A RANDOMIZED PHASE II STUDY OF CHO(E)P VS CC-486-CHO(E)P VS DUVELISIB-CHO(E)P IN PREVIOUSLY UNTREATED CD30 NEGATIVE PERIPHERAL T-CELL LYMPHOMAS

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Eligibility Criteria

- Histologically confirmed diagnosis of PTCL with <10% CD30 expression by immunohistochemistry (see Section 3.3.1)
- Measurable disease as defined by the Lugano criteria
- No prior systemic therapy for lymphoma (excluding corticosteroids)
- Not pregnant and not nursing
- Age ≥ 18 years
- ECOG Performance Status ≤ 2
- Patients with a diagnosis of PTCL subtype histologies other than those specified are excluded (see Section 3.3.1)
- Patients with known CNS involvement are excluded
- No active viral infection with HIV, hepatitis B, or hepatitis C
- No active uncontrolled systemic fungal, bacterial, or viral infection. No concurrent malignancy requiring active therapy within the last 3 years
- Documented LVEF of ≥ 45%
- No significant active cardiac disease within the previous 6 months
- No contraindication to any drug in the chemotherapy regimen, including neuropathy ≥ Grade 2
- No chronic concomitant treatment with strong CYP3A4 inhibitors or inducers

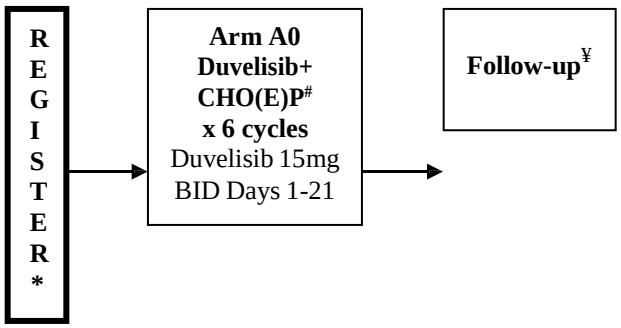
Required Initial Laboratory Values*

Platelet Count	≥ 75,000/mm$^{3\#}$
Absolute Neutrophil Count (ANC)	≥ 1,000/mm^3
AST/SGOT or ALT/SGPT	≤ 3.0 x ULN*
Calc. Creatinine Clearance	≥ 30 mL/min
Total Bilirubin	≤ 2.0 x ULN**

 # ≥ 50,000/mm^3 if secondary to bone marrow involvement from lymphoma per investigator assessment; first 12 patients per arm must have platelet count ≥ 75,000/mm^3

** Except in subjects with documented liver involvement by lymphoma*
*** Unless attributable to Gilbert's Syndrome or documented liver or pancreatic involvement by lymphoma*

Safety Lead-in Schema



* Untreated PTCL, CD30 expression <10% by IHC (excludes ALCL)
\# CHOP/CHOEP [CHO(E)P] given standardly with GSCF support
¥ Patients will be followed for 5 years or until death, whichever comes first.

Safety Lead-In: The first 12 patients on the study will be enrolled in Arm A0 and will receive Duvelisib 15mg BID with CHOP (n=6) or CHOEP (n=6) prior to the randomized study.

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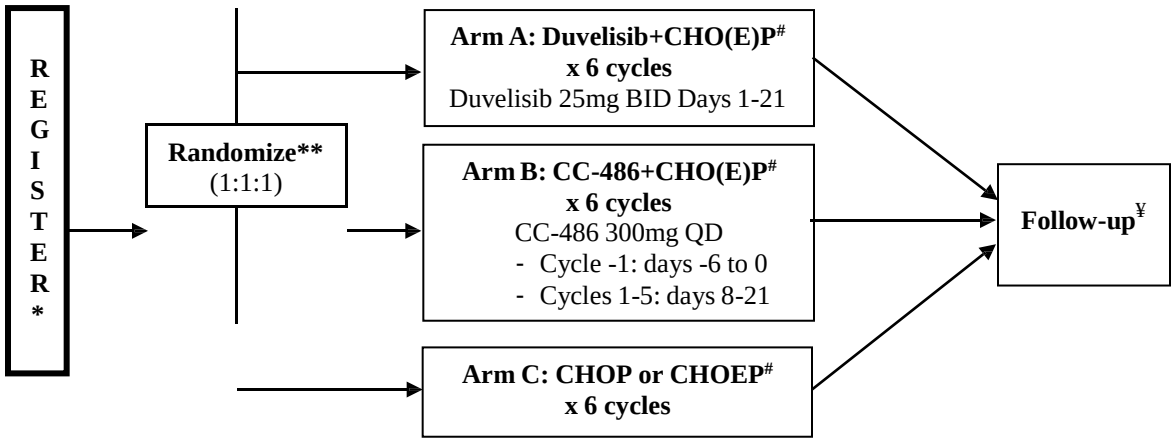
Randomized Phase II Schema



* Untreated PTCL, CD30 expression <10% by IHC (excludes ALCL)

** Stratification: Age (≤ 60 years vs. >60 years); Histologic subtype (AITL/TFH vs. Other) will be added as a stratification factor after the safety check.

\# CHOP/CHOEP [CHO(E)P] given standardly with GSCF support

¥ Patients will be followed for 5 years or until death, whichever comes first.

Phase II Safety Check: The randomized study will have a safety check (the first 12 patients enrolled to each treatment arm) before expanding to the full phase II trial. In arms A, B and C, the safety check will include 6 patients with CHOP chemotherapy and 6 with CHOEP chemotherapy.

Please refer to the full protocol text for a complete description of the eligibility criteria and treatment plan.

2.2.2 To determine the complete remission (CR) rates by FDG PET/CT or CT alone using the Lugano 2014 criteria.

2.2.3 To determine the overall response rate (ORR), duration of response, progression free survival (PFS), event free survival (EFS), and overall survival (OS) of each treatment regimen.

2.2.4 To determine whether designation of follicular helper T-cell phenotype is correlated with response to therapy, PFS, EFS, and OS.

2.2.5 To assess the toxicity profile of the experimental regimens in untreated CD30 negative peripheral T-cell lymphomas using CTCAE and PRO-CTCAE.

3.1 PATIENT SELECTION

For questions regarding eligibility criteria, see the Study Resources page. Please note that the Study Chair cannot grant waivers to eligibility requirements.

3.2 On-Study Guidelines

This clinical trial can fulfill its objectives only if patients appropriate for this trial are enrolled. All relevant medical and other considerations should be taken into account when deciding whether this protocol is appropriate for a particular patient. Physicians should consider the risks and benefits of any therapy, and therefore only enroll patients for whom this treatment is appropriate.

Physicians should consider whether any of the following may render the patient inappropriate for this protocol:

- Psychiatric illness which would prevent the patient from giving informed consent.
- Medical condition such as uncontrolled infection (including HIV), uncontrolled diabetes mellitus or cardiac disease which, in the opinion of the treating physician, would make this protocol unreasonably hazardous for the patient.
- Patients who cannot swallow oral formulations of the agent(s).

In addition:

- Women and men of reproductive potential should agree to use an appropriate method of birth control throughout their participation in this study due to the teratogenic potential of the therapy utilized in this trial. Include as applicable: Appropriate methods of birth control include abstinence, oral contraceptives, implantable hormonal contraceptives or double barrier method (diaphragm plus condom).

3.3 Eligibility Criteria

Use the spaces provided to confirm a patient's eligibility by indicating Yes or No as appropriate. It is not required to complete or submit the following page(s).

When calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test were done on a Monday, the Monday one week later would be considered Day 7.

A female of childbearing potential is a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 12 consecutive months (i.e., has had menses at any time in the preceding 12 consecutive months).

3.2.1 Documentation of Disease

Histologically confirmed diagnosis of PTCL with <10% CD30 expression by immunohistochemistry in the following subtypes (by local review): Nodal T-cell lymphoma with T-follicular helper (TFH) phenotype (TFH-PTCL), follicular T-cell lymphoma, PTCL-NOS, AITL, enteropathy associated T-cell lymphoma, monomorphic epitheliotropic intestinal T-cell lymphoma

- Patients with expression of CD30 in ≥10% of the tumor (based on local immunohistochemistry review) regardless of histology will not be permitted.
- Patients with a diagnosis of other PTCL subtype histologies other than those specified in the inclusion criteria are excluded including large cell transformation of mycosis fungoides
- Patients will be stratified by presence or absence of TFH phenotype (i.e. diagnosis of AITL, TFH-PTCL, follicular T-cell lymphoma) based on local review of pathology. Determination of TFH phenotype can be defined by expression of two or more of the following markers CD10, BCL6, CXCL13, ICOS, and PD1 by immunohistochemistry.

3.2.2 Measurable, FDG avid disease as defined by the Lugano Criteria [26] (see Section 11.0).

3.2.3 Prior Treatment

No prior systemic therapy or radiation therapy for T-cell lymphoma (excluding corticosteroids)

3.2.4 Not pregnant and not nursing, because this study involves an investigational agent whose genotoxic, mutagenic and teratogenic effects on the developing fetus and newborn are unknown.

Therefore, for women of childbearing potential only, a negative urine or serum pregnancy test done ≤ 7 days prior to registration is required.

3.2.5 Age ≥ 18 years

3.2.6 ECOG Performance Status ≤ 2

3.2.7 Required Initial Laboratory Values:

Platelet Count ≥ 75,000/mm^3 (≥50,000/mm^3 if secondary to bone marrow involvement from lymphoma per investigator assessment; the first 12 patients on each arm of the study must have platelets ≥75,000/mm^3 regardless of bone marrow involvement)

Absolute Neutrophil Count (ANC) ≥ 1,000/mm^3

AST/SGOT and ALT/SGPT ≤ 3.0 x ULN*

Calculated Creatinine Clearance ≥ 30 mL/min by Cockcroft-Gault formula

Total Bilirubin ≤ 2.0 x ULN**

* *Except in subjects with documented liver involvement by lymphoma*

** *Except in cases of Gilbert's Syndrome or documented liver or pancreatic involvement by lymphoma*

3.2.8 Archival tissue must be available for submission

3.2.9 Comorbid conditions

- Patients known to have HTLV 1/2 are excluded
- Patients with known central nervous system involvement are excluded
- No active viral infection with HIV, hepatitis B, or hepatitis C. Those who are seropositive (e.g. Hepatitis B core Ab positive) are permitted if they are negative by PCR. Those who are seropositive for hepatitis B and are negative for HBV DNA by PCR must receive concomitant hepatitis B directed antiviral therapy. Those who have hepatitis C Ab positivity who have completed curative therapy for hepatitis C with negative hepatitis C PCR are eligible.
- Human immunodeficiency virus (HIV)-infected patients on effective anti-retroviral therapy with undetectable viral load within 6 months are eligible for this trial.
- No active uncontrolled systemic fungal, bacterial or viral infection (defined as ongoing signs/symptoms related to the infection without improvement despite appropriate antibiotics, antiviral therapy and/or other treatment). Patients with EBV viremia related to their lymphoma are permitted.
- No concurrent malignancy requiring active therapy within the last 3 years with the exception of basal cell carcinoma limited to the skin, squamous cell carcinoma limited to the skin, carcinoma in situ of the cervix, breast or localized prostate cancer. Adjuvant hormonal therapy for cancer previously treated for curative intent is permitted.
- Patients must have documented left ventricular ejection fraction of ≥ 45%.
- No significant active cardiac disease within the previous 6 months including:
  - New York Heart Association (NYHA) class III or IV congestive heart failure
  - Unstable angina or angina requiring surgical or medical intervention; and/or
  - Myocardial infarction
- No contraindication to any drug in the chemotherapy regimen, including neuropathy ≥ Grade 2

3.2.10 Concomitant medications

Chronic concomitant treatment with strong inhibitors of CYP3A4 is not allowed on this study. Patients on strong CYP3A4 inhibitors must discontinue the drug for 14 days prior to registration on the study. See Section 8.1 for more information.

Chronic concomitant treatment with strong CYP3A4 inducers is not allowed. Patients must discontinue the drug 14 days prior to the start of study treatment. See Section 8.1 for more information.

4.1 PATIENT REGISTRATION

4.2 Investigator and Research Associate Registration with CTEP

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and renew their