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Investigational Drug: CPI-613 and Bendamustine

IND Number: 123218

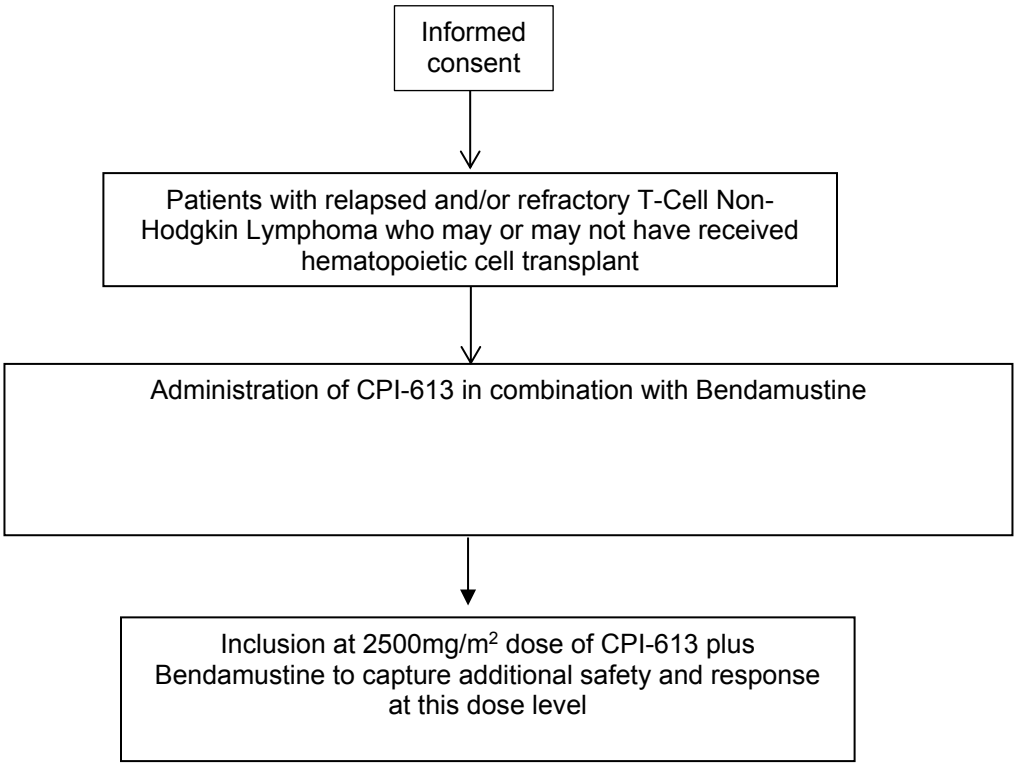
Drug Sponsor: Rafael Pharmaceuticals, Inc.

Participating Institutions: Wake Forest Baptist Comprehensive Cancer Center

Version Date: **11/29/22**

Proprietary and Confidential

SCHEMA



Primary Objectives

Pilot Study to evaluate the feasibility, safety and tolerability of a two day course per cycle of Bendamustine plus CPI-613 in patients with relapsed and refractory T cell non-hodgkin lymphoma.

Exploratory Objectives

To evaluate:

A. Overall response rate (ORR) and disease control rate (DCR) derived from the Lugano classification (Cheson et al. 2014) for PTCL patients and Global Response Score for CTCL (MF/SS) patients (Olson et al. 2011).
B. Duration of response (DOR) derived from the Lugano classification for PTCL patients and Global Response Score for CTCL (MF/SS) patients.
C. Progression-Free-Survival (PFS) derived from Lugano classification for PTCL patients and Global Response Score for CTCL (MF/SS) patients.
D. Overall Survival (OS).
E. Single cell transcriptomics from PMBCs pre- and post-treatment; for correlative analyses of blood PBMC (and possibly excess pre-treatment tumor biopsy) cell population diversity and functional states to reveal potential mechanisms of drug treatment with regard to patient response status

   We recognize that with the limited sample size in this study that these rate estimates will only provide initial information about the rates.

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1.0 STUDY POPULATION AND RATIONALE

Salvage therapy followed by autologous hematopoietic cell transplant (AuHCT) for patients with relapsed or refractory non-hodgkin lymphoma (NHL) is effective only for a subset of patients (Hagberg et al. 2006). For aggressive NHL (i.e., the high-grade B and T-cell NHL that often present as tumors in the lymph nodes), the outcome in relapsed or refractory disease is less optimistic. Relapsed or refractory T-cell non-Hodgkin lymphomas have a poor outcome with median PFS and OS of only 3 months and 6 months respectively.

CPI-613 is a lipoate derivative that targets the pyruvate dehydrogenase complex and has shown activity in hematologic malignancies (Zachar et al. 2011; Pardee et al. 2013). CPI-613 selectively targets the altered form of mitochondrial energy metabolism in tumor cells, causing changes in mitochondrial enzyme activities and redox status which lead to apoptosis, necrosis and autophagy of tumor cells (Zachar et al. 2011). These activities of CPI-613 involve the catalytic and regulatory functions of the pyruvate dehydrogenase complex (PDC), its regulatory kinases (PDKs), and the α-ketoglutarate dehydrogenase complex (KGDHC) (Zachar et al. 2011). The anti-tumor activity of CPI-613 in cell culture of different types of cancer cell lines, animal tumor models and clinical trials against diverse cancers have been documented, particularly against pancreatic cancer (Zachar et al. 2011; Pardee et al, 2011 & 2012; Lee et al. 2011 & 2012; Senzer et al. 2012). CPI-613 is also well-tolerated at doses up to 3,000 mg/m^2, according to a Phase 1 trial in patients with solid tumors and another Phase 1 trial in patients with hematologic malignancies.

Bendamustine has shown single agent activity in the relapsed lymphoma setting with response rates of approximately 50% for B and T cell NHL (Vacirca at al. 2013; Ghesquieres et al. 2013; Damaj et al. 2013).

A phase I dose-escalation study of CPI-613 with bendamustine was recently completed for patients with relapsed or refractory T-cell lymphomas. In this study, subjects received the combination of CPI-613 and bendamustine with CPI-613 given at escalating doses starting at 2,000mg/m^2 over 2 hrs on days 1-4. The study showed that this combination was well-tolerated and a maximum tolerated dose (MTD) was established at 2500 mg/m2 for CPI-613. However, it was noted that the 4-day dosing schedule for CPI-613 on that trial was cumbersome and a barrier to patient enrollment and treatment. We propose a pilot study using the MTD of 2500 mg/m2 for CPI-613 in combination with bendamustine given over an abbreviated schedule for 2 days every 28 days in patients with relapsed/and/or refractory T-cell lymphoma. Correlative studies including single cell sequencing pre-and post-treatment will be performed for marker identification. Results from this pilot study will be used to describe the overall response rate of this regimen in the study population and form the basis for a future phase II clinical trial.

2.0 STUDY OBJECTIVES

2.1 Primary Objectives

Pilot Study to evaluate the feasibility, safety and tolerability of a two day course per cycle of Bendamustine plus CPI-613 in patients with relapsed and refractory T cell non-hodgkin lymphoma.

2.2 Exploratory Objectives

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A. Overall response rate (ORR) and disease control rate (DCR) derived from the Lugano classification (Cheson et al. 2014) for PTCL patients and Global Response Score for CTCL (MF/SS) patients (Olson et al. 2011).
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D. Overall Survival (OS).
E. Single cell transcriptomics from PMBCs pre- and post-treatment; for correlative analyses of blood PBMC (and possibly excess pre-treatment tumor biopsy) cell population diversity and functional states to reveal potential mechanisms of drug treatment with regard to patient response status

We recognize that with the limited sample size in this study that these rate estimates will only provide initial information about the rates.

3.0 PATIENT ELIGIBILITY CRITERIA

3.1 Inclusion Criteria

Patients must meet all of the following inclusion criteria before enrollment:

1. Histologically or cytologically confirmed PTCL (all subtypes) or CTCL (mycosis fungoides/ sezary syndrome) as defined by 2016 World Health Organization (WHO) classification.
2. For patients with PTCL:
    a. Patients must have relapsed/ refractory disease to one or more systemic therapies.
    b. Patients with CD30-positive lymphoma must have received, be ineligible for, or intolerant to brentuximab vedotin.
    c. Patients with limited prior exposure to Bendamustine (less than 2 full cycles or ≤ 480 mg/m^2) may be included, based on PI discretion.

   d. Patients must have measurable disease (e.g., a tumor mass >1 cm or evidence of bone marrow involvement)
3. For patients with CTCL, stage IB- IVB mycosis fungoides or Sezary syndrome are eligible
   a. Patients must have relapsed/ refractory disease to at least one previous systemic therapy. Psoralen plus ultraviolet light therapy (PUVA) is not considered to be a systemic therapy.
4. Male and female patients 18 years of age and older
5. Eastern Cooperative Oncology Group (ECOG) performance status 0-2.
6. Expected survival >3 months
7. Women of child-bearing potential (i.e., women who are pre-menopausal or not surgically sterile) must use accepted contraceptive methods (abstinence, intrauterine device [IUD], oral contraceptive or double barrier device) during the study, and must have a negative serum or urine pregnancy test within 1 week prior to treatment initiation.
8. Fertile men must practice effective contraceptive methods during the study, unless documentation of infertility exists.
9. At least 2 weeks must have elapsed from prior chemotherapy drugs (other than steroids) or radiation
10. At least 6 weeks must have elapsed from prior autologous stem cell transplant and 12 weeks must have elapsed from prior allogeneic stem cell transplant.
11. Laboratory values ≤2 weeks must be:
    a. Adequate hematological function (absolute neutrophil count [ANC] ≥1,500/mm^3, platelets ≥100,000/mm^3). In subjects with known bone marrow involvement, ANC must be ≥ 1000/mm^3 and platelets ≥75,000/mm^3
    b. Adequate hepatic function (aspartate aminotransferase [AST/SGOT] ≤3x upper normal limit [UNL], alanine aminotransferase [ALT/SGPT] ≤3x UNL (≤5x UNL if liver metastases present), bilirubin ≤1.5x UNL).
    c. Adequate renal function (serum creatinine ≤1.5 mg/dL or 133 µmol/L).
12. No evidence of current infection.
13. Mentally competent, ability to understand and willingness to sign the informed consent form.

3.2 Exclusion Criteria

Patients with the following characteristics are excluded:

1. Known cerebral metastases, central nervous system (CNS) or epidural tumor.
2. History of prior malignancy and considered to be at greater than 30% risk of relapse
3. Patients receiving any other standard or investigational treatment for their cancer, or any other investigational agent for any indication, within the past 2 weeks prior to initiation of treatment with study drugs (steroids are allowed)

4. Patients with a history of allogeneic transplant must not have ≥ grade 3 graft-versus-host disease (GVHD) or any clinically significant GVHD requiring systemic immunosuppression.
5. Serious medical illness that would potentially increase patients' risk for toxicity.
6. Pregnant women, or women of child-bearing potential not using reliable means of contraception (because the teratogenic potential of CPI-613 is unknown).
7. Lactating females.
8. Fertile men unwilling to practice contraceptive methods during the study period.
9. Any condition or abnormality which may, in the opinion of the investigator, compromise the safety of patients.
10. Unwilling or unable to follow protocol requirements.
11. Active heart disease including but not limited to symptomatic congestive heart failure, symptomatic coronary artery disease, symptomatic angina pectoris, symptomatic myocardial infarction or symptomatic congestive heart failure.
12. Evidence of current infection.
13. Patients with known HIV infection, hepatitis B, or hepatitis C with positive viral load.
14. Patients who have received cancer immunotherapy of any type within the past 2 weeks prior to initiation of CPI-613 treatment.

3.3 Inclusion of Women and Minorities

Men and women of all races and ethnic groups who meet the above-described eligibility criteria are eligible to participate in this trial.

The study consent form will also be provided in Spanish for Spanish-speaking participants. Based on WFBCCC population estimates, we expect approximately 44.7% of participants to be women. Translating this to our sample size estimate of 12, we plan to enroll at least 5 women. Similarly, we expect approximately 2.8% of study participants to be Hispanic/Latino (N=1). We plan to enroll at least 13% Black or African American (N=2), .5% American Indian/Alaska Native (N=0), .9% Asian (N=1). Should we not meet or exceed these estimates, the PI will engage the Office of Cancer Health Equity to discuss strategies to enhance recruitment in these target populations.

4.0 REGISTRATION PROCEDURES

All patients entered on any WFBCCC trial, whether treatment, companion, or cancer control trial, **must** be linked to the study in EPIC within 24 hours of Informed Consent. Patients **must** be registered prior to the initiation of treatment.

You must perform the following steps in order to ensure prompt registration of your patient:

1. Complete the Eligibility Checklist (Appendix A)
2. Complete the Protocol Registration Form (Appendix B)
3. Alert the Cancer Center registrar by phone, *and then* send the signed Informed Consent Form, Eligibility Checklist and Protocol Registration Form to the registrar, either by fax or e-mail.

Contact Information:

Protocol Registrar PHONE [redacted]
Protocol Registrar FAX [redacted]
Protocol Registrar E-MAIL [redacted]

*Protocol Registration is open from 8:30 AM - 4:00 PM, Monday-Friday.

4. Fax/e-mail ALL eligibility source documents with registration. Patients **will not** be registered without all required supporting documents.

Note: If labs were performed at an outside institution, provide a printout of the results. Ensure that the most recent lab values are sent.

To complete the registration process, the Registrar will:

- assign a patient study number
- assign the patient a dose
- randomize the patient
- other appropriate actions
- register the patient on the study

5.0 Study Outcomes and Study Measures

5.1 Primary Outcome

5.1.1 The primary outcome measure will be feasibility, safety and tolerability of the 2-day dosing regimen of CPI-613 in combination with bendamustine. Feasibility will be defined as 75% of patients being successfully able to complete 80% of their therapy regimens. Toxicity data will be collected on all patients who receive at least one dose of treatment on the study.

5.2 Secondary Outcomes

The following secondary outcomes will be collected and reported for all patients who receive at least one dose of the study medication.

5.2.1 ORR defined as the proportion of patients who achieve a best overall response CR or PR during or following study treatment according to the Lugano classification (Cheson et al. 2014) for PTCL patients and Global Response Score for CTCL (MF/SS) patients (Olson et al. 2011)

5.2.2 DCR defined as the proportion of patients who achieve a best overall response CR, PR, or stable disease (SD). Best overall response of SD must have met the response SD criteria at least once ≥12 weeks after start of study treatment.

5.2.3 DOR will be defined for responders (patients with a best overall response of CR or PR). It is the time from the date of the first documented CR or PR until the date of the first date of progressive disease, or death due to any cause, whichever occurs first. If a patient has not progressed or died by the analysis cutoff date, DOR will be censored at the time of the last adequate tumor assessment on or before the cutoff date

5.2.4 PFS defined as the time from the start of study treatment until the first date of progressive disease, or death due to any cause, whichever occurs first. If a patient has not progressed or died by the analysis cutoff date, PFS will be censored at the time of the last adequate tumor assessment on or before the cutoff date.

5.2.5 OS measured from the start of study treatment until death due to any cause. If a patient is not known to have died at the date of the analysis cut-off, OS will be censored at the last date that:

5.2.5.1 Patient is documented to be alive.

5.2.5.2 At the time of single cell sequencing.

6.0 STUDY PROCEDURES

Table 6-1 (below) provides an overview of the study procedures for Cycles 1-6. Specifics are described in subsequent sections.

Procedures and Assessments	Pre-Study Screen[a]	Cycles 1-6 Each cycle is 28 days long				Follow-Up
		D1	D2	D3	D4	
Informed consent	√					
Medical history, medications, evaluation of symptoms, physical exam	√	√ [b]				
ECOG Performance Status	√	√ [b]				
Pregnancy test for women of child-bearing potential	√	√				
Vital signs	√	√ [c]	√ [c]			
Clinical chemistry	√	√ [d]	√			
LDH	√	√ [d]				
CBC with differential	√	√ [d]				
CPI-613 (2500 mg/m2)		√	√			
Bendamustine (90 mg/m^2) [d]		√	√			
Neulasta				√ [f]	√ [f]	
Research blood samples		√ [g]	√ [g]			√ [g]
Adverse Event Evaluation		√				
Phone contact/EMR Review [g]						√ [g]
For CTCL (MF/SS) patients only						
Dermatology assessment (mSWAT)	√	Repeat after cycles 3 and 6				
Peripheral blood flow cytometry for Sezary cells	√	Repeat after cycles 3 and 6 only if positive at baseline				
PET/CT scan	√	Repeat after cycles 3 and 6 only if positive at baseline				
For PTCL patients only						
Bone marrow biopsy	√	Repeat after cycles 3 and 6 for those with marrow involvement at baseline that cannot be assessed through imaging				
PET/CT scan	√[i]	Repeat after cycles 3 and 6				
Phone contact/EMR Review						√ [h]

MF= Mycosis Fungoides, SS= Sezary Syndrome

[a] Pre-study screening tests, which are also enrollment evaluations, must be performed according the following time frames prior to treatment start:

Within 8 weeks: anti-tumor efficacy assessment. (**Note:** If assessment within this timeframe has already been performed prior to participating in this trial, the results from this assessment can be used). Patients should not have received any additional chemotherapy except steroids after screening PET/CT. If additional chemotherapy has been given, then PET/CT should be repeated prior to enrollment to the study.

Within 2 weeks: medical history, physical exam, vital signs, height, weight, ECOG, evaluation of symptoms and medications, clinical chemistry, CBC with differential, LDH.

Within 1 week: pregnancy test for women of child-bearing potential.

[b] Performed within 5 days prior to each cycle

[c] Vital signs are performed immediately after CPI-613 administration in cycle 1

[d] These tests are performed within 24 hrs prior to dosing of day 1 of CPI-613 with each cycle.

[e] All study assessments will be the same for patients with limited exposure to Bendamustine. All patients will receive baseline scans and have first efficacy scan after 3 full study cycles of CPI- 613 and Bendamustine. Patients will not receive more than 6 total cycles of Bendamustine. Patients with limited prior exposure to Bendamustine (less than 2

cycles ≤480 mg/m^2) will receive a total of 6 cycles of Bendamustine both on and off study. If a patient has had 1 cycle (2 doses) of Bendamustine prior to enrolling on this study, the Bendamustine will be held in Cycle 6. If the patient received 2 cycles of Bendamustine prior to enrolling on this study, the Bendamustine will be held in Cycles 5 and 6.

[f] Neulasta should be given on day 3 or day 4 after Bendamustine, per institutional guidelines. On Body Injector (OBI) is allowed.

[g] Research blood samples are for possible testing of biomarkers, predictors of biological responses, toxicity, genotype vs. drug response relationship, etc. They are to be obtained prior to day 1 and day 2 CPI-613 dosing for each cycle.and at disease progression or study termination, whichever occurs earlier.

[h] Survival and information related to cancer treatment received after the study and disease status is monitored every 3 months via telephone contact or EMR review after treatment termination. Medical record review will coincide with telephone call to obtain information regarding evidence and of relapse (as documented on CT, PET, biopsy, etc).

Table 6-2 (below) provides an overview of the study procedures for maintenance (cycles 7-20). Specifics are described in subsequent sections.

Procedures and Assessments	**Cycles 7-20**				**Follow up (Every 3 months)**
	Each cycle is 28 days long				
	D1	**D2**	**D3**	**D4**	
Medical history, medications, evaluation of symptoms	√ [a]				
ECOG Performance Status	√				
Vital signs	√	√			
Clinical chemistry	√ [b]	√ [b]			
LDH	√				
CBC with differential	√				
Pregnancy test for women of child-bearing potential	√				
CPI-613 (2500 mg/m2 dose)	√	√			
For CTCL (MF/SS) patients only					
Dermatology assessment (mSWAT)	Every 3 months for year 1 of maintenance, then every 6 months AND at progression.				
For PTCT patients only					
CT chest/ abdomen/ pelvis	Every 3 months for year 1 of maintenance, then every 6 months AND at progression.				
Bone marrow biopsy	Only if bone marrow is the primary site of measurable disease at baseline and cannot be evaluated using imaging- repeat every 3 months for year 1 of maintenance, then every 6 months AND at progression.				
Adverse Event Evaluation	√				
Phone contact/EMR Review [c]					√ [c]

[a] Medical history, vital signs, ECOG performance status, evaluation of symptoms, medications: assessed within 5 days prior to each cycle.

[b] Creatinine and BUN to be checked within 24 hours of CPI-613.

[c] Survival and information related to cancer treatment received after the study and disease status is monitored every 3 months via telephone contact or EMR review after treatment termination. Medical record review will also be performed to coincide with the telephone call to obtain information regarding evidence and of relapse (as documented on CT, PET, biopsy, etc).

6.2 Intervention Administration

6.2.1 Pre-Study Screening Tests

Pre-study screening tests must be performed according the following time frames prior to treatment start:

Within 4 weeks: tumor assessments. (**Note:** If assessment within this timeframe has already been performed prior to participating in this trial, the results from this assessment can be used.)

Within 2 weeks: medical history, physical exam, vital signs, height, weight, ECOG, evaluation of symptoms and medications, clinical chemistry, CBC with differential, LDH.

Within 1 week: pregnancy test for women of child-bearing potential.

6.2.2 Safety Assessment

The safety of CPI-613 and Bendamustine will be assessed based on:
- evaluation of symptoms
- vital signs
- ECOG performance status and survival
- clinical chemistry, CBC with differential

The specifics of the safety tests are described in Section 6.3. All safety assessment tests are performed during screening (performed within 2 weeks prior to treatment with CPI-613). Associated with Cycle 1, clinical chemistry, hematology are performed within 24 hours prior to dosing CPI-613, and only creatinine results are needed before dosing CPI-613. Vital signs are performed immediately after CPI-613 administration and re-examined only if clinically indicated. Creatinine and BUN should be checked within 24 hours of every dose of CPI-613. Beyond Cycle 1, physical exam and vital signs, ECOG performance status, evaluation of symptoms and medications will be performed within 5 days prior to each cycle. Clinical chemistry, hematology, will be assessed on Day 1 of each cycle.

6.2.3 Anti-Tumor Efficacy Assessment

Response assessment for CTCL (MF/SS) patients:

Skin lesions and erythema will be evaluated using the Modified Severity Weighted Assessment Tool (mSWAT).

Modified Severity Weighted Assessment (mSWAT) Tool

An mSWAT score is derived by measuring each lesion as a percentage of total body surface area (%TBSA) and multiplying it by a severity-weighting factor (1 =

patch, 2 = plaque, 4 = tumor). All individual numbers are then added to produce a total score.

Body region (%BSA)	Patch*	Plaque*	Tumor*
Head (7%)			
Neck (2%)			
Anterior trunk (13%)			
Arms (8%)			
Forearms (6%)			
Hands (5%)			
Posterior trunk (13%)			
Buttocks (5%)			
Thighs (19%)			
Legs (14%)			
Feet (7%)			
Groin (1%)			
Subtotal of lesion BSA			
Weighting factor	x1	x2	x4
Subtotal lesion BSA x weighting factor			
mSWAT score = summation of each column line above			

Patch = any size lesion without induration or significant elevation above the surrounding uninvolved skin: poikiloderma may be present.

Plaque = any size lesion that is elevated or indurated; crusting, ulceration, or poikiloderma may be present.

Tumor = any solid or nodular lesion ≥1 cm in diameter with evidence of deep infiltration in the skin and/or vertical growth.

Response Criteria for skin, as assessed by mSWAT scores

Response	Definition
CR	100% clearance of skin lesions
PR	50% to 99% clearance of skin disease from baseline without new tumors (T_3) in patients with T_1, T_2, or T_4 only skin disease
SD	<25% increase to <50% clearance in skin disease from baseline without new tumors (T3) in patients with T_1, T_2, or T_4 only skin disease
PD[c]	(1) ≥25% increase in skin disease from baseline or (2) New tumors (T_3) in patients with T_1, T_2, or T_4 only skin disease or (3) Loss of response: in those with CR or PR, increase of skin score of greater than the sum of nadir plus 50% baseline score
Relapse[a]	Any disease recurrence in those with CR

[a] Relapse should be defined as loss of response (as defined for PD) in those with CR, ie, increase of skin score of greater than the sum of nadir plus 50% baseline score

Response Criteria in blood

Peripheral blood flow cytometry for CD4+CD7- and CD4+CD26- cells will be used to assess response in blood.

CR	B0
PR	>50% decrease in quantitative measurements of blood tumor burden from baseline in those with high tumor burden at baseline (B2)
SD	Fails to attain criteria for CR, PR or PD
PD	(1) B0 to B2 or (2) >50% increase from baseline and at least 5,000 neoplastic cells/μL or (3) Loss of response: in those with PR who were originally B2 at baseline, >50% increase from nadir and at least 5,000 neoplastic cells/μL
Relapse	Increase of neoplastic blood lymphocytes to ≥ B1 in those with CR

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

Response Criteria in lymph nodes and viscera

Visceral and nodal disease in CTCL will be evaluated using PET/CT scan and according to the 2014 Lugano Classification as described in Table 6.2.3-2.

Global Overall Response Criteria

The International Society on Cutaneous Lymphomas criteria (Olson et al. 2011) will be used to assess response of cutaneous lymphoma patients. CR, NI, PR, PD and SD are defined as shown in Table 6.2.3-1.

Table 6.2.3-1

Global Response Score					
Global Score*	**Definition**	**Skin**	**Nodes**	**Blood**	**Viscera**
CR	Complete disappearance of all clinical evidence of disease	CR	All categories have CR/NI		
PR	Regression of measurable disease	CR	All categories do not have a CR/NI and no category has a PD		
		PR	No category has a PD and if any category involved at baseline, at least one has a CR or PR		
SD	Failure to attain CR, PR, or PD representative of all disease	PR	No category has a PD and if any category involved at baseline, no CR or PR in any		
		SD	CR/NI, PR, SD in any category and no category has a PD		
PD	Progressive disease		PD in any category		
Relapse	Recurrence disease in prior CR		Relapse in any category		

- Abbreviations: CR, complete response; NI, noninvolved; PR, partial response; PD, progressive disease; SD, stable disease.

Response assessment for PTCL patients:

The Revised Response Criteria for Malignant Lymphoma (Cheson et al. 2014) will be used to stage the disease. Complete response,(CR), partial response (PR),stable disease (SD), and progressive disease (PD) are defined as shown in Table 6.2.3-2. Overall response rate (ORR) (the combined rates of CR and PR) and disease control rate (DCR) (the combined rates of CR, PR and SD) will also be calculated.

Table 6.2.3-2: (Cheson et al. 2014)[1]

Revised Criteria for Response Assessment adapted from Cheson et al. 2014		
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† 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.	Target nodes/nodal masses must regress to ≤ 1.5 cm in LDi 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 At interim, these findings suggest responding disease At end of treatment, these findings indicate residual disease	≥50% decrease in SPD of up to 6 target measurable nodes and extranodal sites When a lesion is too small to measure on CT, assign 5 mm X 5mm as the default value When no longer visible, 0 x 0 mm For a node >5 mm X 5mm,

		but smaller than normal, use actual measurement for calculation
Nonmeasured lesions	Not applicable	Absent/normal, regressed, but no increase Spleen must have regressed by > 50% in length beyond normal
Organ enlargement	Not applicable	
New lesions	None	None
Bone marrow	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 Target nodes/nodal masses, Extranodal lesions	No metabolic response Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	Stable Disease < 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
Non measured 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	Score 4 or 5 with an increase in intensity of uptake from baseline and/or	PPD progression:

masses		
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
Non measured lesions	None	New or clear progression of preexisting non measured lesions
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 perpendicularto 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 difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed 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 $\leq$ mediastinum; 3, uptake > mediastinum but $\leq$ 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.

Survival: Survival (and information related to cancer treatment received after the study and disease status) will be obtained every 3 months via telephone contact after treatment termination. Medical record review will also be performed to coincide with the telephone call to obtain information regarding evidence of relapse (as documented on CT, PET, biopsy, etc).

6.3 Specifics of Tests Performed During the Study

Described below are the specifics of the tests performed in this study.

ECOG Performance Status

The ECOG Performance Status scales (Oken et al 1982) will be used to assess how a patient's disease is progressing and assess how the disease affects the daily living abilities of the patient. These scales are listed in Table 6.3.1-1 (below). The higher the ECOG score, the worse the prognosis.

Table 6.3.1-1: Scales Used in ECOG Performance Status

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Clinical Chemistry, Hematology

Clinical chemistry includes:

glucose	BUN
creatinine	AST/serum glutamic-oxaloacetic transaminase (SGOT)
total protein	ALT/serum glutamic-pyruvic transaminase (SGPT)
albumin	alkaline phosphatase (ALP)
Na^+	CO_2
K^+	total bilirubin
Cl^-	
Mg	
Ca^{+2}	

CBC with differential includes:

white blood count	hemoglobin
differential count	hematocrit
platelet count	

Research blood and optional blood and tissue samples

Research blood samples will be collected pre-treatment on day 1 and day 2 of each cycle prior to CPI-613 dosing, and at disease progression or study termination, whichever occurs earlier. These samples will be 6 mL of whole blood collected into EDTA tubes for single-cell sequencing of peripheral blood mononuclear cells to determine biomarkers and predictors of biological responses and toxicity. Single cell transcriptomics status pre- and post-treatment; for correlative analyses of blood PBMC (and excess pre-treatment tumor biopsy) cell population diversity and functional states to reveal potential mechanisms of drug treatment with regard to patient response status. Additionally, 6 mL of serum will be obtained and "banked" for possible testing of biomarkers in future.

Whole Blood Samples

- Samples (6 mL each) will be collected into a lavender top K2-EDTA 13x100/6ml vacutainer tube
- Invert the tube a minimum of 8 times to mix the anticoagulant (EDTA) completely, then keep sample at room temperature.
- Do not centrifuge, refrigerate or freeze sample.
- Label sample and store at room temperature prior to pick-up by TTPSR personnel (Libby McWilliams).

All optional samples and specimens should be delivered to:

Dr. Wei Zhang (c/o Liz Forbes) (336) 713-7063

Wake Forest Baptist Health

Dept of Cancer Biology: NRC322

Serum Sample

- Collect blood (6 mL) in serum separator tube (6.0 mL, with Polymer gel/Silica activator).
- Gently invert the tube 8-10 times, and let tube sit in an upright position for at least 15-30 minutes at room temperature to allow the blood to clot.

- Within 2 hours from time of collection, spin the tubes at 1000x g using a standard room temperature centrifuge for 10-15 minutes.
- After centrifugation, pipette 1.0 mL aliquots of plasma into each of the 1.8 mL-size polypropylene screw-capped cryovials. Expect to collect between 3-5 cryovials each containing 1.0 mL aliquots of plasma.
- Label the aliquots.
- Quickly freeze the aliquots by placing them either on dry ice or in a –70°C freezer. Store the samples at –70°C or colder.

This sample will be stored in Dr. Kucera's lab for future studies. Please notify Libby McWilliams, the Tumor Procurement Officer, at [redacted] when this sample is drawn.

7.0 STUDY DESIGN

7.1 Treatment Cycles

Each treatment cycle is 4 weeks (see Table 7-1, below). CPI-613 at 2500 mg/m2 is infused intravenously (IV) via a central catheter over 2 hrs on Days 1and 2. Bendamustine at 90 mg/m^2 is infused IV over 10 minutes on Days 1 and 2 of each treatment cycle, given immediately after CPI-613 administration. Each patient will be treated with as many as 6 cycles, if clinically indicated.

Patients with limited prior exposure to Bendamustine (less than 2 cycles or ≤ 480 mg/m2) will receive a total of 6 cycles of Bendamustine both on and off study. If a patient has had 1 cycle (2 doses) of Bendamustine prior to enrolling on this study, the Bendamustine will be held in Cycle 6. If the patient received 2 cycles of Bendamustine prior to enrolling on this study, the Bendamustine will be held in Cycles 5 and 6.

Patients who have a continued response to 6 cycles of treatment with bendamustine and CPI-613 may continue maintenance treatment with CPI-613 alone given on days 1 and 2 every 28 days until disease progression or unacceptable toxicity.

Table 7.1: Timing of CPI-613 and Bendamustine in Each 4-Week Treatment Cycle

	Day 1	Day 2
Week 1	CPI-613 Bendamustine	CPI-613 Bendamustine
Week 2		
Week 3		
Week 4		

7.2 Dosing Delay and Dose Modification

7.2.1 Dosage Adjustment for CPI-613 Related Toxicities

The occurrence of Grade 1 toxicity does not generally require dose modification for subsequent doses for that patient. However, if Grade 2 non-hematologic toxicity (which includes infectious toxicity) develops and is attributed to at least probably related to CPI-613, treatment can resume only after the Grade 2 toxicity has been reduced to Grade 1 or below, and the dose level for subsequent doses for that patient will be reduced by 25% of the dose at which such Grade 2 toxicity occurs. If Grade 3 or 4 non-hematologic toxicity (which includes infectious toxicity) develops, dosing of that patient will be withheld and the patient shall be monitored for recovery from, and reversibility of, such Grade 3 or 4 toxicity. To resume treatment for a patient who has had Grade 3 or 4 toxicity, the Grade 3 or 4 toxicity must be reduced to Grade 1 or below, and the dose level for subsequent doses for that patient will be reduced to 50% of the dose at which such Grade 3 or 4 toxicity occur. If the reduced dose of CPI-613 results in no toxicity, patients may be dose escalated to the prior dose at the discretion of the treating physician.

For adverse events unrelated to serum creatinine elevation or reduction in renal function but are possibly related to CPI-613, the occurrence of Grade 1 toxicity does not generally require dose modification for subsequent doses for that patient. However, if Grade 2 toxicity (other than nausea) probably related to CPI-613 develops, treatment is to be withheld and can resume only after the Grade 2 toxicity has been reduced to Grade 1 or below, and the dose level for subsequent doses for that patient will be reduced by 25% of the dose at which such Grade 2 toxicity occurs. Grade 2 nausea does not require withholding treatment or dose reduction. If Grade 3 or 4 toxicity probably related to CPI-613 develops, dosing of CPI-613 of that patient will be withheld and the patient shall be monitored for recovery from, and reversibility of, such Grade 3 or 4 toxicity. To resume treatment with CPI-613 for a patient who has had CPI-613-related Grade 3 or 4 toxicity, the Grade 3 or 4 toxicity must be reduced to Grade 1 or below, and the dose level for subsequent doses for that patient will be reduced to 50% of the dose at which such Grade 3 or 4 toxicity occurs.

For adverse events related to creatinine elevation, reduction in renal function or mitochondrial inhibition syndrome that are possibly related to CPI-613, dosing of the patient will be withheld even if the severity level is Grade 1 or above. Treatment can resume only after the toxicity has been reduced to Grade 0. The dose level for subsequent doses for that patient will be reduced by 15% if the severity level is of Grade 1, by 25% for Grade 2 toxicity, and by 50% for Grade 3 or 4 toxicity.

Furthermore, if the toxicity possibly related to CPI-613 is acute renal failure and the severity level is Grade 3 or 4, further patient enrollment will be temporarily suspended in order to enable assessment of the following aspects of the trial and implementation of corrective measures or protocol amendment, if necessary:

- compliance of the study sites and investigators to the study protocol
- evaluation of the appropriateness of the procedures for monitoring renal function

Special note for Mitochondrial Inhibition Syndrome.
A. This is a constellation of symptoms that may include high fevers, hypotension, lethargy, pancytopenia, altered mental status and generalized weakness and lactic acidosis. If this occurs or is suspected the recommended treatment until symptoms resolve is:
a. IV L-carnitine 50mg/kg/day in divided doses every 4 hours (i.e. 8.3mg/kg every 4 hours)
b. Folic acid 1mg daily
c. Thiamine 100mg daily

7.2.2 Dosage Adjustment for Bendamustine Related Toxicities

Administration of Bendamustine should be withheld in the event of ≥Grade 4 hematologic toxicity or clinically significant ≥Grade 2 non-hematologic toxicity. Once non-hematologic toxicity has recovered to ≤Grade 1, Bendamustine can be re-initiated at the discretion of the treating physician. For patients experiencing hematologic toxicity, Bendamustine may be re-initiated at the discretion of the treating physician once counts have improved (Absolute Neutrophil Count [ANC] ≥1 x 10^9/L, platelets ≥75 x 10^9/L). However, if the patient has low blood counts related to underlying disease (i.e. bone marrow involvement or splenic sequestration), the Bendamustine can be re-initiated at the discretion of the treatment physician prior to blood count improvement. At that point, dose reduction as described below should be considered:

-Hematologic toxicity Grade 4 toxicity: reduce the dose by 30%.
-Non-hematologic toxicity for clinically significant ≥Grade 3 toxicity: reduce the dose by 30%.

Dose re-escalation in subsequent cycles may be considered at the discretion of the treating physician.

7.4 Duration of Treatment for Each Patient

Treatment with CPI-613 should be continued as long as the treating physician believes there is clinical benefit, unless or until:

- Patients receive an allogeneic stem cell transplant
- Patients exhibit disease progression
- Unacceptable toxicity from CPI-613 in spite of dose reduction
- Patient withdrawal of consent
- Investigator's discretion to withdraw patients from the study because continued participation in the study is not in the patient's best interest.
- Undercurrent illness: a condition, injury, or disease unrelated to the intended disease for which the study is investigating, that renders continuing the treatment unsafe or regular follow-up impossible
- General or specific changes in the patient's condition that renders the patient ineligible for further investigational treatment
- Non-compliance with investigational treatment, protocol-required evaluations or follow-up visits
- Termination of the clinical trial by the sponsor of CPI-613

When terminating treatment during this trial, the investigator should make every effort to contact the patient and to perform a final evaluation. Also, the reason(s) for withdrawal from the study must be recorded.

Upon being taken off the trial, patient's survival and post-study cancer treatment will be monitored by follow up physician visits once patients are removed from trial. All patients will be followed for 5 years post treatment, or until death.

8.0 STUDY DRUGS

8.1 Bendamustine

Bendamustine at 90 mg/m^2 is infused by IV over 10 minutes on Days 1 and 2 of each treatment cycle. Bendamustine is given immediately after CPI-613 administration.

8.2 CPI-613

CPI-613 is to be given as 2-hr IV infusion via a central venous catheter. The starting dose of CPI-613 will be 2500 mg/m2 which was determined to be the MTD in the previous phase I clinical trial.

Description of CPI-613 Drug Product

CPI-613 is provided in 10-mL amber glass vials. Each vial contains 10 mL of CPI-613 at a concentration 50 mg/mL, equivalent to 500 mg of CPI-613. The drug product of CPI-

613 is a clear and colorless solution that is free of any particulate matter.

Handling of CPI-613

CPI-613 is an investigational drug and the toxicity in humans is not fully understood. All necessary precautions in handling potentially toxic chemicals must be strictly adhered to. Gloves and protective clothing must be worn when handling CPI-613. Avoid contact by all modes of exposure. If the solution contacts the skin, it must be washed immediately and thoroughly with soap and water. If the solution comes in contact with mucous membranes, the membranes must be flushed thoroughly with water. Spills should be picked up with absorbent material and the area must be washed at least 3 times with ethyl alcohol followed by water.

CPI-613 drug product is slightly photosensitive (Study# PHO-001). Therefore, after removal of CPI-613 drug product from the amber vials, CPI-613 drug product should be protected from excessive light before administration to patients.

Storage of CPI-613

CPI-613 should be stored under refrigeration, at 2˚-8˚C (36˚-46˚F), except when being prepared for administration.

Administration Route of CPI-613

CPI-613 must be administered IV by infusion, via an IV catheter with D5W running at a rate of about 125-150 mL/hr. To avoid local reactions at and around the site of administration, CPI-613 should be administered via a central venous catheter.

CPI-613 can cause leaching of Diethylhexyl Phthalate (DEHP) from IV infusion sets and IV bags (Study COM-003). Therefore, DEHP-containing IV infusion sets, IV bags or syringes should not be used in mixing or administration of CPI-613. Examples of the IV sets, IV bags and syringes that do not contains DEHP and therefore can be used in the administration of CPI-613 are:

Extension Set for Syringe Pump Use: All extension sets from MED-RX do not contain DEHP.

Syringes: Kendall Monoject syringes, all mono-ject syringes are DEHP free.

IV Infusion Sets:

A compatibility study has been conducted showing that CPI-613 is compatible with 4 commonly used IV infusion sets (Study# COM-001). Therefore, these 4 types of IV

infusion sets, and IV infusion sets that are made with the same materials, can be used to administer CPI-613. These IV infusion sets are:

PVC material - ADDitIV® Primary IV Set with Universal Spike, Backcheck Valve, 2 Injection Sites, DEHP-Free and Latex-Free, 15 drops/mL, REF V14453, B Braun Medical Inc.

Latex material - Interlink® System Secondary Medication Set, 10 drops/mL, 2C7451, Baxter Healthcare Corporation

PVC material - SurshieldTM Safety Winged Infusion Set, 0.19 mL Volume, Latex-Free, DEHP-Free, SV*S25BLS, Terumo Medical Products Hangzhou Co. Ltd.

Polyethylene material - Interlink® System Paclitaxel Set by Baxter HealthCare, Non DEHP-free: Polyethylene tubing with a 0.22 microfilter Item # 2C7558 10 drops/mL

Syringes

Compatibility studies (Studies# COM-001 and COM-002) have shown that CPI-613 drug product (50 mg/mL), and drug product diluted with D5W to various concentrations (1.6-25 mg/mL) are compatible with various types of syringes, as listed below. Therefore, any of these types of syringes, and syringes that are made with the same materials, can be used to administer CPI-613. Also, glass syringes can also be used, since glass (such as glass containers) is compatible with CPI-613 drug product.

Norm-Ject, polyethlyene barrel, polyethylene plunger, latex free (Henke Sass Wolf GMBH) syringes

- Becton Dickinson syringes
- Terumo syringes
- Monoject syringes
- Glass syringes

Reconstitution Process and Administration of CPI-613

CPI-613 must be diluted from 50 mg/mL to 12.5 mg/mL with 5% Dextrose Water (D5W) (i.e., 1 portion of CPI-613 diluted with 3 portions of D5W) prior to administration. The diluted drug product should be visually inspected for clarity. If haziness, precipitate or coloration (other than colorless) is observed, do not use the diluted drug product for dosing. After dilution with sterile D5W, the solution is clear and has a pH of 8.4-8.8. The diluted CPI-613 drug product has been found to be stable for 24 hrs at room temperature and refrigeration temperature (Studies STA-010).

CPI-613 must be administered IV, via an IV catheter that is free flowing and free of air

in the dead space of the IV catheter, to minimize vascular irritation, inflammation and acute toxicity of CPI-613 (Study NCL-049). Accidental co-administration of extra air in the dead space of IV catheters during administration of CPI-613 has demonstrated the potential to induce acute toxicity of CPI-613 according to animal studies (Study NCL-049). Also, accidental leakage of CPI-613 into the perivascular space during IV administration, which prolongs exposure of perivascular tissue to CPI-613, can induce significant local inflammation according to animal studies (Studies NCL-027 and NCL-030). To avoid local reactions at and around the site of administration, CPI-613 must be administered via a central venous catheter.

CPI-613 must not be administered as a bolus, but by infusion, at a rate of ~0.5 mL/min, via a central venous catheter with D5W running at a rate of about 125-150 mL/hr. This is to minimize potential acute toxicity of CPI-613, according to animal studies (Study NCL-049).

The following precautions must be taken when administering CPI-613:

A. Confirmation of the placement of the IV line to ensure a lack of leakage of CPI-613 into the perivascular space.
B. Confirmation that the IV line is free flowing.
C. Confirmation that the IV line is free of dead air space.
D. Dilute CPI-613 drug product with D5W, as instructed in the study protocol.
E. Administer CPI-613 by infusion, not as a bolus.
F. After administration of CPI-613, flush the IV line with ~10 mL of D5W to remove residual CPI-613.
G. To avoid local reactions at and around the site of administration, CPI-613 should be administered via a central venous catheter.

Request for CPI-613

CPI-613 must be requested from Rafael by the Principal Investigator (or authorized designees). CPI-613 may not be used outside the scope of this protocol, nor can it be transferred or licensed to any party not participating in this clinical study. Rafael policy requires that CPI-613 be shipped directly to the institution where the patient is to be treated. Rafael does not permit the transfer of CPI-613 between institutions (unless with prior written approval from Rafael). Requests must be submitted to Rafael by email to [redacted]

The following information must be provided in the request of CPI-613 from Rafael:

- Names of the principal investigator and the requestor (if different)
- Name of the study site
- Name of the pharmacist responsible for receiving and storing CPI-613
- Name of the person and address where CPI-613 is to be shipped to

- Amount (# vials) requested
- Date of request
- Date shipment expected
- Study Protocol (title and protocol#) for which the requested CPI-613 is to be used

Procurement of Investigational Drug

Relevant regulations require investigators to establish a record of the receipt, use and disposition of all investigational products. Investigators may delegate responsibility of drug ordering, storage, accountability and preparation to their designees.

The investigator, or the designee, will be responsible for dispensing and accounting of CPI-613 provided by Rafael and for exercising accepted medical and pharmacy practices.

Records of inventory, dispensation and disposition (vials received, source and dates) must be maintained. In addition, all doses dispensed should be accounted for by recording the date, study number and name, patient identification, patient initials, patient medical record number and balance forward. These records must be maintained and kept at the study site, and will be reviewed by Rafael, or its designee, during periodic monitoring visits.

Disposal of CPI-613

The following procedures are to be taken in disposal of CPI-613:

-During the study, store the used CPI-613 vials (which must be separate from the unused CPI-613 vials) at room temperature in an access-limited area. Alternatively, destroy the used CPI-613 vials according to institutional policy after documentation of the number of used CPI-613 vials and remaining volume in each used vial.

-At the end of the study, deface the label (both used and unused vials) with a permanent marking pen.

-For used CPI-613 vials (if not already destroyed according to institutional policy), after documentation of the number of used CPI-613 units and remaining volume in each container, the used containers should be destroyed at the site according to the institutional procedures for destroying toxic chemicals. A certificate documenting the destruction of used vials must be kept on file.

Calculation of the Amount of CPI-613 for Each Patient

The amount of CPI-613 at each dose level is based on the BSA of the patient. The BSA values will be calculated based on the height and body weight taken during screening

and this BSA value is used throughout the study. This is unless there is a >10% change in the body weight from baseline during the study. At that point, BSA should be revised based on the new body weight and height. The new BSA values will be used from that point on for the remainder of the study, unless there is another >10% change in body weight which will require another revision of the BSA.

8.3 Concomitant Medications and Prophylactic Treatment

Patients cannot receive any standard or investigational treatment (except CPI-613 and Bendamustine) for their cancer, or any other investigational drugs for any indications, while on this study. All concomitant medications (including trade and generic names, dosage and dosing schedule) must be recorded. Concomitant use of anti-emetics is permitted for patients with disease-related nausea. If study subjects experience metallic taste/taste alteration during CPI-613 infusion, which can sometimes lead to nausea and vomiting, patients can take mint candy to minimize the adverse effect. The use of mint candy, and its effectiveness in minimizing metallic taste/taste alteration, should also be recorded.

Special note for Mitochondrial Inhibition Syndrome.

*This is a constellation of symptoms that may include high fevers, hypotension, lethargy, pancytopenia, altered mental status and generalized weakness and lactic acidosis. If this occurs or is suspected the recommended treatment until symptoms resolve is:

a. IV L-carnitine 50mg/kg/day in divided doses every 4 hours (i.e. 8.3mg/kg every 4 hours)
b. Folic acid 1mg daily
c. Thiamine 100mg daily

For Bendamustine, prophylactic treatment for drug-related symptoms can be given according to Package Inserts of the study drugs and clinical practice. Supportive treatment may include anti-emetic, anti-diarrhea, anti-pyretic, anti-allergic, anti-hypertensive, analgesics, antibiotics, allopurinol, and others such as blood products and bone marrow growth factors. Patients may use erythropoietin for chronic anemia. The investigator may utilize erythropoietic factors, or blood or platelet transfusions at their discretion.

9.0 Adverse Events List and Reporting Requirements

9.1 Adverse Event Characteristics

- **CTCAE term (AE description) and grade: The CTEP Active Version of the NCI Common Terminology Criteria for Adverse Events (CTCAE 5.0) will be utilized for AE reporting. The CTEP Active Version of the CTCAE is identified and located on the CTEP website at (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All**

appropriate treatment areas should have access to a copy of the CTEP Active Version of CTCAE.

- **'Expectedness': AEs can be 'Unexpected' or 'Expected' for expedited reporting purposes only.**
- **Attribution of the AE:**
- **Definite – The AE is clearly related to CPI-613.**
- **Probable – The AE is likely related to CPI-613.**
- **Possible – The AE may be related to CPI-613.**
- **Unlikely – The AE is doubtfully related to CPI-613.**
- **Unrelated – The AE is clearly NOT related to CPI-613.**

The Wake Integrated Solution for Enterprise Research (WISER) database will be used for this study to monitor dose level accrual and toxicity-related data. Built-in features within WISER auto-suspend protocol accrual when dose level target accrual is reached or when DLTs reach the protocol-defined limit. Suspension is only lifted following PI review of all adverse events. All grade 3, 4, 5 adverse events should be reported on flowsheets and in WISER regardless of whether they are on the list in 8.2 and 8.3.

All SAEs which are Serious, Possibly Related and Unexpected are required to be reported to Rafael Pharmaceuticals via the provided SAE Reporting Form. All completed forms must be sent to Claudia Moore at Rafael. Rafael will submit any applicable SAEs to the FDA.

SAE reports must be submitted to Rafael by email to: [redacted]

9.2 Adverse Event Characteristics of CPI-613

Possibly related:

- Alkaline phosphatase
- Anorexia
- ALT (SGPT)
- AST (SGOT)
- Bilirubin (hyperbilirubinemia)
- Calcium (hypercalcemia, hypocalcemia)
- *Diarrhea
- Flushing
- Hemoglobin (anemia)
- *Injection site Reaction
- Leukocytes
- Lymphopenia
- *Nausea
- Neutrophils (neutropenia)
- Platelets (thrombocytopenia)
- Potassium
- Sodium
- *Vomiting
- Hematuria

Probably related:

- *Creatinine

Asterisk (*) denotes expected Adverse Events.

9.3 List of adverse events for Bendamustine

Definitely related:

- Myelosuppression.
- Infections (pneumonia, sepsis, septic shock, and death).
- Anaphylaxis and Infusion Reactions (symptoms include fever, chills, pruritus, rash and in rare instances severe anaphylactic and anaphylactoid reactions).
- Tumor Lysis Syndrome.
- Skin Reactions (rash, toxic skin reactions and bullous exanthema).
- Extravasation injury (erythema, marked swelling, and pain).

Probably related:

Other malignancies (pre-malignant and malignant diseases including myelodysplastic syndrome, myeloproliferative disorders, acute myeloid leukemia and bronchial carcinoma)

Possibly related:

- Immune/autoimmune events (uveitis, optic neuritis, pleuritis,serum sickness with polyarticular arthritis, and vasculitis with rash)
- Agitation
- Anorexia
- Arthritis
- Conjunctivitis
- Depression
- Dyspepsia
- Edema
- Hyperkinesia
- Hypertonia
- Hypesthesia
- Hypoglycemia
- Injection site pain
- Insomnia
- Lacrimation disorder
- Malaise
- Nervousness
- Neuritis
- Neuropathy
- Paresthesia
- Somnolence
- Vertigo
- Weight decrease

9.4 Definition of DLT and DLT Evaluation Period

A DLT is defined as follows:

For non-hematological toxicities:

- Any non-hematological toxicity Grade ≥ 3, except for alopecia and nausea uncontrolled by medical management.
- Any Grade ≥ 2 toxicity that does not resolve to Grade ≤ 1 by the start of the next cycle.

For hematologic toxicities:

a. Grade 4 neutropenia lasting more than 5 days
b. Febrile neutropenia of any duration (ANC <1.0 x 10 9/L, fever >38.5◦C)
c. Grade 4 thrombocytopenia, or Grade 3 thrombocytopenia with bleeding or any requirement for platelet transfusion
d. Grade 4 anemia, unexplained by underlying disease

The DLT evaluation period is through Cycle 1 (4 weeks) for each patient.
****NOTE:** Toxicities must continue to be collected during Cycles 2, 3, 4, 5 and 6 for data analysis purposes. This is reiterated on the Adverse Event Form (See Forms Packet).****

9.5 STRC SAE Reporting Requirements

The Data Safety Monitoring Committee (DSMC) is responsible for reviewing SAEs for WFBCCC Institutional studies as outlined in Appendix D. All Adverse Events that occur during protocol intervention and are coded as either 1) unexpected grade 4, 2) unplanned inpatient hospitalization ≥ 24 hours (regardless of grade), or grade 5 (death) must be reported to the DSMC using the using the SAE console in WISER.

All WFBCCC Clinical Protocol and Data Management (CPDM) staff members assisting a Principal Investigator in investigating, documenting and reporting an SAE qualifying for DSMC reporting are responsible for informing a clinical member of the DSMC as well as the entire committee via the email notification procedure of the occurrence of an SAE.

9.6 WFUHS IRB AE Reporting Requirements

IRB (Any unanticipated problems involving risks to subjects or others and adverse events shall be promptly reported to the IRB, according to institutional policy. Reporting to the IRB is required regardless of the funding source, study sponsor, or whether the event involves an investigational or marketed drug, biologic or device. Reportable events are not limited to physical injury, but include psychological, economic and social harm. Reportable events may arise as a result of drugs, biological agents, devices, procedures or other interventions, or as a result of questionnaires, surveys, observations or other interactions with research subjects.

All members of the research team are responsible for the appropriate reporting to the IRB and other applicable parties of unanticipated problems involving risk to subjects or others. The Principal Investigator, however, is ultimately responsible for ensuring the prompt reporting of unanticipated problems involving risk to subjects or others to the IRB. The Principal Investigator is also responsible for ensuring that all reported unanticipated risks to subjects and others which they receive are reviewed to determine whether the report represents a change in the risks and/or benefits to study participants, and whether any changes in the informed consent, protocol or other study-related documents are required.

Any unanticipated problems involving risks to subjects or others occurring at a site where the study has been approved by the WFUHS IRB (internal events) must be reported to the WFUHS IRB within 7 calendar days of the investigator or other members of the study team becoming aware of the event.

Any unanticipated problems involving risks to subjects or others occurring at another site conducting the same study that has been approved by the WFUHS external events) must be reported to the WFUHS IRB within 7 calendar days of the investigator or other members of the study team becoming aware of the event.

Any event, incident, experience, or outcome that alters the risk versus potential benefit of the research and as a result warrants a substantive change in the research protocol or informed consent process/document in order to insure the safety, rights or welfare of research subjects.

10.0 Statistical Considerations

10.1 Analysis of Primary Objective

The primary objectives for this pilot study are to assess the feasibility, safety and tolerability of administering CPI-613, when used in combination with Bendamustine in patients with relapsed and refractory T-cell NHL who have or have not received hematopoietic cell transplant and to evaluate further the safety of CPI-613 and Bendamustine combination.

For each of these primary objectives we will measure proportions of patients and corresponding 95% confidence intervals to gather preliminary estimates of feasibility, safety and tolerability and corresponding levels of variability. Specifically, for the feasibility objective, we will consider a patient as completing therapy if they complete 80% of proposed treatment regimen. Using this pilot study, we will estimate this proportion of patients, and would consider this regimen “feasible” for future studies if at least 75% of patients successfully complete 80% of their therapy regimens. We will then calculate a 95% exact Clopper-Pearson confidence interval for this proportion. Next, for the second primary objectives of safety and tolerability, we will gather additional toxicity data for patients in this trial. We will examine toxicities by patient and by body system. We will calculate proportions of patients who have specific toxicities and also examine the distribution of toxicities by grade across patients. These estimates will provide further useful data for characterizing the safety and tolerability profile of patients taking this combination therapy.

10.2 Exploratory Objectives

All patients who are enrolled and receive any treatment will be considered evaluable for efficacy outcomes in this pilot study regardless of the amount of treatment received.

For these exploratory objectives of evaluating Overall Response Rate (ORR), Disease Control Rate (DCR), Duration Of Response (DOR), Progression-Free-Survival (PFS), and Overall Survival (OS) we will perform descriptive analyses. Given the small sample size expected for this study, evaluation of each of these secondary objectives will be

exploratory in nature. Descriptive statistics will be calculated to describe each of the categorical measures such as Response Rate (RR). In addition, Clopper-Pearson 95% exact confidence intervals will be calculated for each binary outcome. For time to event measures such as OS and PFS Kaplan Meier survival curves will be estimated and median times will be estimated from these curves. Each of these analyses will be performed to generate useful pilot data for planning future studies. The amount of treatment received will be examined in these exploratory analyses as well to determine if there is any association between this level and any of the efficacy outcomes. So for the response rate measures we will examine whether treatment amount is higher (or lower) based on levels of response. Likewise, for time to event analyses we will examine whether treatment amount is associated with outcomes using Cox proportional hazards regression. We recognize that with the small sample size in this pilot study these analyses examining associations between treatment amount and efficacy outcomes will only provide exploratory data to examine these questions.

Single cell transcriptomic status pre- and post-treatment will be assessed and this data will be examining in a descriptive manner. Correlation of blood PBMC (and possibly excess pre-treatment tumor biopsy) cell population diversity and functional states will be examined and seen if there is any relationship between these biomarkers and patient response status. For example, for continuous assessments a two-sample t-test will be performed to compare measures between responders and non-responders. Likewise, for categorical assessments, Fisher's exact tests will be performed to compare rates between responders and non-responders.

10.4 Power and Sample Size

We expect to screen 20 subjects in this study in order to obtain 12 evaluable subjects. With a sample size of 12 patients, a two-sided 95% exact Clopper Pearson confidence interval will have a width of +/- 0.29 if the sample proportion is 0.5. For examining feasibility, we anticipate that the observed rate will be above 75%, so with this value the confidence interval would have a width of +/-0.259 (thus the lower bound would be 0.43. Although, these confidence intervals have relatively large widths, it is felt that this study will still provide useful information to inform the design of future larger studies.

10.5 Accrual Rate

We anticipate accruing at least one patient every 2 months on this protocol and thus expect that accrual for this pilot trial will be completed in ~24-28 months.

10.6 Interim Analysis Plan

There are no interim analyses planned for this study.

11.0 Data Management

Form	Database
Informed Consent	WISER/On Core
Protocol Registration Form	REDCap
Withdrawal of Participation Form	REDCap
Telephone Follow-up/Survival Form	REDCap
Efficacy Assessment Form/Bone Marrow Biopsy	REDCap
Adverse Event Log	REDCap
Medical Record Review Form	REDCap
Vitals/ECOG	REDCap

12.0 Multi-Institutional Monitoring Plan

12.1. SAE Reporting

Each investigator is responsible for submitting SAEs and unexepected AEs to their Institutional Review Board/Ethics Committee according to their institutional guidelines.

Any serious or unexpected event, which occurs to any patient in the course of their treatment on this study or within 30 days following cessation of treatment, must be reported immediately to the Comprehensive Cancer Center of Wake Forest University (WFBCCC) within 24 hours of the investigator learning of its occurrence. When calling to report an event, please clearly state the protocol number (WFBCCC 28314) and the patient identification number, along with the event description and grade. The immediate reports should be followed promptly by detailed, written reports.

A FDA Form 3500 (MEDWATCH) must be sent to WFBCCC for all SAEs which are unexpected, fatal or life-threatening experience and associated with the use of the drug within 48 hours.

The patient must be followed up until clinical recovery is complete and/or laboratory results have returned to normal. This may mean that follow-up will continue after the patient has completed the trial.

12.2. Registration Procedures

All patients must be registered with the WFBCCC Protocol Registrar before enrollment to study. To register a patient, contact the WFBCCC Protocol Registrar Monday through Friday, 8:30AM-4:30PM EST.

12.3. Study Monitoring

Personnel from the WFBCCC Protocol Office will monitor the trial. Clinical Research Associates may periodically visit the investigative site to assure proper conduct of the trial and proper collection of the data. The investigators at each site will allow the monitor to review all source documents used in the preparation of the case reports.

All study forms should be sent to the coordinating site within one week of patient completion.

12.4. Required Documentation

Before the study can be initiated at any site, the following documentation must be provided to the Protocol Office at Wake Forest University Health Sciences.

A. Written documentation of IRB approval of protocol (identified by title, protocol version and date of approval) for each site.
B. IRB membership list
C. Current curricula vitae and documentation of professional licensure of the Principal Investigator and co-Investigators listed on the 1572.
D. U.S. Food and Drug Administration (FDA) Form 1572, signed by the Principal Investigator at the participating center. The names of any sub-investigators at the participating center must appear on this form. Investigators must also complete all regulatory documentation as required by local regulations. This includes any required human subjects training required by the site's local IRB.
E. Human subject protections documentation (e.g. NIH, CITI) for all research personnel (e.g. study coordinators, data managers and other research personnel).
F. IRB approved study informed consent and HIPAA consent form. HIPAA consent language can be included within the study informed consent. Please note that all informed consent forms should be reviewed and approved by the WFU protocol office prior to submission to the site's designated IRB.
G. Laboratory certifications (CAP, CLIAs) and laboratory reference value ranges for each laboratory listed on the site's 1572.
H. Executed clinical research contract
I. Any approval memos from IRB for protocols, continuing reviews, and approved informed consents

J. Signed WFUHS Conflict of Interest Form

12.5 Adherence to the Protocol

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study patient requires alternative treatment, the study shall be conducted exactly as described in the approved protocol. Any deviation from the protocol must have prior approval by the WFBCCC Principal Investigator and must be recorded and explained.

12.6 Amendments to the Protocol

Should amendments to the protocol be required, the amendments will be originated and documented by the Principal Investigator at WFBCCC. The written amendment will be sent to investigators and must be submitted to the IRB at the investigator's site for approval. It should also be noted that when an amendment to the protocol substantially alters the study design or the potential risk to the patient, a revised consent form might be required.

12.7 Record Retention

Study documentation includes all Case Report Forms, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Government agency regulations and directives require that all study documentation pertaining to the conduct of a clinical trial must be retained by the study investigator. In the case of a study with a drug seeking regulatory approval and marketing, these documents shall be retained for at least two years after the last approval of marketing application in an International Conference on Harmonization (ICH) region. In all other cases, study documents should be kept on file until three years after the completion and final study report of this investigational study.

12.8 Obligations of Investigators

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study patients. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and

after study completion.

The Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected and entered onto the flowsheet. Periodically, monitoring visits will be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. At the completion of the study, all case report forms will be reviewed by the Principal Investigator and will require his/her final signature to verify the accuracy of the data.

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Appendix A – Subject Eligibility Checklist

IRB Protocol No.	**WFBCCC Protocol No. WFBCCC 28419**
Study Title: Pilot Study of CPI-613 in Combination with Bendamustine in Patients with Relapsed or Refractory T-Cell Non-Hodgkin Lymphoma	
Principal Investigator: Rahkee Vaidya, M.B.B.S.	

Inclusion Criteria (as outlined in study protocol)	**Criteria is met**	**Criteria is NOT met**	**Source Used to Confirm**
1. Histologically or cytologically confirmed PTCL (all subtypes) or CTCL (mycosis fungoides/sezary syndrome) as defined by 2016 World Health Organization (WHO) classification.	□	□	
2. For patients with PTCL: a. Patients must have relapsed/ refractory disease to one or more systemic therapies. b. Patients with CD30-positive lymphoma must have received, be ineligible for, or intolerant to brentuximab vedotin. c. Patients with limited prior exposure to Bendamustine (less than 2 full cycles or ≤ 480 mg/m^2) may be included, based on PI discretion. d. Patients must have measurable disease (e.g., a tumor mass >1 cm or evidence of bone marrow involvement)	□	□	

3. For patients with CTCL, stage IB- IVB mycosis fungoides or Sezary syndrome are eligible a. Patients must have relapsed/ refractory disease to at least one previous systemic therapy. Psoralen plus ultraviolet light therapy (PUVA) is not considered to be a systemic therapy.	□	□	
4. Male and female patients 18 years of age and older	□	□	
5. Eastern Cooperative Oncology Group (ECOG) performance status 0-2.	□	□	
6. Expected survival >3 months	□	□	
7. Women of child-bearing potential (i.e., women who are pre-menopausal or not surgically sterile) must use accepted contraceptive methods (abstinence, intrauterine device [IUD], oral contraceptive or double barrier device) during the study, and must have a negative serum or urine pregnancy test within 1 week prior to treatment initiation.	□	□	
8. Fertile men must practice effective contraceptive methods during the study, unless documentation of infertility exists.	□	□	
9. At least 2 weeks must have elapsed from prior chemotherapy drugs (other than steroids) or radiation	□	□	

10. At least 6 weeks must have elapsed from prior autologous stem cell transplant and 12 weeks must have elapsed from prior allogeneic stem cell transplant.	□	□	
11. Laboratory values ≤2 weeks must be: a. Adequate hematological function (absolute neutrophil count [ANC] ≥1,500/mm^3, platelets ≥100,000/mm^3). In subjects with known bone marrow involvement, ANC must be ≥ 1000/mm^3 and platelets ≥75,000/mm^3 b. Adequate hepatic function (aspartate aminotransferase [AST/SGOT] ≤3x upper normal limit [UNL], alanine aminotransferase [ALT/SGPT] ≤3x UNL (≤5x UNL if liver metastases present), bilirubin ≤1.5x UNL). c. Adequate renal function (serum creatinine ≤1.5 mg/dL or 133 µmol/L).	□	□	
12. No evidence of current infection.	□	□	
13. Mentally competent, ability to understand and willingness to sign the informed consent form.	□	□	
Exclusion Criteria (as outlined in study protocol)	**Criteria NOT present**	**Criteria is present**	**Source Used to Confirm**

1. Known cerebral metastases, central nervous system (CNS) or epidural tumor.	□	□	
2. History of prior malignancy and considered to be at greater than 30% risk of relapse	□	□	
3. Patients receiving any other standard or investigational treatment for their cancer, or any other investigational agent for any indication, within the past 2 weeks prior to initiation of treatment with study drugs (steroids are allowed)	□	□	
4. Patients with a history of allogeneic transplant must not have ≥ grade 3 graft-versus-host disease (GVHD) or any clinically significant GVHD requiring systemic immunosuppression.	□	□	
5. Serious medical illness that would potentially increase patients' risk for toxicity.	□	□	
6. Pregnant women, or women of child-bearing potential not using reliable means of contraception (because the teratogenic potential of CPI-613 is unknown).	□	□	
7. Lactating females.	□	□	
8. Fertile men unwilling to practice contraceptive methods during the study period.	□	□	
9. Any condition or abnormality which may, in the opinion of the investigator, compromise the safety of patients.	□	□	
10. Unwilling or unable to follow protocol requirements.	□	□	

11. Active heart disease including but not limited to symptomatic congestive heart failure, symptomatic coronary artery disease, symptomatic angina pectoris, symptomatic myocardial infarction or symptomatic congestive heart failure.	□	□	
12. Evidence of current infection.	□	□	
13. Patients with known HIV infection, hepatitis B, or hepatitis C with positive viral load.	□	□	
14. Patients who have received cancer immunotherapy of any type within the past 2 weeks prior to initiation of CPI-613 treatment.	□	□	

This subject is ☐ eligible / ☐ ineligible for participation in this study. (continued on next page)

WISER PID: _____

Signature of research professional confirming eligibility:_____ Date: _____

Signature of Treating Physician: _____

Date: _____

Signature of Principal Investigator**: _____ Date: _____

* Examples of source documents include clinic note, pathology report, laboratory results, etc. When listing the source, please specifically state which document in the medical record was used to assess eligibility. Please also include the date on the document. Example: “Pathology report, 01/01/14” or “Clinic note, 01/01/14”

**Principal Investigator signature can be obtained following registration if needed

Appendix B – Protocol Registration Form

DEMOGRAPHICS

Patient: Last Name: _____ First Name: _____

MRN: ___ ___ ___ ___ ___ ___ ___ ___ DOB (mm/dd/yy): ___ ___ / ___ ___ / ___ ___

Zip Code: ___ ___ ___ ___ ___ SEX: ☐ Male ☐ Female Ethnicity (choose one): ☐ Hispanic ☐Non-Hispanic

Race (choose all that apply): ☐ WHITE ☐BLACK ☐ ASIAN ☐ PACIFIC ISLANDER ☐ NATIVE AMERICAN

Height: ___ ___.___ inches Weight: ___ ___ ___.___lbs.(actual) Surface Area: ___ ___.___m^2

Primary Diagnosis: _____ Date of Diagnosis: ___ ___ /___ ___/___ ___

Performance Status : _____ Stage of Disease: _____

CURRENT DISEASE STATUS AT REGISTRATION: _____

Prior Therapies/ Protocol # if applicable	Start / End Date of Prior Therapy	Best Response (CR, PR, Treatment Failure)	Date of Best Response	Date of Relapse	Duration of Best Response (in Months)
#1 _____	_____/_____	_____	_____	_____	_____
#2 _____	_____/_____	_____	_____	_____	_____
#3 _____	_____/_____	_____	_____	_____	_____
#4 _____	_____/_____	_____	_____	_____	_____

PROTOCOL INFORMATION

Date of Registration: ___ ___ / ___ ___ / ___ ___

MD Name (last) : _____

Date protocol treatment started: ___ ___ / ___ ___ / ___ ___

Informed written consent (consent must be signed prior to registration): ☐ YES ☐ NO

Date Consent Signed: ___ ___ / ___ ___ / ___ ___

PID # (to be assigned by OnCore): ___ ___ ___ ___ ___ ___ ___ ___

Protocol Registrar can be contact by calling 336-713-6767 between 8:30 AM and 4:00 PM, Monday – Friday.
Completed Eligibility Checklist and Protocol Registration Form must be hand delivered, faxed or e-mailed to the registrar at [redacted]

Appendix C Safety and Toxicity Review Committee SOP

Data and Safety Monitoring Committee (DSMC) Serious Adverse Event (SAE) Notification SOP	**Date: 02/11/2021**

Mandatory DSMC SAE Reporting Requirements in WISER

This document describes reporting requirements of adverse events from **WFBCCC Investigator Initiated interventional trials to the Data and Safety Monitoring Committee (DSMC).** A trial is considered a **WFBCCC Investigator Initiated interventional trial** if the following criteria are met:

1) The Principal Investigator (PI) of the trial is a member of a department at the Wake Forest University Baptist Medical Center.
2) WFBCCC is considered as the primary contributor to the design, implementation and/or monitoring of the trial.
3) The trial is designated as "Interventional" using the Clinical Research Categories definitions provided by the NCI in the Data Table 4 documentation. (https://cancercenters.cancer.gov/GrantsFunding/DataGuide#dt4)

There are two distinct types of WFBCCC Investigator Initiated interventional trials based on where patient enrollment occurs. These include:

1) Local WFBCCC Investigator Initiated interventional trials defined as trials where **all patients are enrolled from one of the WFBCCC sites.** These include the main outpatient Cancer Center clinics (located in Winston-Salem) as well as WFBCCC affiliate sites located in Bermuda Run (Davie Medical Center), Clemmons, Lexington, High Point, or Wilkesboro.
2) Multi-Center WFBCCC Investigator Initiated interventional trials defined as trials where patients are enrolled from other sites in addition to WFBCCC sites.

   There are three types of trials that are included in this category:

   a. Trials sponsored by the NCI Community Oncology Research Program (NCORP) that are conducted at multiple sites where the PI is a member of a department at the Wake Forest University Baptist Medical Center.
   b. Trials sponsored by Industry that are conducted at multiple sites and the PI is a member of a department at the Wake Forest University Baptist Medical Center.
   c. Trials sponsored by WFBCCC that are conducted at multiple sites and the PI is a member of a department at the Wake Forest University Baptist Medical Center.

All Adverse Events (AEs) and Serious Adverse Events (SAEs) that occur on any patients enrolled on WFBCCC Investigator Initiated Interventional trials must be entered into the WISER system. The only exception to this requirement is for patients enrolled on NCORP trials at non- WFBCCC sites. AEs and

SAEs for NCORP patients enrolled at WFBCCC sites must be entered into the WISER system. Once these AEs and SAEs are entered in WISER, certain actions must be taken regarding the reporting of specific Adverse Events to the DSMC.

All Adverse Events that occur during protocol intervention (defined below) and are coded as either 1) **unexpected grade 4,** 2) **unplanned inpatient hospitalization > 24 hours (regardless of grade)**, or **grade 5 (death)** must be reported to the DSMC using the using the SAE console in WISER.

A research nurse or clinical research coordinator when made aware that an adverse event meets one of the above criteria has occurred on a WFBCCC Investigator Initiated interventional trial, is responsible for informing a clinical member of the DSMC by phone (or in-person) about the adverse event. The nurse/coordinator should contact the treating physician prior to calling the DSMC clinical member to obtain all details of the SAE, as well as all associated toxicities to be recorded along with the SAE. In addition, this nurse or coordinator is responsible for entering the adverse event information into the SAE console in WISER. Once the adverse event has been entered into the SAE console an email informing the entire DSMC will be generated.

THESE REPORTING REQUIREMENTS APPLY TO any staff member on the study team for a WFBCCC Institutional Interventional trial. Ultimately, the protocol PI has the primary responsibility for AE identification, documentation, grading and assignment of attribution to the investigational agent/intervention. However, when an AE event as described above is observed, it is the responsibility of the person who observed the event to be sure that it is reported to the DSMC.

What is considered during protocol intervention?

During protocol intervention is considered to be the time period while a patient is on study treatment or during the time period within 30 days of last study treatment (even if patient begins a new (non-study) treatment during the 30 days). This window of 30 days should be the standard window to be used in all protocols unless a specific scientific rationale is presented to suggest that a shorter window can be used to identify events. If it is a trial sponsored by Industry and the sponsor requires a longer window for monitoring of SAEs, then the longer window of time specified by the sponsor should be followed.

What is considered as an Unexpected Grade 4 event?

Any grade 4 event that was not specifically listed as an expected adverse event in the protocol should be considered as unexpected. A grade 4 adverse event can be considered to be unexpected if it is an event that would not be expected based on the treatment being received or if it is unexpected based on the health of the patient. In either case, if there is any uncertainty about whether a grade 4 adverse event is expected or unexpected it should be reported to DSMC.

DSMC notification responsibilities of the person (e.g., nurse) handling the reporting/documenting of the SAE in WISER:

1. Make a phone call (or speak in person) to the appropriate clinical member of the DSMC according to the schedule as listed below (page if necessary).
2. Enter a new SAE into the SAE module that is located in the Subject>> CRA Console inWISER WITHIN 24 HOURS of first knowledge of the event. Information can be entered and saved, but the DSMC members will not be notified until a date is entered into the DSMC Notification Date Field. This will ensure that all persons that need to be made aware of the event (i.e., PI, study team members and DSMC members) will be notified; remember to file a copy of the confirmation.
3. Document that the appropriate person(s) on the DSMC has been contacted. Indicate the name of the DSMC clinician that was contacted and the date and time contacted in the Event Narrative field in the SAE console of the particular subject.
4. Document whether or not the protocol should be suspended based on the discussion with the DSMC clinician. This is the major function of the email notification. Enter whether the protocol should be suspended in the Event Narrative Field.
5. Follow up/update the clinical member(s) of DSMC regarding any new developments or information obtained during the course of the SAE investigation and reporting process.

Elements needed to complete the SAE form in the Subject Console in WISER (see Screen Shot 3):

1. Event Date
2. Reported Date
3. Reported by
4. If Grade 5, enter Death Date
5. If Grade 5, enter Death occurred: within 30 days
6. Event Narrative: Brief description (include brief clinical history relevant to this event, including therapies believed related to event). Begin narrative with the DSMC clinician who was notified and Date/Time notified. In addition, state attribution by DSMC clinician as either "Unrelated", "Unlikely", "Possibly", "Probably", or "Definitely". Always include the following here:
    i. DSMC clinician name, date/time contacted and comments
    ii. Date of last dose before the event
    iii. Is suspension of the protocol needed? Y/N
7. Treating Physician comments
8. PI comments, if available
9. Protocol Attribution after discussion with DSMC clinician
10. Outcome (Fatal/Died, Intervention for AE Continues, Migrated AE, Not Recovered/Not Resolved, Recovered/Resolved with Sequelae, Recovered/Resolved without Sequelae, Recovering and Resolving)
11. Consent form Change Required? Y/N
12. SAE Classification ***This is required in order for the email notification to be sent***
13. Adverse Event Details – Enter all details for each AE associated with the SAE.
    a. Course start date

b. Category
c. AE Detail
d. Comments
e. Grade/Severity
f. Unexpected Y/N
g. DLT Y/N
h. Attributions
i. Action
j. Therapy
k. Click ADD to attach the AE Detail to the SAE.

14. Enter Date Notified DSMC -- ***This is required for the email notification to be sent***
15. Click Submit. The auto-generated notification email will disseminate within 5 minutes. If you do not receive an email within 5 minutes, check that you have entered the "Date Notified DSMC" and the "SAE Classification". If these have been entered and the email still has not been received, take a screen shot of the SAE in WISER and immediately email it out to all of the STRC members listed in this SOP. In the subject line, indicate that this is a manual transmission of the SAE in lieu of the auto-generated email. It is required that a notification goes to the DSMC members immediately so that their assessment can be obtained within the 24 hour period requirement. Contact the Cancer Center Programmer/Analyst to alert that there is an issue with the auto-generated email.

The Clinical Members of DSMC to Notify by Phone or Page:

Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday
Lesser	Hughes	Goodman	Reed	Porosnicu	Seegars	Lesser
Hughes	Goodman	Reed	Porosnicu	Seegars	Lesser	Hughes
Goodman	Reed	Porosnicu	Seegars	Lesser	Hughes	Goodman
Reed	Porosnicu	Seegars	Lesser	Hughes	Goodman	Reed
Porosnicu	Seegars	Lesser	Hughes	Goodman	Reed	Porosnicu
Seegars	Lesser	Hughes	Goodman	Reed	Porosnicu	Seegars

[redacted]

[redacted]

Definition of Unavailable:

As a general guideline if the first clinician that is contacted does not respond to the phone call or page within 30 minutes, then initiate contact with the next DSMC clinician listed in the table above on the particular day the SAE is being reported. Allow up to 30 minutes for the new DSMC clinician to respond to a phone call or page before contacting the next member in the table. These times (30 minutes) are a general guideline. Best judgment as a clinical research professional should be used giving considerations of the time of day, severity of the SAE, and other circumstances as to when it is appropriate to contact backup clinicians. If the event occurs near the end of day, then leave messages (voice or email) as appropriate and proceed with submitting the DSMC notification form. It is important to take reasonable steps and to document that some type of contact has been initiated to one or more of the clinical members of DSMC.

DSMC CLINICAN RESPONSIBILITY:

It is the responsibility of the DSMC clinician to review all reported events, evaluate the events as they are reported; and communicate a response to the Investigator, event reporter and the members of DSMC. The review will include but not be limited to the information reported; there may be times when additional information is needed in order for an assessment to be made and further communication directly with the investigator may be warranted. DSMC reserves the right to disagree with the Investigator's assessment. If DSMC does not agree with the Investigator, DSMC reserves the right to suspend the trial pending further investigation. If there is any immediate danger or harm that could be present for a future patient based on the information provided in the DSMC report then an immediate suspension of enrollment should be considered.

AMENDMENTS TO PREVIOUS REPORTS

If all pertinent information is unavailable with the initial submission, once the additional information is available **do not submit a new report**. Rather, go to the original email that was sent to the DSMC and using that email "reply to all". Entitle this new email "**Amendment** for (list date of event and patient ID)" this will avoid duplications of the same event. List the additional information being reported. This information needs to be entered into WISER as well. To do this, go to the Subject console and click SAEs on the left column. Click on the appropriate SAE number that needs updating. Then click Update. This will allow additional information to be added.

Acronyms

AE – Adverse Event

DSMC-Data and Safety Monitoring Committee

SAE-Serious Adverse Event

WFBCCC – Wake Forest Baptist Comprehensive Cancer Center

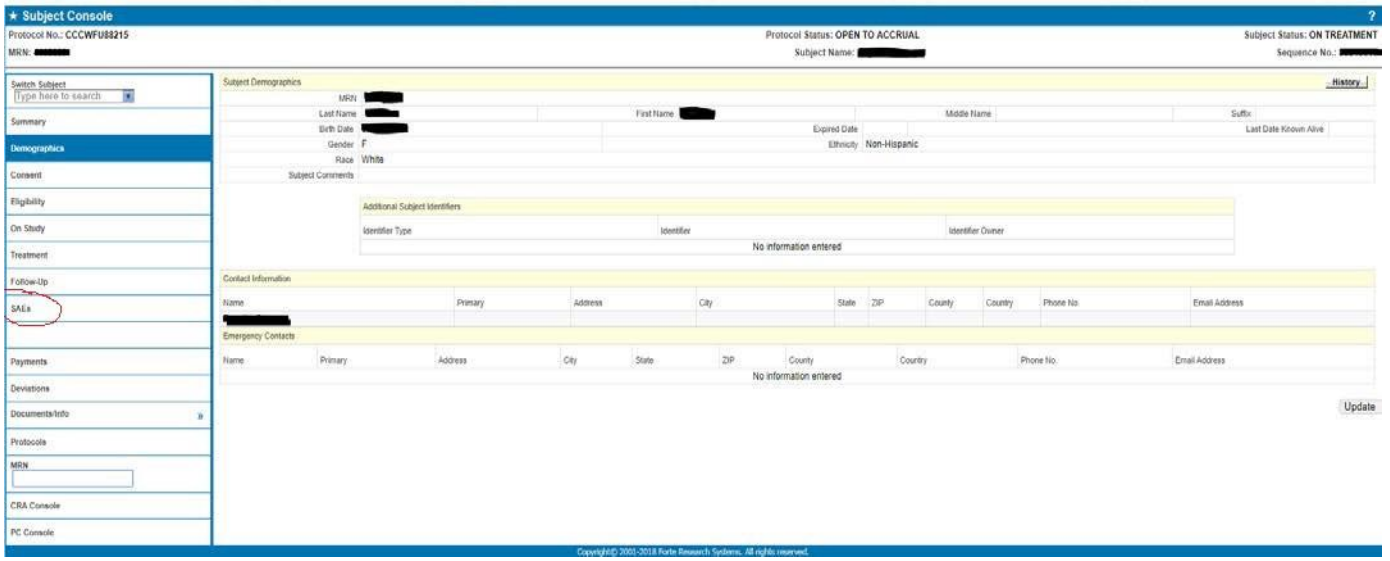
NCI-National Cancer Institute

WISER –Wake Integrated Solution for Enterprise Research

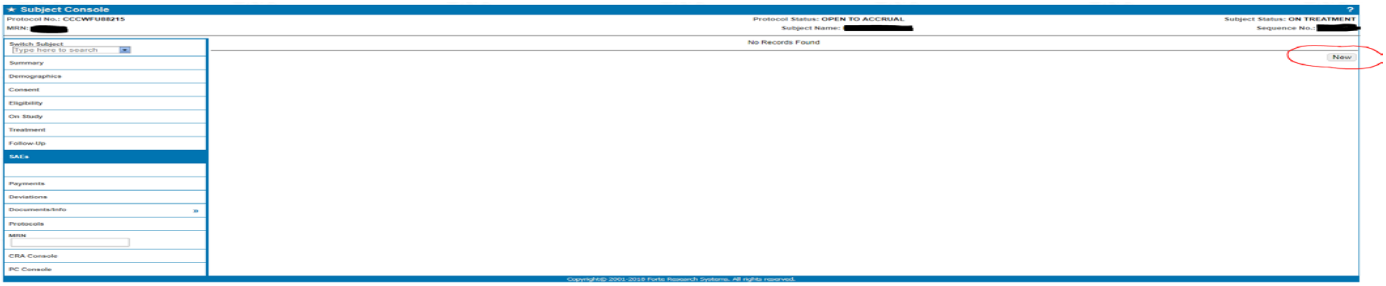
Screen Shots:

The following screen shots come from the SAE Console within the Subject Console in WISER.

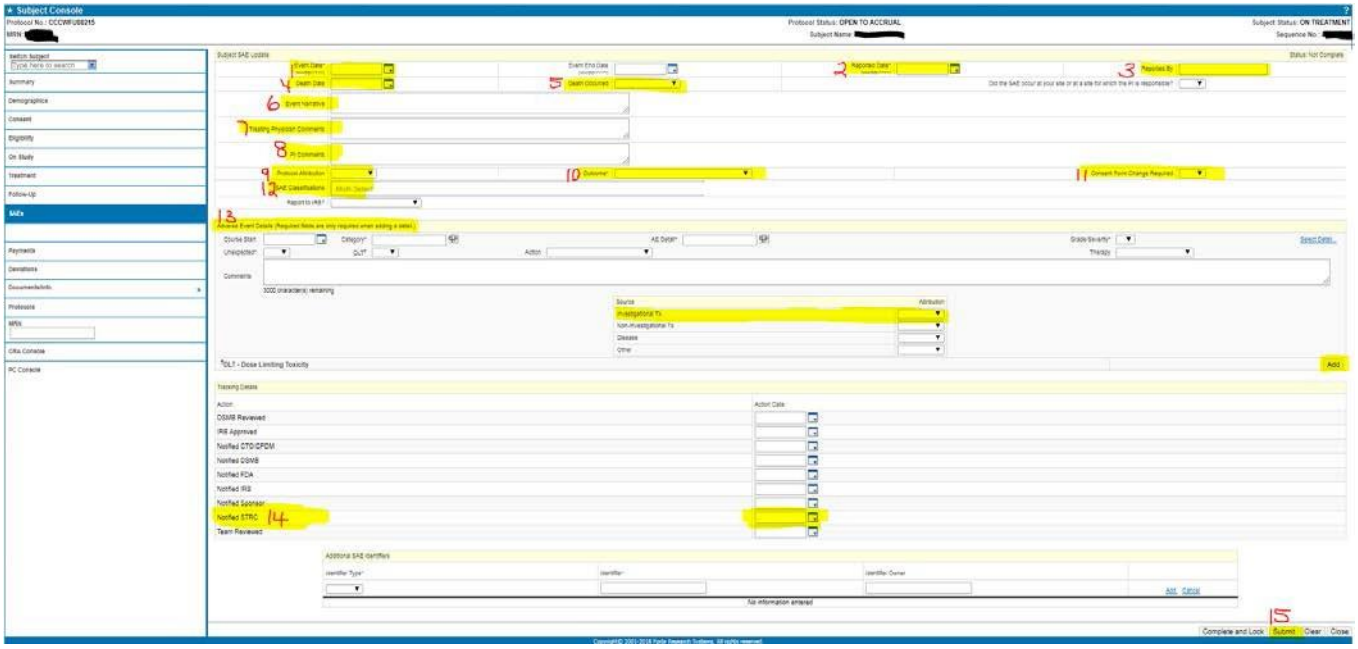
Screen Shot 1:



Screen Shot 2:



Screen Shot 3:



Screen Shot 4: