in months, from the first response of CR or PR to disease progression or death from any cause (DOR)

• The median time, in months, for each of the following:

- The first dose of ALRN-6924 to the first response of CR or PR (TTR)
- The first dose of ALRN-6924 to disease progression or death from any cause (measured at 1 year and beyond) (PFS)
- The first dose of ALRN-6924 to death from any cause (measured at 1 year and beyond) (OS)

Exploratory endpoint:

• The correlation of response with MDM2, MDMX, and/or CDK4 gene copy number and other genetic and protein biomarkers

Study Design

This is a Phase 1/2a open-label, multi-center, dose-escalation and dose expansion study designed to evaluate the safety, tolerability, PK, PD, and anti-tumor effects of ALRN-6924 administered by IV infusion using up to 4 different dosing regimens of a 28- or 21-day cycle (alone or in combination), in patients with advanced solid tumors or lymphomas with WT TP53 (see p53 Status Determination below). In Phase 1 and Phase 2a, patients will receive ALRN-6924 either once weekly for three consecutive weeks for a 28-day cycle (1 and 2 hour infusions may be tested) or twice weekly for two consecutive weeks for a 21-day cycle. In Phase 2a, dosing three times a week for one week over a 21-day cycle will be tested.

This study consists of a Phase 1 Dose Escalation Phase (DEP) and a Phase 2a Dose Expansion Phase (EXP). The DEP is a "3+3" dose escalation design to establish the MTD or the OBD of ALRN-6924. The EXP will enroll up to 5 distinct groups of patients with specific solid tumors and/or lymphomas to further investigate the clinical safety profile and potential efficacy of ALRN-6924 at the MTD, OBD, or in alternate dosing regimens.

In the Phase 2a EXP, peripheral T-cell lymphoma (PTCL) has been selected as one of the diseases to be further studied in up to 3 cohorts to identify the optimal dosing regimen.

Another Phase 2a EXP group will include patients with MDM2 amplified or MDM2/CDK4 co-amplified solid tumors who will receive ALRN-6924 in combination with palbociclib. As these agents have not previously been co-administered, a safety run-in of 6-8 patients will first be enrolled and evaluated by the sponsor and the primary investigators before further patients are permitted to enroll. Patients will receive ALRN-6924 at the previously determined recommended Phase 2 dose for the once-weekly administration schedule (3.1 mg/kg on Days 1, 8, and 15) and palbociclib at an oral dose of 100 mg daily for 21 days (one dose level below the approved oral dose of 125 mg) in a 28-day cycle. Doses of ALRN-6924 and palbociclib may be adjusted for safety or tolerability prior to enrolment of additional patients into this EXP group.

Treatment of patients in the dose escalation and the dose expansion phases of the study will continue until

unacceptable toxicity, patient or physician decision to discontinue therapy or disease progression that is either symptomatic, rapidly progressive, requires urgent intervention, or is associated with a decline in performance status.

TP53 Status Determination and Tumor Sampling Requirements

A central laboratory will be employed to test archived tumor tissue samples or fresh biopsy samples from all patients enrolled in the study for TP53 status using Next-Generation Sequencing (NGS). A fresh biopsy sample will not be obtained if such biopsy poses a significant clinical risk to the patient. To minimize the potential risks from biopsies, the healthcare professional performing the biopsy must ensure that any biopsy performed uses a tumor location that presents a non-significant risk to the patient. Likewise, the healthcare professional performing the biopsy must choose the biopsy procedure that poses the lowest risk to the patient. Examples of significant risk procedures would include (but are not limited to) surgical biopsies of the brain, lung/mediastinum or pancreas.

Starting at DEP Dose Level 4, only patients with tumors WT TP53 will be enrolled. This is based on the proposed mechanism of action of ALRN-6924, which requires WT p53 protein to be pharmacologically active. It may be possible for some tumor cells to harbor a TP53 mutation on one allele, while maintaining WT TP53 on the second allele for TP53 to be pharmacologically active. This hypothesis is supported by in vitro data (unpublished) that demonstrated ALRN-6924 potency in a cell line with one WT TP53 allele and one mutated allele, in a substantial percentage of cells examined. Furthermore, a patient was recently treated with ALRN-6924 and achieved an objective improvement, despite her cancer cells showing only one WT TP53 allele, while lacking any TP53 on the second allele (manuscript under review).

In EXP, beginning with Amendment 6, there will be exceptions from the requirement to obtain central laboratory confirmation of WT p53 status prior to enrollment. The tumor types to be studied during the expansion phase of this clinical trial will be among those with high rates of WT TP53, thus enrollment of patients with mutant or deleted TP53 will be rare. Removal of the requirement to await central laboratory results will allow patients with an urgent need for treatment to participate in the study without enduring the two week delay that occurs while central laboratory testing is performed. Central laboratory testing remains required to confirm WT p53 status.

Phase 1 – Dose Escalation:

In the DEP, patients may meet the TP53 requirement through one of the following scenarios (per the exception to exclusion criterion 1, patients previously treated with an MDM2-inhibitor are also eligible, provided that a biopsy taken after completion of the last treatment with an MDM2-inhibitor meets one of the following):

- Patients may be eligible based on a fresh biopsy or archived tissue that is ≤1 year old. All samples will be tested for TP53 status using NGS at the central laboratory. The central laboratory will determine the TP53 status as expeditiously as possible.
- Upon approval from the medical monitor, patients may also enroll and initiate study treatment based on wildtype TP53 status that was determined by another laboratory. This testing must have been performed on tumor samples obtained no more than one year ago. These archived specimens with previously determined TP53 status must still be submitted for NGS testing at the central laboratory; the central laboratory's result will determine the patient's official classification as either TP53 wildtype or TP53 mutant.

Patients who do not have archived tissue, and for whom a biopsy poses a significant risk, cannot be enrolled.

Phase 2a – Dose Expansion:

In the Phase 2a EXP in PTCL, patients may meet the TP53 requirement through one of the following scenarios:

- Patients need to be tested for TP53 status, using a fresh biopsy or archived tissue that is ≤1 year old. Archived tissue may be used only if the patient did not receive systemic cytotoxic therapy in the interval between tissue collection and the start of treatment with study medication. All samples will be tested for TP53 status using NGS at the central laboratory. The central laboratory will determine the TP53 status as expeditiously as possible. Investigators are encouraged to await the TP53 test result, however, if this is

clinically deemed not to be in the patient's best interest, enrollment and the initiation of study treatment may proceed, prior to the central laboratory result becoming available. Central laboratory testing is still required to confirm WT p53 status.

- Upon approval from the medical monitor, patients may also enroll and initiate study treatment based on wildtype TP53 status that was determined by another laboratory. This testing must have been performed on tumor samples obtained no more than one year ago and the patient must not have received systemic cytotoxic therapy in the interval since the tissue was obtained. These archived specimens with previously determined TP53 status must still be submitted for NGS testing at the central laboratory; the central laboratory's result will determine the patient's official classification as either TP53 wildtype or TP53 mutant.

Patients who do not have archived tissue, and for whom a biopsy poses a significant risk, cannot be enrolled.

In the Phase 2a EXP cohort in MDM2 amplified or MDM2/CDK4 co-amplified solid tumors (ALRN-6924 plus palbociclib):

- Patients must have MDM2 amplified or MDM2/CDK4 co-amplified solid tumors as determined by local, commercial or central assays such as NGS, fluorescent in situ hybridization (FISH) or comparative genomic hybridization (CGH). However, all patients must have fresh or archival tissue submitted to the central laboratory for NGS testing. The central laboratory's results will determine the patient's official classification as MDM2 amplified, MDM2/CDK4 co-amplified, or neither MDM2 amplified nor MDM2/CDK4 co-amplified.
- Mutational analysis of TP53 is not required for this cohort, as TP53 mutations are extremely rare among patients with MDM2 amplifications. However, patients with known mutations or deletions of TP53 will be excluded from study participation. Likewise, patients with known retinoblastoma protein (Rb) mutations will be excluded.

Number of Patients to be Enrolled

Total enrollment of approximately 180 patients is planned for the study. Approximately 75 patients will be enrolled in the DEP for ALRN-6924 as single agent therapy, and approximately 15-25 additional patients for each of the up to five expansion cohorts will be enrolled in the EXP.

Number of Study Sites

Approximately 15 – 25 clinical sites are planned.

Eligibility Criteria

Given the different nature of the individual parts of the protocol, there are 3 distinct sets of inclusion/exclusion criteria described in the following for the Phase 1 dose escalation and the expansion cohorts:

Inclusion Criteria – Phase 1 dose escalation (ALRN-6924 administered as single agent therapy)

Patients must meet all of the following criteria to be considered for participation in this study.

1. Male or female patients age 18 years and older, inclusive, at the time of informed consent

2. Histologically- or cytologically-confirmed solid tumors that are metastatic or unresectable or lymphomas. Standard measures do not exist or are no longer effective for these patients.

3. WT TP53 status for relapsing or treatment-refractory solid neoplasms and lymphomas is mandatory for patients enrolling at Dose Level 4 and higher in Stage 1 of the DEP, as well as for all patients enrolled in Stage 2 of the DEP or in the EXP. In EXP, beginning with Amendment 6, TP53 status still must be determined by the central laboratory, but confirmation of WT TP53 status is not required for enrollment or initiation of study treatment, if the Investigator deems it clinically unacceptable to delay treatment.

4. At least one target lesion that is measurable by either Response Evaluation Criteria in Solid Tumors (RECIST 1.1-

See Appendix K) or by Revised International Working Group Response Criteria for lymphoma patients (IWG 2014 – See Appendix L)

5. Eastern Cooperative Oncology Group (ECOG) performance status 0-1 (See Appendix A)

6. Predicted life expectancy of ≥3 months

7. Adequate hematologic bone marrow function, measured within 7 days prior to the first dose of ALRN-6924, defined as:

- Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L
- Hemoglobin ≥9.0 g/dL
- Platelets $\geq 100 \times 10^9$/L

8. Adequate hepatic function, measured within 7 days prior to the first dose of ALRN-6924, defined as:

- In the absence of disease involvement of the liver: bilirubin ≤1.5 times institutional upper limit of normal (ULN), as well as aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5 times ULN
- In the presence of disease involvement of the liver: bilirubin ≤2 times institutional ULN as well as AST and ALT ≤5 times ULN

9. Adequate renal function, measured within 7 days prior to the first dose of ALRN-6924, defined as:

- Urinalysis with no evidence of +2 or higher proteinuria
- Serum creatinine ≤1.5 times institutional ULN, or calculated creatinine clearance ≥50 mL/min (Cockcroft-Gault formula)

10. Acceptable coagulation profile, measured within 7 days prior to the first dose of ALRN-6924, defined as:

- Prothrombin time (PT) or international normalized ratio (INR) ≤1.5 times ULN
- Activated partial thromboplastin time (aPTT) ≤1.5 times ULN

11. Prior anti-cancer therapies must wash-out such that they can neither cause drug-drug interaction with ALRN-6924 nor interfere with the anti-cancer evaluation of ALRN-6924. Therefore, the wash-out has to meet all the following criteria:

- patients must have recovered from the previous therapy to Grade 1 or baseline of significant toxicities, excluding alopecia, and
- 5 half-lives or 4 weeks (whichever is shorter) must have expired, unless the prior anti-cancer therapy and ALRN-6924 do not interfere with each other's metabolism, and
- 5 half-lives or 4 weeks (whichever is shorter) must have expired, unless the patient unequivocally progressed during the prior anti-cancer therapy

Palliative radiotherapy for bone lesions ≤2 weeks prior to the first dose of ALRN-6924 is acceptable if acute toxicity has resolved

12. Negative serum or urine pregnancy test within 2 days prior to the first dose of ALRN-6924 for women of child-bearing potential, defined as a sexually mature woman who has not undergone a hysterectomy or who has not been naturally post-menopausal for ≥24 consecutive months (i.e., who has had menses any time in the preceding 24 consecutive months)

13. All patients (males and females) of child-bearing potential must agree to use an effective method of birth control (i.e., latex condom, diaphragm, cervical cap, intra-uterine device [IUD], birth control pill, etc.) beginning two weeks prior to the first dose of ALRN-6924 and for 30 days after the last dose of ALRN-6924

14. Ability to understand and willingness to sign a written informed consent form

15. Patients with prostate cancer must continue androgen deprivation therapy, unless such therapy was discontinued 6 months prior to first dose of ALRN-6924

Exclusion Criteria – Phase 1 dose escalation (ALRN-6924 administered as single agent therapy)

Patients who meet any of the following criteria at screening or Day -1 will be excluded:

1. Previous treatment with investigational agents that inhibit MDM2 or MDMX activity with the following exception:

    Patients previously treated with an MDM2-inhibitor are eligible provided that a biopsy taken after completion of the last treatment with an MDM2-inhibitor is confirmed as WT TP53 prior to enrollment.

2. Known hypersensitivity to any study drug component

3. Known and untreated brain metastases. Patients with brain metastases that have been treated and demonstrated to be clinically stable for ≥30 days may be enrolled. Patients with primary central nervous system (CNS) malignancies are excluded.

4. Current, clinically significant coagulopathy or platelet disorder, as determined by the Investigator

5. History of pulmonary embolism within 6 months prior to the first dose of ALRN-6924 or untreated deep venous thrombosis (DVT)

6. Required concurrent use of anti-coagulants or anti-platelet medication, with the exception of aspirin doses ≤ 81 mg/day, low-dose subcutaneous (SC) heparin or SC low-molecular-weight heparin for DVT prophylaxis, or heparin flushes to maintain IV catheter patency.

7. Patients with pre-existing history of or known cardiovascular risk:

- History of acute coronary syndromes within 6 months prior to the first dose of ALRN-6924 (including myocardial infarction, unstable angina, coronary artery bypass graft, angioplasty, or stenting)
- Uncontrolled hypertension
- Pre-existing cardiac failure (New York Heart Association Class III-IV)
- Atrial fibrillation on anti-coagulants
- Clinically significant uncontrolled arrhythmias
- Severe valvulopathy
- Corrected QT (QTc) interval on screening electrocardiogram (ECG) ≥450 msec for males and ≥470 msec for females (QTc >480 msec for any patient with a bundle branch block)

8. Clinically significant gastrointestinal bleeding within 6 months prior to the first dose of ALRN-6924

9. Clinically significant third-space fluid accumulation (e.g., ascites requiring tapping despite the use of diuretics; or pleural effusion that requires tapping or is associated with shortness of breath)

10. Pregnant or lactating females

11. Evidence of serious and/or unstable pre-existing medical, psychiatric, or other condition (including laboratory abnormalities) that could interfere with patient safety or provision of informed consent to participate in this study

12. Active uncontrolled infection including HIV/AIDS or Hepatitis B or C. Patients with primary liver cancer that have positive hepatitis serology but are not demonstrating active viral hepatitis may be considered for enrollment if they meet all other inclusion and no other exclusion criteria.

13. Starting at Dose Level 4 and higher in Stage 1 of the DEP (as well as for all patients enrolling in Stage 2 of the DEP or in the EXP), patients with an Human Papilloma Virus (HPV)-positive malignancy.

14. Known history of another primary malignancy that has not been in remission for ≥2 years. Non-melanoma skin cancer and cervical carcinomas *in situ* or squamous intraepithelial lesions (e.g., cervical intraepithelial neoplasia [CIN] or prostatic intraepithelial/intraductal neoplasia [PIN]) are allowed.

15. Any psychological, sociological, or geographical condition that could potentially interfere with compliance with

the study protocol and follow-up schedule

16. The required use of any concomitant medications that are predominantly cleared by hepatobiliary transporters, organic anion transporter polypeptide [OATP] members OATP1B1 and OATP1B3, on the day of the infusion with ALRN-6924 or within 48 hours after an ALRN-6924 infusion (see Appendix B)

17. Hereditary angioedema of any severity or history of severe or life-threatening angioedema due to any cause.

Inclusion Criteria – Phase 2a dose expansions in PTCL (ALRN-6924 administered as single agent therapy)

Patients must meet all of the following criteria to be considered for participation in this study.

1. Male or female patients age 18 years and older at the time of informed consent

2. A histologically confirmed diagnosis of PTCL based on pathology review at the local institution, using the most recent edition of the WHO Classification of Tumors of Haematopoietic and Lymphoid Tissues as guidance.
The pathology sample must be considered to be adequate, meaning that there must be enough well-preserved, formalin-fixed biopsy material for the pathologist to be able to perform a morphological and immunohistochemical examination so as to in confidence be able to state an unequivocal diagnosis of PTCL. Final diagnoses containing caveats such as "suspicious of" or "presumably" are considered inadequate for a patient to be enrolled in the trial. In addition, a pathology sample must be available for a potential central pathology read.

3. Patients must have relapsed or refractory disease after at least one but not more than 7 prior systemic anticancer regimen.

4. Wildtype TP53 status of T-cell lymphoma cells. Beginning with Amendment 6, TP53 status still must be determined by the central laboratory, but confirmation of WT TP53 status is not required for enrollment or initiation of study treatment, if the Investigator deems it clinically unacceptable to delay treatment.

5. At least one target lesion that is measurable by Revised International Working Group Response Criteria for lymphoma patients (IWG 2014 – See APPENDIX L). Patients with PTCL subtypes that are assessed by alternative criteria must have measurable disease in accordance with those criteria and be approved by the Medical Monitor.

6. Eastern Cooperative Oncology Group (ECOG) performance status 0-1 (See Appendix A)

7. Predicted life expectancy of ≥3 months

8. Adequate hematological bone marrow function, measured within 7 days prior to the first dose of ALRN-6924, defined as:

- Absolute neutrophil count (ANC) $\geq 1.0 \times 10^9$/L
- Platelets $\geq 50 \times 10^9$/L (platelets $< 50 \times 10^9$/L are acceptable if partly caused by autoimmune destruction and/or splenomegaly and/or hepatic disease infiltration)

9. Adequate hepatic function, measured within 7 days prior to the first dose of ALRN-6924, defined as:

- Total bilirubin ≤1.5 x upper normal limit, or ≤ 3 x upper normal limit if documented hepatic infiltration with lymphoma
- Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 x upper normal limit (≤ 5 x ULN if documented hepatic infiltration with lymphoma)

10. Adequate renal function, measured within 7 days prior to the first dose of ALRN-6924, defined as serum creatinine ≤1.5 times institutional ULN, or calculated creatinine clearance ≥50 mL/min (Cockcroft-Gault formula)

11. Acceptable coagulation profile, measured within 7 days prior to the first dose of ALRN-6924, defined as:

- Prothrombin time (PT) or international normalized ratio (INR) ≤1.5 times ULN
- Activated partial thromboplastin time (aPTT) ≤1.5 times ULN

12. Prior anti-cancer therapies must wash-out such that they can neither cause drug-drug interaction with ALRN-6924 nor interfere with the anti-cancer evaluation of ALRN-6924. Therefore, the wash-out has to meet all

the following criteria:

- patients must have recovered from the previous therapy to Grade 1 or baseline of significant toxicities, excluding alopecia, and
- 5 half-lives or 4 weeks (whichever is shorter) must have expired, unless the prior anti-cancer therapy and ALRN-6924 do not interfere with each other's metabolism, and
- 5 half-lives or 4 weeks (whichever is shorter) must have expired, unless the patient unequivocally progressed during the prior anti-cancer therapy

Palliative radiotherapy for bone lesions ≤2 weeks prior to the first dose of ALRN-6924 is acceptable if acute toxicity has resolved

13. Negative serum or urine pregnancy test within 2 days prior to the first dose of ALRN-6924 for women of child-bearing potential, defined as a sexually mature woman who has not undergone a hysterectomy or who has not been naturally post-menopausal for ≥24 consecutive months (i.e., who has had menses any time in the preceding 24 consecutive months)

14. All patients (males and females) of child-bearing potential must agree to use an effective method of birth control (i.e., latex condom, diaphragm, cervical cap, intra-uterine device [IUD], birth control pill, etc.) beginning two weeks prior to the first dose of ALRN-6924 and for 30 days after the last dose of ALRN-6924

15. Ability to understand and willingness to sign a written informed consent form

Exclusion Criteria – Phase 2a dose expansions in PTCL (ALRN-6924 administered as single agent therapy)

Patients who meet any of the following criteria at screening or Day -1 will be excluded:

1. Previous treatment with investigational agents that inhibit MDM2 or MDMX activity

2. Relapse within 75 days of autologous bone marrow transplant.

3. Prior allogeneic stem cell transplantation, unless immunosuppressants are no longer required and there is no active graft versus host disease.

4. Known central nervous system (CNS) lymphoma [computed tomography (CT) or magnetic resonance imaging (MRI) scans are required only if brain metastasis is suspected clinically

5. Known hypersensitivity to any study drug component

6. Current, clinically significant coagulopathy or platelet disorder, as determined by the Investigator

7. Required concurrent use of anti-coagulants or anti-platelet medication, with the exception of aspirin doses ≤ 81 mg/day, low-dose subcutaneous (SC) heparin or SC low-molecular-weight heparin for DVT prophylaxis, or heparin flushes to maintain IV catheter patency.

8. Patients with pre-existing history of or known cardiovascular risk:

- History of acute coronary syndromes within 6 months prior to the first dose of ALRN-6924 (including myocardial infarction, unstable angina, coronary artery bypass graft, angioplasty, or stenting)
- Uncontrolled hypertension
- Pre-existing cardiac failure (New York Heart Association Class III-IV)
- Atrial fibrillation on anti-coagulants
- Clinically significant uncontrolled arrhythmias
- Severe valvulopathy
- Corrected QT (QTc) interval on screening electrocardiogram (ECG) ≥450 msec for males and ≥470 msec for females (QTc >480 msec for any patient with a bundle branch block)

9. Clinically significant gastrointestinal bleeding within 6 months prior to the first dose of ALRN-6924

10. Clinically significant third-space fluid accumulation (e.g., ascites requiring tapping despite the use of diuretics; or pleural effusion that requires tapping or is associated with shortness of breath)

11. Pregnant or lactating females

12. Evidence of serious and/or unstable pre-existing medical, psychiatric, or other condition (including laboratory abnormalities) that could interfere with patient safety or provision of informed consent to participate in this study

13. Active uncontrolled infection, including HIV/AIDS or Hepatitis B or C

14. Known history of another primary malignancy that has not been in remission for ≥1 year. Non-melanoma skin cancer and cervical carcinomas *in situ* or squamous intraepithelial lesions (e.g., cervical intraepithelial neoplasia [CIN] or prostatic intraepithelial/intraductal neoplasia [PIN]) are allowed.

15. Any psychological, sociological, or geographical condition that could potentially interfere with compliance with the study protocol and follow-up schedule

16. The required use of any concomitant medications that are predominantly cleared by hepatobiliary transporters, organic anion transporter polypeptide [OATP] members OATP1B1 and OATP1B3, on the day of the ALRN-6924 infusion or within 48 hours after an ALRN-6924 infusion (see Appendix B)

17. Hereditary angioedema of any severity or history of severe or life-threatening angioedema due to any cause.

Inclusion Criteria – Phase 2a dose expansion in MDM2 amplified or MDM2/CDK4 co-amplified solid tumors (ALRN-6924 plus palbociclib)

Patients must meet all of the following criteria to be considered for participation in this study:

1. Histologically-confirmed solid tumor malignancy:
   a. For which there is no curative treatment and that is relapsed or refractory, following at least one prior line of medical therapy; and
   b. that is either MDM2 amplified or MDM2/CDK4 co-amplified, based on local or central laboratory testing by NGS, FISH, or CGH. Tissue must be available for analysis at a central laboratory, even if enrolling based on alternative (e.g. local or commercial) test results. Alternative laboratory results require approval by the Medical Monitor prior to enrollment. Specimens must have been obtained after any previous exposure to palbociclib or any other CDK4/6 inhibitor.
2. At least one target lesion that is measurable by RECIST 1.1 or RANO or other appropriate response criteria
3. Males and females aged 12 years and older
4. ECOG performance status of 0 to 1
5. Adequate hematopoiesis, defined as:
   a. Absolute neutrophil count (ANC) ≥1.5 × 10^9/L
   b. Hemoglobin ≥9.0 g/dL (without transfusions in the past 2 weeks)
   c. Platelets ≥100 ×10^9/L
   d. Absolute lymphocyte count ≥ 0.5 × 10^9/L
6. Adequate hepatic function, defined as:
   a. In the absence of disease involvement of the liver: bilirubin ≤1.5 times institutional upper limit of normal (ULN), and aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5 times ULN
   b. In the presence of disease involvement of the liver: bilirubin ≤2 times institutional ULN and AST and ALT ≤5 times ULN
7. Adequate renal function, defined as serum creatinine ≤1.5 times institutional ULN, or calculated creatinine clearance ≥50 mL/min (Cockcroft Gault formula)
8. Five half-lives or 4 weeks, whichever is shorter, must have elapsed since any prior anticancer agent was

administered, unless the patient unequivocally progressed during that therapy and the agent would not be expected to interfere with ALRN-6924 or palbociclib metabolism or impede clinical assessments

9. Recovery from the acute toxic effects of all prior therapies to ≤ Grade 1 or baseline, excluding alopecia
10. Provision of informed consent and, where applicable, pediatric assent
11. Agreement to use acceptable methods of pregnancy prevention, if of child-bearing potential

Exclusion Criteria – Phase 2a dose expansion in MDM2 amplified or MDM2/CDK4 co-amplified solid tumors (ALRN-6924 plus palbociclib)

Patients who meet any of the following criteria at screening or Day -1 will be excluded:

1. Tumors with known mutations or deletions in TP53 or Rb
2. Known hypersensitivity to any component of study medication
3. Symptomatic or untreated CNS metastases
4. Pulmonary embolism within the past 6 months or DVT that has not been fully treated.
5. Clinically significant cardiovascular risk factors, including:
    - myocardial infarction, unstable angina, coronary artery bypass grafting, stenting, angioplasty, or acute coronary syndrome in the past 6 months
    - New York Heart Association Class III or IV heart failure
    - clinically significant uncontrolled arrhythmia
    - corrected QT (QTc) interval ≥450 msec for males and ≥470 msec for females (QTc >480 msec for any patient with a bundle branch block)
6. Uncontrolled hypertension
7. Active, uncontrolled infection, including HIV, hepatitis B, or hepatitis C
8. Human papilloma virus (HPV)-positive malignancy.
9. Ascites requiring paracentesis or pleural effusion requiring pleurocentesis or causing dyspnea
10. Hereditary angioedema of any severity or history of clinically significant angioedema, due to any cause
11. Major surgery within 3 weeks prior to the first dose of ALRN-6924
12. History of another malignancy within the past year, excluding nonmelanoma skin cancers, carcinomas in situ, or other malignancies with ≥ 95% 5-year survival
13. Pregnant or lactating females
14. Required use of medications that are primarily cleared by hepatobiliary transporters, including organic anion transporters, OATP1B1 and OATP1B3, and bile salt export pump (BSEP), unless administration is not required on the day of or within 48 hours following ALRN-6924 administration
15. Required use of medications that are strong inhibitors or moderate to strong inducers of CYP3A
16. Administration of any investigational agent, regardless of indication, within the 2 weeks prior to enrollment, unless a minimum of 5 half-lives have elapsed
17. Any medical, psychological, or social condition that would interfere with patient safety or the conduct of the study

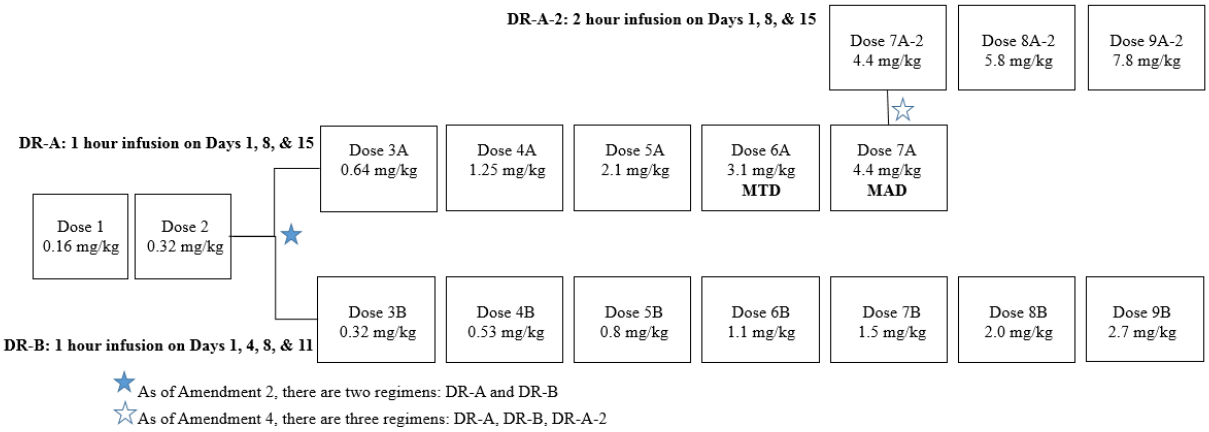
Starting Dose, Dose Escalation, and Dose Reduction

All patients will be dosed with ALRN-6924 at a pre-defined level based on body weight as measured on Day 1 (or up to 3 days prior to Day 1) of each cycle.

Phase 1 – Dose Escalation

Starting at Dose Level (DL) 3 in dose escalation, patients will be sequentially assigned to a treatment arm: Dose Regimen (DR) A will continue testing administration of ALRN-6924 once per week, or Dose Regimen (DR) B testing administration of ALRN-6924 twice per week. For Dose Level 3, DR- A will be enrolled first, DR-B will be enrolled second. The starting dose (DL1) in DEP, based on results from nonclinical toxicology assessments, will be 0.16 mg/kg.

Dose Level and Dose Regimen Schematic – DEP



During the first 2 dose levels, patients will receive ALRN-6924 on Days 1, 8, and 15 of a 28-day cycle. Starting with DL 3, patients in DR- A will continue being treated once a week on Days 1, 8, and 15 of a 28-day cycle, whereas patients in DR- B will be treated twice a week, on Days 1, 4, 8, and 11 of a 21-day cycle. Starting at DL 7A, a modified infusion regimen (DR-A-2) will be explored to mitigate potential infusion reactions.

Treatment Regimen	Infusion Days	Infusion Time	Additional notes
DR-A	1, 8, 15 of a 28-day cycle	1 hour (±15 min)	At the end of the infusion, IV fluids (saline) or oral fluids (500mL – 1000 mL) should be administered unless clinically contraindicated.
DR-A-2	1, 8, 15 of a 28-day cycle	2 hours (±15 min)	At the end of the infusion, IV fluids (saline) or oral fluids (500mL – 1000 mL) should be administered unless clinically contraindicated. Administer dexamethasone (4 mg orally or IV) approximately 4 hours after the end of the infusion in Cycles 1 and 2, and thereafter at the discretion of the investigator.
DR-B	1, 4, 8, 11 for DR-B of a 21-day cycle	1 hour (±15 min)	At the end of the infusion, IV fluids (saline) or oral fluids (500mL – 1000 mL) should be administered unless clinically contraindicated.

A 2-stage dose escalation design will be employed. During the initial Stage 1 Escalation Phase, 100% dose increments will be utilized until ≥1 of 3 patients in a cohort experiences any Grade ≥2 AE that is at least possibly related to study drug. In Stage 2, dose escalation will continue using 3-patient cohorts and the modified Fibonacci sequence (i.e., 67%, 50%, 40%, 33%), until the MTD or an OBD is established. A drug-related AE is an event that is

possibly, probably or definitely attributed to ALRN-6924. Grading of AEs will be defined by the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 (See Appendix O). As drug-related AEs Grade ≥2 occurred in DL-4A (fatigue) and in DL-3B (neutropenia), subsequent dose escalations with DL-5A and DL-4B continued using modified Fibonacci sequence (i.e., 67%, 50%, 40%, and 33%).

Escalation to the next dose level within each DR may proceed in the absence of DLT at the completion of Cycle 1 (treatment cycle = 28 days for DR-A, DR-A-2 and 21 days for DR-B). Escalation to the next dose level within each DR as well as the DR and DL for the EXP cohorts will be decided by a Safety Review Committee (SRC), consisting of the Principal Investigators and Sponsor's Medical Monitor, which will review all available safety information from all patients. As two DLTs have occurred in DR-7A (hypotension and hepatobiliary laboratory abnormalities), there will be no further escalation in DR-A. A new modified infusion regimen was tested (DR-A-2) starting at DR-7A-2. As two DLTs have occurred in DR-7A-2 (anemia and neutropenia), there will be no further escalation in DR-A-2.

Based on review of available safety and PK data during this and other studies with ALRN-6924, dose escalation or modification steps may be adjusted (i.e. increased or decreased) by the SRC to limit the number of patients exposed to sub-therapeutic dose levels as well as to ensure patients' safety.

Within each Dose Regimen cohort:

- If no DLT is observed in a cohort, the subsequent patient group will be enrolled at the next planned dose level of that dose regimen.
- If a DLT is observed in ≥2 of 3 patients at any dose level, no further dose escalation will occur in that DR, and the current dose will be defined as the maximum administered dose (MAD).
- If a DLT is observed in 1 of 3 patients in a cohort at any dose level, then up to 6 patients total will be enrolled in the same DR at that dose level. If a DLT is observed in 2 or more patients in the expanded cohort, then no further dose escalation will occur, and the current dose will be defined as the MAD, unless the SRC decides that there is sufficient clinical uncertainty about the DLTs that warrants the enrollment of up to 6 additional patients. In the event of additionally enrolled patients, if a DLT is observed in 33% or more DLT-evaluable patients in the entire cohort, then no further dose escalation will occur, and the current dose will be defined as the MAD for the dosing regimen under consideration.
- After the MAD is defined, either the previously administered lower dose will be expanded to a total of 6 patients, or an intermediate dose (between the MAD and the previous dose level) will be investigated in a total of 6 patients. The highest dose tolerated in at least 5 of 6 patients (i.e. <33% of DLT-evaluable patients experiencing a DLT) will be defined as the MTD or OBD. Additional patients may be added to further explore the MTD or OBD prior to expansion.

The SRC may hold the dose (e.g., stop dose escalation) at their discretion and enroll additional patients until sufficient safety data are obtained to determine escalation of the current dose level or to confirm a certain dose level as an MTD or OBD.

Dose Level and Dose Regimen – Phase 2a dose expansions

Based on the safety, efficacy and PK/PD profile of ALRN-6924 from the dose escalation portion of the study as well as data from other clinical trials and preclinical data, three dosing regimens of ALRN-6924 administered as single agent therapy (DR-A, DR-B, DR-C) will be tested in Phase 2a EXP in PTCL to determine the optimal dosing regimen.

For patients with MDM2 amplified or MDM2/CDK4 co-amplified solid tumors, patients will receive ALRN-6924 in combination with palbociclib. Palbociclib will be administered at an oral dose of 100 mg daily (Days 1-21) in combination with ALRN-6924, which will be administered at 3.1 mg/kg on Days 1, 8, and 15 of a 28-day cycle (or as otherwise determined during the safety run-in period for this cohort).

The decision to begin palbociclib below the approved dose level of 125 mg is based on the frequency of required

dose reductions, often due to neutropenia. The SRC may consider escalating to the approved palbociclib dose, if palbociclib-related toxicities are not prohibitive and patient benefit is expected to outweigh risk.

Dose Level and Dose Regimen – Phase 2a dose expansions:

Treatment Regimen	Drug and Dose Level	Infusion Days	Infusion Time	Additional notes
DR-A	ALRN-6924 3.1 mg/kg	1, 8, 15 of a 28-day cycle	1 hour (±15 min)	At the end of the infusion, IV fluids (saline) or oral fluids (500 mL – 1000 mL) should be administered, unless clinically contraindicated.
DR-B	ALRN-6924 2.7 mg/kg	1, 4, 8, 11 of a 21-day cycle	1 hour (±15 min)	At the end of the infusion, IV fluids (saline) or oral fluids (500 mL – 1000 mL) should be administered, unless clinically contraindicated.
DR-C	ALRN-6924 3.1 mg/kg [If 3.1 mg/kg is not well tolerated, lower doses may be tested starting at dose levels of -25%]	1, 3, 5 of a 21-day cycle	1 hour (±15 min)	At the end of the infusion, IV fluids (saline) or oral fluids (500 mL – 1000 mL) should be administered, unless clinically contraindicated.
Combination with palbociclib	ALRN-6924 3.1 mg/kg [If 3.1 mg/kg is not well tolerated, up to two dose reductions of 25% may be tested]	1, 8, 15 of a 28-day cycle	1 hour (±15 min)	At the end of the infusion, IV fluids (saline) or oral fluids (500 mL – 1000 mL) should be administered, unless clinically contraindicated.
	Palbociclib 100 mg [If 100 mg is not well tolerated, a reduced dose of 75 mg may be tested.]	1-21 of a 28-day cycle	Oral	Palbociclib should be administered with food. On days when both drugs are administered (Days 1, 8, and 15 of each cycle), palbociclib should be administered at least 6 hours after the infusion of ALRN-6924.

Intra-patient Dose Escalation – Phase 1 Dose Escalation

A patient's dose may be increased to that of a cohort that completed the first cycle without dose-limiting toxicity in ≥33% of DLT-evaluable patients and that has not exceeded the MTD. Intra-patient dose escalations will be allowed provided that the patient completed at least two treatment cycles and did not experience study medication-related toxicity greater than Grade 2 (except for alopecia, electrolyte disturbances responsive to correction within 24 hours,

diarrhea, nausea, fatigue and vomiting that responds to standard medical care). Approval for intra-patient dose escalation must be obtained from the Medical Monitor.

Dose Modifications – Phase 1 dose escalation (ALRN-6924 administered as single agent therapy)

In the event a Grade 4 AE considered related to ALRN-6924 is observed, the patient must be discontinued from the study. Exceptions include Grade 4 neutropenia lasting <3 days, and emesis, diarrhea or electrolyte abnormalities that resolve within 2 days on optimum treatment. For these exceptions, treatment may be delayed for up to 2 weeks to allow resolution of the toxicity (i.e., return to Grade ≤1 or baseline), followed by re-treatment at a reduced dose. Two dose reductions are permitted, a third dose reduction will require evidence of clinical benefit and approval by the Medical Monitor. Relevant labs should be repeated as medically indicated.

In the event a Grade 3 AE considered related to ALRN-6924 is observed (exceptions are Grade 3 fatigue**,** nausea, emesis, diarrhea or clinically insignificant electrolyte abnormalities that resolve within 2 days on optimum treatment), treatment may be delayed for up to 2 weeks to allow resolution of the toxicity, followed by re-treatment at a reduced dose. Two dose reductions are permitted, a third dose reduction will require evidence of clinical benefit and approval by the Medical Monitor. Relevant labs should be repeated as medically indicated.

Following related Grade 3 and Grade 4 AEs (as permitted), the dose for re-treatment will be reduced by 25% intervals (e.g., if the dose is 3.1 mg/kg, the dose will be reduced sequentially to 2.3 mg/kg and 1.7 mg/kg).

For other clinically significant AEs, treatment may be delayed by up to 2 weeks to allow for the resolution of AEs to an acceptable level, and a dose reduction may be made as described above at the discretion of the Investigator in consultation with Sponsor's Medical Monitor. If a patient experiences multiple AEs, decisions on dosing delay or dose reduction will be based on the most severe AE. Any patient who experiences recurrent, clinically significant AEs after one dose reduction may undergo one additional dose reduction. Patients who continue to experience clinically significant AEs after a 2-week delay or the maximum allowed number of dose reductions will be discontinued from study treatment.

Adverse events considered for dose reduction should not include events assessed by the Investigator as exclusively related to underlying disease or other medical condition or concomitant treatment. A patient who experiences an AE considered related to ALRN-6924 that does not meet the requirement for discontinuation may continue on study if the patient is receiving clinical benefit and/or the Investigator feels continued participation is in the best interest of the patient. In such cases, at the Investigator's discretion and in agreement with Sponsor's Medical Monitor, the dose for a patient may be reduced as described above.

A patient who experiences a DLT must continue treatment at a reduced dose level, or discontinue ALRN-6924 treatment (if Grade 4 related AE), as described above at the discretion of the Investigator and in agreement with Sponsor's Medical Monitor until disease progression or unacceptable toxicity. Once the dose has been reduced for a patient, it may not be re-escalated.

Dose Modifications – Phase 2a dose expansions in PTCL (ALRN-6924 administered as single agent therapy)

In the event a non-hematologic Grade 4 AE considered related to ALRN-6924 is observed, the patient must be discontinued from the study. Exceptions include emesis, diarrhea or electrolyte abnormalities that resolve within 2 days on optimum treatment. For these exceptions, treatment may be delayed for up to 2 weeks to allow resolution of the toxicity (i.e., return to Grade ≤1 or baseline), followed by re-treatment at a reduced dose. Relevant labs should be repeated as medically indicated.

In the event a non-hematologic Grade 3 AE considered related to ALRN-6924 is observed (exceptions are Grade 3 fatigue**,** nausea, emesis, diarrhea or clinically insignificant electrolyte abnormalities that resolve within 2 days on optimum treatment), treatment may be delayed for up to 2 weeks to allow resolution of the toxicity, followed by re-treatment at a reduced dose. Relevant labs should be repeated as medically indicated.

For hematologic toxicities, patients must discontinue treatment with ALRN-6924 if

- Neutrophil counts < 0.5 x 10^9/L for > 5 days, or
- Platelet counts < 10 x 10^9/L, or
- Hemoglobin < 6 g/dL (despite RBC transfusion or Erythropoiesis-Stimulating Agent (ESA) administration)

Patients interrupt treatment if

- Neutrophil counts < 0.5 x 10^9/L for ≤ 5 days, or
- Platelet counts < 25 x 10^9/L and >10 x 10^9/L, or
- Hemoglobin < 8 g/dL and > 6 g/dL

After resolution of hematologic toxicity (i.e., return to Grade ≤1 or baseline), patients may continue at a reduced dose. Relevant labs should be repeated as medically indicated.

Following related Grade 3 and Grade 4 AEs (as permitted), the dose for re-treatment will be reduced by 25% intervals (e.g., if the dose is 3.1 mg/kg, the dose will be reduced sequentially to 2.3 mg/kg and 1.7 mg/kg). Two dose reductions are permitted, a third dose reduction will require evidence of clinical benefit and approval by the Medical Monitor.

Dose Modifications – Phase 2a dose expansion in MDM2 amplified or MDM2/CDK4 co-amplified solid tumors (ALRN-6924 plus palbociclib)

Dose modifications of ALRN-6924 will be as described above for the Phase 1 dose escalation. Dose modifications of palbociclib are to be made in accordance with the current approved US prescribing information. In the event that palbociclib administration must be discontinued, the patient may continue to receive ALRN-6924 as a study participant until a criterion for treatment discontinuation has been met. However, if discontinuation of ALRN-6924 is required, patients will be considered to have discontinued study treatment. These patients may continue to receive palbociclib treatment at the investigator's discretion.

Dose Limiting Toxicity Definition during Phase 1 Dose Escalation

A DLT will be defined as any Grade ≥3 AE that is considered possibly, probably, or definitely related to the study drug, with the following exceptions: (1) for fatigue**,** nausea, emesis, diarrhea or mucositis, only Grade ≥3 AE that do not respond within 48 hours to standard supportive/pharmacological treatment will be considered DLT; (2) for electrolyte imbalances, only Grade ≥3 AE that do not respond to correction within 24 hours will be considered DLT; (3) for infusion reactions, only a Grade 3 reaction which caused hospitalization or Grade 4 will be considered DLT. In addition, specific hematologic DLTs are defined as:

• Thrombocytopenia – Grade 4 of any duration, Grade 3 for ≥7 days, or Grade 3 associated with clinically significant bleeding

• Neutropenia – Grade 4 for ≥3 days, or any Grade ≥3 febrile neutropenia

The above criteria will be used to make individual patient determinations regarding dose reductions, interruptions or discontinuation throughout the course of the trial, but DLTs occurring during Cycle 1 will be used to inform safety and tolerability assessments for dose escalation decisions.

Study Drug Administration

ALRN-6924 will be administered as an IV infusion as follows:

Phase 1 Dose Escalation (ALRN-6924 administered as single agent therapy):

- Dose Levels 1 and 2 Dose Regimen A on Days 1, 8, and 15 of each 28-day cycle (1 hour infusion)
- Dose Levels 3 and beyond as follows –
  - Dose Regimen A on Days 1, 8, and 15 in a 28-day cycle (1 hour infusion)

- Dose Regimen B on Days 1 and 4, 8 and 11 in a 21-day cycle (1 hour infusion)
- Dose Regimen A-2 on Days 1, 8, and 15 in a 28-day cycle (2 hour infusion) [starting with Dose Level 7]

Patients who remain on study treatment for 2 years or longer may have their dosing frequency reduced, at the discretion of the investigator (i.e., Days 1 and 15 of a 28-day cycle (DR-A) or Days 1 and 8 of a 21-day cycle (DR-B). In the event that disease control is not maintained, the original dosing schedule may be resumed.

Phase 2a Dose Expansion in PTCL (ALRN-6924 administered as single agent therapy):

- Dose Regimen A 3.1 mg/kg on Days 1, 8, and 15 in a 28-day cycle **(**1 hour infusion)
- Dose Regimen B 2.7 mg/kg on Days 1 and 4, 8 and 11 in a 21-day cycle (1 hour infusion)
- Dose Regimen C 3.1 mg/kg on Days 1, 3 and 5 in a 21-day cycle (1 hour infusion). [If 3.1 mg/kg is not well tolerated, lower doses may be tested starting at dose levels of -25%]

Phase 2a Dose Expansion in MDM2 amplified or MDM2/CDK4 co-amplified solid tumors (ALRN-6924 plus palbociclib):

- ALRN-6924: 3.1 mg/kg **(**1 hour infusion) on Days 1, 8, and 15 in a 28-day cycle plus palbociclib: 100 mg per day orally on Days 1-21 in the same 28-day cycle. It is recommended that palbociclib be administered with food. On days when both drugs are administered (Days 1, 8, and 15 of each cycle), palbociclib should be administered at least 6 hours after the infusion of ALRN-6924.

Following the administration of each dose of ALRN-6924, patients must receive 500 to 1000 mL of IV or oral fluids, unless clinically contraindicated.

Statistical Methods

For each phase of study, results will be summarized by dose level and regimen. Tabulations will be produced for appropriate demographic and baseline clinical characteristics, efficacy, pharmacokinetic, and safety parameters. For categorical variables, summary tabulations of the number and percentage of patients within each category of the parameter will be presented. For continuous variables, the number of patients, mean, median, standard deviation, minimum, and maximum values will be presented. Time-to-event data will be summarized using Kaplan-Meier methodology using 25th, 50th (median), and 75th percentiles with associated 2-sided 95% confidence intervals. Graphical displays will be presented, as appropriate. Results will be evaluated for all patients.

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ACRONYM LIST

ACE	angiotensin converting enzyme
AE	adverse event
AIDS	acquired immunodeficiency syndrome
ALT (SGPT)	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
ARB	angiotensin-receptor blocker
AST (SGOT)	aspartate aminotransferase
AUC	area under the curve
BCRP	breast cancer resistance protein
β-hCG	Beta human chorionic gonadotropin
BrdU	5′-bromo-2′-deoxyuridine (thymidine analog)
BSEP	bile salt export pump
BUN	blood urea nitrogen
CDK4	cyclin-dependent kinase 4
cfDNA	cell free DNA
CFR	Code of Federal Regulations
CGH	comparative genomic hybridization
CIN	cervical intraepithelial neoplasia
C_{max}	maximum concentration
CNS	central nervous system
CO_2	carbon dioxide
CR	complete response
CT	computed tomography
CTC	circulating tumor cells
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
D5W	5% dextrose in water
DEP	dose escalation phase
DL	dose level
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DOR	duration of response
DR	dose regimen
DRF	dose range finding
DVT	deep vein thrombosis
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EOI	end of infusion
ESA	Erythropoiesis-Stimulating Agent
EXP	expansion phase

FDA	Food and Drug Administration
FDG	[^{18}F]-fluorodeoxyglucose
FISH	fluorescent in situ hybridization
FOXM1	Forkhead box protein M1
GCP	good clinical practice
GI	gastrointestinal
GLP	good laboratory practices
HALO	hemotoxicity assays via luminescence output
HERG	human ether-a-go-go-related gene
HER2	human epidermal growth factor receptor 2
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HNSTD	highest non-severely toxic dose
HPV	human papilloma virus
HR	hormone receptor
IB	Investigator's Brochure
IC_{50}	half maximal inhibitory concentration
ICF	informed consent form
ICH	International Council on Harmonisation
IHC	immunohistochemistry
IND	investigational new drug
INR	international normalized ratio
IRB	institutional review board
IUD	intrauterine device
IV	intravenous
IWG	International Working Group
LC-MS-MS	liquid chromatography with tandem mass spectrometry
LD	longest diameter
LDH	lactate dehydrogenase
MAD	maximum administered dose
MDM2	murine double minute 2
MDMX	murine double minute X
MED	minimum efficacious dose
MIC-1	macrophage inhibitory cytokine-1
MNC	mononuclear blood cells
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
N	sample size
NCI	National Cancer Institute
NGS	Next-Generation Sequencing
NK	Natural Killer
OATP	organic anion transporter polypeptide
OBD	optimal biological dose
ORR	overall response rate

OS	overall survival
p21	cyclin-dependent kinase inhibitor p21
p53	Tumor protein p53, cellular tumor antigen p53, phosphoprotein p53 or tumor suppressor p53
PARP	poly-ADP-ribose polymerase
PET	Positron Emission Tomography
PD	pharmacodynamic
PFS	progression-free survival
P-gp	P-glycoprotein
PIN	prostatic intraepithelial/intraductal neoplasia
PK	pharmacokinetics
PR	partial response
PT	prothrombin time
PTCL	peripheral T-cell lymphoma
QTc	corrected QT interval
RANO	Response Assessment in Neuro-Oncology
Rb	retinoblastoma protein
RBC	red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	ribonucleic acid
RNAseq	RNA sequencing
RT-PCR	reverse transcription polymerase chain reaction
SAE	serious adverse event
SC	subcutaneous
SD	stable disease
SOI	start of infusion
SRC	Safety Review Committee
STD_{10}	severely toxic dose in 10% animals
SULT2A1	sulfotransferase family 2A member 1
$t_{1/2}$	half-life
TGI	tumor growth inhibition
TLS	tumor lysis syndrome
T_{max}	time of C_{max}
TP53	the gene that encodes p53
TTR	time to respond
ULN	upper limit of normal
WBC	white blood cell
WT	wild-type

1 BACKGROUND AND STUDY RATIONALE

ALRN-6924 is a synthetic Stapled Peptide designed to disrupt the interaction between the p53 tumor suppressor protein and its predominant endogenous inhibitors, MDM2 and MDMX. For tumors expressing WT p53 protein, pharmacological disruption of the interactions between p53 and MDM2/MDMX offers a means to restore p53-dependent cell cycle arrest and apoptosis, resulting in therapeutic efficacy against human cancers via a novel mechanism. This clinical trial will investigate the safety, tolerability, PK, PD and anti-tumor effects of ALRN-6924 alone or in combination in patients with advanced solid tumors and lymphoma with presumed or confirmed WT TP53.

1.1 Therapeutic Rationale for Inhibiting MDM2/MDMX to Restore p53 Activity

The human transcription factor protein p53 induces cell cycle arrest and apoptosis in response to deoxyribonucleic acid (DNA) damage and cellular stress, thereby playing a critical role in protecting cells from malignant transformation. Inactivation of p53 by deletion, mutation, or through over-expression of its predominant inhibitory proteins MDM2 and MDMX is the single most common defect in human cancers.[1,2] For tumors with WT TP53, pharmacologic disruption of the interactions between p53 and its endogenous suppressors MDM2 and MDMX offers a means to restore p53-dependent cell cycle arrest and apoptosis.[3,4,5,6]

The ability of MDM2 to negatively regulate p53 function is mediated through several mechanisms, including inhibition of p53 transcriptional activity through direct binding, as well as ubiquitination and subsequent proteasomal degradation of the p53 protein.[6,7] Consequently, aberrant MDM2 over-expression and gene amplification results in impaired p53 activity, leading to accelerated cancer development and growth.[1,8]

MDMX lacks the MDM2-like property to initiate p53 degradation, but possesses a similar p53-binding activity that inhibits p53 transcriptional activity. Amplification of MDMX, which appears to correlate with the absence of MDM2 amplification, is observed in many tumor types, including melanoma, breast, head and neck, hepatocellular carcinoma, and retinoblastoma.[6,9,10]

Because MDM2 and MDMX regulate non-overlapping functions of p53, several lines of evidence suggest that selective antagonists targeting only MDM2 have insufficient efficacy, particularly in tumors that express high levels of MDMX.[6,10,11,12,13] A therapeutic approach targeting both MDM2 and MDMX, therefore, is expected to have a higher potential than MDM2-selective molecules to re-activate the p53 pathway in a greater number of tumor types.

In addition to enhanced efficacy, a dual inhibitor against both MDM2 and MDMX has an increased likelihood of achieving a tolerable efficacious dose without causing severe thrombocytopenia, a frequent dose-limiting toxicity (DLT) of MDM2-selective inhibitors in cancer patients.[14] For platelet production to occur, the p53 pathway must be quiescent, with p53 activity suppressed primarily by MDM2 in the bone marrow.[15] A potent inhibitor targeting only MDM2 therefore can significantly interfere with thrombocytopoiesis before achieving anti-tumor efficacy. In contrast, a dual MDM2/MDMX therapeutic approach, by limiting the over-reliance on MDM2 inhibition, has the potential to fully re-activate the p53 pathway in tumor cells before causing dose-limiting thrombocytopenia. Restoration of p53 activity with inhibition of MDMX rather than MDM2 has been shown to be better tolerated in experiments utilizing transgenic and knockout mouse models.[16] Enhancement of p53 activity is not expected to result in adverse

effects in normal non-hematopoietic organs or tissues, as supported by findings in a genetically engineered mouse model.[17]

1.2 Stapled Peptide Technology

Despite the benefits of a dual-inhibition approach, the identification of small molecule dual antagonists with appropriate pharmacological properties has proven challenging, in part due to the structural diversity of the p53-binding regions of MDM2 and MDMX.

One solution lies in converting the α-helical portion of the p53 protein that interacts with MDM2/MDMX into a suitably stable, potent and specific therapeutic agent.[3,18,19] The resulting molecule would be capable of disrupting the interaction between p53 and MDM2/MDMX. Aileron has developed an optimized cross-linking chemistry to lock, or "staple", peptides into α-helices that mimic native protein structures. A Stapled Peptide is generated by standard solid-phase peptide synthesis, followed by a selective bond-forming reaction that results in an all-hydrocarbon cross-link between two non-contiguous, structurally-optimized amino acids. Because proteases recognize and break down peptides only when they are unraveled, the Stapled Peptide technology locks peptides into organized secondary structures and confers resistance to proteolysis. The resulting Stapled Peptide exhibits favorable PK and pharmacological properties, including extended plasma half-life and enhanced potency. A Stapled Peptide also retains the molecular target specificity of its underlying native protein structure. As a result, the Stapled Peptide is anticipated to maintain the function of the target protein being mimicked with a low likelihood of off-target toxicities. In select cases, a Stapled Peptide can be designed to penetrate the cell membrane, thus permitting modulation of specific intracellular protein-protein interactions.[18,20]

1.3 ALRN-6924

ALRN-6924 is a Stapled Peptide clinical candidate designed to disrupt the interaction between p53 and both MDM2 and MDMX.

Despite the structural similarity between MDM2 and MDMX, there are important differences in the p53 binding sites of these proteins that make the development of therapeutic antagonists that can bind to both challenging. By mimicking the natural helical peptide fold of p53, the Stapled Peptide ALRN-6924 binds equipotently to both MDM2 and MDMX. Therefore, ALRN-6924 should be less prone to expected resistance to MDM2-inhibitor therapy. This resistance may result from compensatory mechanisms, such as MDM2 mutation[21] and upregulation of MDMX that may result from selective pressure on MDM2 alone.[22] Stapled Peptides like ALRN-6924 have been shown to overcome resistance to MDM2 inhibition by these mechanisms in preclinical studies.[23,24]

1.4 Nonclinical Experience with ALRN-6924

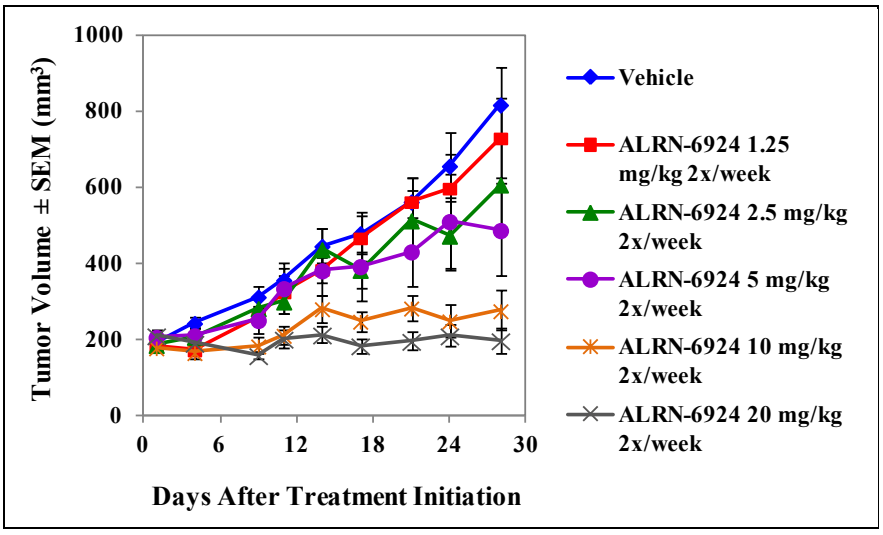
1.4.1 Pharmacology

In vitro biochemical assays, x-ray crystallography and ligand displacement studies confirmed the binding of ALRN-6924 to target molecules MDM2/MDMX. On-target activation of p53-mediated pathways of apoptosis and cell cycle arrest was demonstrated in cancer cells at sub-micromolar concentrations. As expected, the ability of ALRN-6924 to induce cell cycle arrest and apoptotic cell killing was dependent on the presence of WT p53 protein. Proliferation and survival of cell lines with WT p53 protein was sensitive to ALRN-6924, with IC_{50} values ranging from 0.2 to 3.3 μM. In SJSA-1 osteosarcoma cells, the functional consequences of binding of ALRN-6924 to the p53-regulatory site on MDM2 and MDMX

included a concentration-dependent increase in p21 protein, the downstream transcriptional target of p53 and mediator of cell cycle arrest and cellular senescence; and increases in cellular caspase activity, indicative of early apoptotic events. In contrast, ALRN-6924 had no cytotoxic activity in cells lacking a functional p53 signaling pathway. In RKO-E6 cells, in which p53 expression and signaling is suppressed by a stably-transfected human papilloma virus (HPV) E6 oncogene, ALRN-6924 at concentrations exceeding 30 µM was not cytotoxic. ALRN-6924 also did not affect cell viability in SW480 cells, a colorectal cancer cell line with mutated p53 that renders the pathway ineffective. With respect to hematologic cancers, eleven WT TP53 hematologic cancer cell lines (6 lymphoma and 5 leukemia) were evaluated and were highly sensitive to ALRN-6924 intervention as all lines exhibited EC_{50} less than 0.6 µM. Taken together, these lines of evidence suggest effectiveness of ALRN-6924 against both solid and liquid tumor cell lines across multiple histological origins that retain the p53 WT status.

The effect of ALRN-6924 on tumor growth was evaluated in murine xenograft models of human tumors, including human osteosarcoma, breast cancer and melanoma models. Statistically significant tumor growth inhibition (TGI) was observed in each model following IV dosages, and TGI was found to be dose-related in all studies in which a range of dose levels was administered. In particular, ALRN-6924 exhibited consistent efficacy in mice implanted with WT TP53 human tumors that over-express MDM2 (e.g., SJSA-1 osteosarcoma xenograft model) or MDMX (e.g., MCF-7 breast cancer xenograft model). For example, twice-weekly treatment with ALRN-6924 produced a dose-dependent TGI, with a minimum efficacious dose (MED) of 5 mg/kg, in the MCF-7 breast cancer xenograft model (Figure 1). *In vivo* PD assays in this model also demonstrated that ALRN-6924 re-activated the p53 pathway, as shown by decreased tumor cell proliferation, increased p53 protein, increased p21 (a downstream transcriptional target of p53), and increased apoptosis as indicated by an increase in cleaved poly-ADP-ribose polymerase (PARP).

Figure 1: Effect of ALRN-6924 on Tumor Growth in the MCF-7 Breast Cancer Xenograft Model



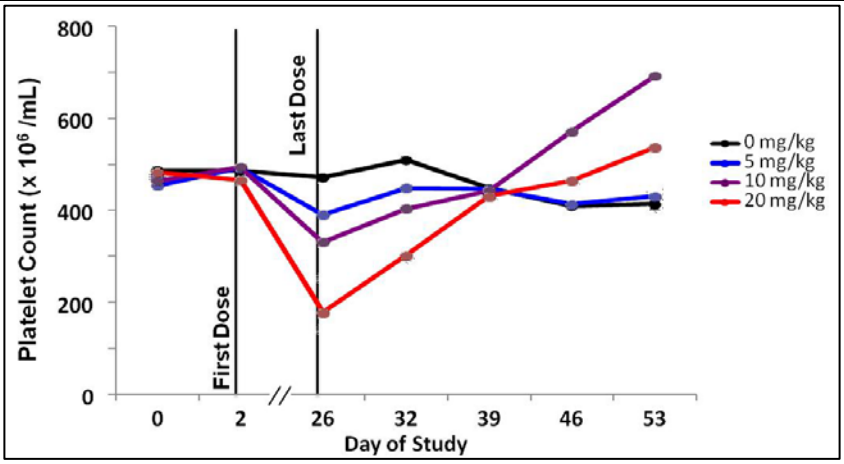
1.4.2 Toxicology and Nonclinical Safety

The pivotal 4-week multiple-dose GLP studies of ALRN-6924 in rats and monkeys utilized twice-weekly IV dosing rather than the once-weekly IV dosing planned as the initial clinical regimen. The studies provided dose- and exposure-related assessments during both dosing and recovery periods, and results

were utilized to define the maximum tolerated doses (MTD) and estimate the severely toxic dose for 10% (STD_{10}) of rats and the highest non-severely toxic dose (HNSTD) in monkeys. All gross and microscopic signs of intolerance (e.g., reduced organ weights, sporadic findings of multi-tissue hemorrhage and hepatic necrosis) and changes in serum chemistry parameters were considered as secondary to red blood cell (RBC), platelet and/or white blood cell (WBC) depletions or anorexia and dehydration in both species. Recovery assessments revealed regenerative and compensatory changes consistent with marrow cell survival and reversibility of all related hematologic and secondary toxicities.

The DLT in both animal species appears to be related to the suppression of hematopoietic cells in the bone marrow, in particular cells of the megakaryocyte lineage, resulting in significant decreases in peripheral blood platelets that demonstrated recovery upon the cessation of dosing (see Figure 2).

Figure 2: Dose-dependent Platelet Response in 4-week Monkey GLP Toxicity Study



Female results shown as representative data

The STD_{10} in rats was defined at 10 mg/kg based on the mortality of one animal in a satellite group for hematology sampling during recovery. The HNSTD in monkeys was defined at 5 mg/kg, based on a complete lack of significant thrombocytopenia at this lowest dose level. However, almost all of the monkeys at the mid- and high-dose levels tolerated ALRN-6924 administration well; only one animal at each of these dose levels developed significant thrombocytopenia (<100,000 x 10^6/ml).

Rats are more sensitive to the bone marrow and hematologic effects of ALRN-6924 than monkeys on the basis of exposures at maximally tolerated doses. Exposure at rat STD_{10} ($AUC_{0-\infty}$=562 µg•hr/mL at 10 mg/kg) was below that of HNSTD in monkeys ($AUC_{0-\infty}$=813 µg•hr/mL at 5 mg/kg). These *in vivo* results correlate with those obtained from *in vitro* hemotoxicity assays via luminescence output (HALO). In these investigations, ALRN-6924 in general inhibited the induced proliferation of bone marrow precursor cells from rats to a greater extent than those from monkeys or humans. IC_{50} values were ~2- to 8-fold higher for rat cells than for monkey or human cells, with the largest difference noted for megakaryocyte colony forming cells, the platelet precursors. These results correlate with *in vivo* findings indicating that rats are more sensitive to the bone marrow and hematologic effects of ALRN-6924 than monkeys on the basis of dose and exposures at maximally tolerated doses. These results also suggest that, in terms of projecting potential bone marrow and hematological toxicity levels in humans, the monkey PK-PD data may be more clinically relevant than the rat data.

ALRN-6924 was negative in genetic toxicology studies, including bacterial mutagenicity (Ames), chromosomal aberrations (human peripheral blood lymphocyte) and *in vivo* micronucleus (rat bone marrow) assays. Safety pharmacology studies were performed to assess the effects of ALRN-6924 on hERG potassium channels *in vitro* and on cardiac function in cynomolgus monkeys. There were no significant adverse findings in these studies.

Compared to the twice-weekly IV dosing schedule utilized in the 4-week GLP toxicity studies, the first-in-human clinical trial of ALRN-6924 will initially assess once-weekly IV dosing for three weeks. In addition, the demonstrated reversibility of ALRN-6924-induced hematologic effects, the ability to detect such findings with routine laboratory measurements, and the availability of effective supportive therapies, all provide additional safety margin in the clinic.

1.4.3 Pharmacokinetics and Absorption, Distribution, Metabolism and Excretion

Pharmacokinetic studies (Table 1) characterize exposure kinetics following single IV administrations of ALRN-6924 in mice, rats and monkeys, including evaluations of two different dosing formulations in rats and monkeys. Using qualified liquid chromatography with tandem mass spectrometry (LC-MS-MS) methods for efficacy models and dose range-finding (DRF) studies, and validated methods for GLP safety studies, exposure was characterized in mice at the MED in efficacy models and in rats and monkeys at tolerated and non-tolerated doses in toxicology studies. Exposures generally increased proportionally with dose, although an apparent plateau was observed at the highest dose of the 4-week monkey toxicology study. No sex-based differences were observed in either species, and no accumulation was observed following multiple doses.

Table 1: Pharmacokinetic Studies Completed with ALRN-6924

Study Type	Description
Analytical Methods Development and Validation	Rat plasma
	Monkey plasma
	Human plasma
	In vitro dosing solutions
	In vivo dosing solutions
	Stability in rat whole blood
	Stability in monkey whole blood
	Method transfer report
Absorption/Kinetics	Single-dose mouse
	Single-dose rat
	Multi-dose rat
	Single-dose rat (2 formulations)
	Single-dose monkey (2 formulations)
Distribution	Plasma protein binding
	Conc.-dependent protein binding
	Substrate for hepatobiliary transporters
Metabolism	Multi-species hepatocytes
	Rat and monkey *in vivo*
Excretion	Rat bile and urine
PK Drug Interactions	CYP enzyme inhibition
	CYP enzyme induction
	Hepatic transporter inhibition

The *in vitro* protein binding of ALRN-6924 was evaluated over a range of concentrations in mouse, rat and monkey plasma, as well as human plasma samples from normal subjects and hypoalbuminemic patients. Protein binding ranged from 92% to 98% in plasma of mice, rats, dogs, monkeys, and humans following incubation of ALRN-6924 at a single concentration of 2 µM, and exceeded 98% in mouse and rat plasma up 250 µM. In human and monkey plasma, free ALRN-6924 fractions of 3-4% were measured at ALRN-6924 concentrations up to 150 µM, corresponding to expected C_{max} values from clinical doses up to 15 mg/kg, rising to 12-14% at concentrations >200 µM. In plasma from hypoalbuminemic patients, a similar rise was seen at >100 µM concentrations of ALRN-6924, corresponding to expected C_{max} values from clinical doses up to 10 mg/kg. The concentration-dependent plasma protein binding provides a possible explanation for the apparent plateau in exposure observed at the high-dose group (20 mg/kg) in the 4-week monkey GLP toxicity study, and suggests less-than-dose-proportional exposure may be seen at very high clinical doses, in particular for patients with hypoalbuminemia.

In vitro studies demonstrated a similar metabolite profile across species, including humans, providing support for the rat and the monkey as suitable species for toxicology studies. Proteolysis is the major biotransformation pathway of ALRN-6924. The predominant metabolite, ALRN-8714, is a 3-amino acid truncation with the cyclic peptide portion intact, and the same metabolite profile was noted in *in vitro* stability studies with mouse, rat, monkey, and human cryopreserved hepatocytes. In a single-dose rat study, hepatobiliary metabolism and elimination represented the predominant clearance pathway for ALRN-6924, with ALRN-8714 being the major excretion product observed in the bile. ALRN-8714 was also observed in the plasma in both the rat and monkey 4-week GLP toxicology studies, with adequate exposures in these studies to provide characterization of its impact on the overall safety profile of ALRN-6924. In the monkey, ALRN-8714 plasma exposure was 10% of the ALRN-6924 AUC, and in the rat, ALRN-8714 exposure was 6% of the ALRN-6924 AUC. Accumulation of ALRN-8714 was not observed with repeated twice-weekly dosing in rats or monkeys.

Inhibition or induction of cytochrome P450 (CYP) enzymes by ALRN-6924 appears to be negligible at clinically-relevant concentrations, although interactions may occur at high exposures of ALRN-6924 with drugs that are predominantly cleared by hepatobiliary transporters (please refer to Appendix B of this protocol or the Investigator's Brochure for additional information).

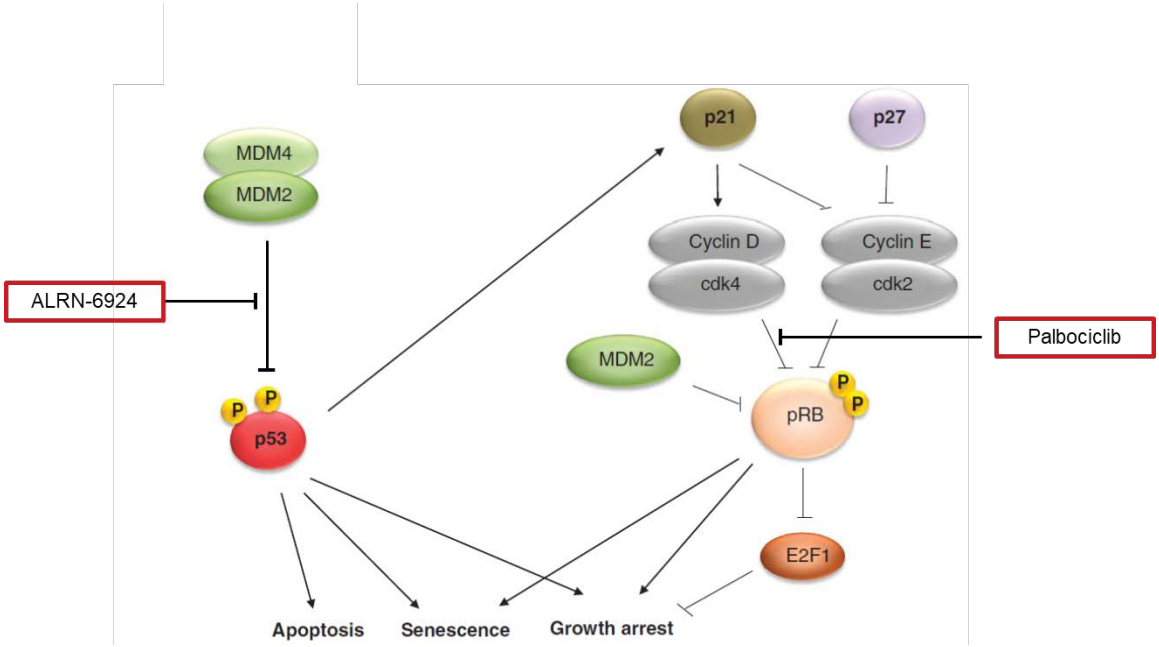
1.4.4 ALRN-6924 Administered in Combination with Palbociclib

1.4.4.1 Pharmacology

Because p53 plays a central role in a variety of signal transduction pathways, including cell cycle, senescence and apoptosis, that are critical to the treatment of cancer, reactivation of p53 by ALRN-6924 can play an important role in combination therapy to provide a greater anti-tumor response than single-agent treatment and minimize resistance to individual drugs.

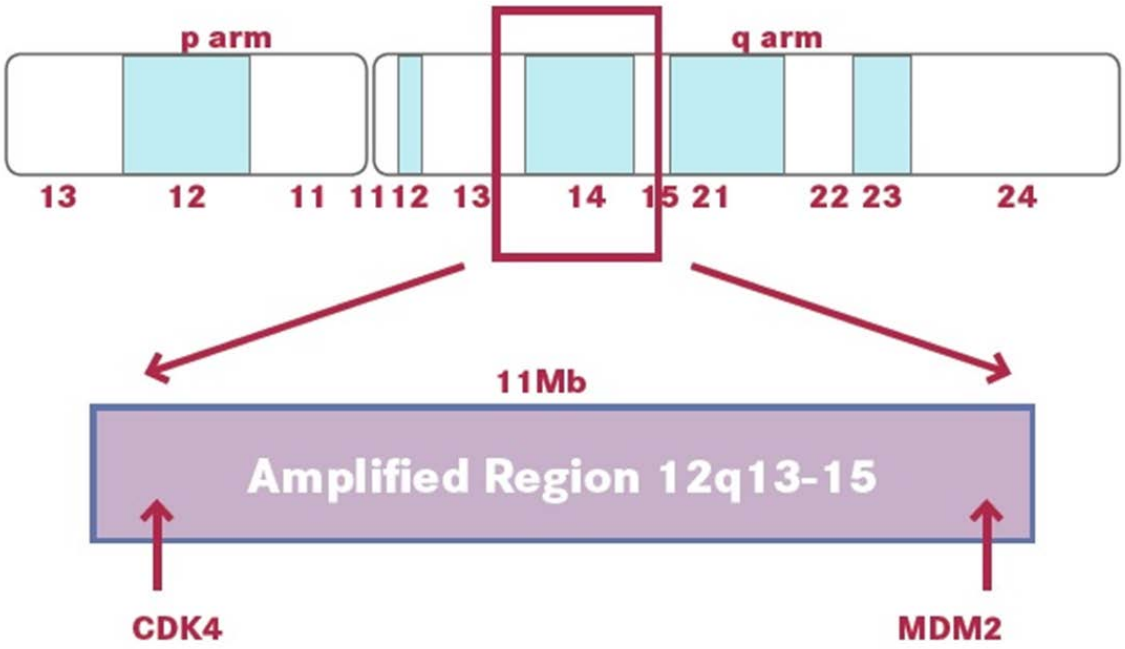
CDK4/6 inhibitors induce apoptosis, senescence, and cell growth arrest via the retinoblastoma protein (Rb) pathway, which converges on the p53 pathway through interrelated mechanisms as shown in Figure 3. Co-amplification of MDM2 and cyclin-dependent kinase 4 (CDK4) (both located on chromosome 12q13 within 11 mega base-pairs only) are oncogenic events, suggesting that combinations of MDM2-inhibitors such as ALRN-6924 and CDK4/6inhibitors such as palbociclib may be synergistic (Figure 4).

Figure 3: Combined Mechanism of Action of ALRN-6924 and Palbociclib



The p53 and Rb pathways converge to trigger apoptosis, senescence, and cell growth arrest (*Adapted from* Lønning and Knappskog, "Mapping genetic alterations causing chemoresistance in cancer: Identifying the roads by tracking the drivers" *Oncogene*. **2013** Nov 14;32(46):5315-30)[25]

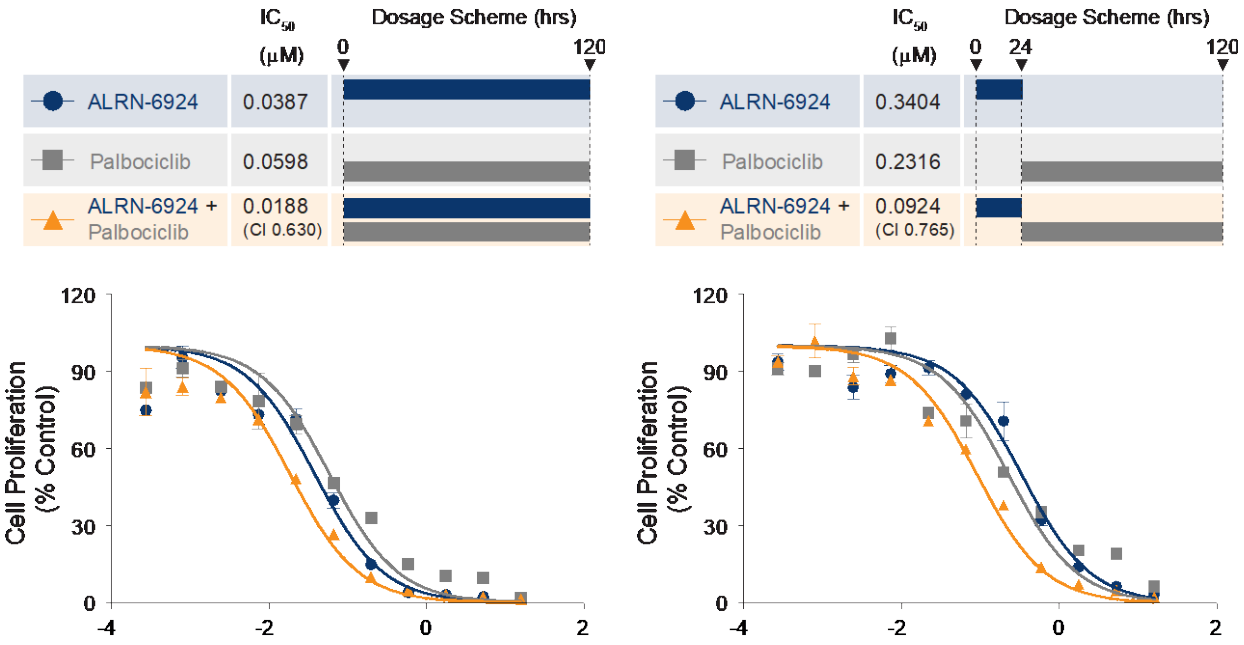
Figure 4: Co-amplification of MDM2 and CDK4



The p53 and Rb pathways are often disabled by MDM2 or CDK4 gene amplification; both genes reside on Chromosome 12 (*Adapted from* B.A. Van Tine, "Multiple Molecular Subtypes of Sarcoma Allow for Orphan Drug Development," *The Journal of Targeted Therapies in Cancer* **2016**)[26]

The anticancer activity of the CDK4/6 inhibitor palbociclib was enhanced by combining with ALRN-6924 in an *in vitro* study. As shown in Figure 5 (left panel), treatment of SJSA1 osteosarcoma cancer cells for 120 hour with ALRN-6924 alone inhibited cellular proliferation with an IC_{50} value of 0.04 µM and treatment with palbociclib alone yielded an IC_{50} of 0.06 µM. However, treatment with increasing concentrations of ALRN-6924 combined with palbociclib in a 1:1 ratio resulted in an improved IC_{50} of 0.02 µM, suggesting additive to synergistic complementarity of the two anticancer agents when dosed together in this MDM2/CDK4-co-amplified cell line. As shown in the right panel of Figure 5, the combination treatment was also effective against SJSA1 cancer cells when ALRN-6924 was administered first, followed by washout and subsequent treatment with palbociclib. This result suggests that the sustained anti-proliferative effects of ALRN-6924 are enhanced by palbociclib.

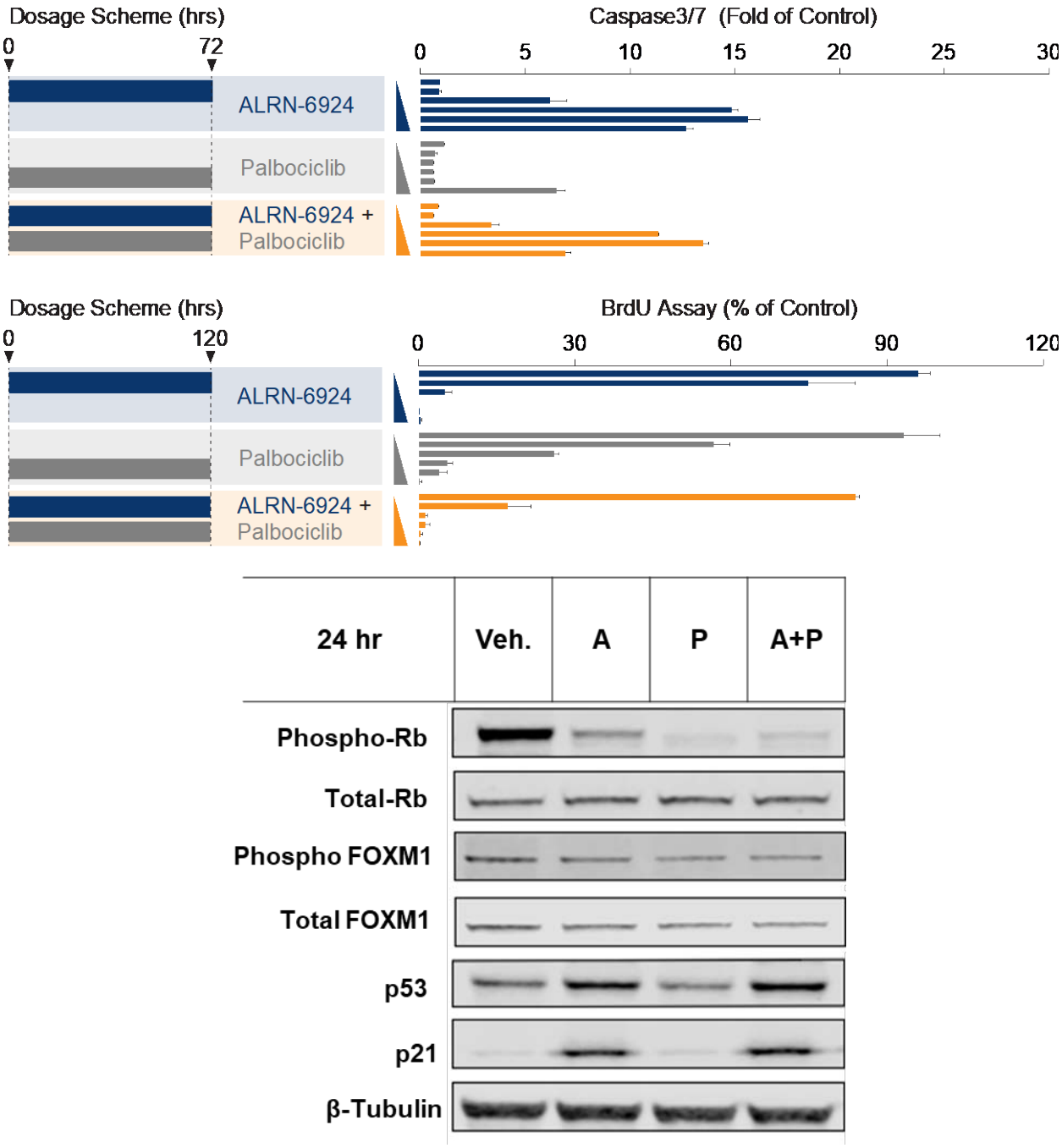
Figure 5: Effect of ALRN-6924 ± Palbociclib on In Vitro Proliferation of MDM2/CDK4-co-amplified SJSA1 Osteosarcoma Cancer Cells



Left panel: Effect of ALRN-6924 ± palbociclib on *in vitro* proliferation of SJSA1 osteosarcoma cancer cells when dosed simultaneously for 120 hours. Right panel: Effect when SJSA1 cells are dosed with ALRN-6924 for 24 hours, washed, then dosed with palbociclib for a further 96 hours.

The mechanism underlying the enhancement of ALRN-6924's anti-proliferative effects when combined with palbociclib was investigated by measuring cell cycle arrest, apoptosis, and the up- and down-regulation of specific molecular markers in cancer cells *in vitro* following single-agent or combination treatment. As shown in Figure 6 (top panel), caspase activation (a measure of apoptosis induction) was evident when both agents were dosed simultaneously in SJSA1 cancer cells. 5'-bromo-2'deoxyuridine (BrdU) incorporation into the DNA of SJSA1 cells was measured to evaluate cell cycle arrest (center panel), with results showing a decrease in cycling cells when treated with the combination. Western blot analysis of phosphorylated Rb, Forkhead box protein M1 (FOXM1), p53, and p21 (bottom panel) all support the conclusion that palbociclib and ALRN-6924 enhance the activity of one another by on-mechanism cell cycle arrest and cancer cell killing in this MDM2/CDK4-co-amplified cell line.

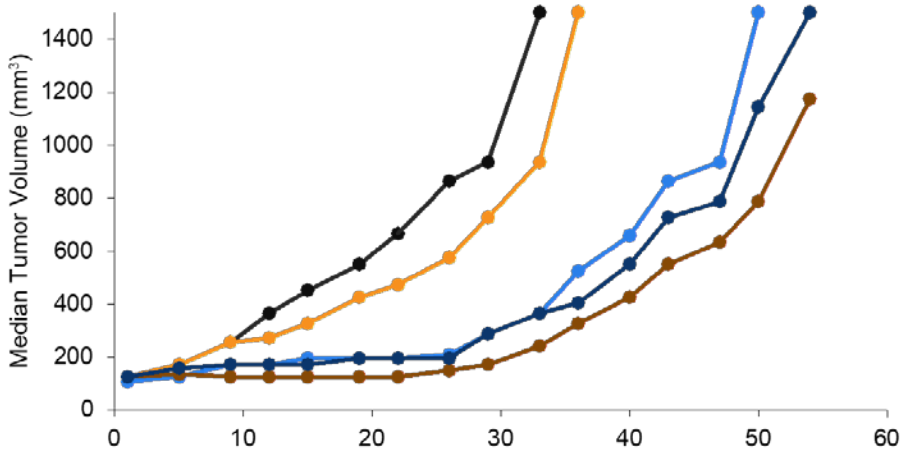
Figure 6: Mechanism of Enhancement of Anti-proliferative Effects of ALRN-6924 when Combined with Palbociclib



Abbreviations: A = ALRN-6924; BrdU = 5'-bromo-2'-deoxyuridine; FOXM1 = Forkhead box protein M1; hr(s) = hour(s); p = palbociclib; p21/53 = Tumor protein 21/53; Rb = retinoblastoma protein; veh = vehicle
Top panel: caspase activation (a measure of apoptosis induction) in SJSA1 cells. Center panel: BrdU incorporation (a measure of cell cycle arrest) in SJSA1 cells. Bottom panel: Western blot analysis of phosphorylated Rb, FOXM1, p53, and p21 in SJSA1 cells following treatment with ALRN-6924 (A), palbociclib (P), or the combination (A+P).

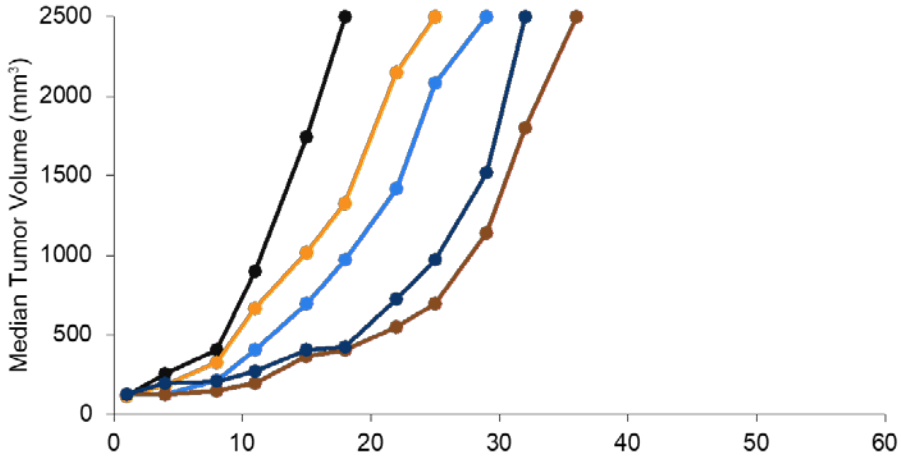
The combination of ALRN-6924 and palbociclib was also tested in MCF-7 and SJSA1 mouse xenograft models. SJSA1 harbors DNA amplification of both MDM2 and CDK4 genes, which neighbor one another on chromosome 12q, while MCF-7 harbors a deletion of the CDKN2A gene, the product of which is a natural inhibitor of MDM2 and CDK4. In these studies, athymic nu/nu mice were xenotransplanted with MCF-7 or SJSA1 cells and then treated with either vehicle, ALRN-6924 alone once-weekly for 21 days, palbociclib alone once daily for 21 days, or a combination of the two agents with ALRN-6924 dosed either 6 hours before or 6 hours after palbociclib on days when both were dosed together. As shown in Figure 7, at the doses administered in this study, the combination of ALRN-6924 and palbociclib yielded 11-31% greater tumor growth inhibition and 17-50% longer time-to-progression than either single agent alone, with administration of ALRN-6924 before palbociclib providing better efficacy in both models.

Figure 7: Effect of Combination of ALRN-6924 and Palbociclib on Tumor Growth in MCF-7 and SJSA1 Mouse Xenograft Models



	%TGI (±SEM) on d22	Median days to >500 mm³	Median days to >1000 mm³
Vehicle	---	19	27
ALRN-6924 20 mg/kg qw x4	30 (9)	22	35
Palbociclib 75 mg/kg qdx22	84 (4)	37	48
ALRN-6924 6h after palbociclib	88 (2)	37	49
Palbociclib 6h after ALRN-6924	95 (3)	42	53

(continued on next page)



	%TGI (±SEM) on d22	Median days to >1000 mm^3	Median days to >2000 mm^3
Vehicle	---	12	16
ALRN-6924 20 mg/kg qw x4	17 (6)	16	21
Palbociclib 75 mg/kg qdx22	51 (9)	18	24
ALRN-6924 6h after palbociclib	71 (3)	25	32
Palbociclib 6h after ALRN-6924	82 (2)	27	34

Top panel: MCF-7 mouse xenograft model. Bottom panel: SJSA1 mouse xenograft model.
Abbreviations: d22 = Day 22; SEM = standard error of the mean; TGI = tumor growth inhibition

1.4.4.2 Pharmacokinetics

No PK interaction is anticipated between ALRN-6924 and palbociclib. The two drugs are metabolized and eliminated by independent mechanisms; namely, proteolytic metabolism with hepatic uptake and biliary excretion for ALRN-6924, while palbociclib is primarily metabolized by CYP3A and sulfotransferase family 2A member 1 (SULT2A1) with the major metabolite in feces as the sulfamic acid conjugate. It is advised to avoid concomitant use of strong CYP3A inhibitors, and moderate and strong CYP3A inducers while on palbociclib therapy. Doses of sensitive CYP3A substrates with a narrow therapeutic index may need to be reduced, as palbociclib may increase their exposures. Palbociclib, at clinically relevant concentrations has a low potential to inhibit transporters P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), OAT1, OAT3, OCT2, OATP1B1 and OATP1B3, and its oral absorption is unlikely to be affected by P-gp and BCRP mediated transport.

Studies with ALRN-6924 indicate a low likelihood of induction or inhibition of CYP enzymes, suggesting any metabolism-based drug-drug interactions between ALRN-6924 and palbociclib are unlikely. Though studies show that ALRN-6924 is an inhibitor of OATP1B1 and OATP1B3 transporters, palbociclib is not known to be a substrate of these transporters, and no hepatobiliary pharmacokinetic drug-drug interactions have been reported for palbociclib. [27]

ALRN-6924 and palbociclib are administered by intravenous and oral routes, respectively, and there will be minimum interaction at the gut level. It is recommended to administer palbociclib with food. Under fed conditions there are no clinically relevant effects of proton pump inhibitors, H2-receptor antagonists, or local antacids on palbociclib exposure.

In nu/nu mice (non-tumor-bearing), the PK of ALRN-6924 was not affected by palbociclib (and vice versa) as shown in Figure 8 and Table 2.

Figure 8: Plasma Concentrations of ALRN-6924 and Palbociclib when Administered Alone or in Combination in Nu/nu Mice

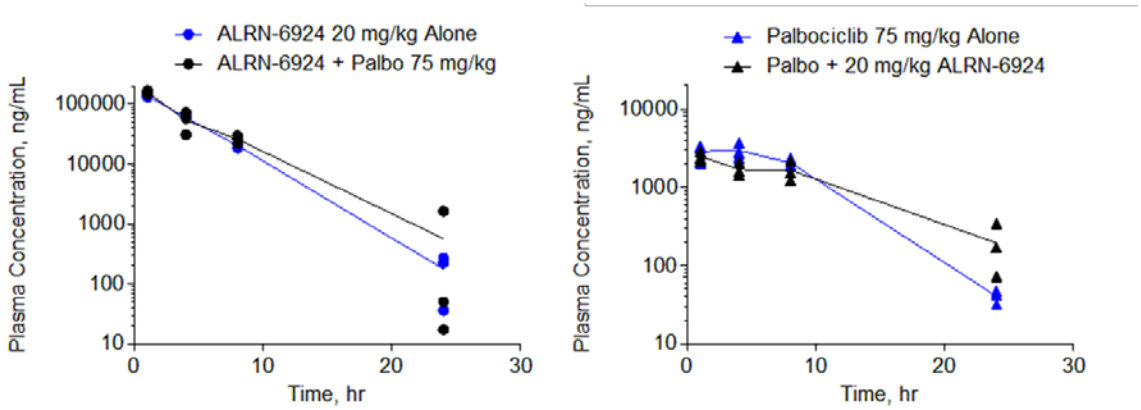


Table 2: Pharmacokinetic Parameters of ALRN-6924 and Palbociclib when Administered Alone or in Combination in Nu/nu Mice

	Alone		Co-administered	
	C_{max} µg/mL	AUC_{last} µg·hr/mL	C_{max} µg/mL	AUC_{last} µg·hr/mL
ALRN-6924	138	686	156	759
Palbociclib	2.9	37	2.6	29

1.5 Clinical Experience with ALRN-6924

There was no clinical experience with ALRN-6924 prior to initiation of this Phase 1/2a study. As of 26 February 2018, a total of 118 patients had received treatment either in the present study or in Study ALRN-6924-1-02, which is an ongoing Phase 1/1b study of ALRN-6924 in patients with acute myeloid leukemia or advanced myelodysplastic syndrome.

1.6 Clinical Experience with Palbociclib

Palbociclib (IBRANCE®) is an inhibitor of CDK4 and CDK6.

Palbociclib has been approved by the FDA for the treatment of hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer in combination with an aromatase inhibitor as initial endocrine based therapy in postmenopausal women; or fulvestrant in women with disease progression following endocrine therapy.

2 STUDY OBJECTIVES

2.1 Phase 1 Dose Escalation (ALRN-6924 administered as single agent therapy)

2.1.1 Primary Objectives

- Evaluate the safety and tolerability of ALRN-6924 in adult patients with advanced solid tumors or lymphomas with WT TP53 who are refractory to or intolerant of standard therapy, or for whom no standard therapy exists
- Determine the DLTs, the MTD or OBD of ALRN-6924 in adult patients with advanced solid tumors or lymphomas

2.1.2 Secondary Objectives

- Describe the PK of ALRN-6924 and its metabolites in blood following single and multiple IV infusions.
- Assess potential patient biomarkers (e.g., p53 status, MDM2 and MDMX expression levels), the effect of ALRN-6924 treatment on these biomarkers, and possible correlation between these biomarkers and clinical response.
- Assess the effect of ALRN-6924 treatment on potential PD biomarkers in tumor biopsy samples including bone marrow aspirates (e.g., p21, caspase, MDM2) and blood samples (e.g., MIC-1), and assess possible correlation between these biomarkers and clinical response.
- Evaluate potential clinical activity of ALRN-6924.
- Investigate the immunogenicity of ALRN-6924.

2.1.3 Exploratory Objectives

- Starting at dose level 3: Assess the effect of ALRN-6924 treatment on potential PD biomarkers (e.g., p21, p53, caspase) in circulating tumor cells (CTC), where detectable, or in mononuclear blood cells (MNC).
- Assess the effects of ALRN-6924 treatment on cell-free DNA from blood.

2.2 Phase 2a Dose Expansion (ALRN-6924 administered as single agent therapy)

2.2.1 Primary Objectives

- Assess overall response rate (ORR)
- Further evaluate the safety and tolerability of ALRN-6924

2.2.2 Secondary Objectives

- Describe the PK of ALRN-6924 and its metabolites in blood following single and multiple IV infusions in patient populations selected for dose expansion with single agent therapy
- Assess duration of response (DOR)
- Assess progression-free survival (PFS)
- Assess overall survival (OS)

- Assess PFS and OS at 1 year
- Assess time to response (TTR)
- Assess the effect of ALRN-6924 treatment on potential pharmacodynamic (PD) biomarkers in tumor biopsy samples (including bone marrow aspirates, where clinically indicated) by measuring potential biomarkers such as p53, p21, caspase, MDM2, MDMX and in blood samples by measuring potential biomarkers such as macrophage inhibitory cytokine-1 [MIC-1] and assessing possible correlation between these biomarkers and clinical outcomes
- Investigate the immunogenicity of ALRN-6924

2.2.3 Exploratory Objectives

- Assess the effects of ALRN-6924 treatment on cell-free DNA from blood.
- Assess the effect of ALRN-6924 treatment on potential PD biomarkers (e.g., p21, p53, caspase) in circulating tumor cells (CTC), where detectable, or in mononuclear blood cells (MNC).
- Assess the effect of ALRN-6924 using alternative response criteria other than the IWG 2014 or RECIST 1.1 criteria

2.3 Phase 2a Dose Expansion in MDM2 Amplified or MDM2/CDK4 Co-amplified Solid Tumors (ALRN-6924 plus palbociclib)

2.3.1 Primary Objectives

- Assess ORR
- Evaluate the safety and tolerability of ALRN-6924 and palbociclib when administered in combination

2.3.2 Secondary Objectives

- Describe the PK of ALRN-6924 (and its metabolites) and palbociclib when administered in combination
- Estimate DOR
- Estimate additional measures of efficacy, including TTR, PFS, OS, and PFS and OS at 1 year

2.3.3 Exploratory Objective

- Explore potential markers of response to treatment with ALRN-6924 and palbociclib

3 INVESTIGATIONAL PLAN

3.1 Study Rationale

ALRN-6924 has demonstrated single-agent anti-tumor activity in multiple animal models of human tumors. These observations, coupled with the documented nonclinical safety profile of ALRN-6924, support the clinical investigation of ALRN-6924 in a variety of human cancer types.

The results of *in vitro* and *in vivo* studies indicate enhanced anti-tumor effects when ALRN-6924 and palbociclib are administered in combination. A Phase 2a expansion cohort will be enrolled to evaluate the combination of ALRN-6924 and palbociclib in patients with MDM2 amplified or MDM2/CDK4 co-amplified solid tumors including, but not limited to, sarcomas, glioblastomas, carcinomas of the breast, and non-small cell lung cancer. The inclusion of patients with glioblastomas is based on non-clinical studies conducted with a similar stapled peptide, ATSP-7041, that evaluated the distribution of this agent in the context of an intact blood-brain barrier.[28] This work demonstrated exposure of the radiolabeled stapled peptide in central nervous system (CNS) tissue in non-tumor-bearing rats, with a 1% brain:plasma ratio for peak concentration and a 1.7% brain:plasma ratio for AUC. In the context of a CNS tumor with disrupted blood-brain barrier, CNS tumor penetration is expected to be substantially higher, as is known for bevacizumab (Avastin®), a high molecular weight monoclonal antibody that is not believed to cross an intact blood-brain barrier, yet is FDA-approved for treatment of primary and metastatic brain tumors.[29] The selection of patients with MDM2-amplified or MDM2/CDK4 co-amplified solid tumors is intended to identify patients who may be more likely to respond to the ALRN-6924 and palbociclib combination regimen, as the products of these amplifications are the targets of the respective agents.

3.2 Study Overview

This is a Phase 1/2a open-label, multi-center, dose-escalation and dose expansion study designed to evaluate the safety, tolerability, PK, PD, and anti-tumor effects of ALRN-6924 administered by IV infusion once weekly for 3 consecutive weeks on Days 1, 8, and 15 of a 28-day cycle (Dose Regimen A or DR-A and DR-A-2), twice weekly for 2 consecutive weeks on Days 1, 4, 8, and 11 of a 21-day cycle (Dose Regimen B or DR-B), or three times weekly for one week on Days 1, 3, and 5 of a 21-day cycle (Dose Regimen C or DR-C) in patients with advanced solid tumors or lymphomas that are anticipated to express WT TP53.

This study consists of a Phase 1 Dose Escalation Phase (DEP) and a Phase 2a Dose Expansion Phase (EXP). The DEP is a "3+3" dose escalation design to establish the MTD or the OBD of ALRN-6924. The EXP will enroll up to 5 distinct groups of patients with specific solid tumors and/or lymphomas to further investigate the clinical safety profile and potential efficacy of ALRN-6924 at the MTD, OBD, or an alternative dosing regimen.

Peripheral T-cell lymphoma (PTCL) has been selected as one of the Phase 2a EXP groups to be further studied; up to 3 cohorts in PTCL may be studied in order to determine the optimal dosing regimen.

Another Phase 2a EXP group will include patients with MDM2 amplified or MDM2/CDK4 co-amplified solid tumors who will receive ALRN-6924 in combination with palbociclib. As these agents have not previously been co-administered, a safety run-in of 6-8 safety evaluable patients will first be enrolled to determine the optimal dosing regimen for the combination.

Treatment of patients in the dose escalation and the dose expansion phases of the study will continue until unacceptable toxicity, patient or physician decision to discontinue therapy, or disease progression that is either symptomatic, rapidly progressive, requires urgent intervention, or is associated with a decline in performance status. Patients receiving clinical benefit may continue on study after a discussion between the Principle Investigator and Medical Monitor.

Starting at Dose Level 4 (DEP), patients with a Human Papilloma Virus (HPV)-positive malignancy will be excluded from enrollment. This is owing to the fact that HPV-infected tumor cells continue to express the viral E6 protein, which is known to cause degradation of p53, hence rendering the expected ALRN-6924-mediated dual inhibition of MDM2/MDMX very unlikely to restore p53 function.

Phase 1 – Dose Escalation (ALRN-6924 administered as single agent therapy)

In DEP, patients may meet the TP53 WT requirement through one of the following scenarios (per the exception to exclusion criterion 1, patients previously treated with an MDM2-inhibitor are also eligible, provided that a biopsy taken after completion of the last treatment with an MDM2-inhibitor meets one of the following):

- Patients may be eligible based on a fresh biopsy or archived tissue that is ≤1 year old. All samples will be tested for TP53 status using Next-Generation Sequencing (NGS) at the central laboratory. The central laboratory will determine the TP53 status as expeditiously as possible.
- Upon approval from the medical monitor, patients may also enroll and initiate study treatment based on wildtype TP53 status that was determined by another laboratory. Again, this testing must have been performed on tumor samples obtained no more than one year ago. These archived specimens with previously determined TP53 status must still be submitted for NGS testing at the central laboratory; the central laboratory's result will determine the patient's official classification as either TP53 wildtype or TP53 mutant.

Patients who do not have archived tissue, and for whom a biopsy poses a significant risk, cannot be enrolled.

In DEP, patients who satisfy all inclusion and exclusion criteria will be enrolled in cohorts of 3 to 6 patients to receive ALRN-6924. ALRN-6924 will be administered by IV infusion in Dose Regimen A over 1 hour (±15 min) on Days 1, 8 and 15 of a 28-day cycle, over 2 hours (±15 min) on Days 1, 8 and 15 of a 28-day cycle in Dose Regimen A-2 starting at Dose Level 7, or in Dose Regimen B over 1 hour (±15 min), starting at Dose Level 3, on Days 1, 4, 8, and 11 of a 21-day cycle. Patients who remain on study treatment for 2 years or longer may have their dosing frequency reduced, at the discretion of the investigator (i.e., Days 1 and 15 of a 28-day cycle (DR-A) or Days 1 and 8 of a 21-day cycle (DR-B). In the event that disease control is not maintained, the original dosing schedule may be resumed.

After the MTD or OBD is established for a particular dosing regimen, additional patients may be enrolled in up to 5 expansion cohorts (approximately 20 patients per expansion cohort) to gain further experience in particular patient or tumor types or to test alternative dosing regimens. Selection of patient or tumor types will be determined in part on the basis of observations made in the dose escalation portion of the study.

Phase 2a – Dose Expansion in PTCL (ALRN-6924 administered as single agent therapy)

Patients may meet the TP53 requirement through one of the following scenarios:

- Patients need to be tested for TP53 status, using a fresh biopsy or archived tissue that is ≤1 year old. All samples will be tested for TP53 status using NGS at the central laboratory. The central laboratory will determine the TP53 status as expeditiously as possible. Investigators are encouraged to await the TP53 test result, however, if this is clinically deemed not to be in the patient's best interest, enrollment and the initiation of study treatment may proceed, prior to the central laboratory result becoming available. Central laboratory testing is still required to confirm WT p53 status.
- Upon approval from the medical monitor, patients may also enroll and initiate study treatment based on wildtype TP53 status that was determined by another laboratory. This testing must have been performed on tumor samples obtained no more than one year ago and the patient must not have received systemic cytotoxic therapy in the interval since the tissue was obtained. These archived specimens with previously determined TP53 status must still be submitted for NGS testing at the central laboratory; the central laboratory's result will determine the patient's official classification as either TP53 wildtype or TP53 mutant.

Patients who do not have archived tissue, and for whom a biopsy poses a significant risk, cannot be enrolled.

ALRN-6924 will be administered by IV infusion in Dose Regimen A over 1 hour (±15 min) on Days 1, 8 and 15 of a 28-day cycle, in Dose Regimen B over 1 hour **(**±15 min) on Days 1, 4, 8, and 11 of a 21-day cycle, and in Dose Regimen C over 1 hour (±15 min) on Days 1, 3, and 5 of a 21-day cycle. For the Dose Regimen C cohort, 6-8 patients will be enrolled in a safety run-in part and the treating investigators, along with the Medical Monitor, will review safety and tolerability through Cycle 1 prior to opening the full DR-C expansion cohort.

Phase 2a – Dose Expansion in MDM2 Amplified or MDM2/CDK4 Co-amplified Solid Tumors (ALRN-6924 plus palbociclib)

Patients enrolled in this cohort must have MDM2 amplified or MDM2/CDK4 co-amplified solid tumors, as determined by local, commercial or central assays such as NGS, fluorescent in situ hybridization (FISH) or comparative genomic hybridization (CGH). However, all patients must have fresh or archival tissue submitted to the central laboratory for NGS testing. The central laboratory's results will determine the patient's official classification as MDM2 amplified, MDM2/CDK4 co-amplified, or neither MDM2 amplified nor MDM2/CDK4 co-amplified.

Mutational analysis of TP53 is not required for this cohort, as TP53 mutations are extremely rare among patients with MDM2 amplifications. However, patients with known mutations or deletions of TP53 will be excluded from study participation. Likewise, patients with known Rb mutations will be excluded, as the cell cycle arrest and senescence response by palbociclib's CDK4/6 inhibition is mediated by Rb, and loss or functional mutation of Rb is specifically associated with resistance to palbociclib.[30]

Enrollment of the first 3 patients in this cohort will be separated in time by at least one week each, to assess for unexpected acute toxicities related to administration of the treatment regimen. ALRN-6924 will be administered by IV infusion over 1 hour (±15 min) on Days 1, 8, and 15 of a 28-day cycle. Palbociclib

will be administered at an oral dose of 100 mg daily for 21 days (one dose level below the approved oral dose of 125 mg) in the same 28-day cycle. A safety run-in group of 6-8 patients will first be enrolled and evaluated before further patients are permitted to enroll. In the event that this regimen is not determined to be safe or tolerable at these dose levels, the dose of ALRN-6924 will be decreased by 25% and/or the dose of palbociclib will be decreased by one dose level (to 75 mg/day), as needed based on the pattern of toxicities encountered. An additional 6-8 patients will be assessed in a safety run-in using the reduced dose level before further enrollment is permitted. One subsequent reduction of the ALRN-6924 dose by 25% may be implemented, if safety and tolerability are still not acceptable. Once the safety run-in is complete, all subsequent patients will be enrolled at the recommended dose level.

Phase 1 and Phase 2a

Safety will be evaluated based on the incidence, severity, duration, causality, seriousness, and type of AE, and changes in the patient's physical examination, vital signs and clinical laboratory results. Investigators will use the NCI CTCAE version 4.03 to assess the severity of AEs. The immunogenicity of ALRN-6924 will be assessed by the measurement of anti-ALRN-6924 antibodies.

If the safety profile appears favorable, the study may be amended in the future to expand existing cohorts or subsets of existing cohorts, add cohorts to test additional cancer types or add cohorts to test other combination treatments with ALRN-6924.

3.2.1 Pharmacokinetic, Pharmacodynamic, and Clinical Activity Assessments

Blood samples will be collected after single and multiple infusions for PK analysis of ALRN-6924 and its metabolites to correlate clinical responses with exposure levels and assess inter-individual variability. Patients receiving ALRN-6924 in combination with palbociclib will also have additional blood samples collected for determination of PK parameters for palbociclib.

Levels of p53 and its endogenous inhibitors MDM2 and MDMX may be assessed before and after exposure to ALRN-6924, and the possible correlation between these biomarkers and outcome or response will be investigated. In the cohort of patients with MDM2 amplified or MDM2/CDK4 co-amplified solid tumors, the correlation of response with MDM2, MDMX, and/or CDK4 gene copy number and other genetic and protein biomarkers will be investigated.

Pharmacodynamics (PD) may be assessed by laboratory-based evaluation of several biomarkers of p53 activation, including levels of p21, caspase and MDM2 in tumor tissue, and where available in CTC, or MNC, as well as MIC-1 in blood, before and after treatment with ALRN-6924. Pharmacodynamic effects on the composition of cell-free DNA from blood may be evaluated.

Results available from previous genetic and biomarker tests, and additional tests of the blood and tumor samples for biomarkers relevant to the safety and efficacy of ALRN-6924 (or ALRN-6924 plus palbociclib) may be investigated for possible correlation with patient outcomes. Any remaining samples collected for PK, biomarker assays, and immunogenicity may be used for exploratory biomarker profiling, sample identification, or additional safety assessments (e.g., anti-drug antibody characterization) as appropriate.

For any cohort that includes adolescents, an assessment of pharmacologic differences between adolescents and adults will be performed.

Phase 1 – Dose Escalation

Clinical Activity:

Clinical activity or response will be evaluated by standard imaging assessments, such as computed tomography (CT), magnetic resonance imaging (MRI), and bone scans. In addition, [^{18}F]-fluorodeoxyglucose positron emission tomography (FDG-PET) or other techniques considered clinically appropriate for the patient's specific disease type can be used. Anti-tumor activity will be assessed using RECIST 1.1 (Appendix K) for patients with solid tumors or using IWG (2014) criteria (Appendix L) for patients with lymphomas. The same imaging technique should be used at each assessment for a patient.

Positron Emission Tomography (PET) Scans:

- For patients with an FDG-avid lymphoma, FDG-PET imaging will be performed at baseline and post-baseline as outlined in IWG 2014 during DEP and in the EXP.
- For solid tumor patients, FDG-PET imaging may be performed at baseline and subsequently post-dose at the first occurrence of stable disease in applicable patients as an adjunct to determine anti-tumor activity, as outlined in RECIST 1.1. (Applicable patients are those who had an evaluable FDG-PET-scan performed prior to starting treatment with study drug.)

NOTE: PET/CT scans may substitute for contrast-enhanced CT scans provided the CT performed as part of a PET–CT is of similar diagnostic quality as a diagnostic CT with IV and oral contrast. As with CT-imaging, the same imaging technique should be used for each patient's PET assessment.

Phase 2a – Dose Expansion

Biopsies:

In the Phase 2a EXP PTCL cohorts, optional biopsies will be taken for PD and p53 status determination purposes: one during screening, one during treatment, and one or more at times of suspected and/or confirmed progression. In the palbociclib combination cohort, if a biopsy is taken for any reason during the study, the samples may be used for further analysis. Samples might be submitted for whole exome sequencing (with a paired germline sample) and RNA sequencing (RNAseq), and results will be compared between pre-treatment and on-treatment, and time of suspected and/or confirmed progression tumor samples for markers of disease response and resistance. Protein expression via immunohistochemistry and RNA expression via quantitative RT-PCR will be examined on specimens obtained prior to beginning treatment, during treatment with ALRN-6924, and then upon suspected and/or confirmed progression. Biopsy details may be found in the Laboratory Manual.

Clinical Activity:

Clinical activity or response will be evaluated by standard imaging assessments, such as computed tomography (CT) and FDG-PET or other techniques considered clinically appropriate for the patient's specific disease type. Anti-tumor activity will be assessed using RECIST 1.1 (Appendix K) for patients with solid tumors, ResponseAssessment in Neuro-Oncology (RANO) for glioblastoma (Appendix M), or IWG (2014) criteria (Appendix L) for patients with lymphomas. The application of additional assessment techniques may also be considered, as appropriate, throughout the conduct of the study. For patients enrolled to the Phase 2a expansion cohort of patients with MDM2 amplified or MDM2/CDK4 co-amplified solid tumors, this will include response criteria that are used to assess anticancer agents that

elicit an immune response, such as iRECIST (see Appendix N)[31] This is owing to the fact that p53-activation has numerous effects on the immune system.[32] The same evaluation technique(s) should be used at each assessment for a patient.

For patients with an FDG-avid lymphoma, FDG-PET imaging will be performed at baseline and post-baseline as outlined in IWG 2014.

NOTE: PET/CT scans may substitute for contrast-enhanced CT scans provided the CT performed as part of a PET–CT is of similar diagnostic quality as a diagnostic CT with IV and oral contrast. As with CT-imaging, the same imaging technique should be used for each patient's PET assessment.

3.3 Number of Patients and Centers

Total enrollment of approximately 180 patients is planned for the study. Approximately 75 patients will be enrolled in the dose escalation portion of the study for ALRN-6924 as single agent therapy, and approximately 15-25 additional patients per expansion cohort will be enrolled in up to 5 expansion cohorts in the expansion part of the study. The expansion cohort of patients with MDM2 amplified or MDM2/CDK4 co-amplified solid tumors is planned to include approximately 10 patients with MDM2/CDK4 co-amplification. In the event that the distribution of patients with MDM2 amplified versus MDM2/CDK4 co-amplified tumors becomes imbalanced, the sponsor may temporarily suspend enrollment to one group to facilitate enrollment in the other.

Approximately 15 to 25 clinical sites are planned.

3.4 Duration of Study

The expected accrual phase is approximately 54 months. The expected follow-up phase is approximately 8 months after the last patient is enrolled, for a total study duration of approximately 62 months.

4 PATIENT POPULATION

The study will enroll adult or adolescent patients with advanced solid tumors or lymphomas who are expected to have WT TP53 and are refractory to or intolerant of standard therapy, or for whom no standard therapy exists. The distinct inclusion/exclusion criteria for each cohort are presented in the remainder of this section.

4.1 Inclusion Criteria – Phase 1 dose escalation (ALRN-6924 administered as single agent therapy)

Patients must meet all of the following criteria to be considered for participation in this study:

1. Male or female patients age 18 years and older, inclusive, at the time of informed consent
2. Histologically- or cytologically-confirmed solid tumors that are metastatic or unresectable or lymphomas. Standard measures do not exist or are no longer effective for these patients.
3. WT TP53 status for relapsing or treatment-refractory solid neoplasms and lymphomas is mandatory for patients enrolling at Dose Level 4 and higher in Stage 1 of the DEP as well as for all patients enrolled in Stage 2 of the DEP or in the EXP. In EXP, beginning with Amendment 6, TP53 status still must be determined by the central laboratory, but confirmation of WT TP53 status is not required for enrollment or initiation of study treatment, if the Investigator deems it clinically unacceptable to delay treatment.
4. At least one target lesion that is measurable by RECIST 1.1 in patients with solid tumors or by IWG (2014) criteria in patients with lymphoma.
5. ECOG performance status 0-1
6. Predicted life expectancy of ≥3 months
7. Adequate hematologic bone marrow function, measured within 7 days prior to the first dose of ALRN-6924, defined as:
   - ANC $\geq 1.5 \times 10^9$/L
   - Hemoglobin ≥9.0 g/dL
   - Platelets $\geq 100 \times 10^9$/L
8. Adequate hepatic function, measured within 7 days prior to the first dose of ALRN-6924, defined as:
   - In the absence of disease involvement in the liver: bilirubin ≤1.5 times institutional ULN as well as AST and ALT ≤2.5 times ULN
   - In the presence of disease involvement in the liver: bilirubin ≤2 times ULN as well as AST and ALT ≤5 times ULN
9. Adequate renal function, measured within 7 days prior to the first dose of ALRN-6924, defined as:
   - Urinalysis with no evidence of +2 or higher proteinuria

- Serum creatinine ≤1.5 times institutional ULN or calculated creatinine clearance ≥50 mL/min (Cockcroft-Gault formula)

10. Acceptable coagulation profile, measured within 7 days prior to the first dose of ALRN-6924, defined as:
    - PT or INR ≤1.5 times ULN
    - aPTT ≤1.5 times ULN
11. Prior anti-cancer therapies must wash-out such that they can neither cause drug-drug interaction with ALRN-6924 nor interfere with the anti-cancer evaluation of ALRN-6924. Therefore, the wash-out has to meet all the following criteria:
    - patients must have recovered from the previous therapy to Grade 1 or baseline of significant toxicities, excluding alopecia, and
    - 5 half-lives or 4 weeks (whichever is shorter) must have expired, unless the prior anti-cancer therapy and ALRN-6924 do not interfere with each other's metabolism, and
    - 5 half-lives or 4 weeks (whichever is shorter) must have expired, unless the patient unequivocally progressed during the prior anti-cancer therapy

    Palliative radiotherapy for bone lesions ≤2 weeks prior to the first dose of ALRN-6924 is acceptable if acute toxicity has resolved
12. Negative serum or urine pregnancy test within 2 days prior to the first dose of ALRN-6924 for women of child-bearing potential, defined as a sexually mature woman who has not undergone a hysterectomy or who has not been naturally post-menopausal for ≥24 consecutive months (i.e., who has had menses any time in the preceding 24 consecutive months)
13. All patients (males and females) of child-bearing potential must agree to use an effective method of birth control (i.e., latex condom, diaphragm, cervical cap, IUD, birth control pill, etc.) beginning two weeks before the first dose of ALRN-6924 and for 30 days after the last dose of ALRN-6924
14. Ability to understand and willingness to sign a written informed consent form
15. Patients with prostate cancer must continue androgen deprivation therapy, unless such therapy was discontinued 6 months prior to first dose of ALRN-6924

4.2 Exclusion Criteria – Phase 1 dose escalation (ALRN-6924 administered as single agent therapy)

Patients who meet any of the following criteria at screening or Day -1 will be excluded:

1. Previous treatment with investigational agents that inhibit MDM2 or MDMX activity with the following exception:

   Patients previously treated with an MDM2-inhibitor are eligible provided that a biopsy taken after completion of the last treatment with an MDM2-inhibitor is confirmed as WT TP53 prior to enrollment.
2. Known hypersensitivity to any study drug component

3. Known and untreated brain metastases. Patients with brain metastases that have been treated and demonstrated to be clinically stable for ≥30 days may be enrolled. Patients with primary CNS malignancies are excluded.
4. Current, clinically significant coagulopathy or platelet disorder, as determined by the Investigator
5. History of pulmonary embolism within 6 months prior to the first dose of ALRN-6924 or untreated DVT
6. Required concurrent use of anti-coagulants or anti-platelet medication, with the exception of aspirin doses ≤81 mg/day, low-dose SC heparin or SC low-molecular-weight heparin for DVT prophylaxis, or heparin flushes to maintain IV catheter patency.
7. Patients with pre-existing history of or known cardiovascular risk:
    - History of acute coronary syndromes within 6 months prior to the first dose of ALRN-6924 (including myocardial infarction, unstable angina, coronary artery bypass graft, angioplasty, or stenting).
    - Uncontrolled hypertension
    - Pre-existing cardiac failure (New York Heart Association class III-IV)
    - Atrial fibrillation on anti-coagulants.
    - Clinically significant uncontrolled arrhythmias
    - Severe valvulopathy.
    - Corrected QTc interval on screening ECG ≥450 msec for males and ≥470 msec for females (QTc >480 msec for any patient with a bundle branch block).
8. Clinically significant gastrointestinal bleeding within 6 months prior to the first dose of ALRN-6924.
9. Clinically significant third-space fluid accumulation (e.g., ascites requiring tapping despite the use of diuretics, or pleural effusion that requires tapping or is associated with shortness of breath).
10. Pregnant or lactating females.
11. Evidence of serious and/or unstable pre-existing medical, psychiatric or other condition (including laboratory abnormalities) that could interfere with patient safety or provision of informed consent to participate in this study.
12. Active uncontrolled infection, including HIV/AIDS or hepatitis B or C in the absence of hepatocellular carcinoma. Patients with primary liver cancer that have positive hepatitis serology but are not demonstrating active viral hepatitis may be considered for enrollment if they meet all other inclusion and no other exclusion criteria.
13. Starting at Dose Level 4 and higher of Stage 1 of the DEP, as well as for all patients enrolling in Stage 2 of the DEP or in the EXP, patients with an HPV-positive malignancy.

14. Known history of another primary malignancy that has not been in remission for ≥2 years. Non-melanoma skin cancer and cervical carcinomas *in situ* or squamous intraepithelial lesions (e.g., CIN or PIN) are allowed.

15. Any psychological, sociological, or geographical condition that could potentially interfere with compliance with the study protocol and follow-up schedule.

16. The required use of any concomitant medications that are predominantly cleared by hepatobiliary transporters, OATP members OATP1B1 and OATP1B3, on the day of the ALRN-6924 infusion or within 48 hours after an ALRN-6924 infusion.

17. Hereditary angioedema of any severity or history of severe or life-threatening angioedema, due to any cause

4.3 Inclusion Criteria – Phase 2a dose expansions in PTCL (ALRN-6924 administered as single agent therapy)

1. Male or female patients age 18 years and older, inclusive, at the time of informed consent
2. A histologically confirmed diagnosis of PTCL based on pathology review at the local institution, using the most recent edition of the WHO Classification of Tumors of Haematopoietic and Lymphoid Tissues as guidance.

   The pathology sample must be considered to be adequate, meaning that there must be enough well-preserved, formalin-fixed biopsy material for the pathologist to be able to perform a morphological and immunohistochemical examination so as to in confidence be able to state an unequivocal diagnosis of PTCL. Final diagnoses containing caveats such as "suspicious of" or "presumably" are considered inadequate for a patient to be enrolled in the trial. In addition, a pathology sample must be available for a central pathology read.
3. Patients must have relapsed or refractory disease after at least one but not more than 7 prior systemic anticancer regimens.
4. WT TP53 status of t-cell lymphoma cells. Beginning with Amendment 6, TP53 status still must be determined by the central laboratory, but confirmation of WT TP53 status is not required for enrollment or initiation of study treatment, if the Investigator deems it clinically unacceptable to delay treatment.
5. At least one target lesion that is measurable by Revised International Working Group Response Criteria for lymphoma patients (IWG 2014 - See Appendix L). Patients with PTCL subtypes that are assessed by alternative criteria must have measurable disease in accordance with those criteria and be approved by the Medical Monitor.
6. Eastern Cooperative Oncology Group (ECOG) performance status 0-1 (See Appendix A)
7. Predicted life expectancy of ≥3 months
8. Adequate hematological bone marrow function, measured within 7 days prior to the first dose of ALRN-6924, defined as:

   - Absolute neutrophil count (ANC) ≥1.0 x 10^9/L

- Platelets ≥50 $\times 10^9$/L (platelets <50 x 10^9/L are acceptable if partly caused by autoimmune destruction and/or splenomegaly and/or hepatic disease infiltration)

9. Adequate hepatic function, measured within 7 days prior to the first dose of ALRN-6924, defined as:
    - Total bilirubin ≤1.5 x upper normal limit, or ≤ 3 x upper normal limit if documented hepatic infiltration with lymphoma
    - Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 x upper normal limit (≤ 5 x upper normal limit if documented hepatic infiltration with lymphoma)
10. Adequate renal function, measured within 7 days prior to the first dose of ALRN-6924, defined as serum creatinine ≤1.5 times institutional ULN, or calculated creatinine clearance ≥50 mL/min (Cockcroft-Gault formula)
11. Acceptable coagulation profile, measured within 7 days prior to the first dose of ALRN-6924, defined as:
    - Prothrombin time (PT) or international normalized ratio (INR) ≤1.5 times ULN
    - Activated partial thromboplastin time (aPTT) ≤1.5 times ULN
12. Prior anti-cancer therapies must wash-out such that they can neither cause drug-drug interaction with ALRN-6924 nor interfere with the anti-cancer evaluation of ALRN-6924. Therefore, the wash-out has to meet all the following criteria:
    - patients must have recovered from the previous therapy to ≤Grade 1 or baseline of significant toxicities, excluding alopecia, and
    - 5 half-lives or 4 weeks (whichever is shorter) must have expired, unless the prior anti-cancer therapy and ALRN-6924 do not interfere with each other's metabolism, and
    - 5 half-lives or 4 weeks (whichever is shorter) must have expired, unless the patient unequivocally progressed during the prior anti-cancer therapy

    Palliative radiotherapy for bone lesions ≤2 weeks prior to the first dose of ALRN-6924 is acceptable if acute toxicity has resolved
13. Negative serum or urine pregnancy test within 2 days prior to the first dose of ALRN-6924 for women of child-bearing potential, defined as a sexually mature woman who has not undergone a hysterectomy or who has not been naturally post-menopausal for ≥24 consecutive months (i.e., who has had menses any time in the preceding 24 consecutive months)
14. All patients (males and females) of child-bearing potential must agree to use an effective method of birth control (i.e., latex condom, diaphragm, cervical cap, intra-uterine device [IUD], birth control pill, etc.) beginning two weeks prior to the first dose of ALRN-6924 and for 30 days after the last dose of ALRN-6924
15. Ability to understand and willingness to sign a written informed consent form

4.4 Exclusion Criteria – Phase 2a dose expansions in PTCL (ALRN-6924 administered as single agent therapy)

1. Previous treatment with investigational agents that inhibit MDM2 or MDMX activity
2. Relapse within 75 days of autologous bone marrow transplant.
3. Prior allogeneic stem cell transplantation, unless immunosuppressants are no longer required and there is no active graft versus host disease.
4. Known central nervous system (CNS) lymphoma [computed tomography (CT) or magnetic resonance imaging (MRI) scans are required only if brain metastasis is suspected clinically
5. Known hypersensitivity to any study drug component
6. Current, clinically significant coagulopathy or platelet disorder, as determined by the Investigator
7. Required concurrent use of anti-coagulants or anti-platelet medication, with the exception of aspirin doses ≤ 81 mg/day, low-dose subcutaneous (SC) heparin or SC low-molecular-weight heparin for DVT prophylaxis, or heparin flushes to maintain IV catheter patency.
8. Patients with pre-existing history of or known cardiovascular risk:
    - History of acute coronary syndromes within 6 months prior to the first dose of ALRN-6924 (including myocardial infarction, unstable angina, coronary artery bypass graft, angioplasty, or stenting)
    - Uncontrolled hypertension
    - Pre-existing cardiac failure (New York Heart Association Class III-IV)
    - Atrial fibrillation on anti-coagulants
    - Clinically significant uncontrolled arrhythmias
    - Severe valvulopathy
    - Corrected QT (QTc) interval on screening electrocardiogram (ECG) ≥450 msec for males and ≥470 msec for females (QTc >480 msec for any patient with a bundle branch block)
9. Clinically significant gastrointestinal bleeding within 6 months prior to the first dose of ALRN-6924
10. Clinically significant third-space fluid accumulation (e.g., ascites requiring tapping despite the use of diuretics; or pleural effusion that requires tapping or is associated with shortness of breath)
11. Pregnant or lactating females
12. Evidence of serious and/or unstable pre-existing medical, psychiatric, or other condition (including laboratory abnormalities) that could interfere with patient safety or provision of informed consent to participate in this study
13. Active uncontrolled infection, including HIV/AIDS or Hepatitis B or C

14. Known history of another primary malignancy that has not been in remission for ≥1 year. Non-melanoma skin cancer and cervical carcinomas in situ or squamous intraepithelial lesions (e.g., cervical intraepithelial neoplasia [CIN] or prostatic intraepithelial/intraductal neoplasia [PIN]) are allowed.
15. Any psychological, sociological, or geographical condition that could potentially interfere with compliance with the study protocol and follow-up schedule
16. The required use of any concomitant medications that are predominantly cleared by hepatobiliary transporters, organic anion transporter polypeptide [OATP] members OATP1B1 and OATP1B3, on the day of the ALRN-6924 infusion or within 48 hours after an ALRN-6924 infusion (see Appendix B)
17. Hereditary angioedema of any severity or history of severe or life-threatening angioedema, due to any cause.

4.5 Inclusion Criteria - Phase 2a Dose Expansion in MDM2 Amplified or MDM2/CDK4 Co-amplified Solid Tumors (ALRN-6924 plus palbociclib)

1. Histologically-confirmed solid tumor malignancy:
   a. for which there is no curative treatment and that is relapsed or refractory following at least one prior line of medical therapy; and
   b. that is either MDM2 amplified or MDM2/CDK4 co-amplified, based on local or central laboratory testing by NGS, FISH, or CGH. Tissue must be available for analysis at a central laboratory, even if enrolling based on alternative (e.g., local or commercial) test results. Alternative laboratory results require approval by the Medical Monitor prior to enrollment. Specimens must have been obtained after any previous exposure to palbociclib or any other CDK4/6 inhibitor.
2. At least one target lesion that is measurable by RECIST 1.1 or RANO or other appropriate response criteria
3. Males and females aged 12 years and older
4. ECOG performance status of 0 to 1
5. Adequate hematopoiesis, defined as:
   a. Absolute neutrophil count ≥1.5 × 10^9/L
   b. Hemoglobin ≥9.0 g/dL (without transfusions in the past 2 weeks)
   c. Platelets ≥100 ×10^9/L
   d. Absolute lymphocyte count ≥ 0.5 × 10^9/L
6. Adequate hepatic function, defined as:
   a. In the absence of disease involvement of the liver: bilirubin ≤1.5 times institutional ULN, and AST and ALT ≤2.5 times ULN

b. In the presence of disease involvement of the liver: bilirubin ≤2 times institutional ULN and AST and ALT ≤5 times ULN

7. Adequate renal function, defined as serum creatinine ≤1.5 times institutional ULN, or calculated creatinine clearance ≥50 mL/min (Cockcroft Gault formula)
8. Five half-lives or 4 weeks, whichever is shorter, must have elapsed since any prior anticancer agent was administered, unless the patient unequivocally progressed during that therapy and the agent would not be expected to interfere with ALRN-6924 or palbociclib metabolism or impede clinical assessments
9. Recovery from the acute toxic effects of all prior therapies to ≤ Grade 1 or baseline, excluding alopecia
10. Provision of informed consent and, where applicable, pediatric assent
11. Agreement to use acceptable methods of pregnancy prevention, if of child-bearing potential

4.6 Exclusion Criteria - Phase 2a Dose Expansion in MDM2 Amplified or MDM2/CDK4 Co-amplified Solid Tumors (ALRN-6924 plus palbociclib)

1. Tumors with known mutations or deletions in TP53 or Rb
2. Known hypersensitivity to any component of study medication
3. Symptomatic or untreated CNS metastases
4. Pulmonary embolism within the past 6 months or DVT that has not been fully treated.
5. Clinically significant cardiovascular risk factors, including:
   - myocardial infarction, unstable angina, coronary artery bypass grafting, stenting, angioplasty, or acute coronary syndrome in the past 6 months
   - New York Heart Association Class III or IV heart failure
   - clinically significant uncontrolled arrhythmia
   - corrected QT (QTc) interval ≥450 msec for males and ≥470 msec for females (QTc >480 msec for any patient with a bundle branch block)
6. Uncontrolled hypertension
7. Active, uncontrolled infection, including HIV, hepatitis B, or hepatitis C
8. HPV-positive malignancy.
9. Ascites requiring paracentesis or pleural effusion requiring pleurocentesis or causing dyspnea
10. Hereditary angioedema of any severity or history of clinically significant angioedema, due to any cause
11. Major surgery within 3 weeks prior to the first dose of ALRN-6924
12. History of another malignancy within the past year, excluding nonmelanoma skin cancers, carcinomas in situ, or other malignancies with ≥ 95% 5-year survival

13. Pregnant or lactating females
14. Required use of medications that are primarily cleared by hepatobiliary transporters, including organic anion transporters, OATP1B1 and OATP1B3, and bile salt export pump (BSEP), unless administration is not required on the day of or within 48 hours following ALRN-6924 administration
15. Required use of medications that are strong inhibitors or moderate to strong inducers of CYP3A
16. Administration of any investigational agent, regardless of indication, within the 2 weeks prior to enrollment, unless a minimum of 5 half-lives have elapsed
17. Any medical, psychological, or social condition that would interfere with patient safety or the conduct of the study

4.7 Removal of Patients from Study Therapy

A patient may be removed from the study therapy for a variety of reasons, including:

- Disease progression that is either symptomatic, rapidly progressive, required urgent intervention, or associated with a decline in performance status
- Unacceptable adverse event(s)
- Intercurrent illness that prevents further participation
- Patient refusal to continue treatment through the study and/or consent withdrawal for study participation
- Patient unable or unwilling to comply with study requirements
- Pregnancy or failure to use adequate birth control
- General or specific changes in the patient's condition that render the patient unacceptable for further treatment in this study in the judgment of the Investigator

Under no circumstance will care of a withdrawn patient be adversely affected by a decision to withdraw or be withdrawn from the study.

4.8 Patient Replacement

Any patient who completes screening and does not receive a dose of ALRN-6924 (single agent cohorts) or at least one dose each of ALRN-6924 and palbociclib (MDM2 amplification and MDM2/CDK4 co-amplification cohort) will be replaced. A patient in the dose escalation portion of the study or a safety run in group who discontinues the study prior to completion of the first cycle for reasons other than safety, or who does not receive all required doses in the first cycle for reasons other than safety, will be replaced. A patient in the dose expansion portion of the study who discontinues study participation prior to the completion of the first cycle of treatment for any reason or who does not receive all required doses in the first cycle may be replaced. Patients who are not confirmed by the central laboratory to have met all molecular requirements for their given cohort may be replaced.

5 TREATMENT PLAN

5.1 Study Drug Description

ALRN-6924

The study drug for ALRN-6924-1-01 is the investigational agent ALRN-6924. Details on the administration, dispensing, return, and destruction of ALRN-6924 will be provided in the Pharmacy Binder.

ALRN-6924 drug product is a frozen or refrigerated liquid product supplied in single-use glass vials in a single dose strength of 75 mg in 5.0 mL, dissolved in 20 mM sodium phosphate, 240 mM trehalose, 300 ppm Polysorbate 20, pH 7.5. Each vial contains recoverable 5.0 mL and is filled with formulated ALRN-6924 to 5.5 ± 0.2 mL. ALRN-6924 for Injection is stored as frozen product at -15º to -25° C or refrigerated product at 2º to 8° C.

Palbociclib

For the Phase 2a cohort with MDM2 amplified or MDM2/CDK4 co-amplified solid tumors, palbociclib will be provided to patients as capsules for oral use.

Palbociclib will be administered on an outpatient basis. Patients will be provided with a diary to record time of palbociclib administration on each dosing day. In order to assess treatment compliance, the numbers of palbociclib capsules that were dispensed and returned by the patient will be recorded. Any dose reductions or interruptions, and the reason for these actions, will also be recorded.

5.2 Preparation of ALRN-6924

Specific instructions for acquisition and storage of ALRN-6924 and preparation of the final dosing solution will be provided in the Pharmacy Binder. Briefly, ALRN-6924 is introduced into an IV infusion bag containing D5W; this will be known as ALRN-6924 Dosing Solution and will be provided by the site pharmacy for administration to the patient. ALRN-6924 Dosing Solution will be labeled with the ALRN-6924-1-01 Patient Identification Number. The investigative staff will confirm this information and its relevancy to the intended patient. The start of the ALRN-6924 infusion must begin within 6 hours of dilution into 250-mL D5W, and the infusion bag shall remain at room temperature until use.

5.3 Study Drug Administration

The investigational agent ALRN-6924 as well as palbociclib (IBRANCE®) will be provided by Aileron and distributed to clinical sites. Patients should begin treatment with study drug within 21 days following the start of clinical screening. Issues that would cause treatment delays should be discussed with Sponsor's Medical Monitor.

Treatment of patients in the dose escalation and the dose expansion phases of the study will continue until unacceptable toxicity, patient or physician decision to discontinue therapy, or disease progression that is either symptomatic, rapidly progressive, requires urgent intervention, or is associated with a decline in performance status. Patients receiving clinical benefit despite evidence of suspected or confirmed PD may continue on study after a discussion between the Principle Investigator and Medical Monitor.

ALRN-6924 will be administered by IV infusion in D5W. The pre-defined dose will be calculated for each patient based on body weight at the start of each cycle. During the first two cycles, ALRN-6924 should be administered in the morning to allow observation of delayed infusion reactions.

Phase 1 Dose Escalation:

Treatment Regimen	**Infusion Days**	**Infusion Time**	**Additional notes**
DR-A	1, 8, 15 of a 28-day cycle	1 hour (±15 min)	At the end of the infusion, IV fluids (saline) or oral fluids (500 mL – 1000 mL) should be administered, unless clinically contraindicated.
DR-A-2	1, 8, 15 of a 28-day cycle	2 hours (±15 min)	At the end of the infusion, IV fluids (saline) or oral fluids (500 mL – 1000 mL) should be administered, unless clinically contraindicated. Administer dexamethasone (4 mg orally or IV) approximately 4 hours after the end of the infusion in Cycles 1 and 2, and thereafter at the discretion of the investigator.
DR-B	1, 4, 8, 11 of a 21-day cycle	1 hour (±15 min)	At the end of the infusion, IV fluids (saline) or oral fluids (500 mL – 1000 mL) should be administered, unless clinically contraindicated.

In DEP, ALRN-6924 will not be administered outside of the planned schedule in Cycle 1 (i.e., there are no planned windows for dose days). Follow-up visits on non-dosing days have windows, however, at the Investigator's discretion, it may be necessary to conduct a study visit on an alternative day than described in this schedule in order to protect the safety, rights, or welfare of the patient. If this is the situation, the Investigator will confer with and obtain approval from the Medical Monitor.

Patients in the DEP who remain on study treatment for 2 years or longer may have their dosing frequency reduced (i.e., Days 1 and 15 of a 28-day cycle for DR-A and Days 1 and 8 of a 21-day cycle for DR-B), at the discretion of the investigator. In the event that disease control is lost, the original administration schedule may be resumed, at the discretion of the investigator.

Phase 2a Dose Expansion:

Treatment Regimen	Drug and Dose Level	Dosing Days	Infusion Time	Additional notes
DR-A	ALRN-6924 3.1 mg/kg	1, 8, 15 of a 28-day cycle	1 hour (±15 min)	At the end of the infusion, IV fluids (saline) or oral fluids (500 mL – 1000 mL) should be administered, unless clinically contraindicated.
DR-B	ALRN-6924 2.7 mg/kg	1, 4, 8, 11 of a 21-day cycle	1 hour (±15 min)	At the end of the infusion, IV fluids (saline) or oral fluids (500 mL – 1000 mL) should be administered, unless clinically contraindicated.
DR-C	ALRN-6924 3.1 mg/kg [If 3.1 mg/kg is not well tolerated, lower doses may be tested starting at dose levels of -25%]	1, 3, 5 of a 21-day cycle	1 hour (±15 min)	At the end of the infusion, IV fluids (saline) or oral fluids (500 mL – 1000 mL) should be administered, unless clinically contraindicated.
Combination with palbociclib	ALRN-6924 3.1 mg/kg [If 3.1 mg/kg is not well tolerated, up to two dose reductions of 25% may be tested]	1, 8, 15 of a 28-day cycle	1 hour (±15 min)	At the end of the infusion, IV fluids (saline) or oral fluids (500 mL – 1000 mL) should be administered, unless clinically contraindicated.
	Palbociclib 100 mg [If 100 mg is not well tolerated, reduction to a 75 mg dose may be tested.]	1-21 of a 28-day cycle	Oral	Palbociclib should be administered with food. On days when both drugs are administered (Days 1, 8, and 15 of each cycle), palbociclib should be administered at least 6 hours after the infusion of ALRN-6924.

5.4 Management of Toxicities

5.4.1 Toxicities Related to ALRN-6924

Usual supportive medicines used as standard-of-care are allowed, with the exception of growth factors during DEP Cycle 1. All supportive medications and medications to treat toxicities must be recorded in the electronic case report form (eCRF).

5.4.1.1 Management of Infusion-Related Reactions

For the management of Grade 1-2 infusion-related reactions:

- Stop the infusion for 15–30 minutes.
- Measure vital signs at least once every 5 minutes until symptoms abate.
- Consider administering diphenhydramine 25–50 mg IV or equivalent.
- If symptoms abate, re-start the infusion at one-half the previous rate.
- Additional medical measures, such as the administration of selective anti-histamines (e.g., cimetidine 300 mg or ranitidine 50 mg IV) or corticosteroids (e.g., dexamethasone 20 mg IV) may be considered for reactions that do not abate after 15 minutes.
- If symptoms do not abate 30 minutes after the administration of medical measures, discontinue the day's ALRN-6924 treatment.

In the case of a prior infusion-related reaction controlled by above medical management, subsequent ALRN-6924 infusions should include premedication at least 30 minutes before the start of ALRN-6924 infusion.

For the management of Grade 3+ infusion-related reactions:

- Stop the infusion.
- Measure vital signs at least once every 5 minutes until symptoms abate.
- Consider administering the following:
  - Diphenhydramine 50 mg IV
  - Cimetidine 300 mg or ranitidine 50 mg IV
  - Dexamethasone 20 mg IV
  - Epinephrine 0.5 mg SC
  - Albuterol inhaler as needed for bronchospasm
- Additional agents may be administered per institutional guidelines for the treatment of infusion-related reactions.

Patients experiencing Grade 3 hypersensitivity reactions that require hospitalization or any Grade 4 hypersensitivity reactions that are related to ALRN-6924 infusion should be discontinued from study treatment and not rechallenged.

5.4.1.2 Angioedema

Follow standard clinical practice when suspecting angioedema symptoms during treatment with ALRN-6924. If the administration of antihistamines and corticosteroids does not resolve symptoms, consider the administration of icatibant, a bradykinin B2-receptor inhibitor approved in the US and Europe for the treatment of hereditary angioedema. In the event of signs of airway obstruction, epinephrine has to be immediately available and the patient must be in the care of a clinician who can provide emergency airway management.

Patients being treated with ALRN-6924 should be educated about the symptoms of angioedema and urged to tell their care team immediately, should such symptoms develop.

5.4.1.3 Management of Tumor Lysis Syndrome (TLS)

There is a potential for TLS in patients with lymphoma, especially those with large tumor burden, pre-dose elevated lactate dehydrogenase and leukocyte counts, renal dysfunction, or dehydration. TLS can be caused by treatment-induced abrupt cancer cell disintegration. It is usually observed shortly after initiating treatment.

Laboratory TLS is defined as a 25% increase in the levels of serum uric acid, potassium, or phosphorus or a 25% decrease in calcium levels.

Prophylaxis and management of TLS for at risk patients during this clinical trial must include :

- Laboratory assessments of the blood prior to each ALRN-6924 administration during Cycle 1:
    - Electrolytes, including potassium, phosphorus, and calcium
    - Creatinine
    - Uric acid
    - Lactate dehydrogenase
- Administration of allopurinol or an alternative uric acid-lowering agent throughout Cycle 1.
- Antiemetics should be optimized, to prevent poor oral intake and fluid losses from vomiting. Hydration status should be monitored closely and intravenous fluids should be administered as indicated, to prevent or treat dehydration.
- ALRN-6924 must be withheld, if TLS is suspected, and not resumed until electrolyte aberrations and renal function have stabilized and uric acid has been reduced to within normal limits.
- Patients should be hospitalized for closer monitoring and management, if clinically indicated in the judgment of the investigator.

These actions should be continued beyond Cycle 1, if the patient remains at risk, in the judgment of the investigator.

Additional prophylaxis and/or management should be implemented in accordance with local standard of care practices.

5.4.2 Toxicities Related to Palbociclib

For patients in the palbociclib combination cohort, palbociclib-related toxicities should be managed as described in the current approved US prescribing information. All supportive medications and medications to treat toxicities must be recorded in the eCRF.

5.5 Registering and Enrolling Patients on Study, Assignment of Dose Level

5.5.1 Patient Registration

Prior to registration and any study-specific evaluations being performed, adult patients must have given written informed consent; for pediatric patients, written informed consent from parent(s) or legal guardian and pediatric assent for the study must have been provided. All patients must have completed the pre-study evaluations. Patients must meet all of the eligibility requirements listed in Section 4. Each patient will be assigned a unique identification code prior to enrollment.

See the Study Operations Binder for further information on Patient Enrollment.

5.5.2 Staggered Cohort Enrollment Scheme for Dose Level 1 (DEP)

A staggered cohort enrollment scheme will be employed in the first dose cohort (Dose Level 1), in which each patient completes one week of study treatment before the next patient will be enrolled in this cohort. There will be no mandated waiting period between patients enrolled in Dose Level 2 and higher.

5.5.3 Assignment of Dose Level (DEP)

Cohorts of three to six patients will receive ALRN-6924 per dose level and per dose regimen, i.e. DR-A, DR-A-2 and DR-B. At the discretion of the Investigator and Medical Monitor, a fourth patient may be enrolled in the initial group of 3 patients per dose regimen (DR) to help manage patient allocation across multiple sites. If this occurs, the first 3 patients to complete Cycle 1 in the current DR will be used to assess dose limiting toxicities. However, all available data from the 4th patient will be reviewed at the time of the dose level and regimen Safety Review Meeting (Refer to Section 8.10.1). In the event that a drug-related DLT is observed in one of the first 3 patients of a dose level in a dose regimen, and after discussion among the Investigators and Sponsor's Medical Monitor, additional patients will be enrolled into the study for a total of 6 patients at the same dose level in the same dose regimen.

5.6 Dose Escalation Criteria (DEP)

In the absence of >33% of patients experiencing a drug-related DLT, escalation to the next dose level for a given treatment arm may proceed when all of the following have occurred:

- At the completion of Cycle 1 (treatment cycle = 28 days for DR-A and DR-A-2 or treatment cycle = 21 days for DR-B),
- The Safety Review Meeting is convened during which the Safety Review Committee (SRC), consisting of the Investigators and Sponsor's Medical Monitor, has reviewed all available safety data for all patients in the cohort and confirms that the next planned dose level is appropriate; and
- The Sponsor Medical Monitor issues written documentation of the decision to proceed to the next planned dose level of a dose regimen.

It is important to note that despite the absence of >33% of patients experiencing a DLT, the next dose level may be less than the planned dose level if the Investigators and Sponsor's Medical Monitor agree that a more conservative dose escalation approach is warranted or would be in the best interest of the patients. The SRC may hold the dose (e.g., stop dose escalation) at their discretion and enroll additional patients until sufficient safety data are obtained to determine escalation of the current dose level or to confirm a certain dose as an MTD or OBD.

5.7 Planned Dose Levels

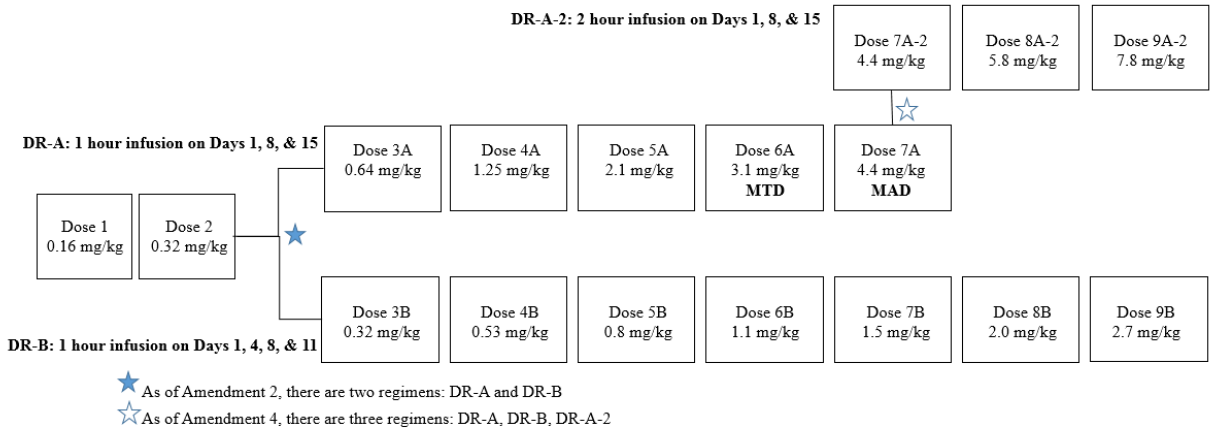
5.7.1 Dose Levels for the Dose Escalation Portion of the Study

In the Dose Escalation portion of the study, increasing dose levels of ALRN-6924 will be evaluated in cohorts of 3-6 DLT-evaluable patients per dose regimen. Patients enrolled in Cohort 1 receive ALRN-6924 at Dose Level 1 (0.16 mg/kg). Based on allometric scaling, at 0.16 mg/kg dose in humans, the predicted AUC (50 µg•hr/mL) is approximately 9% of the rat AUC at STD_{10} and approximately 6% of the AUC at the monkey HNSTD as described in Section 1.4.

In the absence of DLT in >33% of DLT-evaluable patients in either DR, subsequent cohorts of 3 to 6 patients will receive escalated doses until the MTD or an OBD is established for each dose regimen.

A 2-stage dose escalation design will be employed. During the initial Stage 1 Escalation Phase, 100% dose increments will be utilized until ≥1 of 3 patients in a cohort experiences any Grade ≥2 AE that is at least possibly related to study drug. Study drug-related AEs Grade ≥2 occurred in DL-4A (fatigue) and in DL-3B (neutropenia). Therefore, per protocol, Stage 2 has been implemented for subsequent dose escalations starting with DL-5A and DL-4B. Dose escalation will continue using 3-patient cohorts and the modified Fibonacci sequence (i.e., 67%, 50%, 40%, 33%), until the MTD or an OBD is established. As two DLTs have occurred in DR-7A (hypotension and hepatobiliary laboratory abnormalities), there will be no further dose escalation in DR-A. A new modified infusion regimen was tested (DR-A-2) starting at dose level 7A-2 (=4.4 mg/kg body-weight). As two DLTs have occurred in DR-7A-2 (anemia and neutropenia), there will be no further escalation in DR-A-2.

Figure 9: Dose Level and Dose Regimen Schematic



The observation of DLT(s) will be used to make individual patient determinations regarding dose reductions, interruptions or discontinuation throughout the course of the trial, but DLTs occurring during Cycle 1 will be used to inform safety and tolerability assessments for dose escalation decisions.

If DLTs are observed in the first cohort, the dose will be de-escalated to Dose Level -1. If DLTs are observed at Dose Level -1, the dose will be de-escalated to Dose Level -2. If DLTs are observed at Dose Level -2, other dose levels may be considered and implemented after discussions among the Investigators and Sponsor's Medical Monitor.

It is anticipated that at least 3 patients will be treated at each dose level per treatment arm. If no patients experience a DLT, then the subsequent 3 patients will be treated at the next planned dose level.

If DLT is observed in ≥2 of 3 patients in either treatment DRs at any dose level, no further dose escalation will occur in that DR, and the current dose will be defined as the maximum administered dose (MAD).

If DLT is observed in 1 of 3 patients in a cohort at any dose level, then up to 6 patients total will be enrolled at that same DR at that dose level. If DLT is observed in ≥2 patients in the expanded cohort, then no further dose escalation will occur, and the current dose will be defined as the MAD, unless the SRC decides that there is sufficient clinical uncertainty about the DLTs that warrants the enrollment of up to 6 additional patients. In the event of additionally enrolled patients, if a DLT is observed in 33% or more DLT-evaluable patients in the entire cohort, then no further dose escalation will occur, and the current dose will be defined as the MAD for the dosing regimen under consideration. After the MAD is defined, either the previously administered lower dose will be expanded to a total of 6 patients, or an intermediate (between the MAD and the next lower dose level) will be investigated in up to 6 patients. The highest dose tolerated without DLT in at least 5 of 6 patients (i.e. <33% of DLT-evaluable patients experiencing a DLT) in a cohort from one treatment arm will be defined as the MTD for that treatment arm. Additional patients may be added to further explore the MTD or OBD prior to expansion.

Based on review of available safety and PK data during this and other studies with ALRN-6924, dose escalation or modification steps may be adjusted (i.e. increased or decreased) by the SRC to limit the number of patients exposed to sub-therapeutic dose levels as well as to ensure patients' safety. Additional patients may be added to further explore safety at a dose level or to confirm a certain dose as an MTD or OBD.

5.7.2 Dose Levels for the Expansion Portion of the Study

The EXP will enroll up to 5 distinct groups of patients with specific solid tumors and/or lymphomas to further investigate the clinical safety profile and potential efficacy of ALRN 6924 at the MTD, OBD, or an alternative dosing regimen. PTCL has been selected as one of the EXP groups to be further studied; up to 3 cohorts in PTCL may be studied in order to determine the optimal dosing regimen. Another Phase 2a EXP group will include patients with MDM2 amplified or MDM2/CDK4 co-amplified solid tumors who will receive ALRN-6924 in combination with palbociclib.

<u>Phase 2a Expansion in PTCL</u>

Two DLTs were observed at DL-7A (hypotension and hepatobiliary laboratory abnormalities) rendering DL-7A the maximum administered dose whereas in DL-6A, only one DLT was observed (fatigue) in six DLT-evaluable patients. Furthermore, a complete remission has been observed in a PTCL patient at DL-5A (2.1 mg/kg). Therefore, the first selected dose and schedule for the Phase 2a expansion in PTCL is

3.1 mg/kg on Days 1, 8, and 15 of a 28 day cycle (DL-6A). Alternative dosing regimens to be tested may include 2.7 mg/kg on Days 1, 4, 8, and 11 of a 21 day cycle (DR-B) and 3.1 mg/kg on Days 1, 3, and 5 of a 21 day cycle (DR-C). Six to 8 patients will be enrolled in DR-C in a run-in part and the treating investigators, along with the Medical Monitor, will review safety and tolerability through Cycle 1 prior to opening the full DR-C expansion cohort. Lower dose levels for DR-C, in 25% reductions in the starting dose, may be assessed if the safety and tolerability of 3.1 mg/kg are not acceptable. Should this occur, 6-8 patients will again be enrolled into a run-in part and the treating investigators and Medical Monitor will meet again to review all patients prior to opening the full DR-C expansion cohort. For each dose level assessed during the run-in part, the SRC will use the DLTs defined in Phase 1 as a guide for determining safety.

Phase 2a Expansion in MDM2 amplified or MDM2/CDK4 co-amplified solid tumors

ALRN-6924 and palbociclib have not previously been co-administered in humans. Therefore, for the Phase 2a cohort of patients with MDM2 amplified or MDM2/CDK4 co-amplified solid tumors, a safety run-in group of 6-8 patients will first be enrolled and evaluated by the sponsor and the primary investigators before further patients are permitted to enroll. The SRC will use the DLTs defined in Phase 1 and the toxicity profile of palbociclib (in accordance with the package insert) as a guide for assessing safety.

Enrollment of the first 3 patients in this cohort will be separated in time by at least one week each, to assess for unexpected acute toxicities related to administration of the treatment regimen. Patients will receive ALRN-6924 at the previously determined recommended Phase 2 dose for the once-weekly administration schedule (3.1 mg/kg on Days 1, 8, and 15) and palbociclib at an oral dose of 100 mg daily for 21 days (one dose level below the approved oral dose of 125 mg) in a 28-day cycle. In the event that this regimen is not determined to be safe or tolerable at these dose levels, the dose of ALRN-6924 will be decreased by 25% and/or the dose of palbociclib will be decreased by one dose level (to 75 mg/day), as needed based on the pattern of toxicities encountered, and an additional 6-8 patients will be assessed in a safety run-in using the reduced dose level, before further enrollment is permitted. Subsequent reductions of the ALRN-6924 dose by 25% may be implemented if safety and tolerability are still not acceptable. The decision to begin palbociclib below the approved dose level is based on the frequency of required dose reductions, often due to neutropenia. The SRC may consider adjusting to the approved palbociclib dose, if palbociclib-related toxicities are not prohibitive and patient benefit is expected to outweigh risk. Once the safety run-in is complete, all subsequent patients will be enrolled at the recommended dose level.

5.7.3 Intra-Patient Dose Escalation- Phase 1 Dose Escalation

A patient's dose may be increased to that of a cohort that completed the first cycle without dose-limiting toxicity in ≥ 33% of DLT-evaluable patients and that has not exceeded the MTD. Intra-patient dose escalations will be allowed provided that the patient completed at least two treatment cycles and did not experience study medication-related toxicity greater than Grade 2 (except for alopecia, electrolyte disturbances responsive to correction within 24 hours, diarrhea, nausea, fatigue and vomiting that responds to standard medical care). Approval for intra-patient dose escalation must be obtained from the Medical Monitor.

5.8 Dose and Schedule Adjustments for Toxicity

5.8.1 Dose Modifications – Phase 1 dose escalation (ALRN-6924 administered as single agent therapy)

In the event a Grade 4 AE considered related to ALRN-6924 is observed, the patient must be discontinued from study treatment. Exceptions include Grade 4 neutropenia lasting <3 days, and emesis, diarrhea or electrolyte abnormalities that resolve within 2 days on optimum treatment. For these exceptions, treatment may be delayed for up to 2 weeks to allow resolution of the toxicity (i.e., return to Grade ≤1 or baseline), followed by re-treatment at a reduced dose. Two dose reductions are permitted; a third dose reduction will require evidence of clinical benefit and approval by the Medical Monitor. Relevant labs should be repeated as medically indicated.

In the event a Grade 3 AE considered related to ALRN-6924 is observed (exceptions are Grade 3 fatigue, nausea, emesis, diarrhea or clinically insignificant electrolyte abnormalities that resolve within 2 days on optimum treatment), treatment may be delayed for up to 2 weeks to allow resolution of the toxicity, followed by re-treatment at a reduced dose. Two dose reductions are permitted, a third dose reduction will require evidence of clinical benefit and approval by the Medical Monitor. Relevant labs should be repeated as medically indicated.

Dose modifications for re-treatment following related Grade 3 and Grade 4 AEs (as permitted): patients will be re-treated at the preceding dose level (per Figure 9).

For other clinically significant AEs, treatment may be delayed by up to 2 weeks to allow for the resolution of AEs to an acceptable level, and may continue treatment at a reduced dose level as described above at the discretion of the Investigator in consultation with Sponsor's Medical Monitor. If a patient experiences multiple AEs, decisions on dosing delay or dose reduction will be based on the most severe AE. Any patient who experiences recurrent, clinically significant AE after one dose reduction may undergo one additional dose reduction. Patients who continue to experience clinically significant AEs after a 2-week delay or the maximum allowed number of dose reductions will be discontinued from the study.

Adverse events considered for dose reduction should not include the events assessed by the Investigator as exclusively related to underlying disease or other medical condition or concomitant treatment. A patient who experiences an AE considered related to ALRN-6924 that does not meet the requirement for discontinuation may continue on study if the patient is receiving clinical benefit and/or the Investigator feels continued participation is in the best interest of the patient. In such cases, at the Investigator's discretion and in agreement with Sponsor's Medical Monitor, the dose for a patient may be reduced as described above.

A patient who experiences a DLT must continue treatment at a reduced dose level, or discontinue ALRN-6924 treatment (if Grade 4 related AE), as described above at the discretion of the Investigator and in agreement with Sponsor's Medical Monitor until disease progression or unacceptable toxicity. Once the dose has been reduced for a patient, it may not be re-escalated.

5.8.2 Dose Modifications – Phase 2a dose expansions in PTCL (ALRN-6924 administered as single agent therapy)

In the event a non-hematologic Grade 4 AE considered related to ALRN-6924 is observed, the patient must be discontinued from the study. Exceptions include emesis, diarrhea or electrolyte abnormalities that resolve within 2 days on optimum treatment. For these exceptions, treatment may be delayed for up to 2 weeks to allow resolution of the toxicity (i.e., return to Grade ≤1 or baseline), followed by re-treatment at a reduced dose. Relevant labs should be repeated as medically indicated.

In the event a non-hematologic Grade 3 AE considered related to ALRN-6924 is observed (exceptions are Grade 3 fatigue, nausea, emesis, diarrhea or clinically insignificant electrolyte abnormalities that resolve within 2 days on optimum treatment), treatment may be delayed for up to 2 weeks to allow resolution of the toxicity, followed by re-treatment at a reduced dose. Relevant labs should be repeated as medically indicated.

For hematologic toxicities, patients must discontinue treatment with ALRN-6924 if

- Neutrophil counts < 0.5 x 10^9/L for > 5 days, or
- Platelet counts < 10 x 10^9/L, or
- Hemoglobin < 6g/dL (despite RBC transfusion or Erythropoiesis-Stimulating Agent (ESA) administration)

Patients must interrupt treatment if

- Neutrophil counts < 0.5 x 10^9/L for ≤ 5 days, or
- Platelet counts < 25 x 10^9/L and >10 x 10^9/L, or
- Hemoglobin < 8 g/dL and > 6 g/dL

After resolution of hematologic toxicity (i.e., return to Grade ≤1 or baseline), patients may continue at a reduced dose. Relevant labs should be repeated as medically indicated.

Following related Grade 3 and Grade 4 AEs (as permitted), the dose for re-treatment will be reduced by 25% intervals (e.g., if the dose is 3.1 mg/kg, the dose will be reduced sequentially to 2.3 mg/kg and 1.7 mg/kg). Two dose reductions are permitted, a third dose reduction will require evidence of clinical benefit and approval by the Medical Monitor.

5.8.3 Dose Modifications – Phase 2a Dose Expansion in MDM2 Amplified or MDM2/CDK4 Co-amplified Solid Tumors (ALRN-6924 plus palbociclib)

Dose modifications of ALRN-6924 will be as described in Section 5.8.1. Dose modifications of palbociclib should be made in accordance with the current approved US prescribing information.

In the event that palbociclib administration must be discontinued, the patient may continue to receive ALRN-6924 as a study participant until one of the criteria for treatment discontinuation has been met. However, if discontinuation of ALRN-6924 is required, patients will be considered to have discontinued study treatment. Those patients may continue to receive palbociclib treatment at the Investigator's discretion.

5.9 Toxicity, DLT and MTD Evaluation

5.9.1 Toxicity Grading Criteria

Toxicity grading is based on NCI CTCAE v4.03.

5.9.2 Definition of Dose-Limiting Toxicity

A DLT will be defined as any Grade ≥3 AE that is considered to be possibly, probably, or definitely related to the study drug, with the following exceptions: (1) for fatigue, nausea, emesis, diarrhea or mucositis, only Grade ≥3 AE that do not respond within 48 hours to standard supportive/pharmacological treatment will be considered DLT; (2) for electrolyte imbalances, only Grade ≥3 AE that do not respond to correction within 24 hours will be considered DLT; (3) for infusion reactions, only a Grade 3 reaction which caused hospitalization or Grade 4 will be considered a DLT. In addition, specific hematologic DLTs are defined as:

• Thrombocytopenia – Grade 4 of any duration, Grade 3 for ≥7 days, or Grade 3 associated with clinically significant bleeding

• Neutropenia – Grade 4 for ≥3 days, or any Grade ≥3 febrile neutropenia

The above criteria will be used to make individual patient determinations regarding dose reductions, interruptions or discontinuation throughout the course of the trial, but DLTs occurring during Cycle 1 will be used to inform safety and tolerability assessments for dose escalation decisions.

5.9.3 Definition of Maximum Tolerated Dose

The MTD is defined as the dose at which ≤1 of 6 patients experiences a treatment-related toxicity that qualifies as a DLT, with the next higher dose having ≥2 of up to 6 patients experiencing a DLT.

The MTD will not be established until all patients enrolled in the cohort have completed Cycle 1, discontinued treatment or had a dose reduction. Previously established tolerability of a dose level will be reevaluated if toxicities that would have been DLTs in Cycle 1 are observed in later cycles.

5.9.4 Definition of Optimal Biological Dose (OBD)

For each treatment arm, the safety review committee might identify an OBD for a selected patient population before the MTD is reached. Such OBD would be derived from the evaluation of available safety, PK, PD, and preliminary efficacy information from the dose escalation portion of the study.

5.10 Concomitant Medications and Therapies

5.10.1 Permitted and Recommended Medications

Any changes in documented, permitted concomitant medications taken within 28 days of beginning treatment with ALRN-6924, or at the beginning of the clinical trial, or permitted concomitant medications added during the time the patient is participating in this study (through End-of-Treatment Visit or receipt of a subsequent therapy) must be recorded in the eCRF. All supportive medications and medications to treat toxicities as listed in Section 5.4 must be recorded in the eCRF.

Patients treated with ALRN-6924 have experienced nausea and vomiting. The administration of antiemetics, including 5HT3 antagonists, is recommended prior to and for 72 hours following

ALRN-6924 administration. For patients receiving palbociclib, additional antiemetic administration may be required.

Patients who experience neutropenia after Cycle 1 of DEP or at any time during EXP may receive myeloid growth factors at the discretion of the investigator.

5.10.2 Prohibited Medications and Medications Requiring Special Consideration

Other agents and treatments as outlined in Section 4, including concurrent anti-tumor therapy of any kind or any other investigational agent, are excluded. In the event that a patient is deriving clinical benefit from study treatment, but requires concurrent anticancer surgery or radiation therapy, that patient may continue on the study with permission of the Medical Monitor. The PI and medical monitor will determine the required duration of ALRN-6924 and/or palbociclib interruption, to allow for such treatments. Efficacy measures will be censored, as of the time of any such permitted concurrent therapy.

Although they are not prohibited, it is strongly recommended that alternative antihypertensive agents be used in place of ACE inhibitors and ARBs during treatment with ALRN-6924. It cannot be excluded that concomitant treatment with these agents and ALRN-6924 may increase the risk for developing angioedema. Note that this does not change the requirement to hold ARBs for 48 hours following the administration of ALRN-6924, due to a known pharmacokinetic interaction that decreases clearance of the ARB.

Any concomitant medications that are predominantly cleared by hepatobiliary transporters, OATP members OATP1B1 and OATP1B3, on the day of the ALRN-6924 infusion and within 48 hours after an ALRN-6924 infusion are prohibited (Appendix B), including the sartan class of angiotensin receptor blockers (ARBs).

For patients with MDM2 amplified or MDM2/CDK4 co-amplified solid tumors who are receiving ALRN-6924 in combination with palbociclib, strong CYP3A inhibitors and moderate to strong CYP3A inducers are prohibited. Patients should not consume grapefruit products while receiving palbociclib.

5.11 Packaging, Labeling, and Storage

The ALRN-6924 study vials will be labeled according to the local law and legislation. A copy of the labels will be filed and stored in the trial master files and can be made available to the study sites upon request.

ALRN-6924 for Injection is stored as frozen product at -15º to -25° C or refrigerated product at 2º to 8° C.

Palbociclib should be stored as described in the current approved US prescribing information.

5.12 Drug Accountability

The Principal Investigator is responsible for ensuring accountability for the investigational agent ALRN-6924, including reconciliation of drugs and maintenance of drug records.

Upon receipt of ALRN-6924, the clinical study site will check for accurate delivery and acknowledge receipt by signing (or initialing) and dating the documentation provided and returning it to the Sponsor or Sponsor's designee. A copy will be retained in the Investigator site file.

The receipt, dispensing, administration, and return of ALRN-6924 will be recorded on the appropriate drug accountability forms, and an accurate accounting will be available for verification by the Sponsor monitor at each monitoring visit.

Investigational agent accountability records will include:

- Confirmation of delivery to the site
- Inventory at the site
- Dispensing for each patient
- Return or alternative disposition of unused study drug
- Dates, quantities, batch numbers, expiry dates, and the Patient Identification Number for the study.

The Sponsor monitor will periodically review the investigational agent accountability forms to verify drug accountability and compliance. Drug accountability and destruction instructions are outlined in the Pharmacy Binder.

6 STUDY PROCEDURES

6.1 Schedule of Study Events

The schedule of study activities (including assessments, tests, exams, disease assessments, collection of tissue specimens, and study drug administration) beginning with molecular screening and continuing throughout the study are provided in the appendices starting with Appendix C.

Phase 1 dose escalation: During the first 2 dose levels, patients will receive ALRN-6924 on Days 1, 8, and 15 of a 28-day cycle. Starting with DL 3, patients in treatment DR-A and DR-A-2 (starting at DL7) will continue being treated once a week on Days 1, 8, and 15 of a 28-day cycle, whereas patients in DR-B will be treated twice a week, on Days 1 and 4, 8 and 11 of a 21-day cycle. Dose escalation proceeds based on safety parameters and review as described in Sections 5.5.3, 5.6, and 8.10.1 and each DR is independent of each other. All data regardless of DR and DL will be collated and available for each Safety Review Meeting.

Phase 2a dose expansion:

- Patients with PTCL: up to 3 single agent dosing regimens will be tested: DR-A (Days 1, 8, and 15 of a 28-day cycle); DR-B (Days 1, 4, 8, and 11 of a 21-day cycle); and DR-C (Days 1, 3, and 5 of a 21-day cycle).
- Patients with MDM2 amplified or MDM2/CDK4 co-amplified solid tumors: ALRN-6924 (DR-A) will be administered in combination with palbociclib in a 28-day cycle (see Appendix I and Appendix J).

Refer to the Pharmacy Binder for detailed instructions on how to prepare and administer ALRN-6924. For instructions on administration of palbociclib, refer to the current approved US prescribing information.

6.2 Informed Consent and Pediatric Assent

Informed consent will be collected prior to any study specific procedures. This may be accomplished by using an Informed Consent Form (ICF) specific to molecular screening followed by an ICF for the main study, or may be a combined form covering both molecular screening and the main study.

For any cohort in which adolescents are eligible to enroll, pediatric assent may be required in accordance with local laws and regulations. Informed consent must be provided by a legally-acceptable representative if the age of majority has not been reached. A minor who reaches the age of majority during study participation must be reconsented to confirm their agreement with continued participation.

6.3 Biopsies

A fresh or archival biopsy taken pre-dose must be sent to the central laboratory for TP53 and/or MDM2 and CDK4 amplification testing. See Section 3.2 and the Laboratory Manual for details. For patients in the PTCL expansion cohorts, an additional pre-treatment tumor sample is required to be available for central pathology read (if requested).

In the Phase 2a EXP PTCL cohorts, optional biopsies will be taken for PD purposes as well as for TP53 testing: during screening, during treatment, and at times of suspected progression. In the palbociclib combination cohort, if a biopsy is taken for any reason during the study, the samples may be used for further analysis. See the Laboratory Manual for details. Samples might be submitted for whole exome sequencing (with paired germline samples) and RNA sequencing (RNAseq), and results will be compared

between pre-treatment and on-treatment, and times of suspected progression. Tumor samples will be examined for markers of disease response and resistance. Protein expression via immunohistochemistry and RNA expression via quantitative RT-PCR may be examined on specimens obtained prior to beginning treatment, during treatment with ALRN-6924, and then upon suspected progression.

6.4 Germline DNA

To be collected via a buccal swab only for patients in Phase 2a EXP PTCL cohorts who consent to optional biopsies. See the Laboratory Manual for details.

6.5 Medical and Disease History

The medical history is to include demographic information, cancer history, including disease duration, previous treatment regimens, and toxicities, as well as information about the patient's non-malignancy-related history and all prior surgeries.

6.6 Vital signs

Includes blood pressure, pulse, respiration rate, and body temperature. Collection times are indicated in the schedule of events. Additional vital signs will be collected at the discretion of the investigator.

6.7 Electrocardiograms

Screening and predose ECGs (if required) are to be performed in triplicate (5-10 min between readings). ECGs are to be performed after the patient has been supine for at least 10 minutes. All ECGs should be performed with the patient in the same physical position. Postdose ECGs (if required) are to be performed in triplicate (5-10 min between readings) only if patient has a QTc that is a) >500 msec; b) increased by 60 msec over pre-dose; or c) decreased by 50 msec below pre-dose recording.

6.8 Physical Examination

Full physical examination to be performed at Screening, Day 1 pre-dose, and End of Treatment; all other physical examinations (if required) may be symptom-directed. Weight to be collected at Screening and on Day 1 (or up to 3 days prior to Day 1) of each cycle. Height is to be obtained only at the Screening visit.

6.9 Laboratory Assessments

Laboratory assessments to be performed locally may include:

- Clinical chemistry (glucose, calcium, albumin, total protein, sodium, potassium, CO_2, chloride, phosphate, BUN [blood urea nitrogen], serum creatinine, uric acid, alkaline phosphatase, ALT, AST, LDH, total and direct bilirubin).
- Hematology (complete blood count, platelets and differential).
- Urinalysis (dipstick measurement [pH, specific gravity, protein, glucose, ketones, nitrite, leukocyte esterase] with microscopic analysis, if results of the dipstick indicate additional testing required).
- Coagulation (PT, INR, aPTT).
- Serum or urine pregnancy test (Beta human chorionic gonadotropin [β-hCG]) for women of child-bearing potential.

- At select visits, lymphocyte subset testing will be performed (B-cells, T-cells including CD4 and CD8, natural killer [NK] cells).
- C-reactive protein, fibrinogen, and reticulocytes will also be collected at select visits.
- HPV testing of tumor tissue from cancers likely to be HPV-positive: to be performed dependent upon cancer type, including (but not limited to) cervical cancer, oropharyngeal cancer, head and neck squamous cell cancers or anal cancer.
- HIV, Hepatitis B and C testing

6.10 Disease Assessments/Imaging

RECIST 1.1- or iRECIST- (for solid tumor patients), RANO- (for glioblastoma patients), or IWG 2014- (for lymphoma patients) compliant imaging scans, photographs, physical examination, and/or laboratory-based assays (e.g., prostate specific antigen) for patients with relevant disease indications will be obtained at baseline (within 21 days of Cycle 1 Day 1) and for objective anti-tumor activity as outlined below. The same type of imaging, physical examination, or laboratory-based assay procedure should be used for each assessment for a patient. In EXP, all study images must be available to be sent for central imaging read, if requested.

After dosing commences, perform tumor assessment as follows:

- DR-A, DR-A-2, combination (ALRN-6924 plus palbociclib): Images will be obtained prior to the start of Cycle 3 and every other cycle thereafter, e.g., prior to Cycles 5, 7, and 9.
- DR-B, DR-C: Images will be obtained prior to the start of Cycle 4 and every third cycle thereafter, e.g., prior to Cycles 7, 10, and 11.
- In DEP, after 1 year of treatment, assessments will be obtained at approximately 3 month intervals. After 2 years of treatment, assessments will be obtained at approximately 4 month intervals or per standard of care. In EXP, the frequency of imaging will not change after 1 year of treatment.
- End of Treatment assessments are required only if the patient did not have a tumor assessment within the prior 6-8 weeks.

6.11 Concomitant Medications

Concomitant medications (current medications and those taken within 28 days of Cycle 1, Day 1) through the end of treatment visit or until start of subsequent anticancer therapy.

6.12 PK and PD Assessments

Refer to the Laboratory Binders for specimen collection, processing, storage, and shipment procedures.

Blood samples for PK and PD assessments will be collected at the timepoints shown in the tables below. Patients who are already enrolled in the expansion and consent to this testing will have blood drawn at their next available cycle (i.e. if the next available cycle is Cycle 4, they will follow the PK/PD Cycle 1 testing at Cycle 4 [with the exception of germline DNA and cfDNA testing which remains on the below schedule], and will follow the below indicated Cycle 2 testing at Cycle 5).

DR-A, DR-A-2 (ALRN-6924 single agent therapy)

Screening		**PK**	**PD**
During screening			cfDNA
Cycle 1		**PK**	**PD**
Day 1	within one hour before start of infusion (SOI)	X	MIC-1 CTC (select sites only) Germline DNA (EXP only)
	End of Infusion (EOI) (+5 min)	X	
	30 min after EOI (± 5 min)	X	
	1 hr after EOI (±5 min)	X	
	2 hr after EOI (±10 min)	X	
	4 hr after EOI (±10 min)	X	MIC-1 CTC (select sites only)
	8 hr after EOI (±2 hours)	X	MIC-1 CTC (select sites only)
Day 2	24 hours (±4 hr) after SOI day prior	X	MIC-1 CTC (select sites only)
Day 3 (DEP only)	48 hours (±4 hr) after SOI	X	MIC-1
Cycle 2		**PK**	**PD**
Day 15	EOI (+5 min)	X	
	1 hr after EOI (±5 min)	X	
	4 hr after EOI (±10 min)	X	
Day 16 (DEP only)	24 hours (±4 hr) after SOI day prior	X	
Cycle 5		**PK**	**PD**
Day 1	within one hour before SOI		cfDNA
End of Treatment		**PK**	**PD**
End of Treatment			cfDNA

DR-B (ALRN-6924 single agent therapy)

Screening		**PK**	**PD**
During screening			cfDNA
Cycle 1		**PK**	**PD**
Day 1	within one hour before SOI	X	MIC-1 CTC (select sites only) Germline DNA (EXP only)
	EOI (+5 min)	X	
	30 min after EOI (± 5 min)	X	
	1 hr after EOI (±5 min)	X	
	2 hr after EOI (±10 min)	X	
	4 hr after EOI (±10 min)	X	MIC-1 CTC (select sites only)
	8 hr after EOI (±2 hours)	X	MIC-1 CTC (select sites only)
Day 2	24 hours (±4 hr) after SOI day prior	X	MIC-1 CTC (select sites only)
Day 3 (DEP only)	48 hours (±4 hr) after SOI	X	MIC-1
Day 4	within one hour before SOI	X	MIC-1
Cycle 2		**PK**	**PD**
Day 11	EOI (+5 min)	X	
	1 hr after EOI (±5 min)	X	
	4 hr after EOI (±10 min)	X	
Day 12 (DEP only)	24 hours (±4 hr) after SOI day prior	X	
Cycle 5		**PK**	**PD**
Day 1	within one hour before SOI		cfDNA
End of Treatment		**PK**	**PD**
End of Treatment			cfDNA

DR-C (ALRN-6924 single agent therapy)

Screening		**PK**	**PD**
During screening			cfDNA
Cycle 1		**PK**	**PD**
Day 1	within one hour before SOI	X	MIC-1 Germline DNA CTC (select sites only)
	EOI (+5 min)	X	
	30 min after EOI (± 5 min)	X	
	1 hr after EOI (±5 min)	X	
	2 hr after EOI (±10 min)	X	
	4 hr after EOI (±10 min)	X	MIC-1 CTC (select sites only)
	8 hr after EOI (±2 hours)	X	MIC-1 CTC (select sites only)
Day 2 (optional)	24 hours (±4 hr) after SOI day prior		MIC-1 CTC (select sites only)
Day 3	within one hour before SOI	X	MIC-1
	EOI (+5 min)	X	
Day 5	within one hour before SOI	X	MIC-1
	EOI (+5 min)	X	
	1 hr after EOI (±5 min)	X	
	2 hr after EOI (±10 min)	X	
Day 8	Any time	X	MIC-1
Cycle 2		**PK**	**PD**
Day 5	within one hour before SOI	X	
	EOI (+5 min)	X	
	1 hr after EOI (±5 min)	X	
	2 hr after EOI (±10 min)	X	
Cycle 5		**PK**	**PD**
Day 1	within one hour before SOI		cfDNA
End of Treatment		**PK**	**PD**
End of Treatment			cfDNA

ALRN-6924 plus palbociclib

Timepoint		PK		PD
		ALRN-6924	Palbociclib	
During screening				cfDNA
Cycle 1				
Day 1	within one hour before start of ALRN-6924 infusion (SOI)	X		
	End of Infusion (EOI) (+5 min)	X		
	30 min after EOI (± 5 min)	X		
	1 hr after EOI (±5 min)	X		
	2 hr after EOI (±10 min)	X		
	4 hr after EOI (±10 min)	X		
Day 2	24 hrs (±2 hr) after EOI Day 1/ 18 hrs (±2 hr) after Day 1 palbociclib dose	X	X	
Day 8	within one hour before ALRN-6924 SOI	X	X	
	EOI (+5 min)	X	X	
Day 15	within one hour before ALRN-6924 SOI	X	X	
	EOI (+5 min)	X	X	
Day 22	Any time	X	X	
Cycle 5				
Day 1	within one hour before SOI			cfDNA
End of Treatment				
End of Treatment	Any time			cfDNA

6.13 End of Treatment and End of Study

Approximately 30 days (+/- 5 days) after the last dose of study drug, an end of treatment visit will be conducted. For patients in Phase 1, this visit will be the same as the end of study. Patients in Phase 2 will remain on study and be followed for survival and subsequent therapies.

7 STATISTICAL CONSIDERATIONS

Full details will be included in the Statistical Analysis Plan.

7.1 General Considerations

The primary objectives of this Phase 1/2a study are to determine the MTD or OBD and DLT(s) of ALRN-6924 administered by IV infusion on Days 1, 8 and 15 (DEP DR-A and DR-A-2) of a 28-day cycle or Days 1, 4, 8, 11 (DEP DR- B) of a 21-day cycle, in patients with advanced solid tumors or lymphoma and to further investigate the clinical safety profile and efficacy of ALRN-6924 (administered alone or in combination with other agents) in expansion cohorts (Phase 2a) which will include an additional dosing cohort of ALRN-6924 administered by IV infusion on Days 1, 3, and 5 (DR- C) of a 21-day cycle. Statistical analyses will be descriptive in nature and will account for all dose levels and regimens studied. Where applicable, analyses will include a description of adolescent versus adult data.

7.2 Patient Disposition and Characteristics

The baseline characteristics of patients enrolled will be summarized. All patients who received study treatment will be accounted for, including patients who died or withdrew from study treatment during the study.

7.3 Safety Analysis

The safety population will include all patients who have received at least one dose of ALRN-6924. Adverse events, vital sign measurements, clinical laboratory information and concomitant medication usage will be tabulated. All toxicities will be summarized by severity based on the NCI CTCAE version 4.03 and relationship to treatment. Serious adverse events will be listed separately. Graphical displays will be provided where useful in the interpretation of results. Statistical analyses will be descriptive in nature and will account for all dose levels and regimens studied.

7.4 Pharmacokinetic Analysis

Levels of ALRN-6924 and its metabolite (and other agents given in combination with ALRN-6924) will be measured in blood samples collected at specific timepoints. Pharmacokinetic data will be tabulated and summarized by individual patient and collectively by dose level for each dose regimen. Graphical displays will be provided where useful in the interpretation of results.

7.5 Pharmacodynamic Analysis

Levels of p53, MDM2, MDMX, p21 and caspase will be measured in tumor specimens collected before beginning treatment, during Cycle 1 or Cycle 2 and at suspected disease progression. MIC-1 and CTCs will be measured in blood samples. Pharmacodynamic effects on the composition of cell free DNA from blood will be evaluated. Pharmacodynamic data will be tabulated and summarized by individual patient and collectively by dose level. Graphical displays will be provided where useful in the interpretation of results.

7.6 Clinical Activity Analysis

To evaluate clinical activity, response rates and duration of response based on RECIST 1.1, IWG 2014, RANO, iRECIST, or other appropriate or exploratory criteria will be analyzed.

In DEP, the efficacy evaluable population will consist of patients who:

- Received at least one dose of ALRN-6924 at a dose level at least 0.8 mg/kg per infusion
- Have at least one post-baseline evaluation or had clinical progression and
- Are TP53 wild type or indeterminate (as assessed by the central lab, and if not assessed by central laboratory, as assessed by the local laboratory)

In the single agent EXP cohorts, the efficacy evaluable population will consist of patients who:

- Received at least one dose of ALRN-6924
- Have at least one post-baseline evaluation or had clinical progression and
- Are TP53 wild type (as assessed by the central lab)

In the EXP cohort of patients with MDM2 amplified or MDM2/CDK4 co-amplified solid tumors, the efficacy evaluable population will consist of patients who:

- Received at least one dose each of ALRN-6924 and palbociclib
- Have at least one post-baseline evaluation or had clinical progression and
- Are confirmed to have MDM2 amplification (with or without CDK4 co-amplification) with TP53 and Rb wild type (as assessed by the central lab)

A descriptive analysis of other evidence of anti-tumor activity or other clinical benefit will be provided based on clinical, radiographic or other appropriate assessment of efficacy or clinical anti-tumor activity.

Overall response rate, duration of response, and time to response will be assessed in DEP as well as in EXP.

Additional clinical activity analyses in the Phase 2a dose expansion will include OS and PFS and OS at 1 year. Time-to-event endpoints will be calculated from the time of first administration of ALRN-6924 (Day 1) until the stated event or end of study.

8 SAFETY

The Investigator and the Sponsor are responsible for monitoring the safety of patients who have entered the study. To capture the most potentially relevant safety information during a clinical trial, it is important that Investigators record accurate AE terms on the eCRF.

8.1 Adverse Event Definitions

8.1.1 Adverse Event

An AE includes any noxious, pathological, or unintended change in anatomical, physiological, or metabolic functions as indicated by physical signs, symptoms, and/or laboratory changes occurring in any phase of the clinical study whether or not temporally associated with the administration of study medication and whether or not considered related to the study medication. This definition includes an exacerbation of pre-existing medical conditions or events, intercurrent illnesses, hypersensitivity reactions, drug interactions, or clinically significant laboratory findings.

An AE does not include the following:

- Medical or surgical procedures, e.g., tooth extraction, transfusion, surgery (The medical condition that leads to the procedure is to be recorded as an AE.)
- Pre-existing conditions or procedures present or detected at the start of the study that do not worsen
- Hospitalization for elective surgeries or for other situations in which an untoward medical event has not occurred
- Abnormal laboratory value, unless it is clinically significant according to the Investigator, requires intervention, or results in a delay, discontinuation or change in the dose of study drug
- Overdose of study drug or concomitant medication unaccompanied by signs/symptoms; if sign/symptoms occur, the final diagnosis should be recorded as an AE.
- Pregnancy by itself, unless a complication occurs during pregnancy leading to hospitalization; in this case, the medical condition that leads to the hospitalization is to be recorded as the AE.
- A significant worsening of the disease under investigation including death which is captured as an efficacy parameter in this study and, thus, is not recorded as an AE.

8.1.2 Serious Adverse Event

A serious adverse event (SAE) is defined as an adverse event that results in any of the following outcomes:

- Death
- Life-threatening adverse experience (i.e., immediate risk of death from the event as it occurred; this does not include an adverse event that, had it occurred in a more serious form, might have caused death)
- Persistent or significant disability/incapacitation
- Inpatient hospitalization or prolongation of existing hospitalization

- Congenital anomaly/birth defect

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based on medical judgment, they may jeopardize the patient or may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Hospitalizations due to the underlying disease will not be reported as an SAE unless there is reason to suspect a causal relationship with the study drug.

8.1.3 Unexpected Adverse Event

An AE or suspected adverse reaction is considered "unexpected" if it is not listed in the ALRN-6924 Investigator's Brochure or is not listed at the specificity or severity that has been observed; or, is not consistent with the risk information described in the protocol or elsewhere. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the Investigator's Brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the Investigator's Brochure listed only cerebral vascular accidents.

"Unexpected," as used in this definition, also refers to AEs or suspected adverse reactions that are mentioned in the Investigator's Brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of ALRN-6924 but are not specifically mentioned as occurring with ALRN-6924.

8.2 Adverse Event Reporting Period

The AE reporting period begins from the date of the first study drug administration and ends 30 days after the last dose of study drug or a subsequent anticancer therapy is started, whichever occurs first. See Section 8.4 for information about reporting SAEs. Information regarding the follow up of AEs can be found in Section 8.5.

8.3 Recording of Adverse Events

Each AE should be recorded in standard medical terminology on the AE eCRF page. Whenever possible, the AE should be evaluated and reported as a diagnosis rather than as individual signs or symptoms. For example, cough, runny nose, sneezing, sore throat, and head congestion should be reported as 'upper respiratory infection'. If a definitive diagnosis is not possible, the individual signs and symptoms should be recorded. Dates of start (onset) and stop (recovery), action taken, and outcome will be recorded in the AE eCRF page.

An abnormal laboratory value will not be considered as an AE unless it is 1) assessed as clinically significant by the Investigator, 2) requires intervention, or 3) results in a delay, discontinuation or change in the dose of study treatment. A clinically significant abnormal laboratory value will not be considered an AE if it is determined to be related to the study condition or concomitant conditions, e.g., diabetes, of which the Investigator was previously aware and have not worsened. An abnormal laboratory value considered as an AE will be recorded on the AE page or module.

The Investigator will evaluate all AEs with regard to maximum intensity and relationship to study drug, as follows.

8.3.1 Maximum Intensity

Maximum intensity should be assigned using one of the severity grades as outlined in the NCI CTCAE v4.03; if the AE is not specifically listed in CTCAE v4.03, use the following grades:

- Grade 1: mild
- Grade 2: moderate
- Grade 3: severe/disabling
- Grade 4: life-threatening
- Grade 5: death

8.3.2 Relationship to Study Treatment

The degree of certainty with which an AE is attributed to study treatment (or alternative causes, e.g., natural history of the underlying diseases, concomitant therapy, etc.) will be determined by how well the event can be understood in terms of known pharmacology of ALRN-6924 (or agents administered in combination with ALRN-6924) and/or reaction of similar nature previously observed with ALRN-6924 or similar drugs. Each AE will be assigned one of the following five categories:

- *Unrelated:* There is not a temporal relationship to study drug administration (e.g., too early, too late, study drug not taken), or there is a reasonable causal relationship to another drug, concurrent illness, or circumstance.
- *Unlikely related:* There is a temporal relationship to study drug administration, but there is not a reasonable causal relationship between study drug and the AE (i.e., it is doubtful the AE is related to study drug); could be reasonably explained by other factors, including underlying disease, complications, concomitant drugs, or concurrent treatment.
- *Possibly related:* There is a reasonable temporal sequence from administration of the drug (e.g., occurred in a time frame relevant to administration of study drug, including the outcome after withdrawal of study medication, if applicable); or for which the possibility of the study drug being the causative factor (e.g., existence of similar reports attributed to the suspected drug and its analogues; reactions attributable to the pharmacological effect) could not be excluded, although other factors such as underlying disease, complications, concomitant drugs, or concurrent treatment are presumable.
- *Probably related:* There is a reasonable temporal sequence from administration of the drug (including the course after withdrawal of the drug); and for which the possibility of factors other than the drug, such as underlying disease, complications, concomitant drugs, or concurrent treatment, could not be excluded as the cause.
- *Definitely related:* Follows a clear temporal sequence from administration of the study drug; could not be possibly explained by the known characteristics of the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient; disappears or decreases on cessation or reduction in dose of the study drug; reappears or worsens when the study drug is re-administered; or follows a response pattern known to be associated with administration of the study drug.

8.4 Adverse Event Reporting

Each AE is to be reported by the Investigator as serious or non-serious according to the definitions above. This classification that determines the regulatory reporting procedures to be followed is described in Table 5.

Table 5: Reporting Guidelines for Adverse Events

Gravity of AE	Reporting Time to Sponsor	Type of Report
Serious	Within 24 hours after the site becomes aware of the event	Initial SAE Report
	Within 4 working days after the site becomes aware of the event	Completed SAE Report
Non-Serious	Per AE eCRF page	Completed AE eCRF page

Any SAE, regardless of relationship to study treatment that occurs during therapy or within 30 days after the last dose of study treatment must be reported to the Sponsor within 24 hours after the site becomes aware of the event. The Investigator is encouraged to discuss with the study Medical Monitor any adverse experiences for which the issue of reportability is unclear or questioned. The initial report should be followed by submission of a more detailed SAE Report within 4 working days of the site's knowledge of the event.

If the SAE occurs more than 30 days following administration of the last dose of study treatment, SAEs should be reported only if considered related to study treatment. In the event of patient death, the reason for death should be recorded as the SAE, with 'death' recorded as the outcome on the SAE eCRF module.

The SAE also will be recorded as an AE on the AE eCRF page. Note: the SAE Report is different from the AE eCRF page. In areas of both forms where the same data are reported, the forms will be completed in a consistent manner. For example, the same term should be used for the AE on both forms, with the same start and stop dates, action taken, outcome, etc.

An SAE Report should be prepared with as much available information concerning the event as possible so that a written report can be filed with the appropriate regulatory authorities. If causality cannot be determined definitively at the time of the SAE occurrence, it is important to notify the Sponsor within the timeline stated above, and to attribute the relationship as 'Not Assessable' (only applicable for the initial SAE Report). When new significant information is obtained and the outcome and attribution of the event is known, the Investigator will communicate this in a follow-up SAE Report. This relevant information will be provided in a timely manner to allow reporting to regulatory authorities within the required reporting period. Any SAE follow-up information requested by the Sponsor should be provided in a timely manner.

As necessary, the SAE Report should be accompanied by relevant pages from the eCRFs, e.g., medical history, AEs, concomitant medications. Additional information may be requested by Sponsor in an expedited manner to ensure that the initial reporting of the SAE made to the regulatory authorities complies with the required time frame. The Sponsor may be required to collect and report additional

information to the regulatory authorities in a follow-up report, containing a final evaluation of the event, including copies of hospital reports, autopsy reports, or other relevant information.

The Sponsor will provide information regarding SAEs and IND safety reports to Investigators for notification of IRBs in accordance with FDA regulations.

8.5 Adverse Event and Serious Adverse Event Follow-Up

All AEs and SAEs observed while a patient is receiving study treatment should be followed until resolution, return to baseline, or it is deemed that further recovery is unlikely. For patients who have discontinued study treatment, all AEs and SAEs that occur within 30 days after the last administration of study treatment or withdrawal from the study must be reported unless the patient starts new anticancer therapy. Any AE or SAE deemed related to study drug should be followed until resolution or stabilization, or until the patient starts new therapy. All measures required for AE management and the ultimate outcome of the AE will be recorded in the source document and eCRF.

For SAEs occurring from the patient's first administration of study treatment, during the study or within 30 days of the last administration of study drug, the Investigator should submit follow-up reports to the Sponsor regarding the status of the SAE and the patient's subsequent course. Follow-up reports should be submitted until the SAE has subsided, until the condition stabilizes (in the case of persistent impairment), the patient receives alternative therapy, or the patient dies.

8.6 Ongoing Safety Evaluation

During DEP, a study safety evaluation will be conducted on a regular (monthly) basis by teleconference, led by the Sponsor's Medical Monitor and participating Principal Investigators. All available dose exposure, dose-limiting toxicity, AE/SAE profiles and clinical laboratory abnormalities, and other safety measures will be reviewed during each convened meeting. Patient accrual will not be interrupted during the regularly scheduled safety evaluations.

The same process will be followed for the assessment of safety run-ins conducted during the EXP; however, these safety evaluations will be triggered by the accrual of a target number of safety evaluable patients, rather than occurring on a monthly basis.

8.7 Pregnancy

Any pregnancy diagnosed during the study, or that occurs within 30 days after stopping study medication, must be reported immediately to the Investigator. Pregnancy, in and of itself, is not regarded as an adverse event, unless there is suspicion that study medication may have interfered with the effectiveness of a contraceptive medication. If the patient becomes pregnant while on-study, the study drug should be immediately discontinued. Pregnancy information about a female patient or a female partner of a male patient should be reported immediately from the time the Investigator first becomes aware of a pregnancy or its outcome. This will be performed by the Investigator completing a Pregnancy Form.

Any pregnancy complication, spontaneous abortion, elective termination of a pregnancy for medical reasons, outcome of stillbirth, congenital anomaly/birth defect, or serious adverse event in the mother will be recorded as an SAE and will be reported as described in Section 8.4.

8.8 Medication Errors

A medication error for this study is defined as any accidental incorrect administration of a medicinal product. The error may be related to the administration of a wrong medication, nature of the medication, route of administration, dosage or frequency of the treatment as specified in this protocol (including omission of one or more administrations).

- Medication errors with concomitant medication treatment will not be recorded in the CRF unless they result in an AE.
- Medication errors with the study medication that result in an AE will be captured as an AE in the CRF.
- Medication errors with the study medication resulting in an overdose, incorrect route of administration, or administration with the incorrect study drug will be reported to Safety Desk as soon as they are known regardless of whether or not a subsequent AE has occurred.

8.9 Overdose

An overdose with ALRN-6924 for this clinical trial is defined as an accidental or intentional overdose with ALRN-6924 regardless of whether it is associated with an AE (even if not fulfilling a seriousness criterion), and is to be reported to Safety Desk within 24 hours from the time the Investigator first becomes aware of its occurrence following the same process as described for SAEs.

There is no known antidote available in case of ALRN-6924 overdose. Overdose should be managed aggressively with close monitoring and administration of prophylactic and symptomatic therapies to prevent or correct potential side effects.

For information regarding overdose of palbociclib, refer to the current approved US prescribing information.

8.10 Data and Safety Review Process

8.10.1 Review Process

This study is a Phase 1/2a dose escalation study designed to determine the safety and the MTD or OBD of ALRN-6924 in patients with advanced solid tumors or lymphoma. Therefore, each dose escalation will be based on observed toxicities and AEs. The safety of ALRN-6924 within each patient cohort will be reviewed prior to initiation of the next cohort. Escalation to the next dose level may proceed in the absence of DLT when all of the following have occurred:

- At the completion of Cycle 1 (DR-A or DR-A-2, treatment cycle = 28 days and DR-B, treatment cycle = 21 days),
- The Safety Review Meeting has been convened, during which the Safety Review Committee, consisting of the Investigators and Sponsor's Medical Monitor, has reviewed and considered all available safety data for all patients in the cohort and confirms that the next planned dose level is appropriate; and
- The Sponsor Medical Monitor issues written documentation of the decision to proceed to the next planned dose level.

In Phase 2a EXP, an additional dosing regimen will be explored in the PTCL cohorts. Six to 8 patients will be enrolled in DR-C in a run-in part and the treating investigators, along with the Medical Monitor, will review safety and tolerability through Cycle 1, prior to opening the full DR-C expansion cohort. Lower dose levels for DR-C may be assessed if the safety and tolerability of 3.1 mg/kg are not acceptable. Should this occur, 6-8 patients will again be enrolled in to a run-in part and the treating investigators and Medical Monitor will meet again to review all patients, prior to opening the full DR-C expansion cohort.

In the Phase 2a EXP cohort with MDM2 amplified or MDM2/CDK4 co-amplified solid tumors who will receive ALRN-6924 in combination with palbociclib, a safety run-in group of 6-8 patients will first be enrolled to determine the optimal dosing regimen for the combination. Safety and tolerability will be evaluated by the sponsor and the primary investigators before further patients are permitted to enroll.

Ongoing safety monitoring during the study will be provided through frequent teleconferences. The Investigators, clinical research staff, and Sponsor's Medical Monitor will review toxicities and AEs for all patients via regularly scheduled teleconference. Schedule and frequency of teleconferences may be adjusted to reflect enrollment rate and safety observations.

8.10.2 Oversight Responsibilities

The Sponsor will be responsible for routine monitoring of this study. The Sponsor also will be responsible for ensuring that ongoing communication is maintained between the Sponsor's Medical Monitor, Investigators and clinical research staff at each site, emphasizing the need for vigilance, particularly in the areas of safety and adherence to eligibility criteria. The Sponsor will ensure that all safety, AE and efficacy data are readily available and shared among the clinical sites. The Sponsor will also coordinate teleconferences to review safety information and document decisions regarding determination of MTD, DLT and dose escalation, as well as any decisions related to the exploration of DR-C in PTCL cohorts, and the combination of ALRN-6924 and palbociclib in the MDM2/CDK4 amplified solid tumor cohort.

The Sponsor's Medical Monitor will review the safety information as it becomes available on an ongoing basis for each patient. The Sponsor's Medical Monitor will review all SAEs occurring during the study and ensure that reports are provided to all clinical sites and the FDA, in compliance with FDA guidelines.

The Sponsor is obligated to report the progress and safety of the study annually to the FDA.

9 STUDY MANAGEMENT

9.1 Investigator Responsibilities

9.1.1 Data Management

The Investigator is responsible for ensuring completion and maintenance of adequate and accurate eCRFs and source documentation. Source documentation constitutes original records, which may include: progress notes, medication administration records, laboratory reports, discharge summaries, etc. All eCRFs should be completed in their entirety with source documents and other printed records stored in a confidential and locked location. The Investigator must sign the Investigator's statement in each patient's eCRF indicating that the data reported are accurate.

9.1.2 Protocol Adherence

Each Investigator must adhere to the protocol as detailed in this document and agrees that any changes to the protocol must be approved by the Sponsor prior to seeking approval from the IRB. Each Investigator will be responsible for enrolling only those patients who have met protocol eligibility criteria.

9.1.3 Study Drug Accountability

The Investigator is responsible for study drug provided to his/her site. All investigational study drug, ALRN-6924, required for completion of this study will be provided by the Sponsor. The recipient will acknowledge receipt of the drug indicating shipment content and condition. Damaged supplies will be replaced. Accurate records of all study drug dispensed from and returned to the study site are to be maintained. The study site must supply a copy of their drug destruction policy to the Sponsor before authorization for destruction can be granted.

9.2 Monitoring

The Sponsor is responsible for ensuring the proper conduct of the study with regard to ethics, protocol adherence, site procedures, integrity of the data, and applicable laws and/or regulations. At regular intervals during the study and following completion of the study, the Sponsor's study monitors will contact the study site via visits to the site, telephone calls, and letters in order to review study progress, eCRF completion, and address any concerns or questions regarding the study conduct. During monitoring visits, the following aspects of study conduct will be carefully reviewed: Patient recruitment, informed consent of patients, patient compliance with study procedures, source data verification, drug accountability, use of concomitant therapy by patients, AE and SAE documentation and reporting, and quality of data. Records pertaining to these aspects are expected to be kept current.

9.3 Audits and Inspections

The Sponsor and its designees, a regulatory authority, or an IRB (or any designees of these organizations) may visit the study site at any time during the study or after completion of the study to perform audits or inspections. The purpose of a sponsor audit or regulatory inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted according to the protocol, GCP, ICH guidelines, and any other applicable regulatory requirements. Investigators should contact the Sponsor immediately if contacted by a regulatory agency about an inspection at their site.

9.4 Protocol Amendments

Any amendments to the protocol will be prepared by the Sponsor. With the exception of amendments to address immediate safety concerns, all amendments must be submitted to the IRB for approval prior to implementation. In some instances, an amendment requires changes to the informed consent form, which also must be submitted for IRB approval prior to administration to patients. If any changes to the eCRF are required, the Sponsor will issue supplemental or revised eCRF pages in the electronic data capture system.

9.5 Record Keeping

9.5.1 Health Insurance Portability Accountability Act of 1996

The Investigator agrees to comply with all applicable federal, state, and local laws and regulations relating to the privacy of patient health information, including, but not limited to, the Standards for Individually Identifiable Health Information, 45 Code of Federal Regulations (CFR) Parts 160 and 164 (the Health Insurance Portability Accountability Act of 1996 [HIPAA] Privacy Regulation). The Investigator shall ensure that study patients authorize the use and disclosure of protected health information in accordance with HIPAA Privacy Regulation and in a form satisfactory to the Sponsor.

9.5.2 Financial and Regulatory Disclosures

The Investigator shall provide to the Sponsor sufficient accurate financial information to support submission of complete and accurate financial certification or disclosure statements to the FDA. The Investigator shall also provide a current, signed curriculum vitae and a completed Form 1572. The Investigator shall promptly update this information if any relevant changes occur in the course of the study or for one year following completion of the study.

9.5.3 Access to Original Records

It is an expectation of regulatory authorities that monitors, auditors, and representatives of national and international government regulatory agency bodies have access to original source documentation to ensure data integrity. “Original” in this context is defined as the first documentation of an observation and does not differentiate between hard copy and electronic records.

9.5.4 Retention of Study Documents

Study-related records must be retained for 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 in an ICH region, or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by applicable regulatory requirements or by an agreement with the sponsor.

The Investigator must not destroy any study-related records without receiving approval from the Sponsor. The Investigator must notify the Sponsor in the event of accidental loss or destruction of any study records. If the Investigator leaves the institution where the study was conducted, the Sponsor must be contacted to arrange alternative record storage options.

10 ETHICAL CONSIDERATIONS

This study will be conducted in accordance with current US FDA regulations, ICH GCP guidelines, the principles of the Declaration of Helsinki, and local ethical and legal requirements.

10.1 Informed Consents and Pediatric Assents

There are 2 Informed Consent Forms (ICFs) that may be provided to each site: one molecular screening ICF and one clinical study ICF. Some sites may combine these into one ICF.

For each type of ICF, sample ICFs will be provided to each site. No major deviations may be made from the sample ICFs. The Sponsor or designee will review the draft ICFs before they are finalized, and the final IRB-approved documents must be provided to the Sponsor for regulatory purposes. If the ICFs omit the template provisions authorizing the Sponsor and its representatives and designees to have access to study participant-identifiable health information in accordance with 45 CFR Part 164, a separate written authorization complying with 45 CFR Part 164 must be prepared for review and approval by the Sponsor before use.

The ICFs must be signed by the patient or the patient's legal guardian before his or her participation in the study, including prior to any study-specific activities or procedures. A copy of each ICF must be provided to the patient or the patient's legal guardian. If necessary, the ICFs will be provided in a certified translation of the local language.

Pediatric assent may also be required, according to local laws and regulations, in order for an adolescen to enroll in a cohort for which adolescents are eligible.

Signed consent forms and, where applicable, assent forms, must remain in each patient's study file and must be available for verification by study monitors or authorized regulatory representatives at any time.

10.2 Institutional Review Board

This protocol, the ICFs, relevant supporting information and all types of patient recruitment or advertisement information must be submitted to the IRB for review and must be approved before the study is initiated. Any amendments to the protocol must also be approved by the IRB prior to implementing changes in the study.

The Investigator is responsible for keeping the IRB apprised of the progress of the study and of any changes made to the protocol, minimally on an annual basis. The Investigator must also keep the IRB informed of any significant AEs.

10.3 Confidentiality

The information obtained during the conduct of this clinical study is confidential, and disclosure to third parties other than those noted below is prohibited. Information obtained during the conduct of this study will be collected, processed, and transmitted to or for the benefit of the Sponsor in accordance with applicable law, as discussed below. Information contained therein will be maintained in accordance with applicable law protecting patient privacy and may be inspected by the clinical researcher, the researcher's staff, the Sponsor and its representatives, to check, process, evaluate, and use the information collected during the study. Processing, evaluation or use of the information will be performed by a health professional for medical purposes and/or by those operating under a duty of confidentiality that is equivalent to that of a health professional.

Information will be transmitted and processed as the Sponsor may direct, including to the Sponsor and its representatives in the United States or elsewhere. Information obtained from the study will be used by the Sponsor in connection with the development of the study drug, including possible filing of applications with governmental authorities for marketing approval and for other pharmaceutical and medical research purposes. The Study Investigator is obliged to provide the Sponsor with complete test results and all data developed in this study and, in this regard, will obtain all necessary patient or other authorizations. This information may be disclosed to other physicians who are conducting similar studies and to the FDA/applicable regulatory agencies as deemed necessary by the Sponsor. Patient-specific information may be provided to other appropriate medical personnel only with the patient's permission or as required or permitted by applicable law.

All Investigators and research study personnel who process information from the study must agree to take appropriate measures to prevent unauthorized or unlawful processing or disclosure of data. To ensure compliance with current Federal Regulations and the ICH GCP guidelines, data generated by this study must be available for inspection upon request by representatives of the FDA, national and local health authorities, the Sponsor and the IRB for each study site.

The Sponsor intends to pursue publication of the results of the study in cooperation with the Investigators, subject to the terms and conditions of the clinical trial agreement between the Sponsor and Investigators. Sponsor approval is required for publication of any data subsets. Final authorship will be determined at least in part based on the number of qualified patients enrolled by each center. Patient names and other personal data relating to an identified or identifiable patient (such as photographs, audio, videotapes or other factors specific to physical, physiological, mental, economic, cultural or social identity) may not be disclosed in any publication without prior written authorization from the Sponsor and the patient.

11 ADMINISTRATIVE STRUCTURE OF THE STUDY

The Sponsor or its designated representative will be responsible for data management, data summary and/or analysis, and preparation of a clinical study report.

Clinical laboratory parameters (hematology, serum chemistry, coagulation, urinalysis, pregnancy test, tumor markers) will be assessed by local laboratories and results recorded by the site staff on the appropriate eCRF pages.

Laboratory-based pharmacodynamic and pharmacokinetics assessments will be conducted at a central laboratory designated by the Sponsor, unless such assessments are specifically allowed to be performed by local laboratories with appropriate capabilities.

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APPENDIX A: Assessment of Performance Status - ECOG

ECOG Performance Status*	Criteria	Karnofsky Score
0	Fully active; able to carry on all pre-disease performance without restriction	90-100%
1	Restricted in physically strenuous activity but ambulatory	70-80%
2	Ambulatory and capable of self-care, but unable to carry out any work activities	50-60%
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours	30-40%
4	Completely disabled	10-20%

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APPENDIX B: Marketed Drug Products with a Predominant Hepatobiliary Transporter Clearance Mechanism; Marketed Drug Products that May Cause CYP3A-mediated Drug-drug Interactions with Palbociclib

Marketed Drug Products with a Predominant Hepatobiliary Transporter Clearance Mechanism

Because of *in vitro* findings of transporter enzyme inhibition (e.g., OATP1B1, OATP1B3, BSEP) at concentrations that may be clinically relevant (e.g., at C_{max} of high-dose levels of ALRN-6924), the possibility of drug-drug interactions of ALRN-6924 with medications that are predominantly cleared by hepatobiliary transporters should be considered. In particular, methotrexate and statins (e.g., atorvastatin, rosuvastatin) should not be dosed on the day of the ALRN-6924 infusion and within 48 hours after an ALRN-6924 infusion. Additional medications that may be affected by co-administration with ALRN-6924 are listed below, however, this list may not be all inclusive and the investigator should consult with a pharmacist, or other professional resource, to identify other medications that may be cleared in this manner. The Sponsor's Medical Monitor should be contacted if there are questions regarding the concomitant use of drugs with a predominantly hepatobiliary transporter clearance mechanism. Table is not meant to be fully comprehensive and inclusive of all medications.

Asunaprevir	Methotrexate
Atorvastatin	Olmesartan
Bosentan	Pravastatin
Caspofungin	Repaglinide
Cerivastatin	Rifampin
Danoprevir	Rosuvastatin
Eluxadoline	Simvastatin
Eprosartan	Simiprevir
Fexafenadine	Tacrolimus
Fimasartan	Telmisartan
Fluvastatin	Thyroxine
Grazoprevir	Valsartan
Irbesartan	Velpatasvir
Lovastatin	Voxilsprevir
Losartan	

Marketed Drug Products that May Cause CYP3A-mediated Drug-drug Interactions with Palbociclib

Note: The following is not an exhaustive list. Please check for the potential liability of the drug to be co-administered drug for CYP3A-mediated drug-drug interaction before use.

Strong CYP3A Inhibitors[1]
Clarithromycin
Indinavir
Itraconazole
Ketoconazole
lopinavir/ritonavir
Nefazodone
Nelfinavir
Posaconazole
Ritonavir
Saquinavir
Telaprevir
Telithromycin
Voriconazole
Also avoid – Grape fruit and Grapefruit Juice
Strong CYP3A Inducers[2]
Phenytoin
Rifampin
Carbamazepine
Enzalutamide
St John's Wort
Sensitive CYP3A Substrates[3]
Alfentanil
Cyclosporine
Dihydroergotamine
Ergotamine
Everolimus
Fentanyl
Pimozide
Quinidine
Sirolimus
Tacrolimus

[1] Avoid concomitant use of strong CYP3A inhibitors. If co-administration of palbociclib with a strong CYP3A inhibitor cannot be avoided, reduce the dose of palbociclib.

[2] Avoid concomitant use of strong CYP3A inducers.

[3] The dose of the sensitive CYP3A substrate with a narrow therapeutic index may need to be reduced as palbociclib may increase their exposure.

APPENDIX C: Dose Regimen A and A-2 - Study Activities Through Cycle 1 - ALRN single agent therapy

	Molecular Screen	Clinical Screen -21 days	Within 7 days prior to Day 1	Day 1		Day 2	Day 3 DEP only	Day 8 EXP: ± 1 d		Day 15 EXP: ± 1 d		Day 16	Day 22[15] ±1 d
				Pre-Dose	Post-Dose			Pre-Dose	Post-Dose	Pre-Dose	Post-Dose		
Written informed consent	See 6.2	See 6.2											
Medical and disease history		X											
Demographics		X											
Tumor biopsy or archive tissue sample	See 3.2[1]												
Eligibility		X	X										
Blood test for HIV, hepatitis B and C		X											
HPV test[3]		X											
Serum or urine pregnancy test			Within 2 days prior to Day 1										
Vital signs[4]		X	X	X	X	X	X	X	X	X	X	X	X
Physical exam[5]		X		X				X		X			
12-lead ECG[6]		X		X	X								
Laboratory assessments – chemistry		X	X[2]	X		X	X	X		X		X	
Laboratory assessments – hematology		X	X[2]	X		X	X	X		X		X	X
Laboratory assessments - coagulation		X	X[2]	X		X	X	X		X		X	
Laboratory assessments - urinalysis		X	X[2]	X		X	X	X		X		X	
Laboratory assessments – lymphocyte subset testing			X			X		X					
Laboratory assessments – CRP, fibrinogen			X	X		X	X	X		X		X	
Laboratory assessments – reticulocytes				X									
Blood Collection – immunogenicity				X[7]									
Blood Collection - PD assessments-MIC-1				X[7]	X[7]	X[8]	X[9]						
Blood Collection - PD assessments-CTC DEP and select sites in EXP				X[7]	X[7]	X[8]							
Blood Collection - PK assessments				X[7]	X[7]	X[8]	X[9]						
Blood Collection –cell-free DNA	X												

	Molecular Screen	Clinical Screen -21 days	Within 7 days prior to Day 1	Day 1		Day 2	Day 3 DEP only	Day 8 EXP: ± 1 d		Day 15 EXP: ± 1 d		Day 16	Day 22[15] ±1 d
Germline DNA sample[10]				X									
ECOG Performance Status		X	X					X		X			
Biopsy for biomarker assessments /p53 status												X[1]	
Tumor Assessment/Imaging[11]		X											
ALRN-6924 dosing[12]				X				X		X			
Concomitant medications[13]		X	X	X	X	X	X	X	X	X	X	X	X
AE assessment[14]					X	X	X	X	X	X	X	X	X

DEP: For Days 1 through 16, no pre-specified visit windows exist to ensure timely safety follow-up and PK/PD sampling. However, at the Investigator's discretion, it may be necessary to conduct a study visit on an alternative day than described in this schedule in order to protect the safety, rights, or welfare of the patient. If this is the situation, the Investigator will confer with and obtain approval from the Medical Monitor.

[1] A pre-treatment biopsy or archival sample is required for p53 testing. For patients with a study biopsy performed immediately prior to enrollment, optional needle biopsy to be performed within 24 hours of Cycle 1 Day 15 infusion OR Cycle 2 Day 15 infusion. Decision to be made at the discretion of the Investigator. In EXP, optional biopsies include pre-treatment, during treatment, and one or more at times of suspected and/or confirmed progression.

[2] Can be omitted if screening laboratory assessments are performed within 7 days of the first dose of ALRN-6924. Screening/within 7 day assessments are to be used for eligibility assessment.

[3] HPV status must be determined for tumors that are associated with HPV infection, including (but not limited to) cervical cancers, oropharyngeal cancer, head and neck squamous cell cancers or anal cancer, unless HPV status of the tumor is already known and documented.

[4] Blood pressure, pulse, respiration rate, body temperature.

Cycle 1, Days 1, 8, 15: On the days of drug administration vital signs will be recorded pre-dose (within 30 minutes prior to SOI) and at the following timepoints:

During infusion:

DR-A (one hour infusion): 15 min (± 3 min) and 30 min (± 3 min)

DR-A-2 (two hour infusion): 30 min (± 3 min) and 60 min (± 3 min)

Post-infusion: At EOI (±5 min), 1 hr (±5 min) and 2 hr (±10 min), 4 hrs (±10 min) following EOI. On Cycle 1 Day 1 additional timepoints include 6 hrs (±10 min) and 8 hrs (±10 min) following EOI. Additional vital signs will be collected at the discretion of the investigator.

[5] Full physical examination to be performed at Screening, Day 1 Predose, and End of Treatment; all other physical examinations may be symptom directed. Height and weight to be collected on Day 1.

[6] ECGs to be performed after the patient has been supine for at least 10 minutes. Readings should be performed with the patient in the same physical position. Screening and pre-dose ECG recording should be taken in triplicate with 5-10 minutes between readings. Thereafter, subsequent readings on that same day will be performed in triplicate only if patient has a QTc that is a) >500 msec; b) increased by 60 msec over pre-dose; or c) decreased by 50 msec below pre-dose value. Timepoints on Cycle 1, Day 1: Pre-dose (within 30 minutes prior to infusion), end of infusion (EOI +5 min) and at 1 (± 5 min) and 2 hr (±10 min) after EOI.

[7] PD (MIC-1 and CTC): Within 1 hour before the start of infusion (SOI), and 4 (±10 min) and 8 hours (±2 hours) after EOI.

PK: Within 1 hour before SOI; at EOI (+5 min) and at 30 min (±5 min), 1 hour (±5 min), 2 (±10 min), 4 (±10 min) and 8 hours (±2 hours) after EOI.

Immunogenicity: Within 1 hour before the SOI on Day 1.

Patients who are already enrolled in the expansion and consent to this PD/PK testing will have blood drawn at their next available cycle (i.e. if the next available cycle is Cycle 4, they will follow the PK/PD Cycle 1 testing at Cycle 4, and will follow the indicated Cycle 2 testing at Cycle 5).

[8] PD (CTC and MIC-1) and PK: blood should be collected 24 hours (±4 h) after the initiation of Day 1 infusion.
[9] DEP only: PD (MIC-1 only) and PK: blood should be collected 48 hours (±4 h) after the initiation of Day 1 infusion.
[10]In patients consenting to optional biopsies, buccal swab for germline DNA (EXP only)
[11] RECIST 1.1- (for solid tumor patients) or IWG 2014- (for lymphoma patients) compliant imaging for disease assessment and tumor measurements as well as laboratory-based assays (e.g., prostate specific antigen) for patients with relevant disease indications.
[12] During the first two cycles, ALRN-6924 should be administered in the morning to allow observation of delayed infusion reactions. In dosing regimen DR-A, ALRN-6924 will be infused over 1 hour (±15 min). In dosing regimen DR-A-2, ALRN-6924 will be infused over 2 hours (±15 min), with dexamethasone (4 mg orally or IV) administered 4 hours after the end of infusion to mitigate potential infusion reactions. At the end of the infusion for both DR-A and DR-A-2, IV fluids (saline) or oral fluids (500mL – 1000 mL) should be administered unless clinically contraindicated.
[13] All concomitant medications taken within 28 days of beginning the study (Cycle 1 Day 1) until 30 days after last infusion or start of subsequent therapy must be reported in the relevant eCRF pages, including supportive care drugs and drugs used for treatment of AEs or chronic diseases.
[14] AE reporting begins at the point of the first ALRN-6924 infusion until 30 days after last infusion or start of subsequent therapy; until all drug-related toxicities and ongoing SAEs have resolved, whichever is later; or until the Investigator assesses AEs as “chronic” or “stable.”
[15]This visit will be performed for all patients in DEP and performed in EXP only if the patient has experienced any grade 3 neutropenia, anemia or thrombocytopenia while on study, regardless of the relationship to ALRN-6924

APPENDIX D: Dose Regimen A and A-2 - Study Activities Cycle 2 and Beyond - ALRN single agent therapy

	Day 1[1] ±3 d		**Day 8** ±1 d		**Day 15** ±1 d		**Day 16**[8] ±2 d	**At the end of cycles 2, 4, 6, etc.**	**End-of-Treatment** 30 ± 5 d after last dose or at study withdrawal	**Long-Term Follow Up (EXP only)**[16]
	Pre-dose	Post-dose	Pre-dose	Post-dose	Pre-dose	Post-dose				
Serum or urine pregnancy									X	
Vital signs[2]	X	X	X	X	X	X	X		X	
Physical exam[3]	X		X		X				X	
12-lead ECG[4]	X	X							X	
Laboratory assessments – chemistry[5]	X				X		X		X	
Laboratory assessments – hematology[5]	X		X		X		X		X	
Laboratory assessments – coagulation[5]	X				X		X		X	
Laboratory assessments – urinalysis[5]	X				X		X		X	
Laboratory assessments – CRP, fibrinogen	Cycle 2 only				Cycle 2 only		Cycle 2 only			
Collection of blood for immunogenicity[6]	Cycle 2, 3, 5 only								X	
Blood Collection - PK assessments					Cycle 2 only[7]	Cycle 2 only[7]	Cycle 2: DEP only[7]			
Blood Collection - cell-free DNA[6]	Cycle 5 only								X	
ECOG Performance status[9]	X		X		X				X	
Biopsy for biomarker assessments /p53 status[10]							X		X	
Tumor Assessment/Imaging[11]								X	X[12]	
ALRN-6924 dosing[13]	X		X		X					
Concomitant medications[14]	X	X	X	X	X	X	X		X	
AE assessment[15]	X	X	X	X	X	X	X		X	
Phone calls or other contact										X

[1] "Day 29" = Day 1 of next cycle for patients continuing treatment. Day 1 pre-dose evaluations for Cycle 2 and subsequent cycles are to be done within 3 days prior to next cycle drug administration.

[2] Blood pressure, pulse, respiration rate, body temperature. For patients on > 1 year, this procedure is no longer a mandatory study procedure:

On the days of drug administration (Days 1, 8, 15 of each cycle) vital signs will be recorded pre-dose (within 30 minutes prior to SOI) and at the following timepoints:

During infusion:

DR-A (one hour infusion): 15 min (± 3 min) and 30 min (± 3 min)

DR-A-2 (two hour infusion): 30 min (± 3 min) and 60 min (± 3 min).

Post-infusion: At EOI (±5 min) and as clinically indicated following EOI. In cycle 2 only, vital signs will be collected at 1 hr (±5 min), 2 hrs (±10 min) and 4 hrs (±10 min) following EOI. Additional vital signs will be collected at the discretion of the investigator.

[3] Full physical examination to be performed at End of Treatment visit; all other physical examinations may be symptom directed. For patients on > 1 year, this procedure is no longer a mandatory study procedure. Weight to be collected at Day 1 (+/- 3 days) of each cycle.

[4] ECGs to be performed after the patient has been supine for at least 10 minutes. Readings should be performed with the patient in the same physical position. Pre-dose ECG recording should be taken in triplicate with 5-10 minutes between readings. Thereafter, subsequent readings on that same day will be performed in triplicate only if patient has a QTc that is a) >500 msec; b) increased by 60 msec over pre-dose; or c) decreased by 50 msec below pre-dose value. Timepoints on Day 1 of new cycle: At pre-dose (within 30 minutes prior to infusion) and EOI (+5 min). For patients on > 1 year, this procedure is no longer a mandatory study procedure.

[5] For patients on > 1 year, the required labs are: full labs to be collected on Day 1, and hematology only at Day 15

[6] Within 1 hour before SOI

[7] PK (Cycle 2 only): Day 15-collect at EOI (+5 min) and at 1 hour (±5 min) and 4 hours (±10 min) after the end of infusion. Patients who are already enrolled in the expansion and consent to this PD/PK testing will have blood drawn at their next available cycle (i.e. if the next available cycle is Cycle 4, they will follow the PK/PD Cycle 1 testing at Cycle 4, and will follow the indicated Cycle 2 testing at Cycle 5).

PK (Cycle 2 only): DEP only - Day 16 - Blood should be collected 24 hours (±4 h) after the initiation of Day 15 infusion.

[8] Day 16 visit should only be completed for Cycle 2; this visit to be completed in DEP and only in EXP if the optional biopsy is performed

[9] For patients on > 1 year, this is no longer a mandatory study procedure

[10] Cycle 2 biopsy not performed if collected in specified timepoint in Cycle 1. For patients with a study biopsy performed immediately prior to enrollment, optional needle biopsy to be performed within 24 hours of Cycle 1 Day 15 infusion OR Cycle 2 Day 15 infusion; decision to be made at the discretion of the Investigator. In EXP, optional biopsies include pre-treatment, during treatment, and one or more at times of suspected and/or confirmed progression.

[11] To be performed at end of even-numbered cycles (Cycle 2, Cycle 4, Cycle 6, etc.) prior to start of the next treatment cycle. RECIST 1.1 (APPENDIX K) measurements for patients with solid tumors; IWG 2014 (APPENDIX L) measurements for patients with lymphoma. In DEP, after 1 year, assessments will be obtained at approximately 3 month intervals. After 2 years, assessments will be obtained at approximately 4 month intervals or per standard of care. In EXP, the frequency of imaging will not change after 1 year of treatment.

[12] Same method used as baseline. Perform only if no tumor assessment was performed within 6-8 weeks prior.

[13] During the first two cycles, ALRN-6924 should be administered in the morning to allow observation of delayed infusion reactions. In dosing regimen DR-A, ALRN-6924 will be infused over 1 hour (±15 min). In dosing regimen DR-A-2, ALRN-6924 will be infused over 2 hours (±15 min), with dexamethasone (4 mg orally or IV) administered 4 hours after the end of infusion to mitigate potential infusion reactions. At the end of the infusion for both DR-A and DR-A-2, IV fluids (saline) or oral fluids (500mL – 1000 mL) should be administered unless clinically contraindicated.

[14] All concomitant medications taken within 28 days of beginning the study (Cycle 1 Day 1) until 30 days after last infusion or start of subsequent therapy must be reported in the relevant eCRF pages, including supportive care drugs and drugs used for treatment of AEs or chronic diseases.

[15] AE reporting begins at the point of the first ALRN-6924 infusion and continues until 30 days after last infusion or start of subsequent therapy; until all drug-related toxicities and ongoing SAEs have resolved, whichever is later; or until the Investigator assesses AEs as “chronic” or “stable.”

[16] EXP only: Phone calls or other contact should be made approximately every 2 months following end of treatment visit to assess survival status and collect information on subsequent therapies

APPENDIX E: Dose Regimen B - Study Activities Through Cycle 1

	Molecular Screen	Clinical Screen -21 days	Within 7 days prior to Day 1	Day 1		Day 2	Day 3[9]	Days 4 and 8 EXP: ± 1 d		Day 11 EXP: ± 1 d		Day 12 DEP only	Day 15 ± 1 d EXP only	Day 18 ± 1 d DEP only
				Pre-Dose	Post-Dose			Pre-Dose	Post-Dose	Pre-Dose	Post-Dose			
Written informed consent	See 6.2	See 6.2												
Medical and disease history		X												
Demographics		X												
Tumor biopsy or archive tissue sample	See 3.2[1]													
Eligibility		X	X											
Blood test for HIV, hepatitis B and C		X												
HPV test[3]		**X**												
Serum or urine pregnancy test			Within 2 days prior to Day 1											
Vital signs[4]		X	X	X	X	X	X	X	X	X	X	X	X	X
Physical exam[5]		X		X				X		X				
12-lead ECG[6]		X		X	X									
Laboratory assessments – chemistry		X	X[2]	X		X	X	X		X		X	X	
Laboratory assessments – hematology		X	X[2]	X		X	X	X		X		X	X	X
Laboratory assessments - coagulation		X	X[2]	X		X	X	X		X		X	X	
Laboratory assessments - urinalysis		X	X[2]	X		X	X	X		X		X	X	
Laboratory assessments – lymphocyte subset testing			X			X		X						
Laboratory assessments – CRP, fibrinogen			X	X		X	X	X		X		X	X	
Laboratory assessments – reticulocytes				X										
Blood Collection - immunogenicity				X[7]										
Blood Collection - PD assessments-MIC-1				X[7]	X[7]	X[8]	X[9]	X[9]						
Blood Collection - PD assessments-CTC DEP and select sites in EXP				X[7]	X[7]	X[8]								
Blood Collection - PK assessments				X[7]	X[7]	X[8]	X[9]	X[9]						

	Molecular Screen	Clinical Screen -21 days	Within 7 days prior to Day 1	Day 1		Day 2	Day 3[9]	Days 4 and 8 EXP: ± 1 d		Day 11 EXP: ± 1 d		Day 12 DEP only	Day 15 ± 1 d EXP only	Day 18 ± 1 d DEP only
Blood Collection – cell-free DNA	X													
Germline DNA sample[10]				X										
ECOG Performance Status		X	X					X		X				
Biopsy for biomarker assessments/p53 status							EXP: Day 3 or 10[1]					DEP: X[1]		
Tumor Assessment/Imaging[11]		X												
ALRN-6924 dosing[12]				X				X		X				
Concomitant medications[13]		X	X	X	X	X	X	X	X	X	X	X	X	X
AE assessment[14]					X	X	X	X	X	X	X	X	X	X

DEP: For Days 1 through 12, no pre-specified visit windows exist to ensure timely safety follow-up and PK/PD sampling. However, at the Investigator's discretion, it may be necessary to conduct a study visit on an alternative day than described in this schedule in order to protect the safety, rights, or welfare of the patient. If this is the situation, the Investigator will confer with and obtain approval from the Medical Monitor.

[1] A pre-treatment biopsy or archival sample is required for p53 testing. For patients with a study biopsy performed immediately prior to enrollment, optional needle biopsy to be performed within 24 (DEP) or 48 (EXP) hours of Cycle 1 Day 11 infusion OR Cycle 2 Day 11 infusion. In EXP, optional biopsies include pre-treatment, during treatment, and one or more at times of suspected and/or confirmed progression.

[2] Can be omitted if screening laboratory assessments are performed within 7 days of the first dose of ALRN-6924. Screening/within 7 day assessments are to be used for eligibility assessment.

[3] HPV status must be determined for tumors that are associated with HPV infection, including (but not limited to) cervical cancers, oropharyngeal cancer, head and neck squamous cell cancers or anal cancer, unless HPV status of the tumor is already known and documented.

[4] Blood pressure, pulse, respiration rate, body temperature.

Cycle 1, Days 1, 4, 8, 11: On the days of drug administration vital signs will be recorded pre-dose (within 30 minutes prior to SOI) and at the following timepoints:

During infusion: 15 min (± 3 min) and 30 min (± 3 min)

Post-infusion: At EOI (±5 min), 1 (±5 min), 2 hrs (±10 min) and 4 hrs (±10 min) following EOI. On Cycle 1 Day 1 additional timepoints include 6 hrs (±10 min) and 8 hrs (±10 min) following EOI. Additional vital signs will be collected at the discretion of the investigator.

[5] Full physical examination to be performed at Screening, Day 1 Predose and End of Treatment; all other physical examinations may be symptom directed. Weight to be collected at Day 1.

[6] ECGs to be performed after the patient has been supine for at least 10 minutes. Readings should be performed with the patient in the same physical position. Screening and pre-dose ECG recording should be taken in triplicate with 5-10 minutes between readings. Thereafter, subsequent readings on that same day will be performed in triplicate only if patient has a QTc that is a) >500 msec; b) increased by 60 msec over pre-dose; or c) decreased by 50 msec below pre-dose value. Timepoints on Cycle 1, Day 1: Pre-dose (within 30 minutes prior to infusion), end of infusion (EOI +5 min) and at 1 (±5 min) and 2 hours (±10 min) after EOI.

[7] PD (MIC-1 and CTC): within 1 hour before the start of infusion (SOI) and 4 (± 10 min) and 8 hr (± 2 hours) after EOI.

PK: Within 1 hour before SOI; at EOI (+5 min) and at 30 min (± 5 min), 1 hour (±5 min), 2 (± 10 min), 4 (± 10 min) and 8 hours (±2 hours) after EOI.

Immunogenicity: Within 1 hour before the SOI on Day 1.

[8] PD (CTC and MIC-1) and PK: Day 2: Collect blood samples 24 hours (±4 h) after the initiation of Day 1 infusion.

[9] PD (MIC-1 only) and PK: Day 3 (Day 3 for DEP only): Collect blood samples 48 hours (±4 h) after the initiation of Day 1 infusion. Day 4: Collect blood samples within 1 hour prior to SOI. Visit to be completed in EXP only if biopsy performed. In EXP, PK and PD not collected at this visit.

[10] In patients consenting to optional biopsies, buccal swab for germline DNA (EXP only)

[11] RECIST 1.1 - (for solid tumor patients) or IWG 2014- (for lymphoma patients) compliant imaging for disease assessment and tumor measurements as well as laboratory-based assays (e.g., prostate specific antigen) for patients with relevant disease indications.

[12] During the first two cycles, ALRN-6924 should be administered in the morning to allow observation of delayed infusion reactions. ALRN-6924 will be infused over 1 hour (±15 min). At the end of the infusion, IV fluids (saline) or oral fluids (500mL – 1000 mL) should be administered unless clinically contraindicated.

[13] All concomitant medications taken within 28 days of beginning the study (Cycle 1 Day 1) until 30 days after last infusion or start of subsequent therapy must be reported in the relevant eCRF pages, including supportive care drugs and drugs used for treatment of AEs or chronic diseases.

[14] AE reporting begins at the point of the first ALRN-6924 infusion and continues until 30 days after last infusion or start of subsequent therapy; until all drug-related toxicities and ongoing SAEs have resolved, whichever is later; or until the Investigator assesses AEs as “chronic” or “stable.”

APPENDIX F: Dose Regimen B - Study Activities Cycle 2 and Beyond

	Day 1[1] ±3 d		Day 3 EXP only [9]	Day 4 and 8 ±1 d		Day 11 ±1 d		Day 12[15] DEP only	Day 15[16] EXP only	After last dose in cycles 3, 6, 9 etc.	End-of-Treatment 30 + 5 d after last dose or at study withdrawal	Long-Term Follow Up [17] (EXP only)
	Pre-dose	Post-dose		Pre-dose	Post-dose	Pre-dose	Post-dose					
Serum or urine pregnancy											X	
Vital signs[2]	X	X		X	X	X	X	X	X		X	
Physical exam[3]	X			X		X					X	
12-lead ECG[4]	X	X									X	
Laboratory assessments – chemistry[5]	X					Starting at Cycle 4		X	X		X	
Laboratory assessments – hematology[5]	X			X		Starting at Cycle 4		X	X		X	
Laboratory assessments – coagulation[5]	X							X			X	
Laboratory assessments – urinalysis[5]	X							X			X	
Laboratory assessments – CRP, fibrinogen	Cycle 2 only					Cycle 2 only		Cycle 2 only				
Collection of blood for immunogenicity[6]	Cycle 2, 3, 5 only										X	
Blood Collection - PK assessments						X[7]	X[7]	X[7]				
Blood Collection- cell-free DNA[6]	Cycle 5 only										X	
ECOG Performance status[8]	X			X		X					X	
Biopsy for biomarker assessments /p53 status			Day 3 or 10[9]					X[9]			X[9]	
Tumor Assessment/Imaging										X[10]	X[11]	

	Day 1[1] ±3 d		Day 3 EXP only [9]	Day 4 and 8 ±1 d		Day 11 ±1 d		Day 12[15] DEP only	Day 15[16] EXP only	After last dose in cycles 3, 6, 9 etc.	End-of-Treatment 30 + 5 d after last dose or at study withdrawal	Long-Term Follow Up [17] (EXP only)
ALRN-6924 dosing[12]	X			X		X						
Concomitant medications[13]	X	X		X	X	X	X	X	X		X	
AE assessment[14]	X	X		X	X	X	X	X	X		X	
Phone calls or other contact												X

[1] "Day 22" = Day 1 of next cycle for patients continuing treatment. Day 1 pre-dose evaluations for Cycle 2 and subsequent cycles are to be done within 3 days prior to next cycle drug administration.

[2] Blood pressure, pulse, respiration rate, body temperature. On the days of drug administration (Days 1, 4, 8, and 11 of each cycle) vital signs will be recorded pre-dose (within 30 minutes prior to SOI) and at the following timepoints:

(During infusion) 15 min (± 3 min) and 30 min (± 3 min);

(Post-infusion) At EOI (±5 min) and as clinically indicated following EOI. For patients on > 1 year, this procedure is no longer a mandatory study procedure.

In cycle 2 only, vital signs will be collected at 1 hr (±5 min), 2 hrs (±10 min) and 4 hrs (±10 min) following EOI. Additional vital signs will be collected at the discretion of the investigator.

[3] Full physical examination to be performed at End of Treatment; all other physical examinations may be symptom directed. For patients on > 1 year, this procedure is no longer a mandatory study procedure. Weight to be collected at Day 1 (+/- 3 days) of each cycle.

[4] ECGs to be performed after the patient has been supine for at least 10 minutes. Readings should be performed with the patient in the same physical position. Screening and pre-dose ECG recording should be taken in triplicate with 5-10 minutes between readings. Thereafter, subsequent readings on that same day will be performed in triplicate only if patient has a QTc that is a) >500 msec; b) increased by 60 msec over pre-dose; or c) decreased by 50 msec below pre-dose value. Timepoints on Day 22 of prior cycle or Day 1 of new cycle: At pre-dose (within 30 minutes prior to infusion) and EOI (+5 min). For patients on > 1 year, this procedure is no longer a mandatory study procedure.

[5] For patients on > 1 year, the required labs are: full labs to be collected on Day 1, and hematology only at Day 11

[6] Within 1 hour before SOI

[7] PK (Cycle 2 only): Day 11 collect at EOI (+5 min) and at 1 hour (±5 min) and 4 hours (±10 min) after the end of infusion.

DEP only: PK (Cycle 2 only): Day 12 visit should be conducted and blood should be collected 24 hours (±4 h) after the initiation of Day 11 infusion.

[8] For patients on > 1 year, this procedure is no longer a mandatory study procedure.

[9] Cycle 2 biopsy not performed if collected in specified timepoint in Cycle 1. For patients with a study biopsy performed immediately prior to enrollment, optional needle biopsy to be performed within 24 hours (DEP) or 48 hours (EXP) of Cycle 1 Day 11 infusion OR Cycle 2 Day 11 infusion. In EXP, optional biopsies include pre-treatment, during treatment, and one or more at times of suspected and/or confirmed progression.

[10] To be performed at end of odd-numbered cycles (Cycle 3, 6, 9, etc.) prior to start of the next treatment cycle. RECIST 1.1 (APPENDIX K) measurements for patients with solid tumors; IWG 2014 (APPENDIX L) measurements for patients with lymphoma. In DEP, after 1 year, assessments will be obtained at approximately 3 month intervals. After 2 years, assessments will be obtained at approximately 4 month intervals or per standard of care. In EXP, the frequency of imaging will not change after 1 year of treatment.

[11] Same method used as baseline. Perform only if no tumor assessment was performed within 6-8 weeks prior.

[12] During the first two cycles, ALRN-6924 should be administered in the morning to allow observation of delayed infusion reactions. ALRN-6924 will be infused over 1 hour (±15 min). At the end of the infusion, IV fluids (saline) or oral fluids (500mL – 1000 mL) should be administered unless clinically contraindicated.

[13] All concomitant medications taken within 28 days of beginning the study (Cycle 1 Day 1) until 30 days after last infusion or start of subsequent therapy must be reported in the relevant eCRF pages, including supportive care drugs and drugs used for treatment of AEs or chronic diseases.

[14] AE reporting begins at the point of the first ALRN-6924 infusion until 30 days after last infusion or start of subsequent therapy; until all drug-related toxicities and ongoing SAEs have resolved, whichever is later; or until the Investigator assesses AEs as "chronic" or "stable."

[15] Day 12 visit should only be completed for Cycle 2

[16] Day 15 visit to be completed in Cycles 1-3 and then at the discretion of the investigator

[17] EXP only: Phone calls or other contact should be made approximately every 2 months following end of treatment visit to assess survival status and collect information on subsequent therapies

APPENDIX G: Dose Regimen C - Study Activities Through Cycle 1

	Molecular Screen	Clinical Screen -21 days	Within 7 days prior to Day 1	Day 1		Day 2[15]	Days 3 ± 1 d		Day 5 ± 1 d		Day 8 ± 1 d	Day 15 ± 1 d
				Pre-Dose	Post-Dose		Pre-Dose	Post-Dose	Pre-Dose	Post-Dose		
Written informed consent	See 6.2	See 6.2										
Medical and disease history		X										
Demographics		X										
Tumor biopsy or archive tissue sample	See 3.2[1]											
Eligibility		X	X									
Blood test for HIV, hepatitis B and C		X										
HPV test[3]		X										
Serum or urine pregnancy test			Within 2 days prior to Day 1									
Vital signs[4]		X	X	X	X	X	X	X	X	X	X	X
Physical exam[5]		X		X			X		X		X	X
12-lead ECG[6]		X		X	X							
Laboratory assessments – chemistry		X	X[2]	X		X	X[7]		X[7]		X[7]	X[7]
Laboratory assessments – hematology		X	X[2]	X		X	X[7]		X[7]		X[7]	X[7]
Laboratory assessments - coagulation		X	X[2]	X		X						
Laboratory assessments - urinalysis		X	X[2]	X		X						
Laboratory assessments – lymphocyte subset testing			X						X			
Laboratory assessments – CRP, fibrinogen			X	X		X	X		X		X	X
Laboratory assessments – reticulocytes				X								
Blood Collection - immunogenicity				X[8]								
Blood Collection - PD assessments-MIC-1				X[8]	X[8]	X[9]	X[10]		X[10]		X[10]	
Blood Collection - PD assessments-CTC (select sites only)				X[8]	X[8]	X[9]						
Blood Collection - PK assessments				X[8]	X[8]		X[10]	X[10]	X[10]	X[10]	X[10]	

	Molecular Screen	Clinical Screen -21 days	Within 7 days prior to Day 1	Day 1		Day 2[15]	Days 3 ± 1 d		Day 5 ± 1 d		Day 8 ± 1 d	Day 15 ± 1 d
Blood Collection – cell-free DNA	X											
Germline DNA sample[11]				X								
ECOG Performance Status		X	X				X		X			
Biopsy for biomarker assessments/p53 status						Day 2 or 4[1]						
Tumor Assessment/Imaging[12]		X										
ALRN-6924 dosing[13]				X			X		X			
Concomitant medications[14]		X	X	X	X	X	X	X	X	X		X
AE assessment[15]					X	X	X	X	X	X		X

[1] For patients with a study biopsy performed immediately prior to enrollment, needle biopsy to be performed within 24 hours after Day 1 infusion OR Day 3 infusion; decision to be made at the discretion of the Investigator and only for patients with a study biopsy prior to their study participation. A pre-treatment biopsy or archival sample is required for p53 testing. For patients with a study biopsy performed immediately prior to enrollment, optional needle biopsy to be performed within 24 hours of Cycle 1 Day 1 infusion OR Day 3 infusion. Biopsy may also be performed at visit 2. Decision to be made at the discretion of the Investigator. In EXP, optional biopsies include pre-treatment, during treatment, and one or more at times of suspected and/or confirmed progression.

[2] Can be omitted if screening laboratory assessments are performed within 7 days of the first dose of ALRN-6924. Screening/within 7 day assessments are to be used for eligibility assessment.

[3] HPV status must be determined for tumors that are associated with HPV infection, including (but not limited to) cervical cancers, oropharyngeal cancer, head and neck squamous cell cancers or anal cancer, unless HPV status of the tumor is already known and documented.

[4] Blood pressure, pulse, respiration rate, body temperature.

Cycle 1, Days 1, 3, 5: On the days of drug administration vital signs will be recorded pre-dose (within 30 minutes prior to SOI) and at the following timepoints:

During infusion: 15 min (± 3 min) and 30 min (± 3 min)

Post-infusion: At EOI (±5 min), 1 (±5 min), 2 hrs (±10 min) and 4 hrs (±10 min) following EOI. On Cycle 1 Day 1 additional timepoints include 6 hrs (±10 min) and 8 hrs (±10 min) following EOI. Additional vital signs will be collected at the discretion of the investigator.

[5] Full physical examination to be performed at Screening, Day 1 Predose and End of Treatment; all other physical examinations may be symptom directed. Weight to be collected at Day 1.

[6] ECGs to be performed after the patient has been supine for at least 10 minutes. Readings should be performed with the patient in the same physical position. Screening and pre-dose ECG recording should be taken in triplicate with 5-10 minutes between readings. Thereafter, subsequent readings on that same day will be performed in triplicate only if patient has a QTc that is a) >500 msec; b) increased by 60 msec over pre-dose; or c) decreased by 50 msec below pre-dose value. Timepoints on Cycle 1, Day 1: Pre-dose (within 30 minutes prior to infusion), end of infusion (EOI +5 min) and at 1 (±5 min) and 2 hours (±10 min) after EOI.

[7] Days 3 and 5: Perform hematology and the following chemistries: glucose, sodium, potassium, CO2, chloride, BUN [blood urea nitrogen], serum creatinine

Day 8 and 15: Perform hematology and clinical chemistry.

[8] PD (MIC-1 and CTC): within 1 hour before the start of infusion (SOI) and at 4 (± 10 min) and 8 hours (± 2 hours) after EOI.

PK: Within 1 hour before SOI; at EOI (+5 min) and at 30 min (± 5 min), 1 hour (±5 min), 2 (± 10 min), 4 (± 10 min) and 8 hours (±2 hours) after EOI.

Immunogenicity: Within 1 hour before the SOI on Day 1.

[9] PD (MIC-1 and CTC): Day 2: Collect blood samples 24 hours (±4 h) after the initiation of Day 1 infusion. Complete visit only if CTCs are being collected, or if optional biopsy being conducted.

[10] PD (MIC-1 only): Day 3 and 5: Collect blood samples within 1 hour prior to SOI.

PK Day 3: Collect blood samples within one hour prior to SOI and at EOI (±5 min)

PK Day 5: Within 1 hour before SOI; at EOI (+5 min), at 1 hour (±5 min), 2 (± 10 min) hours post EOI
PD (MIC-1 only) and PK: Day 8: Collect blood samples at any time

[11] In patients consenting to optional biopsies, buccal swab for germline DNA (EXP only)

[12] RECIST 1.1- (for solid tumor patients) or IWG 2014- (for lymphoma patients) compliant imaging for disease assessment and tumor measurements as well as laboratory-based assays (e.g., prostate specific antigen) for patients with relevant disease indications.

[13] During the first two cycles, ALRN-6924 should be administered in the morning to allow observation of delayed infusion reactions. ALRN-6924 will be infused over 1 hour (±15 min). At the end of the infusion, IV fluids (saline) or oral fluids (500mL – 1000 mL) should be administered unless clinically contraindicated. Patients should receive ALRN-6924 within 1 day of the scheduled dose, but must not receive ALRN-6924 on consecutive dosing days.

[14] All concomitant medications taken within 28 days of beginning the study (Cycle 1 Day 1) until 30 days after last infusion or start of subsequent therapy must be reported in the relevant eCRF pages, including supportive care drugs and drugs used for treatment of AEs or chronic diseases.

[15] AE reporting begins at the point of the first ALRN-6924 infusion until 30 days after last infusion or start of subsequent therapy; until all drug-related toxicities and ongoing SAEs have resolved, whichever is later; or until the Investigator assesses AEs as “chronic” or “stable.

APPENDIX H: Dose Regimen C - Study Activities Cycle 2 and Beyond

	Day 1[1] ±3 d		**Day 2[9]**	**Day 3 ± 1 d**		**Day 5 ± 1 d**		**Day 8 ± 1 d**	**Day 15[15] ± 1 d**	**After last dose in cycles 3, 6, 9 etc.**	**End-of-Treatment 30 + 5 d after last dose or at study withdrawal**	**Long-Term Follow Up [16]**
	Pre-dose	Post-dose		Pre-dose	Post-dose	Pre-dose	Post-dose					
Serum or urine pregnancy											X	
Vital signs[2]	X	X		X	X	X	X	X	X		X	
Physical exam[3]	X			X		X			X		X	
12-lead ECG[4]	X	X									X	
Laboratory assessments – chemistry[5]	X							X	X		X	
Laboratory assessments – hematology[5]	X							X	X		X	
Laboratory assessments – coagulation[5]	X										X	
Laboratory assessments – urinalysis[5]	X										X	
Laboratory assessments – CRP, fibrinogen	Cycle 2 only							Cycle 2 only	Cycle 2 only		X	
Collection of blood for immunogenicity[6]	Cycle 2, 3, 5 only										X	
Blood Collection - PK assessments						Cycle 2 only[7]	Cycle 2 only[7]					
Blood Collection- cell-free DNA[6]	Cycle 5 only										X	
ECOG Performance status[8]	X			X		X					X	
Biopsy for biomarker assessments /p53 status			Day 2 or 4[9]								X[9]	
Tumor Assessment/Imaging										X[10]	X[11]	
ALRN-6924 dosing[12]	X			X		X						
Concomitant medications[13]	X	X		X	X	X	X	X	X		X	

	Day 1[1] ±3 d		Day 2[9]	Day 3 ± 1 d		Day 5 ± 1 d		Day 8 ± 1 d	Day 15[15] ± 1 d	After last dose in cycles 3, 6, 9 etc.	End-of-Treatment 30 + 5 d after last dose or at study withdrawal	Long-Term Follow Up [16]
AE assessment[14]	X	X		X	X	X	X	X	X		X	
Phone calls or other contact												X

[1] "Day 22" = Day 1 of next cycle for patients continuing treatment. Day 1 pre-dose evaluations for Cycle 2 and subsequent cycles are to be done within 3 days prior to next cycle drug administration.

[2] Blood pressure, pulse, respiration rate, body temperature. On the days of drug administration (Days 1, 3 and 5 of each cycle) vital signs will be recorded pre-dose (within 30 minutes prior to SOI) and at the following timepoints:

(During infusion) 15 min (± 3 min) and 30 min (± 3 min);

(Post-infusion) At EOI (±5 min) and as clinically indicated following EOI. For patients on > 1 year, this procedure is no longer a mandatory study procedure.

In cycle 2 only, vital signs will be collected at 1 hr (±5 min), 2 hrs (±10 min) and 4 hrs (±10 min) following EOI. Additional vital signs will be collected at the discretion of the investigator.

[3] Full physical examination to be performed at End of Treatment; all other physical examinations may be symptom directed. For patients on > 1 year, this procedure is no longer a mandatory study procedure. Weight to be collected at Day 1 (+/- 3 days) of each cycle.

[4] ECGs to be performed after the patient has been supine for at least 10 minutes. Readings should be performed with the patient in the same physical position. Screening and pre-dose ECG recording should be taken in triplicate with 5-10 minutes between readings. Thereafter, subsequent readings on that same day will be performed in triplicate only if patient has a QTc that is a) >500 msec; b) increased by 60 msec over pre-dose; or c) decreased by 50 msec below pre-dose value. Timepoints on Day 1 of new cycle: At pre-dose (within 30 minutes prior to infusion) and EOI (+5 min). For patients on > 1 year, this procedure is no longer a mandatory study procedure.

[5] For patients on > 1 year, the required labs are: full labs to be collected on Day 1, and hematology only at Day 8.

[6] Within 1 hour before SOI

[7] PK (Cycle 2 only): Collect within 1 hour before SOI, at EOI (±5 min), 1 hour (±5 min), and 2 hours (±10 min) after the end of infusion.

[8] For patients on > 1 year, this procedure is no longer a mandatory study procedure.

[9] Cycle 2 biopsy not performed if collected in Cycle 1. For patients with a study biopsy performed immediately prior to enrollment, optional needle biopsy to be performed within 24 hours of Cycle 2 Day 1 infusion OR Day 3 infusion; decision to be made at the discretion of the Investigator. Visit to be performed only if biopsy performed. In EXP, optional biopsies include pre-treatment, during treatment, and one or more at times of suspected and/or confirmed progression.

[10] To be performed at end of odd-numbered cycles (Cycle 3, 6, 9, etc.) prior to start of next treatment cycle. RECIST 1.1 (APPENDIX K) measurements for patients with solid tumors; IWG 2014 (APPENDIX L) measurements for patients with lymphoma. In EXP, the frequency of imaging will not change after 1 year of treatment.

[11] Perform only if no tumor assessment was performed within 6-8 weeks prior.

[12] During the first two cycles, ALRN-6924 should be administered in the morning to allow observation of delayed infusion reactions. ALRN-6924 will be infused over 1 hour (±15 min). At the end of the infusion, IV fluids (saline) or oral fluids (500mL – 1000 mL) should be administered unless clinically contraindicated. Patients should receive ALRN-6924 within 1 day of the scheduled dose, but must not receive ALRN-6924 on consecutive dosing days.

[13] All concomitant medications taken within 28 days of beginning the study (Cycle 1 Day 1) until 30 days after last infusion or start of subsequent therapy must be reported in the relevant eCRF pages, including supportive care drugs and drugs used for treatment of AEs or chronic diseases.

[14] AE reporting begins at the point of the first ALRN-6924 infusion until 30 days after last infusion or start of subsequent therapy; until all drug-related toxicities and ongoing SAEs have resolved, whichever is later; or until the Investigator assesses AEs as "chronic" or "stable."

[15] Day 15 visit to be completed in Cycles 1-3 and then at the discretion of the investigator.

[16] Phone calls or other contact should be made approximately every 2 months following end of treatment visit to assess survival status and collect information on subsequent therapies

APPENDIX I: Combination ALRN-6924 plus Palbociclib - Study Activities Through Cycle 1

	Screening -21 days	Day 1		Day 2	Day 8 ± 1 d		Day 15 ± 1 d		Day 22 ±1 d
Procedure		Pre- Dose	Post-Dose		Pre- Dose	Post- Dose	Pre- Dose	Post- Dose	
Written informed consent/pediatric assent	X								
Medical and disease history	X								
Demographics	X								
Tumor biopsy or archive tissue sample (NGS testing)	X								
Eligibility	X								
HPV test (tumor)[1]	X								
Serum or urine pregnancy test	X								
Vital signs[2]	Within 7 days prior to Day 1	X	X	X	X	X	X	X	X
Physical exam[3]	X	X							
12-lead ECG[4]	X								
Laboratory assessments – chemistry	Within 7 days prior to Day 1	X		X	X		X		X
Laboratory assessments – hematology	Within 7 days prior to Day 1	X		X	X		X		X
Laboratory assessments - coagulation	Within 7 days prior to Day 1	X		X	X		X		X
Laboratory assessments – reticulocytes		X							
Blood Collection – immunogenicity		Within 1 hour before SOI							
Blood Collection- cell-free DNA	X								
Blood Collection - PK assessments		X[5]		X[5]	X[5]		X[5]		X[5]
ECOG Performance Status	Within 7 days prior to Day 1	X			X		X		
Tumor Assessment/Imaging	Within 28 days prior to Day 1								
ALRN-6924 dosing[6]		X			X		X		
Palbociclib dosing[6]		Administered orally on Days 1 to 21 of each 28-day cycle with food							
Patient diary[7]		Record daily during palbociclib dosing							

	Screening -21 days	Day 1	Day 2	Day 8 ± 1 d	Day 15 ± 1 d	Day 22 ±1 d
Concomitant medications	Within 28 days prior to C1D1 until 30 days after last infusion or start of subsequent therapy					
AE assessment		AE collection period begins with first dose of ALRN-6924 until 30 days post last dose or start of subsequent therapy				

[1] HPV status must be determined only for tumors that are associated with HPV infection, including (but not limited to) cervical cancers, oropharyngeal cancer, head and neck squamous cell cancers or anal cancer, unless HPV status of the tumor is already known and documented.

[2] Blood pressure, pulse, respiration rate, body temperature.
Cycle 1, Days 1, 8, 15: On the days of drug administration vital signs will be recorded pre-dose (within 30 minutes prior to SOI) and at the following timepoints:
During infusion: 15 min (± 3 min) and 30 min (± 3 min)
Post-infusion: At EOI (±5 min), 1 hr (±5 min) and 2 hr (±10 min), 4 hrs (±10 min) following EOI. On Cycle 1 Day 1 additional timepoints include 6 hrs (±10 min) and 8 hrs (±10 min) following EOI.
Additional vital signs will be collected at the discretion of the investigator.

[3] Full physical examination to be performed at Screening (including height), Day 1 Predose, and End of Treatment; all other physical examinations may be symptom directed. Weight to be collected on Day 1.

[4] ECGs to be performed after the patient has been supine for at least 10 minutes. Readings should be performed with the patient in the same physical position. ECG recording should be taken in triplicate with 5-10 minutes between readings.

[5] PK timepoints are as follows:

- Cycle 1 Day 1: ALRN-6924 samples: within 1 hour before SOI; at EOI (+5 min) and at 30 min (±5 min), 1-hour (±5 min), 2 (±10 min), and 4 (±10 min) hours after EOI.
- Cycle 1 Day 2: ALRN-6924 sample: 24 hours (±2 hours) post EOI; palbociclib: 18 hours (±2 hours) post dose
- Cycle 1 Day 8 and 15: ALRN-6924 samples: within 1 hour before SOI; at EOI (+5 min), Palbociclib samples: within 1 hour before SOI; at EOI (+5 min) of ALRN-6924 dosing.
- Cycle 1 Day 22: palbociclib: any time on Day 22

[6] During the first two cycles, ALRN-6924 should be administered in the morning to allow observation of delayed infusion reactions. ALRN-6924 will be infused over 1 hour (±15 min). At the end of the infusion, IV fluids (saline) or oral fluids (500mL – 1000 mL) should be administered unless clinically contraindicated. On days when both drugs are administered (Days 1, 8, and 15), palbociclib should be administered at least 6 hours following the infusion of ALRN-6924. It is recommended that palbociclib be administered with food at approximately the same time each day.

[7] Patients to record time of palbociclib administration in diary. In addition, the number of capsules dispensed and returned should be recorded for each patient.

APPENDIX J: Combination ALRN-6924 plus Palbociclib - Study Activities Cycle 2 and Beyond

	Day 1[1] ±3 d		Day 8 ±1 d		Day 15 ±1 d		End-of-Treatment 30 ± 5 d after last dose or at study withdrawal	Long-Term Follow Up[11]
Procedure	Pre-dose	Post-dose	Pre-dose	Post-dose	Pre-dose	Post-dose		
Serum or urine pregnancy							X	
Vital signs[2]	X	X	X	X	X	X	X	
Physical exam[3]	X						X	
Biopsy (NGS testing)[4]	X							
Laboratory assessments – chemistry[5]	X				X		X	
Laboratory assessments – hematology[5]	X		X		X		X	
Laboratory assessments – coagulation[5]	X				X		X	
Collection of blood for immunogenicity[6]	Cycle 2, 3, 5 only						X	
Blood Collection- cell-free DNA[6]	Cycle 5 only						X	
ECOG Performance status[7]	X		X		X		X	
P53 status	If a biopsy is collected at any time on study, p53 testing should be performed							
Tumor Assessment/Imaging	Performed at end of even-numbered cycles (Cycle 2, 4, 6, etc.) prior to start of the next treatment cycle. After 1 year on treatment may be assessed after every third cycle, at the discretion of the investigator						X[8]	
ALRN-6924 dosing[9]	X		X		X			
Palbociclib dosing[9]	Administered orally on Days 1 to 21 of each 28-day cycle with food							
Patient diary[10]	Record daily during palbociclib dosing							
Concomitant medications	Within 28 days prior to C1D1 until 30 days after last infusion or start of subsequent therapy						X	
AE assessment							X	
Phone calls or other contact								X

[1] "Day 29" = Day 1 of next cycle for patients continuing treatment. Day 1 pre-dose evaluations for Cycle 2 and subsequent cycles are to be done within 3 days prior to next cycle drug administration.

[2] Blood pressure, pulse, respiration rate, body temperature. For patients on > 1 year, this procedure is no longer a mandatory study procedure.
On the days of drug administration (Days 1, 8, 15 of each cycle), vital signs will be recorded pre-dose (within 30 minutes prior to SOI) and at the following timepoints:
During infusion: 15 min (± 3 min) and 30 min (± 3 min)
Post-infusion: At EOI (±5 min) and as clinically indicated following EOI.
Additional vital signs will be collected at the discretion of the investigator.

[3] Weight to be collected at Day 1 (or up to 3 days prior to Day 1) of each cycle.

[4] Biopsies are not required per protocol however if a biopsy is taken during the study a sample should be submitted to the central laboratory for next generation sequencing

[5] For patients on > 1 year, the required labs are: full labs to be collected on Day 1, and hematology only at Day 15

[6] Within 1 hour before SOI

[7] For patients on > 1 year, this is no longer a mandatory study procedure

[8] Same method used as baseline. Perform only if no tumor assessment was performed within 6-8 weeks prior.

[9] During the first two cycles, ALRN-6924 should be administered in the morning to allow observation of delayed infusion reactions. ALRN-6924 will be infused over 1 hour (±15 min). At the end of the infusion, IV fluids (saline) or oral fluids (500mL – 1000 mL) should be administered unless clinically contraindicated. On days when both drugs are administered (Days 1, 8, and 15), palbociclib should be administered at least 6 hours following the infusion of ALRN-6924. It is recommended that palbociclib be administered with food at approximately the same time each day.

[10] Patients to record time of palbociclib administration in diary. In addition, the number of capsules dispensed and returned should be recorded for each patient.

[11] Phone calls or other contact should be made approximately every 2 months following end of treatment visit to assess survival status and collect information on subsequent therapies.

APPENDIX K: RECIST 1.1 – Assessment of Clinical Activity for Patients with Solid Tumors

Although response is not the primary endpoint of this study, patients with measurable disease will be assessed at baseline and during the study by standard criteria. Patients should be reevaluated after receiving 2 cycles of study therapy and then after every 2 cycles thereafter. In the event objective response (PR or CR) is noted, changes in tumor measurements must be confirmed by repeat assessments that should be performed at least 4 weeks after the criteria for response are first met. For stable disease (SD), follow-up measurements must meet the SD criteria at least 5 weeks after study entry.

1. Definitions

Response and progression will be evaluated in this study using the international criteria (version 1.1) proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee [Eur J Cancer. 45 (2009) 228-247]. Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in RECIST 1.1. Note: Lesions are either measurable or non-measurable using the criteria provided below. The term "evaluable" in reference to measurability will not be used because it does not provide additional meaning or accuracy.

1.1 Measurable Disease

Measurable disease is defined by the presence of at least one measurable lesion. Measurable lesions are defined as those that can be accurately measured in at least one dimension [longest diameter (LD) in the plane of measurement to be recorded] with a minimum size of:

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm)
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest x-ray

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness no greater than 5 mm).

1.2 Non-measurable Disease

All other lesions (or sites of disease), including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis) are considered non-measurable disease. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, abdominal masses/abdominal organomegaly identified by physical exam and not followed by CT or MRI.

Bone lesions, cystic lesions and lesions previously treated with local therapy must be considered as follows:

Bone lesions:

- Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques (i.e., CT or MRI) can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- 'Cystic lesions' thought to represent cystic metastases can be considered measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with prior local treatment:

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion.

1.3 Target Lesions

All measurable lesions up to a maximum of two lesions per organ and five lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. The baseline sum diameters will be used as reference by which to characterize the objective tumor response.

1.4 Lymph Node Assessment

For lymph nodes, measurements should be made of the short axis, which is defined as perpendicular to the LD of node assessed in the plane of measurement:

- Target lesion if short axis ≥ 15 mm
- Non-target lesion if short axis is ≥ 10 but < 15 mm
- Normal if short axis < 10 mm

For baseline, add the actual short axis measurement to the sum of LD of non-nodal lesions.

1.5 Non-target Lesions

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required and these lesions should be followed as "present," "absent," or in rare cases "unequivocal progression." In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case report form (e.g., 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

2. Guidelines for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.

Clinical lesions. Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended. When lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may be reviewed at the end of the study.

Chest x-ray. Chest CT is preferred over chest x-ray, particularly when progression is an important endpoint. Lesions on chest x-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

Conventional CT and MRI. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness > 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is acceptable in certain situations (e.g., for body scans).

Ultrasound (US). US should not be used to measure tumor lesions. US examinations cannot be reproduced in their entirety for independent review at a later date because they are operator dependent. If new lesions are identified by US, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT.

Endoscopy, Laparoscopy. The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.

Tumor markers. Tumor markers alone cannot be used to assess objective tumor response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Cytology, Histology. These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g., residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain).

3. Response Criteria

3.1 Evaluation of Target Lesions

Complete Response (CR):	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.
Partial Response (PR):	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
Progressive Disease (PD):	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of one or more new lesions is also considered progression.
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

3.1.1 Assessment of Target Lymph Nodes

Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline exam), even if the nodes regress to below 10 mm on study. In order to qualify for CR, each node must achieve a short axis < 10 mm. For PR, SD and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

3.1.2 Target Lesions that Become "too small to measure"

All lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g., 2 mm). If it is the opinion of the radiologist that the lesion has disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned.

3.1.3 Lesions that Split or Coalesce on Treatment

When non-nodal lesions fragment, the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter should be the maximal longest diameter for the 'coalesced lesion.'

3.2 Evaluation of Non-target Lesions

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

Non-CR/Non-PD:	Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.
Progressive Disease (PD):	Unequivocal progression of existing non-target lesions (The appearance of one or more new lesions is also considered progression). To achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation.

3.3 New Lesions

The finding of a new lesion should be unequivocal (i.e., not attributed to differences in scanning technique, change in imaging modality, or findings thought to represent something other than tumor, such as a 'new' healing bone lesion). A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. If a new lesion is equivocal, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm this is definitely a new lesion, then progression should be declared using the date of the initial scan.

3.4 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best overall response assignment will depend on findings of both target and non-target disease and will also take into consideration the appearance of new lesions. Furthermore, depending on the nature of the study, it may also require confirmatory measurement. Specifically, in non-randomized trials where response is the primary endpoint, confirmation of PR or CR is needed to deem either one the "best overall response."

It is assumed that at each protocol-specified time point, a response assessment occurs. The following table provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline.

Time point response: Patients with target (± non-target) disease

Target Lesions	Non-target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR / non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD
CR=complete response, PR=partial response, SD=stable disease PD=progressive disease, NE=inevaluable			

Complete or partial responses may be claimed only if the criteria for each are confirmed by a repeat assessment at least 4 weeks later. In this circumstance, the best overall response can be interpreted as shown in the following table:

Best overall response when confirmation of CR and PR required

Overall response First time point	Overall response Subsequent time point	BEST overall response
CR	CR	CR
CR	PR	SD, PD or PR*
CR	SD	SD provided minimum criteria for SD duration met, otherwise PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE
NE	NE	NE

CR=complete response; PR=partial response; SD=stable disease; PD=progressive disease; NE=inevaluable

* If CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in the fact patient had PR, not CR, at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

4. Confirmatory Measurement/Duration of Response

4.1 Confirmation

To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed at least 4 weeks after the criteria for response are first met. In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval at 5 weeks.

4.2 Duration of Overall Response

The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

4.3 Duration of Stable Disease

Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

APPENDIX L: International Working Group Revised Response Criteria for Malignant Lymphoma (IWG) (2014)

"Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma - The Lugano Classification"

Cheson, B.D., Fisher, R.I., Barrington, S.F., Cavalli, F., Schwartz, L.H., Zucca, E., Lister, T.A. (September 20, 2014). Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma - The Lugano Classification. *Journal of Clinical Oncology*: 32(27), 3059-3067.

The published criteria authored by Cheson et al. may be viewed and/or downloaded by accessing the following website:
http://jco.ascopubs.org/cgi/doi/10.1200/JCO.2013.54.8800 (Abstract)

Full Text, page 3062

Table 2. Revised Staging System for Primary Nodal Lymphomas Stage

Involvement		Extranodal (E) Status
Limited		
I	One node or a group of adjacent without nodal	Single extranodal lesions nodes involvement
II	Two or more nodal groups on the side of the diaphragm	Stage I or II by nodal same extent with limited contiguous extranodal involvement
II bulky*	II as above with "bulky" disease	Not applicable
Advanced		
III	Nodes on both sides of the diaphragm; nodes above the diaphragm with spleen involvement	Not applicable
IV	Additional noncontiguous extralymphatic involvement	Not applicable

NOTE. Extent of disease is determined by positron emission tomography– computed tomography for avid lymphomas and computed tomography for nonavid histologies. Tonsils, Waldeyer's ring, and spleen are considered nodal tissue.
*Whether stage II bulky disease is treated as limited or advanced disease may be determined by histology and a number of prognostic factors.

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Table 3. Revised Criteria for Response Assessment

Response and Site	PET-CT–Based Response	CT-Based Response
Complete	Complete metabolic response	Complete radiologic response (all of the following)
Lymph nodes and extralymphatic sites	Score 1, 2, or 3* with or without a residual mass on 5PS†	Target nodes/nodal masses must regress to < 1.5 cm in LDi
	It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (eg, with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake	No extralymphatic sites of disease
Nonmeasured lesion	Not applicable	Absent
Organ enlargement	Not applicable	Regress to normal
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, IHC negative
Partial	Partial metabolic response	Partial remission (all of the following)
Lymph nodes and extralymphatic sites	Score 4 or 5† with reduced uptake compared with baseline and residual mass(es) of any size	≥ 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites
	At interim, these findings suggest responding disease	When a lesion is too small to measure on CT, assign 5 mm × 5 mm as the default value
Nonmeasured lesions		
Organ enlargement	At end of treatment, these findings indicate residual disease	When no longer visible, 0 × 0 mm
		For a node > 5 mm × 5 mm, but smaller than normal, use actual measurement for calculation
New lesions	Not applicable	
Bone marrow	Not applicable	Absent/normal, regressed, but no increase
		Spleen must have regressed by > 50% in length beyond normal
	None	None
	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan	Not applicable
No response or stable disease	No metabolic response	Stable disease
Target nodes/nodal masses, extranodal lesions	Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	< 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
Nonmeasured lesions	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesions	None	None
Bone marrow	No change from baseline	Not applicable
Progressive disease	Progressive metabolic disease	Progressive disease requires at least 1 of the following
Individual target nodes/nodal masses	Score 4 or 5 with an increase in intensity of uptake from baseline and/or	PPD progression:
Extranodal lesions	New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	An individual node/lesion must be abnormal with: LDi > 1.5 cm and Increase by ≥ 50% from PPD nadir and An increase in LDi or SDi from nadir 0.5 cm for lesions < 2 cm 1.0 cm for lesions > 2 cm In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (eg, a 15-cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline New or recurrent splenomegaly
Nonmeasured lesions	None	New or clear progression of preexisting nonmeasured lesions

(continued on following page)

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Table 3. Revised Criteria for Response Assessment (continued)

Response and Site	PET-CT–Based Response	CT-Based Response
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	Regrowth of previously resolved lesions A new node > 1.5 cm in any axis A new extranodal site > 1.0 cm in any axis; if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma
Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

Abbreviations: 5PS, 5-point scale; CT, computed tomography; FDG, fluorodeoxyglucose; IHC, immunohistochemistry; LDi, longest transverse diameter of a lesion;
MRI, magnetic resonance imaging; PET, positron emission tomography; PPD, cross product of the LDi and perpendicular diameter; SDi, shortest axis perpendicular to the LDi; SPD, sum of the product of the perpendicular diameters for multiple lesions.

*A score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid undertreatment). Measured dominant lesions: Up to six of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in two diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (eg, liver, spleen, kidneys, lungs), GI involvement, cutaneous lesions, or those noted on palpation. Nonmeasured lesions: Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be diffi to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confi and followed by imaging. In Waldeyer's ring or in extranodal sites (eg, GI tract, liver, bone marrow), FDG uptake may be greater than in the mediastinum with complete metabolic response, but should be no higher than surrounding normal physiologic uptake (eg, with marrow activation as a result of chemotherapy or myeloid growth factors).

†PET 5PS: 1, no uptake above background; 2, uptake ::: mediastinum; 3, uptake > mediastinum but ::: liver; 4, uptake moderately > liver; 5, uptake markedly higher than liver and/or new lesions; X, new areas of uptake unlikely to be related to lymphoma.

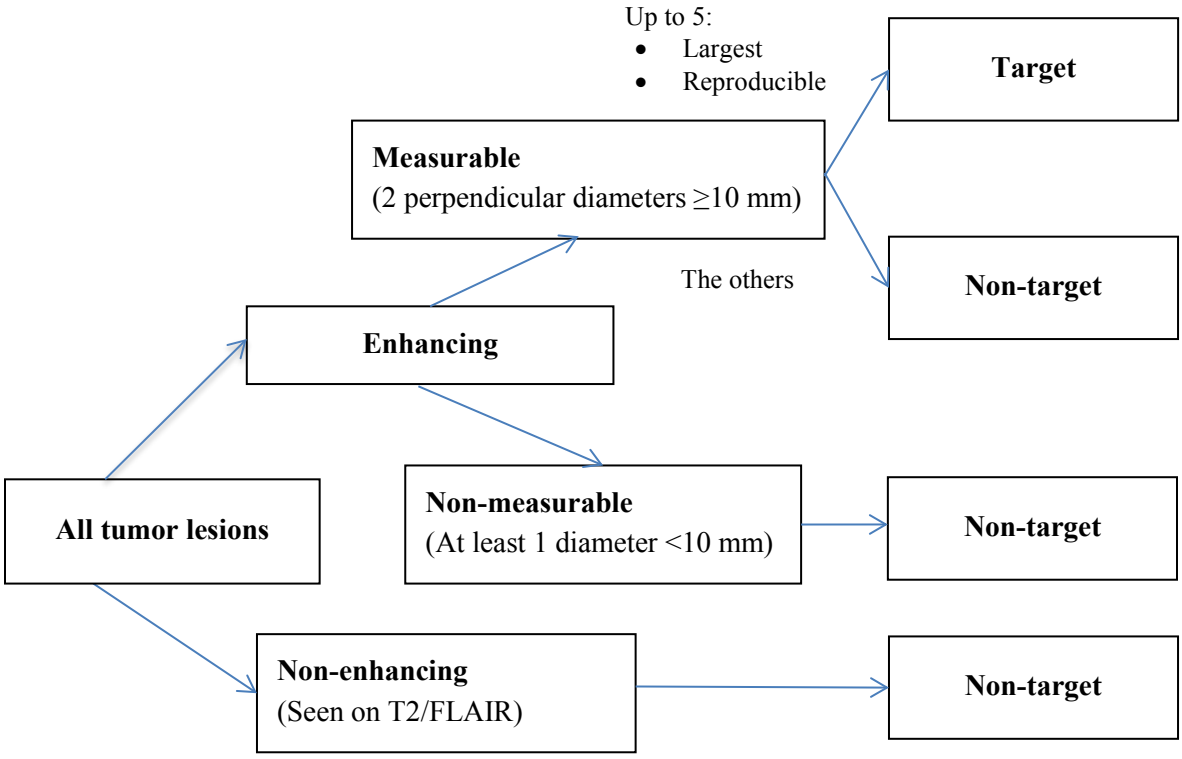
APPENDIX M: Response Assessment in Neuro-Oncology (RANO) Criteria

"Updated Response Assessment Criteria for High-Grade Gliomas: Response Assessment in Neuro-Oncology Working Group"

Wen PY, Macdonald DR, Reardon DA, Cloughesy TF, Sorensen AG, Galanis E, DeGroot J, Wick W, Gilbert MR, Lassman AB, Tsien C, Mikkelsen T, Wong ET, Chamberlain MC, Stupp R, Lamborn KR, Vogelbaum MA, van den Bent MJ, Chang SM. Updated response assessment criteria for high-grade gliomas: Response Assessment in Neuro-Oncology Working Group. J Clin Oncol. 2010;28(11):1963-72.

The published criteria may be viewed and/or downloaded by accessing the following website:
http://ascopubs.org/doi/full/10.1200/JCO.2009.26.3541

Selection of target lesions:
To evaluate changes in brain tumors using the RANO criteria, up to 5 enhancing lesions identified on baseline T1 (T1 relaxation time constant)-weighted images are measured and monitored for response over time.



Summary of response criteria:

Criterion	Complete Response	Partial Response	Stable Disease	Progressive Disease
T1 enhancing disease	None	≥ 50% ↓	< 50% ↓ but <25% ↑	≥ 25% ↑[a]
T2/FLAIR	Stable or ↓	Stable or ↓	Stable or ↓	↑[a]
New lesion	None	None	None	Present[a]
Corticosteroids	None	Stable or ↓	Stable or ↓	NA[b]
Clinical status	Stable or ↑	Stable or ↑	Stable or ↑	↓[a]
Requirement for response	All	All	All	Any

Abbreviation: FLAIR = fluid-attenuated inversion recovery; NA=not applicable
a Progression occurs when this criterion is present.
b Increase in corticosteroids alone will not be taken into account in determining progression in the absence of persistent clinical deterioration.

APPENDIX N: iRECIST Response Criteria

"iRECIST: Guidelines for Response Criteria for Use in Trials Testing Immunotherapeutics"

Seymour, L., Bogaerts, J., Perrone, A., Ford, R., Schwartz, L.H., Mandrekar, S., et al. (2017). iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. *Lancet Oncol, 18(3)*, e143-e152. DOI: https://doi.org/10.1016/S1470-2045(17)30074-8

The published criteria may be viewed and/or downloaded by accessing the following website: http://recist.eortc.org/wp-content/uploads/2017/03/Supplementary-material_iRECIST_Seymour-et-al_revision_FINAL_clean_nov25.pdf

APPENDIX O: NCI Common Terminology Criteria for Adverse Events, Version 4.03

Version 4.03 of the NCI CTCAE, dated 14 June 2010, may be viewed and/or downloaded by accessing the following website:

http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf