Weill Cornell Medicine NewYork-Presbyterian

A Multi-center Phase II Study of CC486-CHOP in Patients with Previously Untreated Peripheral T-cell Lymphoma

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Confidentiality Statement

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List of Abbreviations

AE	Adverse Event
AESI	Adverse events of special interest
CFR	Code of Federal Regulations
CRF	Case Report Form
CTSC	Clinical Translational Science Center
DSMB	Data Safety Monitoring Board
DSMP	Data Safety Monitoring Plan
DDPCR	Digital Droplet PCR
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act of 1996
HRBFA	Human Research Billing Analysis Form
HUD	Humanitarian Use Device
ICF	Informed Consent Form
IDE	Investigational Device Exemption
IND	Investigational New Drug
IP	Investigational Product
IRB	Institutional Review Board
PHI	Protected Health Information
PI	Principal Investigator
REDCap	Research Electronic Data Capture
SAE	Serious Adverse Event
SUSAR	Suspected Unexpected Serious Adverse Reaction
UAP	Unanticipated Problem
WCM	Weill Cornell Medicine

Table of Contents

PROTOCOL SUMMARY 4

SCHEMA 7

STUDY PROCEDURES 8

1. STUDY OBJECTIVES 10
   1.1 Primary Objective 10
   1.2 Secondary Objectives 10
   1.3 Exploratory Objectives 10

2. BACKGROUND 10
   2.1 Peripheral T-cell Lymphoma 10
   2.2 Investigational Agent 11
      2.2.1 CC-486 11
      2.2.2 CHOP 12
   2.3 Rationale 13
   2.4 Correlative Studies Background 14

3. SUBJECT SELECTION 15
   3.1 Study Population 15
   3.2 Inclusion Criteria 15
   3.3 Exclusion Criteria 16

4. REGISTRATION PROCEDURES 17

5. STUDY PROCEDURES 18
   5.1 Study Design 18
   5.1 Schedule of Evaluations 18
      5.1.1 Screening Visit 18
      5.1.2 Treatment Phase 19
         5.1.2.1 Cycle 1, Day -6 19
         5.1.2.2 Cycle 1-6, Day 1 19
         5.1.2.3 Cycle 1-5, Day 8 and Cycle 1-2, Day 15 19
      5.1.3 Treatment Discontinuation 20
      5.1.4 Follow-up Phase 20
   5.2 Treatment Administration 21
      5.2.1 CC-486 Administration 21
      5.2.2 CHOP Administration 21
      5.2.3 Growth Factors 21
      5.2.4 CNS Prophylaxis 21
      5.2.5 Tumor Lysis Management 22
   5.3 General Concomitant Medication and Supportive Care Guidelines 22
      5.3.1 Recommended Concomitant Medications/Procedures 22
      5.3.2 Prohibited Concomitant Medications/Procedures 22

5.4 Duration of Therapy and Criteria for Removal from Study 22
5.5 Duration of Follow Up 23

6. DOSING DELAYS/DOSE MODIFICATIONS 23
6.1 Hematologic Requalification and Dose Adjustment 23
6.2 CC-486 Dose Levels 25
6.3 CHOP Dose Modification 26

7. PHARMACEUTICAL INFORMATION 26
7.1 CC-486 26
7.1.1 Description 26
7.1.2 Availability 27
7.1.3 Agent Ordering 27
7.1.4 Agent Accountability 27
7.1.5 Side Effects 27
7.2 Cyclophosphamide 28
7.2.1 Description and Mode of Action 28
7.2.2 Availability and Accountability 28
7.2.3 Clinical Use 28
7.2.4 Side Effects 28
7.3 Doxorubicin 28
7.3.1 Description and Mode of Action 28
7.3.2 Availability and Accountability 28
7.3.3 Clinical Use 29
7.3.4 Side Effects 29
7.4 Vincristine 29
7.4.1 Description and Mode of Action 29
7.4.2 Availability and Accountability 29
7.4.3 Clinical Use 29
7.4.4 Side Effects 30
7.5 Prednisone 30
7.5.1 Description and Mode of Action 30
7.5.2 Availability and Accountability 30
7.5.3 Clinical Use 30
7.5.4 Side Effects 30

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9. MEASUREMENT OF EFFECT 32
9.1 Response Criteria 32
9.2 Duration of Response 35
9.3 Progression-Free Survival (PFS) 35
9.4 Overall Survival (OS) 35

10. DATA REPORTING / REGULATORY CONSIDERATIONS 35
10.1 Data Collection 35
10.2 Regulatory Considerations 36

11. STATISTICAL CONSIDERATIONS 36
11.1 Study Design 36
11.2 Sample Size 36
11.3 Analysis Plan for Endpoints 37
11.3.1 Primary Endpoints 37
11.3.2 Secondary Clinical Endpoints 37
11.3.3 Laboratory Correlates 37

12. ADVERSE EVENT REPORTING REQUIREMENTS 37
12.1 Adverse Event Definition 37
12.1.1 Adverse Event Characteristics and Related Attributions 38
12.1.2 Recording of Adverse Events 38
12.1.3 Reporting of AE to WCM IRB 39
12.2 Definition of SAE 39
12.2.1 Reporting of SAE to IRB 40
12.2.2 Reporting of SAE to FDA 40
12.2.3 Reporting of SAE to Celgene 42
12.3 IND Annual Reports 43
12.4 AE/SAE Follow Up 43

13. DATA AND SAFETY MONITORING PLAN (DSMP) 43

14. REFERENCES 43

APPENDIX A: COCKCROFT-GAULT ESTIMATION OF CRCL 47

APPENDIX B: INTERNATIONAL PROGNOSTIC INDEX (IPI) SCORE 48

APPENDIX C: PERFORMANCE STATUS CRITERIA 49

APPENDIX D: NEW YORK HEART ASSOCIATION (NYHA) CLASSIFICATION FOR CONGESTIVE HEART FAILURE 50

APPENDIX E: DEAUVILLE CRITERIA FOR PET SCAN INTERPRETATION 51

APPENDIX F: RECOMMENDATIONS FOR MANAGEMENT OF TREATMENT-INDUCED DIARRHEA 52

APPENDIX G: CORRELATIVE STUDIES LABORATORY INSTRUCTIONS 53

PROTOCOL SUMMARY

Full Title:
A Multi-center Phase II Study of CC486-CHOP in Patients with Previously Untreated Peripheral T-cell Lymphoma

Short Title:
CC486-CHOP for Untreated Peripheral T-cell Lymphoma

Clinical Phase:
Phase II

Principal Investigator:
Jia Ruan, M.D., Ph.D.

Sample Size:
N=20

Accrual Ceiling:
The study will screen up to 25 patients to account for screening failure and early drop out.

Study Population:
Key inclusion criteria include:

- Histologically confirmed diagnosis of PTCL of the following subtypes:
    - Nodal T-cell lymphoma with T-follicular helper (TFH) phenotype*
        a. Angioimmunoblastic T-cell lymphoma
        b. Follicular T-cell lymphoma
        c. PTCL/NOS, T-follicular helper (TFH) variant
    - PTCL-NOS
    - Anaplastic large cell lymphoma, ALK negative
    - Anaplastic large cell lymphoma, ALK positive with IPI > 2
    - Adult T-cell leukemia / lymphoma

  *: Nodal TCL with TFH phenotype will represent at least 2/3 of the total enrollment.
- No prior systemic therapy for lymphoma
- Measurable disease defined by a tumor mass ≥ 1.5 cm in one dimension and measurable in two dimensions
- Age 18-80 years
- ECOG performance status ≤ 2
- Required initial laboratory parameters:
  Absolute neutrophil count (ANC) ≥ 1500 cells/mm^3 (1000 if BM involvement)
  Platelet count ≥ 75,000 cells/mm^3 (50,000 if BM involvement)
  Calculated creatinine clearance ≥ 30 ml/min by Cockcroft-Gault formula
  Total bilirubin ≤ 2.0 x ULN
  AST/SGOT or ALT/SGPT ≤ 3.0 x ULN

- LVEF ≥ 50%

Key exclusion criteria include:

- Known central nervous system (CNS) involvement by lymphoma
- Known HIV disease
- Known seropositivity for or active viral infection with hepatitis B virus (HBV) or hepatitis C virus (HCV). Seropositive HBV patients are eligible if they are negative for HBV DNA by PCR and receive concomitant antiviral therapy.
- Prior history of malignancies other than PTCL unless the patient has been disease free for ≥ 5 years. Exceptions include basal cell carcinoma or squamous cell carcinoma of the skin; carcinoma in situ of cervix; carcinoma in situ of breast, or localized prostate cancer
- Pregnant or breastfeeding females
- Patients with active uncontrolled infections
- Patient is receiving other systemic anti-neoplastic or investigational drugs
- Known GI disorders interfering with absorption and metabolism of oral CC-486
- Patients with bulky disease who require immediate cyto-reductive chemotherapy

Accrual Period:
1/2018 – 1/2020

Study Design:
This is a phase II, multi-center study to determine the efficacy and safety of first-line CC-486 plus CHOP in patients with PTCL who have received no prior systemic therapy. The study has a sample size of 20, and follows two-stage minimax design for primary efficacy analysis.

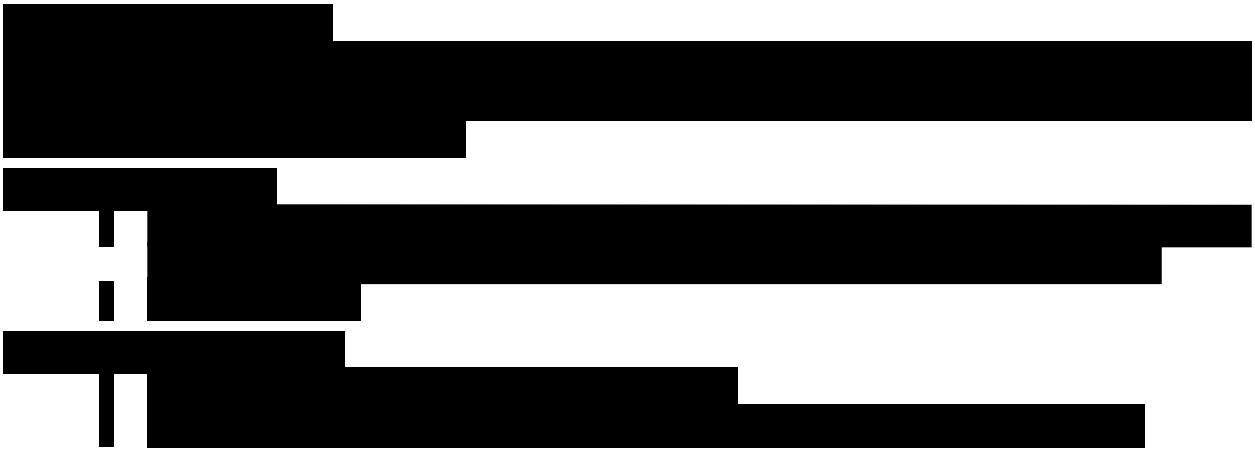
Study Duration:
The study includes 6 cycles (~18 weeks) of treatment and 2 years of follow-up. The projected end date is 12/31/2022. Patients achieving complete remission will be evaluated every 6 months for 2 years or until disease progression. Patients who have disease progression will be contacted every 6 months to assess for survival status.

Study Agent/ Intervention Description:

- Standard dose CHOP will be provided on day 1 of each cycle and repeat every 3 weeks for a total of 6 cycles.
- CC486 at 300 mg daily will be administered orally from day -6 to day 0 for cycle 1 priming, and on days 8-21 following cycles 1-5.
- Patients in CR/PR following 6 cycles of treatment have the option to proceed to consolidative autologous stem cell transplant.

Primary Objective:
To determine the complete response rate (CR) of CC486-CHOP in PTCL by 2014 International Working Group (IWG) criteria, and the Deauville Criteria for scan interpretation. CR rate after cycle 6 will be used for the purpose of interim efficacy analysis.

Secondary Objectives:
To determine overall response rate (ORR), safety, survival (progression-free survival and overall survival), and time to next treatment.



Endpoints:

- The primary end point is to determine CR rate. CR rate after cycle 6 of treatment will be used for interim and final efficacy analysis.
- The secondary endpoints include progression-free survival (PFS), overall survival (OS), and time to next treatment.

SCHEMA

Eligibility

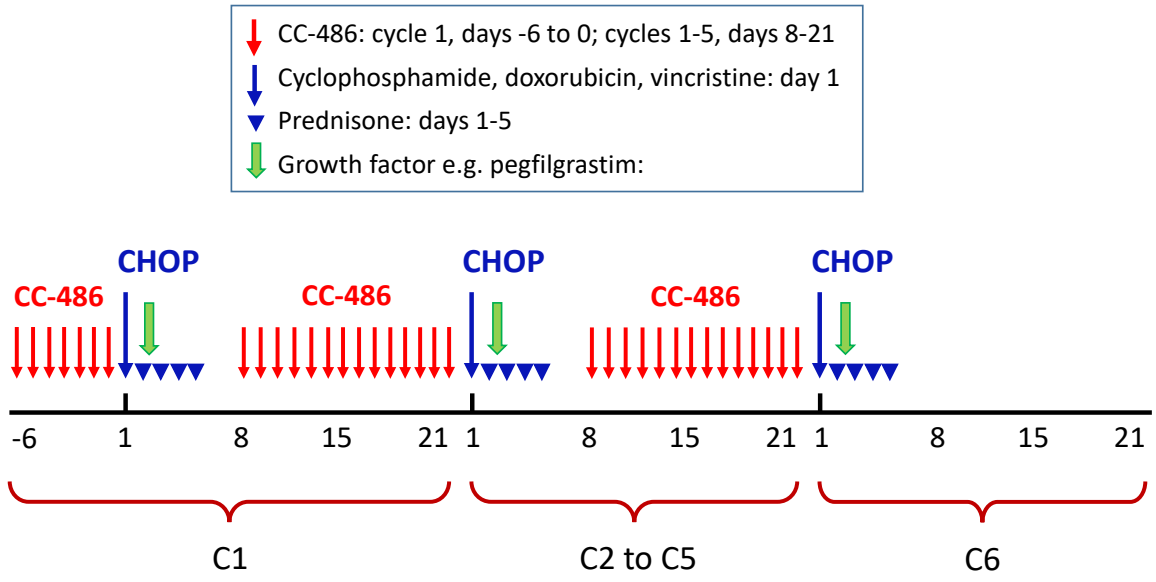
Diagnosed with one of the following PTCL histologic subtypes:

- Nodal T-cell lymphoma with T-follicular helper (TFH) phenotype (tumor cells must express 2 or 3 TFH-related antigens, including PD1, CD10, BCL6, CXCL13, ICOS, SAP and CCR5) *
    a. Angioimmunoblastic T-cell lymphoma
    b. Follicular T-cell lymphoma
    c. PTCL/NOS, T-follicular helper (TFH) variant
- PTCL-NOS
- Anaplastic large cell lymphoma, ALK negative
- Anaplastic large cell lymphoma, ALK positive with IPI >2
- Adult T-cell leukemia / lymphoma

*: Nodal TCL with TFH phenotype will represent at least 2/3 of the total enrollment.

Must have measurable disease and no prior systemic treatment

Treatment



Response Assessment

- Response assessed with imaging (either NM PET/CT or diagnostic CT with contrast) after cycles 3 and 6 and then every 6 months thereafter if in CR for 2 years.
- Patients in CR/PR following 6 cycles of treatment have the option to proceed to consolidative stem cell transplant.

STUDY PROCEDURES

Table 1 Schedule of Study Procedures[1]

Procedures	**Screening**	**Treatment Phase**				**End of Treatment**	**Follow-up Phase**
		Cycle 1, Day -6	Cycle 1-6, Day 1	Cycle 1-5, Day 8,	Cycle 1-2, Day 15	28 days from last dose	Q6m for 2 years if CR, or until POD[6]
Informed consent	X						
Medical history	X						
Physical exam with vital signs	X	X	X	X	X	X	X
ECOG performance status	X	X	X			X	X
IPI score	X						
LVEF assessment[2]	X					X	
12-lead ECG[3]	X						
Concomitant medications	X	X	X	X	X	X	
AE assessment		Continuous from C1D-6 until 28 days after last dose					
Staging							
Lymph node biopsy[4]	X						
Bone marrow study[5]	X					X	
Diagnostic CT (MRI)[6]	X		Cycle 3, between days 15 and 21			X	X[6]
PET[6]	X					X	
Laboratory studies							
CBC with differential	X	X	X	X	X	X	X
CMP including LFT	X	X	X	X	X	X	X
LDH, uric acid, phosphate	X	X	X	X	X	X	X
PT, aPTT	X						
Creatinine clearance[7]	X						
Pregnancy test[8]	X	X	X			X	
HIV Ab	X						
HTLV-1 Ab	X						
EBV viral DNA[9]	X		X[9]			X[9]	
HBsAg, HBsAb, HBcAb	X						
HBV viral DNA[10]	X		X[10]			X[10]	
HCV Ab	X						
Exploratory biomarkers							

FFPE LN/tumor biopsy/Archival tissue[4]	X						
Fresh LN/tumor biopsy (optional)[11]		X	X				
Blood sample[12]		X	X	X[12]	X[12]		

[1] Unless otherwise specified, all screening requirements are within 28 days, all other assessments and procedures are +/- 3 days.
[2] Left ventricular ejection fraction will be performed by standard methods (either by multi-gated acquisition [MUGA] scan or echocardiogram) at Screening and End of Treatment to evaluate doxorubicin toxicity. Screening assessment may be acceptable within 3 months prior to starting study treatment.
[3] 12-lead ECG is performed at screening/baseline and as clinically indicated.
[4] All subject must have pre-treatment diagnostic unstained FFPE biopsy slides available demonstrating PTCL (archival tissue has no time limit); additionally, one-time buccal swab collection for germline control should occur at screening, on treatment or off treatment.
[5] Screening bone marrow biopsy may be acceptable within 3 months prior to starting study treatment. During the study bone marrow biopsy is required only if the patient has otherwise fulfilled the criteria for CR.
[6] Tumor assessment will be by means of PET/CT (CT with diagnostic quality) at Screening (within 6 weeks of starting study treatment) and End of Treatment after completion of therapy. CT scan with contrast or MRI will be performed between Days 15 and 21 of Cycle 3 during treatment, and during Follow-up Phase every 6 months for 2 years assuming patient has achieved CR. Additional PET/CT imaging every 3 months during Follow-up Phase for patients in PR is recommended at discretion of treating investigator.
[7] Creatinine clearance (CrCl) is estimated using the Cockcroft-Gault formula where CrCl (mL/min) = (140 – age)(weight [kg]) / 72 (serum creatinine [mg/dL]; for females, the formula is multiplied by 0.85 (Cockcroft, 1976). Creatinine clearance should be calculated using actual body weight.
[8] Pregnancy tests for females of childbearing potential. A female of childbearing potential (FCBP) 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 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months). Serum pregnancy test with sensitivity of at least 25 mIU/mL is to be obtained in females of childbearing potential (FCBP) at Screening and Cycle 1 Day -6; remaining pregnancy tests may be serum or urine at the Investigator's discretion. A serum pregnancy test must be done within 72 hours prior to Cycle 1 Day -6 of starting study therapy and either serum or urine pregnancy test on Day 1 of every cycle in Treatment Period (except Cycle 1) and at Treatment Discontinuation.
[9] If a subject has EBV viremia at Screening, EBV viral DNA will be measured on day 1 of each cycle and End of Treatment.
[10] All patients must be screened for hepatitis B before starting treatment. Carriers of hepatitis B should be closely monitored, including HBV DNA testing at Screening, day 1 of each cycle and End of Treatment. For patients with evidence of prior HBV infection, HBV suppressive therapy is strongly recommended.
[11] Fresh core lymph node/tumor biopsies are collected before and after the CC-486 Cycle 1 priming course. The pre CC-486 biopsy on Cycle 1 Day -6 can be replaced by a Screening biopsy if the frozen sample is collected according to the Laboratory Manual (see Section 8). The post CC-486 priming biopsy is collected on Cycle 1 Day 1 prior to the administration of CHOP.
[12] Correlative study blood samples will be collected at on cycle 1 day -6, and days 1, 8, 15 of cycles 1 and 2.

1. STUDY OBJECTIVES

1.1 Primary Objective

To determine the complete response rate (CR) of CC486-CHOP in PTCL by 2014 International Working Group (IWG) criteria, and the Deauville Criteria for scan interpretation. CR rate after cycle 6 will be used for the purpose of interim efficacy analysis.

1.2 Secondary Objectives

To determine overall response rate (ORR), safety, survival (progression-free survival and overall survival), and time to next treatment.

2. BACKGROUND

2.1 Peripheral T-cell Lymphoma

Peripheral T-cell lymphomas (PTCL) are a heterogeneous group of non-Hodgkin lymphomas (NHL), encompassing 5-10% NHL in western countries with a higher incidence of 15-20% in Asia and South America [1,2]. The most prevalent nodal T-cell lymphomas include PTCL-NOS, angioimmunoblastic T-cell lymphoma (AITL), and anaplastic large cell lymphoma (ALCL). Despite divergent cells of origin and mechanisms of lymphomagenesis, PTCL therapy has historically followed the treatment framework for aggressive B-cell NHL, in part due to lack of dedicated prospective studies. CHOP is the most commonly prescribed initial treatment for systemic PTCL. With the exception of ALK-positive ALCL, CHOP generally provides ORR of 60-80%, CR of 30-40%, and long-term survival measured by 5-yr OS in the range of 20-30% [3-5]. While autologous stem cell transplant may extend PFS for some patients (3- and 5-yr PFS 40-50%), relapse remains common [4,6]. There are tremendous unmet needs in developing novel frontline therapy for PTCL to improve response quality and duration, ultimately better survival.

Emerging genetic studies with gene expression profiling (GEP) and next generation sequencing (NGS) have shown recurrent mutations in PTCL including *Tet methylcytosine dioxygenase 2*

(*TET2)*, *isocitrate dehydrogenase 2* (*IDH2)*, *DNA (cytosine-5)-methyltransferase 3A* (*DNMT3A)*, and *Ras homolog gene family, member A (RHOA)*, which contribute to lymphomagenesis and may represent the target of tailored therapies such as epigenetic modifiers [2]. Aberrant DNA methylation patterns have been characterized in PTCL subtypes, providing insight into potential targets for clinical application of demethylation agents. Nodal Peripheral T-cell lymphoma with T-follicular helper (TFH) phenotype, which includes AITL and a subset of PTCL/NOS variant with follicular helper T-cell (TFH), have recurrent mutations affecting *RHOA*, *TET2*, *DNMT3A*, and *IDH2*. Integrative analysis of gene expression and promoter methylation revealed recurrently hypermethylated genes involved in T-cell receptor signaling and T-cell differentiation that likely contribute to lymphomagenesis in AITL [7,8], providing a strong rationale for considering the use of hypomethylating agents in AITL treatment. Other PTCL subtypes that have demonstrated differential hypermethylation associated with disease and progression include ALCL, ATLL, and extranodal NK-T cell lymphoma [9-12].

In preclinical interventional studies, treatment of ATLL cell lines with azacitidine (AZA) restored expression of epigenetically silenced tumor suppressor genes include p14ARF and p16INK4a, and induced growth inhibition of lymphoma cells [13]. In ALCL cell lines xenografts, low-dose treatment with 5-aza-2'-deoxycytidine led to apoptosis and cell cycle arrest in vitro and in vivo [14]. 5-AZA treatment of ALCL PDTX led to global hypomethylation [9]. Decitabine treatment of NK cell lines was associated with re-expression of selected methylated and epigenetically silenced genes, which sensitized these cell lines to chemotherapy-induced apoptosis [12]. Combination of hypomethylating agents and HDAC inhibitors was shown to be synergistic in cell lines and in vivo xenograft models of T-cell lymphoma [15].

In human PTCL patients, a retrospective French cohort study reported clinical outcome of 19 patients with R/R PTCL treated with 5-AZA. Treatment consisted of subcutaneous daily injection of 75 mg/m² 5-AZA for 7 consecutive days every 28-day cycle, until progression or unacceptable toxicity. Ten patients had previous or concomitant diagnosis of myelodysplastic syndrome, mostly (9/10) chronic myelomonocytic leukemia (CMML). Patients received a median number of 3 cycles of 5-AZA. Overall response rate (ORR) was 53% (10/19), significantly higher in AITL patients than in patients with other PTCL entities (9/12, 75% *vs*. 1/7, 15%, p=0.0198). Five patients with AITL achieved CR, leading to a CR rate of 42% in AITL. Responses in 7 out of 9 AITL patients appeared to be durable. *TET2* was sequenced in 14 patients and was mutated in 8/10 (80%) AITL and 1/4 (25%) other PTCL; 8/8 AITL patients who responded to 5-AZA treatment were *TET2* mutated. [16-18].

2.2 Investigational Agent

2.2.1 CC-486

Azacitidine, an analog of the pyrimidine nucleoside cytidine, has effects on cell differentiation, gene expression, and deoxyribonucleic acid (DNA) synthesis and metabolism. Azacitidine promotes antineoplastic activity via two mechanisms – as an epigenetic modifier of DNA methylation by inhibition of DNA methyltransferase at low doses, and as a direct cytotoxic agent by incorporation into DNA and RNA at high doses. Vidaza® (azacitidine for injection), which

can be administered by the intravenous (IV) or subcutaneous (SC) routes, is approved by the US Food and Drug Administration (FDA) for myelodysplasia (MDS). Vidaza is also approved by the European Commission (EU) for intermediate-2 (INT-2) and high-risk MDS, CMMoL, and AML with multilineage dysplasia. An oral formulation of azacitidine (CC-486) has been developed and is currently being evaluated in clinical trials, either as a single agent or in combination with other drugs, for the treatment of hematological and solid malignancies. CC-486 is not yet approved by any regulatory agency worldwide for any indication. For a comprehensive overview of both Vidaza® and CC-486, please refer to the IB.

The safety, pharmacokinetics, and pharmacodynamics of oral azacitidine in subjects with MDS, chronic myelomonocytic leukemia (CMMoL), or AML was evaluated in a phase 1/2, open-label dose escalation trial [19,20]. Dose levels of 120, 180, 240, 300, 360, 480, and 600 mg were evaluated in Part 1 of the study, while Part 2 further evaluated safety, tolerability and efficacy of 14-day and 21-day once daily (QD) treatment. A total of 131 subjects were enrolled of which 127 received CC-486. Median time to peak plasma levels was 1 hour with maximum effect on global DNA methylation at day 15 of each cycle. From Part 2 of the study, the dose of 300 mg QD for 14 or 21 days was considered safe and tolerable and was carried forward in Phase 3 studies in AML and MDS. The most frequently observed non-hematologic TEAEs included GI symptoms of diarrhea, nausea, constipation, and vomiting. The dose levels of 200 mg and 300 mg were further supported by clinical and pharmacodynamics data from a Phase 1 study (AZA-ST-001), in which CC-486 was administered for a total of 14 out of 21-days as a priming agent in combination with cytotoxic agents of carboplatin or nab-paclitaxel in solid tumor patients [21]. In an ongoing phase 1, open-label trial of frontline oral azacitidine (CC-486) plus R-CHOP in subjects with large B-cell lymphoma or follicular lymphoma or transformed lymphoma (NCT02343536), the dose level of 300 mg QD for 14 days out of 21-day cycle was found to be effective with manageable safety profile for administration with R-CHOP regimen in frontline aggressive lymphoma patients [22].

2.2.2 CHOP

CHOP is the most commonly prescribed initial therapy for PTCL, despite results showing that it is largely ineffective and that the majority of PTCL patients have an inferior outcome compared with their B-cell counterparts receiving CHOP, with the exception of ALK positive ALCL. In the collaborative International T-cell Lymphoma Project which evaluated a cohort of 1,314 previously untreated cases of PTCL and NKTCL from 22 centers worldwide diagnosed between 1990 and 2002, over 85% patients received an anthracycline-containing regimen. The 5-year OS for PTCL-NOS, AITL, and NKTCLs was 32% compared with 14% for ATLL. ALCL, ALK positive, demonstrated 5-year OS of 70%, compared to 49% with ALCL, ALK negative [1]. Contemporary real world studies appear to confirm the treatment practice and clinical outcome in PTCL. In the Swedish lymphoma registry study which reviewed 755 PTCL patients diagnosed during the 10-year period between 2000 and 2009, 84% patients receiving chemotherapy were treated with CHOP or CHOEP, ORR was 70% among the evaluable patients, and <17% patients were planned for autologous stem cell transplant (ASCT) in first remission [23]. In the US multicenter cohort study including 341 newly diagnosed PTCL patients enrolled from 2000 to 2011 at 9 US academic centers, 70% patients received CHOP, ORR was 73%, 3-year PFS and OS were 32% and 52% respectively, and 10% patients underwent ASCT in first remission [24]. Adding etoposide to CHOP in the form of CHOEP may improve EFS but not OS in younger PTCL patients [23,25].

Although CHOP is largely inadequate and anthracycline may not be essential [1], there is a paucity of prospective randomized trials comparing alternative chemotherapy combinations with CHOP in frontline setting, given disease rarity and heterogeneity. The majority of information regarding the efficacy of alternative regimens is based on retrospective or phase 2 data with historical comparisons. Examples of single arm phase 2 studies with intensive or non-anthracycline based combination included the CyclOBEAP [26] and PEGS regimens [27]. A randomized phase 3 trial by GOELAMS compared VIP-reinforced-ABVD to standard CHOP, demonstrating that VIP-rABVD was not superior to CHOP/21 in terms of EFS as first-line treatment of PTCL [5]. To date, standard dose CHOP remains the reference regimen in PTCL treatment. Exception to CHOP backbone applies to extranodal NK/T cell lymphoma which requires incorporation of asparaginase and radiation, and hepatosplenic T cell lymphoma which responds to intensive chemotherapy such as ICE or IVAC and early consolidative stem cell transplant.

To improve efficacy of CHOP, there are a number of phase 1/2 and phase 3 prospective studies aiming to incorporate novel agents into chemotherapy backbone. In CD30+ PTCL, based on phase 1 data which showed high CR rate (88%) with brentuximab vedotin plus CHP [28], the phase 3 randomized Echelon-2 study (NCT01777152) assesses survival and response rates in CD30+ PTCL patients receiving experimental brentuximab vedotin plus CHP versus standard CHOP. High CR rate (51%) was achieved in a phase 1b/II study of CHOP plus romidepsin [29], which forms the basis for the ongoing phase 3 LYSARC study (NCT01796002) evaluating survival and response with Ro-CHOP vs CHOP. The current study aims to evaluate efficacy and safety of incorporating hypomethylating agent CC-486 into CHOP backbone for chemo-sensitization. ASCT is permitted in first remission.

2.3 Rationale

Given the enrichment of mutations in epigenetic modifiers in T-cell lymphoma subtypes which leads to an overall hyper-methylated state, chemo-sensitization with azacitidine in combination with CHOP appears to be an attractive therapeutic mechanism.

Oral azacitidine (CC-486) has been studied in subjects with myelodysplastic syndrome/acute myelogenous leukemia (MDS/AML) and as monotherapy or in combination with chemotherapeutic agents in subjects with solid tumors and lymphoma. The dose levels of 200 mg and 300 mg were selected based on the following available clinical and pharmacodynamic evidence: (i) a minimum exposure to CC-486 up to 300 mg daily for 7 days, and ideally 14 days or longer [19], resulted in detectable changes in the methylation pattern of the DNA in the peripheral blood mononuclear cells of subjects treated with CC-486 given as single agent and in combination with cytotoxic agents; and (ii) preliminary data from AZA-ST-001 (Phase 1) combination study of CC-486, administered at doses of 200 mg or 300 mg in combination with carboplatin and with nab-paclitaxel (on a different schedule than proposed in this study) demonstrated an acceptable safety profile for a Phase 2 dose [21].

The schedule of azacitidine administration relative to the administration of CHOP has been evaluated in 2 lymphoma studies. In a phase 1 study in patients with high risk DLBCL, the combination of azacitidine administered subcutaneously daily for 5 days as priming followed by

R-CHOP was shown to be tolerable and yielded a high rate of complete remission. Pre- and post-azacitidine treatment biopsies confirmed genomic demethylation and chemosensitization [30]. Currently, a phase I trial evaluating the combination of CC486, an oral form of azacitidine, plus R-CHOP in patients with previously untreated DLBCL and transformed B-cell NHLs (NCT02343536) has reached the recommended dose level of CC-486 of 300 mg for 14 days in combination with standard dose R-CHOP for dose expansion phase, demonstrating the safety and feasibility of the CC-486 plus CHOP combination in frontline setting [22]. We propose a phase 2 study to assess the efficacy and safety of CC-486 plus CHOP as initial therapy for PTCL, prioritizing enrollment of patients with T-follicular helper (TFH) phenotype and acquired genetic predisposition to chemo-sensitization by hypomethylation agent. Correlative biomarker studies are prospectively planned in conjunction with the study treatment to guide future trial design with novel epigenetic modifying agents.

[redacted]

3. SUBJECT SELECTION

3.1 Study Population

Adults with previously untreated peripheral T-cell lymphoma who meet the inclusion and exclusion criteria will be eligible for participation in this study.

3.2 Inclusion Criteria

- Histologically confirmed diagnosis of PTCL of the following subtypes:
    - Nodal T-cell lymphoma with T-follicular helper (TFH) phenotype (tumor cells must express 2 or 3 TFH-related antigens, including PD1, CD10, BCL6, CXCL13, ICOS, SAP and CCR5)*
        a. Angioimmunoblastic T-cell lymphoma
        b. Follicular T-cell lymphoma
        c. PTCL/NOS, T-follicular helper (TFH) variant
    - PTCL-NOS
    - Anaplastic large cell lymphoma, ALK negative
    - Anaplastic large cell lymphoma, ALK positive with IPI > 2
    - Adult T-cell leukemia / lymphoma

  *: Nodal TCL with TFH phenotype will represent at least 2/3 of the total enrollment.
- No prior systemic therapy for lymphoma
- Measurable disease defined by a tumor mass ≥ 1.5 cm in one dimension and measurable in two dimensions
- Age 18-80 years
- ECOG performance status ≤ 2
- Required initial laboratory parameters:
    - Absolute neutrophil count (ANC) ≥ 1500 cells/mm^3 (1000 if secondary to lymphoma BM involvement per investigator assessment)
    - Platelet count ≥ 75,000 cells/mm^3 (50,000 if secondary to lymphoma BM involvement per investigator assessment)
    - Hemoglobin ≥ 8 g/dL
    - Calculated creatinine clearance ≥ 30 ml/min by Cockcroft-Gault formula
    - Total bilirubin ≤ 2.0 x ULN except in cases of Gilberts Syndrome, or documented liver of pancreatic involvemebt by lymphoma
    - AST/SGOT or ALT/SGPT ≤ 3.0 x ULN except in subjects with documented liver involvement by lymphoma
    - Alkaline phosphatase < 2.5 x ULN
- LVEF ≥ 50%

- Understand and voluntarily sign an ICF prior to any study related assessments and procedures are conducted.
- Able to adhere to the study visit schedule and other protocol requirements.
- Negative serum pregnancy test within 72 hours before starting study treatment on Cycle 1 Day -6 for females of childbearing potential (FCBP).

  A female of child-bearing potential, defined as a sexually mature woman who: 1) has not undergone a hysterectomy (the surgical removal of the uterus) or bilateral oophorectomy (the surgical removal of both ovaries) or, 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time during the preceding 24 consecutive months), may participate providing they agree to the following conditions:

  - Either commit to complete abstinence from heterosexual contact (which must be reviewed on a monthly basis) or agree to the use of a physician-approved contraceptive method (oral, injectable, or implantable hormonal contraceptive; tubal ligation; intrauterine device; barrier contraceptive with spermicide; or vasectomized partner) without interruption, while on CC-486 (including dose interruptions); and for 3 months following the last dose of IP; and
  - A medically supervised serum pregnancy test with sensitivity of at least 25 mIU/mL is to be obtained in females of childbearing potential (FCBP) at Screening and Cycle 1 Day -6; remaining pregnancy tests may be serum or urine at the Investigator's discretion. A serum pregnancy test must be done within 72 hours prior to Cycle 1 Day -6 of starting study therapy and either serum or urine pregnancy test on Day 1 of every cycle in Treatment Period (except Cycle 1) and at Treatment Discontinuation. The subject may not receive IP until the Investigator has verified that the result of the pregnancy test is negative.
- Male subjects with a female partner of childbearing potential must either commit to complete abstinence or agree to the use of a physician-approved contraceptive method throughout the course of the study and avoid fathering a child during the course of the study and for 3 months following the last dose of the IP.

3.3 Exclusion Criteria

- Known central nervous system (CNS) involvement by lymphoma
- Active viral infection with HIV or hepatitis type B or C (seropositive HBV patients are eligible if they are negative for HBV DNA by PCR and receive concomitant antiviral therapy).
- Prior history of malignancies other than PTCL unless the patient has been disease free for ≥ 5 years from the signing of the ICF. Exceptions include basal cell carcinoma or squamous cell carcinoma of the skin; carcinoma in situ of cervix; carcinoma in situ of breast, or localized prostate cancer
- Significant active cardiac disease within the previous 6 months including (**Appendix D**):
  - 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
- 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)
- Abnormal coagulation parameters (PT >15 seconds, aPTT>40 seconds, and/or INR >1.5)
- Known or suspected hypersensitivity to azacitidine or mannitol
- Contraindication to any drug in the chemotherapy regimen, and specifically
  - LVEF <50%
  - Corrected QT interval >480 msec (using the Fridericia formula)
  - Neuropathy ≥ Grade 2
- Pregnant or breast feeding females. (Lactating females must agree not to breast feed while taking azacitidine)
- Patient is receiving other systemic anti-neoplastic investigational drugs
- Known GI disorders interfering with absorption and metabolism of oral CC-486
- Patients with advanced malignant hepatic tumors
- Any significant medical condition, laboratory abnormality, or psychiatric illness that would prevent the subject from participating in the study
- Patients with bulky disease who require immediate cyto-reductive chemotherapy

[redacted]

5. STUDY PROCEDURES

5.1 Study Design

This is a single arm phase II study to evaluate the safety and efficacy of CC486 plus CHOP as initial therapy for peripheral T-cell lymphoma, prioritizing enrollment of patients with T-follicular helper (TFH) phenotype and acquired genetic predisposition to chemo-sensitization by hypomethylation agent. Study treatment will include 6 cycles of CC-486 plus CHOP.

5.1 Schedule of Evaluations

Screening assessments and all scheduled study visits and assessments are outlined in **Table 1**.

5.1.1 Screening Visit

Study screening begins when the subject signs the written informed consent document (ICD). All screening assessments and baseline evaluations must be completed within 28 days prior to the start of Cycle 1 Day -6 treatment, unless otherwise specified.

- All patients must have pre-treatment diagnostic unstained FFPE biopsy slides available demonstrating PTCL (archival tissue has no time limit)
- Bone marrow aspirate and core biopsy (within 3 months prior to starting study treatment)
- Physical examination with history, vital signs including weight, height and performance status
- Concomitant medications
- 12-lead Electrocardiogram
- ECHO or MUGA scan to show EF of ≥ 50% (within 3 months prior to starting study treatment)
- PET scan (within 6 weeks prior to starting study treatment)
- CT scan (or MRI) of neck/chest/abdomen/pelvis (and other areas if indicated to evaluate sites of disease involvement) (within 6 weeks prior to starting study treatment)
- Complete blood count (CBC) with differential
- Serum chemistries to include CMP, LDH, phosphate and uric acid
- Coagulation profile with PT and aPTT
- Creatinine clearance

- Hepatitis B/C screening
- HIV, HTLV-1, EBV testing
- Pregnancy test (for female of childbearing potential)

5.1.2 Treatment Phase

5.1.2.1 Cycle 1, Day -6

- Physical examination with vital signs and performance status
- AE assessment
- Concomitant medications
- CBC with differential
- Serum chemistries to include CMP, LDH, phosphate and uric acid
- Pregnancy test (for female of childbearing potential)
- Optional fresh lymph node/tumor biopsy (can be replaced by a screening biopsy if the frozen sample is collected according to the Laboratory Manual, see **Section 8.1.1**)
- Correlative blood samples

5.1.2.2 Cycle 1-6, Day 1

- Physical examination with vital signs and performance status
- AE assessment
- Concomitant medications
- CBC with differential
- Serum chemistries to include CMP, LDH, phosphate and uric acid
- Pregnancy test (for female of childbearing potential)
- HBV viral DNA in HBcAb positive, asymptomatic carrier
- EBV viral DNA in subject with EBV viremia at baseline
- Optional fresh lymph node/tumor biopsy **(Cycle 1 only)**
- Correlative blood samples **(Cycles 1 and 2 only)**

5.1.2.3 Cycle 1-5, Day 8 and Cycle 1-2, Day 15

- Physical examination with vital signs
- AE assessment
- Concomitant medications

- CBC with differential
- Serum chemistries to include CMP, LDH, phosphate and uric acid
- CT scan (or MRI) of neck/chest/abdomen/pelvis (and other areas if indicated to evaluate sites of disease involvement) between days 15 and 21 of cycle 3
- Correlative blood samples **(Cycles 1 and 2 only)**

5.1.3 Treatment Discontinuation

At treatment discontinuation, subjects will undergo off study evaluations within 28 days of last dose.

- Physical examination with vital signs and performance status
- AE assessment
- Concomitant medications
- CBC with differential
- Serum chemistries to include CMP, LDH, phosphate and uric acid
- HBV viral DNA in HBcAb positive, asymptomatic carrier
- EBV viral DNA in subject with EBV viremia at baseline
- Pregnancy test (for female of childbearing potential)
- ECHO or MUGA scan
- CT scan (or MRI) of neck/chest/abdomen/pelvis (and other areas if indicated to evaluate sites of disease involvement)
- PET scan for response assessment
- Bone marrow aspiration and core biopsy (unilateral) only if otherwise in complete remission (not repeated once negative)

5.1.4 Follow-up Phase

Patients will have follow-up evaluations every 6 months for 2 years or until progression of disease, whichever occurs first. At each follow-up evaluation, the patient will have the following:

- Physical examination with vital signs and performance status
- CBC with differential
- Serum chemistries to include CMP, LDH, phosphate and uric acid
- CT scan (or MRI) of neck/chest/abdomen/pelvis (and other areas if indicated to evaluate

sites of disease involvement)

- PET scan at shorter interval than 6 months (e.g. 3 months) for patients in PR at discretion of investigator
- Survival and subsequent anti-lymphoma treatment information

5.2 Treatment Administration

5.2.1 CC-486 Administration

CC-486 at 300 mg once daily is to be administered Cycle 1, Day -6 to 0 and Cycles 1 to 5, Day 8 to 21. Antiemetic prophylaxis is recommended before dosing. Subject should take CC-486 with approximately 240 mL (8 ounces) of room temperature water. CC-486 may be taken on an empty stomach or with food. If CC-486 is taken with food, a light meal (not more than 600 calories) may be eaten before or after administration. All efforts should be made to administer CC-486 on all scheduled days of the Cycle 1 priming dosing (7 days, Cycle 1 Day -6 to Cycle 1 Day 0) and the Cycle 1-5 dosing (14 days, Day 8-21). A dose missed earlier in a day can be administered later that day as long as it is taken at least 8 hours before the next scheduled dose. Any missed dose should not be taken beyond the last scheduled day of CC-486 administration for the cycle, but should be returned by the subject for CC-486 accountability. If vomiting occurs after a dose of CC-486 is administrated, that dose should not be made up later that day. The subject should continue with the dosing schedule on the next day and inform the Investigator about the vomiting event at the next visit.

5.2.2 CHOP Administration

CHOP is to be administered on Days 1 to 5 of Cycles 1-6. Chemotherapy can be administer within +72h or -24h of Day 1 of each scheduled Cycle. Preparation and infusion rate are according to the package insert and local practice. The doses to be used are:
Cyclophosphamide: 750 mg/m2 IV on day 1
Doxorubicin: 50 mg/m2 IV on day 1
Vincristine: 1.4 mg/m2 IV (not to exceed 2.0 mg total) on day 1
Prednisone: 100 mg PO days 1-5

5.2.3 Growth Factors

Growth factors are mandatory per standard of care. Either pegfilgrastim, lenograstim or filgrastim can be used. Pegfilgrastim must be administered a minimum of 24 hours after Day 1 of CHOP and 5 days before the start of CC-486. Filgrastim or lenograstim should be started a minimum of 24 hours after Day 1 and stopped 24 hours before start of CC-486.

5.2.4 CNS Prophylaxis

Decisions regarding CNS staging and prophylaxis will be at the discretion of the treating investigator. If CNS prophylaxis is deemed appropriate it will be with intrathecal methotrexate, cytarabine, or liposomal cytarabine, at the discretion of the treating investigator.

5.2.5 Tumor Lysis Management

All patients should receive prophylaxis for TLS before the initiation of the first dose of CC-486. Prophylaxis will include appropriate hydration, administration of an agent to reduce uric acid, such as allopurinol (or rasburicase IV for high risk patients with elevated uric acid levels before treatment). Laboratory results including electrolyte values will be assessed on a weekly basis during cycle 1 of treatment.

5.3 General Concomitant Medication and Supportive Care Guidelines

5.3.1 Recommended Concomitant Medications/Procedures

Subjects should receive full supportive care, including transfusions of blood and blood products, antibiotics, analgesics, and antiemetics when appropriate during treatment phase.

- It is strongly recommended that all subjects receive a dose of a prophylactic antiemetic, preferably a 5-HT3 antagonist, 30 minutes prior to each dose of CC-486.
- Growth factor prophylaxis is required for all subjects and will be provided and administered by the investigative site a minimum of 24 hours after chemotherapy (Day 2 of CHOP) and at least 5 days before any dose of CC-486 for pegfilgrastim, and stopped one day before CC-486 for lenograstim or filgrastim.
- Prophylaxis against pneumocystis jiroveci is required but choice and dose of agent will be selected by the Investigator according to local practice and provided by the investigative site.
- Asymptomatic carriers of Hepatitis B with negative HBV DNA should receive lamivudine, tenofovir, or entecavir during therapy and until at least 6 months beyond completion of therapy.
- Other anti-infection prophylaxis (eg, acyclovir, levofloxacin, and other premedications) will be selected by the Investigator according to local practice and provided by the investigative site.
- Treatment with antidiarrheal medications should be prescribed for non-infectious diarrhea. Pre-medication with antidiarrheal medication for subsequent doses of CC-486 may be appropriate at the investigator's discretion (See **Appendix F**).

5.3.2 Prohibited Concomitant Medications/Procedures

Any anti-cancer therapy is prohibited 28 days prior to Day 1 dosing and during the entire Treatment Period of the study. An exception applies for subjects with bulky disease and/or rapidly progressing systemic symptoms, whereby treatment with 1 mg/kg/day prednisone, or equivalent, is permitted at the discretion of the Investigator. No other anthracycline may be substituted for doxorubicin.

5.4 Duration of Therapy and Criteria for Removal from Study

Study treatment will include 6 cycles of CC-486 plus CHOP. Subjects who meet the following criteria should be discontinued from the study:

- Withdraw of consent
- Inability of subject to comply with study requirements
- Determination by the investigator that it is no longer safe for the subject to continue therapy
- Disease progression

- Pregnancy or a positive pregnancy test

Subjects who complete less than 1 cycle of treatment and discontinue treatment for reasons other than toxicity will be replaced.

5.5 Duration of Follow Up

The Follow-up Period for each subject begins upon study treatment discontinuation. This includes subjects who complete the full course of treatment, who discontinue treatment due to progression, toxicity, as well as those who withdraw consent from study treatment. Subjects will be followed for response, progression, subsequent anti-lymphoma therapies, and survival according to the schedule described in Table 1, until disease progression or 2 years from end of treatment, whichever occurs first.

6. DOSING DELAYS/DOSE MODIFICATIONS

6.1 Hematologic Requalification and Dose Adjustment

In order to ensure adequate administration of the CHOP regimen while limiting toxicity, hematologic requalification and dose adjustment rules will be followed as detailed in **Table 2**.

Table 2: Hematologic Requalification and Dose Adjustments.

Date of Assessment	**If Any of the Following Are Present:**	**Then, Take the Following Action**
Day -6 Cycle 1 CC-486	ANC < 1,500 cells/mm3 (1.5 x 10^9/L) ANC < 1,000 cells/mm3 (1.0 x 10^9/L) due to lymphoma bone marrow involvement. Platelet Count < 75,000/mm^3 (100 x 10^9/L) Platelet Count < 50,000/mm^3 (100 x 10^9/L) due to lymphoma bone marrow involvement Hb < 8 g/dL	Cannot initiate CC-486 study treatment as per Exclusion Criteria.
	Any other exclusion criteria	
Day 1 Cycles 1-6 CHOP and growth factors	<u>Hematologic Requalification/Dose Delay Criteria</u> ANC < 1,000 cells/mm^3 (1.0 x 10^9/L) (≥ Grade 3) unless due to lymphoma in marrow Platelet count < 50,000 cells/mm^3 (60 x 10^9/L) unless due to lymphoma in marrow.	Hold CHOP. Reassess a maximum one week later, and resume CHOP if recovered
	Other AEs	

Date of Assessment	**If Any of the Following Are Present:**	**Then, Take the Following Action**
	IP, CC-486 related diarrhea or vomiting Grade 2 or worse despite adequate medical intervention Any other unacceptable CHOP related AE except for vincristine-related. For Cycles 2 to 6, any IP related non-hematologic Grade 3 or more toxicity not resolved to Grade 2 or less	For non-hematologic AEs considered to be related to CC486, CHOP can be started when AE resolved to grade 2 or less. For non-hematologic AE related to CHOP, delay or discontinue CHOP at investigator discretion.
Day 8 to 14 Cycles 1-5 CC-486	<u>Hematologic Requalification/Dose Delay Criteria</u> Grade 3 neutropenia (ANC < 1000 cells/mm^3 (1.0×10^9/L) with fever (temperature > 38.5°C)	Hold CC-486. 1. Monitor CBC at least every 7 days until requalification criteria is met. CC-486 can be restarted at the time requalification is met on the dosing day. 2. If by Day 15 the requalification criteria is met, a subject can complete the remainder of the CC-486 dosing Day 15 to Day 21 (7 days). If requalification criteria is NOT met on Day 15, suspend CC-486 for the remainder of the current cycle, and reduce by one dose level at next cycle.
	If delay 7-14 days in start of CHOP in current cycle:	Restart CC-486 on Day 8 of this cycle at next reduced dose level.
	If delay > 14 days in start of CHOP in current cycle: If delay > 21 days in start of CHOP in current cycle, or >2 occurrences of >14 days delay in start of CHOP	Hold CC-486 during entire cycle and reduce by one dose level at next cycle. Discontinue CC486 permanently
	Other AEs	For non-hematologic Grade ≥3 AEs considered to be related to CC-486, if held, can be restarted at

Date of Assessment	If Any of the Following Are Present:	Then, Take the Following Action
		the next lower dose when AE is resolved to Grade 2 or less.
Day 15 - 21 Cycle 1-5 CC-486	<u>Hematologic Requalification/Dose Delay Criteria</u> ANC < 750 cells/mm³ (0.75 x 10^9/L) and day 8 Platelet count < 50,000 cells/mm³ (50 x 10^9/L) unless due to lymphoma bone marrow involvement per investigator assessment	Hold CC-486 until next cycle. 1. First occurrence: Restart CC-486 at same dose level at next cycle. 2. Second occurrence: Reduce CC-486 by one dose level at next cycle. 3. Third occurrence: Discontinue CC-486 4. Dose delays occurring during both days 8-14 and days 15-21 of the same cycle: Hold CC-486 for the remainder of the current cycle, and reduce by one dose level at next cycle.
	If >14 day delay in start of CHOP in current cycle:	Hold CC-486 for entire cycle and reduce by one dose level at next cycle.
	If > 21 day delay in start of CHOP in current cycle, or >2 occurrences of >14 day delay in start of CHOP	Discontinue CC486 permanently
	Other AEs	For grade ≥ 3 non-hematologic AEs considered to be related to CC-486, if held, can be restarted at the next lower dose when AE is resolved to Grade 2 or less.

6.2 CC-486 Dose Levels

Dose reductions for CC-486 are described in **Table 3**.

Table 3: CC-486 Dose Level Reductions

Dose Level	Current Dose	One Level Dose Reduction
0	300 mg QD	200 mg QD
-1	200 mg QD	150 mg QD
-2	150 mg QD	100 mg QD
-3	100 mg QD	None
QD = once daily; QOD = every other day.		

6.3 CHOP Dose Modification

With the exception of vincristine, the dose level for cyclophosphamide, doxorubicin, and prednisone may not be modified. For cytopenia, the CC-486 dose adjustments or cycle delay rules for CHOP should be implemented as per **Table 2**.

The vincristine dose may be modified according to **Table 4** and **Table 5**. Dose delay for peripheral neuropathy due to vincristine per Table 4 does not prevent continuing treatment with the other drugs on schedule. If the subject cannot tolerate the lowest level of vincristine, it is acceptable to continue on study with chemotherapy plus CC-486 without vincristine.

Table 4: Dose Modification Rules - Vincristine

CTCAE Toxicity Grade	Action Required
Peripheral neuropathy Newly developed ≥ Grade 3 (applies only to those neuropathies which begin or worsen while on study)	Hold (interrupt dose) When the toxicity resolves to ≤ Grade 2 or to baseline, restart at the next lower dose level

CTCAE= Common Terminology Criteria for Adverse Events.

Table 5: Dose Reduction Levels-Vincristine

Starting Dose	1.4 mg/m^2 (maximum of 2.0 mg total)
Level -1 Dose	1.0 mg max

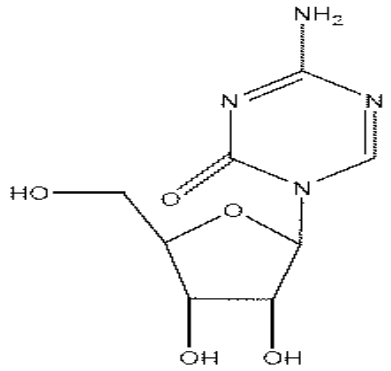
7. PHARMACEUTICAL INFORMATION

7.1 CC-486

7.1.1 Description

CC-486 contains AZA, which is a pyrimidine nucleoside analog of cytidine. It differs from cytidine in having nitrogen in the 5-position of the heterocyclic ring. It has the following chemical structure:

Chemical Structure of Azacitidine



Azacitidine is (4-amino-1-β-D-ribofuranosyl-s-triazin-2(1*H*)-one).

The empirical formula is $C_8H_{12}N_4O_5$. The molecular weight is 244 amu.

7.1.2 Availability

Different formulations of oral azacitidine (CC-486) have been developed and are being used in clinical studies. The oral azacitidine formulations may use any of the following excipients: mannitol USP, silicified microcrystalline cellulose NF, crospovidone NF, magnesium stearate NF, croscarmellose sodium, vitamin E TPGS NF, methacrylic acid copolymer (enteric coating) NF, Opadry coating, triethyl citrate NF, talc USP, hydroxypropyl cellulose NF, and hard gelatin capsule. Azacitidine capsules contain 100 mg of the active ingredient only.

7.1.3 Agent Ordering

CC-486 will be supplied by Celgene in appropriate strengths for oral administration. Investigational product will be supplied as labeled blister cards. Store the CC-486 oral formulation as directed on the label. Procedures for proper handling and disposal should be applied according to standards established at each facility for cytotoxic drugs.

7.1.4 Agent Accountability

CC-486 Inventory Records – The investigator, or a responsible party designated by the investigator, will maintain a careful record of the inventory and disposition of all agents received from Celgene on a Drug Accountability Record Form (DARF).

7.1.5 Side Effects

The most common AEs reported during the azacitidine clinical trials reflect the underlying nature of the disease and the cytotoxic properties of azacitidine. The most commonly reported adverse reactions with azacitidine treatment were hematological reactions including anemia, thrombocytopenia, neutropenia, febrile neutropenia, and leukopenia, gastrointestinal events including nausea, vomiting, abdominal pain, constipation, and diarrhea. For the most frequently reported TEAEs (≥ 10% of subjects), the highest incidence of first occurrence was observed within Cycles 1-2. In general, no clinically relevant differences were seen when the safety data were analyzed for age, gender, or disease subtypes. The most common adverse reactions can be managed through delays or dose decrease of azacitidine and/or supportive measures. The overall safety profile of azacitidine from the ongoing clinical studies is consistent with that described in the IB; however, diarrhea may be more frequent and/or more severe in patients receiving orally-

administered azacitidine.

7.2 Cyclophosphamide

7.2.1 Description and Mode of Action

Cyclophosphamide is an alkylating agent that prevents cell division primarily by cross-linking DNA strands. Cyclophosphamide is considered cell cycle phase non-specific. Cyclophosphamide is bio-transformed principally in the liver to active alkylating metabolites that cross-link to tumor-cell DNA. Please refer to the FDA-approved package insert for product information, extensive preparation instructions, and a comprehensive list of adverse events.

7.2.2 Availability and Accountability

Cyclophosphamide is commercially available as 100 mg, 200 mg, 500 mg, 1 gm, or 2 gm vials in 5, 10, 25, 50, and 100 ml of water respectively, resulting in a solution of 20 mg/ml. Shake vials and warm slightly in lukewarm water to facilitate dissolution. Intact vials should be stored at room temperature. Reconstituted and diluted solutions are stable for 24 hours at room temperature and 6 days if refrigerated. Procedures for proper handling and disposal should be applied according to standards established at each facility for cytotoxic drugs.

7.2.3 Clinical Use

The desired dose is diluted into 100-500 ml of 5% dextrose or 0.9% normal saline for IV administration usually over 15-45 minutes.

7.2.4 Side Effects

Myelosuppression, hemorrhagic cystitis (patients must be well-hydrated before, during, and after treatment and have adequate renal function). Syndrome of inappropriate antidiuretic hormone (SIADH), fatigue, alopecia, anorexia, nausea, vomiting, hyperuricemia, azospermia, amenorrhea, cardiotoxicity (myocardial necrosis) usually at doses higher than those used in this study

7.3 Doxorubicin

7.3.1 Description and Mode of Action

Doxorubicin is a cytotoxic anthracycline antibiotic isolated from cultures of *Streptomyces peucetius* var. *caesius*. Doxorubicin binds to nucleic acids, presumably by specific intercalation of the planar anthracycline nucleus with the DNA double helix, which inhibits nucleotide replication and action of DNA and RNA polymerases. Doxorubicin also inhibits topoisomerase II. Free radical formation has been implicated in doxorubicin cardiotoxicity by means of Cu (II) and Fe (III) reduction at the cellular level. Doxorubicin does not cross the blood brain barrier. Please refer to the FDA-approved package insert for doxorubicin for product information, extensive preparation instructions, and a comprehensive list of adverse events.

7.3.2 Availability and Accountability

Doxorubicin is commercially available in 10, 20, 50, an 100 mg vials as a red-orange lyophilized powder which has a storage stability of at least two years – see expiration date on vial. After adding the diluent, the vial should be shaken and the contents allowed to dissolve. The reconstituted solution is stable for 7 days at room temperature and 15 days under refrigeration (2

to 8° C) when protected from light. It should be protected from exposure to sunlight. Discard any of the unused solution from single dose vials. Unused solutions of the multiple dose vial remaining beyond the recommended storage times should be discarded.

7.3.3 Clinical Use

The vials should be reconstituted with sodium chloride injection, USP (0.9%) to give a final concentration of 2 mg/ml. Doxorubicin should be slowly administered into the tubing of a freely running intravenous infusion of Sodium Chloride Injection, USP, or 5% Dextrose Injection, USP. The tubing should be attached to a Butterfly needle inserted preferably into a large vein. Push of bolus administration should be done over 5 – 10 minutes through the side arm of a free flowing IV line. Care must be taken not to infiltrate doxorubicin, as it is a tissue vesicant. If extravasation occurs: stop the infusion; aspirate blood solution from the injection site; disconnect the syringe/IV bag from the catheter; inject 0.5 ml of hydrocortisone phosphate mixed in 2 mL NS into the catheter; remove the catheter/needle; apply ice packs 30'QID to the area for one day. Doxorubicin is not compatible with heparin so it should not be administered through a heparin-lock.

7.3.4 Side Effects

Hematologic: Leukopenia (dose-limiting), thrombocytopenia, anemia. Nadir in 10-14 days with recovery usually in 21 days.
Dermatologic: alopecia (usually complete; reversible) radiation recall reactions; increased sensitivity to sunlight.
Gastrointestinal: nausea and vomiting (doxorubicin is generally considered moderately to highly emetogenic), anorexia, diarrhea, mucositis (stomatitis, esophagitis).
Cardiovascular: cardiomyopathy may occur and is related to total cumulative lifetime dose. The risk for cardiomyopathy increases with total doses > 450 mg/m2. ECG changes and less often, arrhythmias, are seen. Rarely, sudden death has occurred.
Other: Red discoloration of urine for 24-48 hours after drug administration. Doxorubicin is a vesicant and can cause tissue necrosis if extravasated, especially at the concentration usually employed for bolus injections (i.e., 2 mg/mL).

7.4 Vincristine

7.4.1 Description and Mode of Action

Vincristine sulfate, USP is a vincaleukoblastine, 22-oxo-, sulfate (1:1) salt of an alkaloid obtained from a common flowering herb, the periwinkle plant (*Vinca rosea* Linn). The mechanism of action of Oncovin has been related to the inhibition of microtubule formation in the mitotic spindle, resulting in an arrest of dividing cells at the metaphase stage. Please refer to the FDA-approved package insert for vincristine sulfate for product information, extensive preparation instructions, and a comprehensive list of adverse events.

7.4.2 Availability and Accountability

Vincristine is commercially available in 1, 2, and 5 mg vials (1 mg/mL). Vials should be refrigerated and protected from light.

7.4.3 Clinical Use

Administer without further dilution by rapid IV bolus in the side arm of a newly started IV line or

rapid IV bolus or continuous infusion through a central venous catheter. Care must be taken not to infiltrate vincristine, as it is a tissue vesicant. If extravasation occurs: stop the infusion; aspirate blood solution from the injection site; disconnect the syringe/IV bag from the catheter; inject 1 mL of hyaluronidase (150 units/ml) into the catheter; remove the catheter/needle; apply dry heat 30'QID to the area for one day.

7.4.4 Side Effects

The most common toxicity associated with vincristine is neurotoxicity. Peripheral manifestations of neurotoxicity include: numbness of extremities, paresthesias, loss of deep tendon reflexes, neuropathic pain and muscle weakness. GI manifestations of neurotoxicity include constipation, and adynamic ileus. Cranial nerve manifestations include: diplopia, hoarseness, tinnitus, jaw pain (the latter usually occurring with the first dose of vincristine). Orthostatic hypotension & SIADH may also be seen. Vincristine is a vesicant and may cause tissue necrosis upon extravasation. This is more likely with bolus injections as opposed to dilute infusions

7.5 Prednisone

7.5.1 Description and Mode of Action

Prednisone is a potent synthetic glucocorticoid that affects almost every body system. It has anti-inflammatory, immunosuppressant, and minimal mineralocorticoid activity, and antineoplastic properties. As an antineoplastic agent, prednisone may bind to specific proteins (receptors) within the cell forming a steroid-receptor complex. Binding of the receptor-steroid complex with nuclear chromatin alters mRNA and protein synthesis within the cell. Please refer to the FDA-approved package insert for prednisone for product information and a comprehensive list of adverse events.

7.5.2 Availability and Accountability

Prednisone is commercially available in 5, 10, 20, and 50 mg scored tablets and in an oral solution containing 1 mg of prednisone/ml. All forms are stable at room temperature.

7.5.3 Clinical Use

Administer orally with meals to minimize indigestion or GI irritation.

7.5.4 Side Effects

Side effects likely to be encountered with intermittent high doses include: GI (dyspepsia, ulceration), insomnia, and hyperglycemia. Occasionally a "withdrawal syndrome" after short-term high doses, such as in this study, manifest muscle aches and pains. Immunosuppression with risk of infection is also seen.

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9. MEASUREMENT OF EFFECT

Response and progression will be evaluated in this study using the Lugano criteria for lymphoma response.[33] The response assessment time points are: once between Days 15 and 21 of Cycle 3 and at the end of cycle 6 (or at treatment discontinuation). Subjects entering the Follow-up Period will have CT scans every 6 months for up to 2 years or until disease progression. If an additional CT scan is performed earlier than the specified time points due to changes in the subject's clinical status, please also perform an additional response assessment at that time. Once a subject has progressed, no further response assessments are required.

PET-CT. PET-CT is the preferred imaging modality. At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for response assessment. However, if the site can document that the CT performed as part of a PET-CT is of sufficient quality to allow for measurement of target lesions, then the CT portion of the PET-CT can be used for response assessment.

Conventional CT and MRI. This guideline has defined measurability of lesions on CT scan based on the assumption that CT thickness is 5mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size of a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations.

9.1 Response Criteria

Response and Site	**PET-CT–Based Response**	**CT-Based Response**
Complete	Complete metabolic response	Complete radiologic response (all of the following)
Lymph nodes and extralymphatic sites	Score 1, 2, or 3.*_ with or without a residual mass on 5PS.†	Target nodes/nodal masses must regress to ≤ 1.5 cm in LDi
	It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (eg, with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake	No extralymphatic sites of disease
Nonmeasured	Not applicable	Absent

Response and Site	PET-CT–Based Response	CT-Based Response
lesion		
Organ enlargement	Not applicable	Regress to normal
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, IHC negative
Partial	Partial metabolic response	Partial remission (all of the following)
Lymph nodes and extralymphatic sites	Score 4 or 5† with reduced uptake compared with baseline and residual mass(es) of any size	≥ 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites
	At interim, these findings suggest responding disease	When a lesion is too small to measure on CT, assign 5 mm × 5 mm as the default value
	At end of treatment, these findings indicate residual disease	When no longer visible, 0 × 0 mm
		For a node > 5 mm × 5 mm, but smaller than normal, use actual measurement for calculation
Nonmeasured lesions	Not applicable	Absent/normal, regressed, but no increase
Organ enlargement	Not applicable	Spleen must have regressed by > 50% in length beyond normal
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	No metabolic response	Stable disease
Target nodes/nodal masses, extranodal lesions	Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	< 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
Nonmeasured lesions	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression

Response and Site	PET-CT–Based Response	CT-Based Response
New lesions	None	None
Bone marrow	No change from baseline	Not applicable
Progressive disease	Progressive metabolic disease	Progressive disease requires at least 1 of the following
Individual target nodes/nodal masses	Score 4 or 5 with an increase in intensity of uptake from baseline and/or	PPD progression:
Extranodal lesions	New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	An individual node/lesion must be abnormal with: LDi > 1.5 cm and Increase by ≥ 50% from PPD nadir and An increase in LDi or SDi from nadir 0.5 cm for lesions ≤ 2 cm 1.0 cm for lesions > 2 cm In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (eg, a 15-cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline New or recurrent splenomegaly
Nonmeasured lesions	None	New or clear progression of preexisting nonmeasured lesions
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	Regrowth of previously resolved lesions A new node > 1.5 cm in any axis A new extranodal site > 1.0 cm in any axis; if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma
Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

- Abbreviations: 5PS, 5-point scale; CT, computed tomography; FDG, fluorodeoxyglucose; IHC, immunohistochemistry; LDi, longest transverse diameter of a lesion; MRI, magnetic resonance imaging; PET, positron emission tomography; PPD, cross product of the LDi and perpendicular diameter; SDi, shortest axis perpendicular to the LDi; SPD, sum of the product of the perpendicular diameters for multiple lesions.
- * A score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid

undertreatment). Measured dominant lesions: Up to six of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in two diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (eg, liver, spleen, kidneys, lungs), GI involvement, cutaneous lesions, or those noted on palpation. Nonmeasured lesions: Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be 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 ≤ mediastinum; 3, uptake > mediastinum but ≤ liver; 4, uptake moderately > liver; 5, uptake markedly higher than liver and/or new lesions; X, new areas of uptake unlikely to be related to lymphoma.

9.2 Duration of Response

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

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

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

9.3 Progression-Free Survival (PFS)

PFS is defined as the duration of time from start of treatment to time of documentation of progression or death from any cause.

9.4 Overall Survival (OS)

OS is defined as the duration of time from start of treatment to death from any cause.

10. DATA REPORTING / REGULATORY CONSIDERATIONS

10.1 Data Collection

REDCap will be used to capture all treatment, toxicity, efficacy, and adverse event data for all enrolled patients.

REDCap (Research Electronic Data Capture) is a free data management software system that is fully supported by the Weill-Cornell Medical Center CTSC. It is a tool for the creation of customized, secure data management systems that include Web-based data-entry forms, reporting tools, and a full array of security features including user and group based privileges, authentication using institution LDAP system, with a full audit trail of data manipulation and export procedures. REDCap is maintained on CTSC-owned servers that are backed up nightly and support encrypted (SSL-based) connections. Nationally, the software is developed, enhanced and supported through a multi-institutional consortium led by the Vanderbilt University CTSA.

10.2 Regulatory Considerations

All protocol amendments and consent form modifications will be made by the Principal Investigator. Celgene will have the opportunity to review and approve the changes prior to submission of these changes to the local IRB and distribution to participating sites.

11. STATISTICAL CONSIDERATIONS

11.1 Study Design

This is an exploratory phase II study to study the safety and efficacy of CC486 + CHOP in patients with mature peripheral T-cell lymphoma. If the data from this trial provide evidence of efficacy in this patient population, the treatment will be considered for further investigation. A total of 20 patients (17 eligible and evaluable patients) will be enrolled on this trial, with at least 2/3 of the subjects having T-cell lymphoma with T-follicular helper (TFH) phenotype.

11.2 Sample Size

The primary endpoint for this study will be the complete response rate (CR). Sample size recommendations for the phase II design are determined according to Simon's two-stage Minimax design [34]. We project a complete response proportion of 35%, below which the response will be unacceptable, and a complete response proportion of 60%, above which the combination regimen will be considered worthy of further exploration. The null hypothesis that the complete response proportion is less than or equal to 35% will be tested against the alternative hypothesis that the complete response proportion is greater than or equal to 60%.

The sample size computations were performed assuming 10% level of significance and 80% power. In the first stage, 13 patients (at least 2/3 of subjects with T-cell lymphoma with T-follicular helper (TFH) phenotype) will enter the study. If 4 or fewer achieve CR, the study will be terminated early and declared to have a negative result. If 5 or more patients achieve CR, enrollment will be extended to 17 patients. At Stage 2, the treatment will be declared effective and worthy of further testing if 9 or more patients achieve CR among the 17 patients (at least 2/3 of subjects with T-cell lymphoma with T-follicular helper (TFH) phenotype) entered. This two-stage design yields a ≥ 0.80 probability of a positive result if the true percentage of complete responders is $\geq 60\%$. It yields a ≥ 0.90 probability of a negative result if the true percentage of complete responders is $\leq 35\%$. Assuming 15% are unevaluable/ineligible, we anticipate that a total of 20 patients will be enrolled in study (assuming we proceed to the second stage).

Table 1. Numbers of complete responders required to accept or reject H_0 at each stage. Under

this design, H_0 will not be rejected at Stage 1.

	N	Accept H_0	Reject H_0
Stage 1	13	≤ 4	---
Stage 2	17	≤ 8	≥ 9

Table 2. Summary of 90% confidence intervals for potential complete response rates. To allow for a 15% ineligibility rate, we will accrue 20 patients to this study.

No. responses in 17 eligible patients	Complete response rate	90% CI
8	0.470	0.306, 0.639
9	0.529	0.360, 0.693
10	0.588	0.416, 0.745
11	0.647	0.474, 0.795

11.3 Analysis Plan for Endpoints

11.3.1 Primary Endpoints

The primary endpoint of complete response rate will be estimated and a 95% confidence interval will be estimated via Clopper-Pearson exact binomial method.

11.3.2 Secondary Clinical Endpoints

With adequate follow-up time, secondary endpoints of progression-free survival (PFS), overall survival (OS), and time to next treatment will be assessed by Kaplan-Meier survival analysis and 95% confidence intervals will be calculated using Greenwood's formula. PFS will be defined as the time from first treatment day until objective or symptomatic progression or death. OS will be defined as the time from first treatment day until death.

The frequency of subjects experiencing toxicities will be tabulated. Toxicities will be assessed and graded according to CTCAE v. 4.0 terminology. Exact 95% confidence intervals around the toxicity proportions will be calculated to assess the precision of the obtained estimates.

[redacted]

12. ADVERSE EVENT REPORTING REQUIREMENTS

12.1 Adverse Event Definition

An adverse event (AE) is any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an investigational medicinal product (IMP) or other protocol-imposed

intervention, regardless of attribution.

This includes the following:

- AEs not previously observed in the patient that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with NHL that were not present prior to the AE reporting period
- Complications that occur as a result of protocol-mandated interventions
- Preexisting medical conditions (other than the condition being studied) judged by the investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period

All subjects will be monitored for AEs during the study. Assessments may include monitoring of any or all of the following parameters: the subject's clinical symptoms, laboratory, pathological, radiological or surgical findings, physical examination findings, or findings from other tests and/or procedures.

All AEs will be recorded by the Investigator from the time the subject initiates study treatment until 28 days after the last dose of investigational product and those SAEs made known to the Investigator at any time thereafter that are suspected of being related to study treatment. AEs and serious adverse events (SAEs) will be recorded on the AE page of the CRF and in the subject's source documents. All SAEs must be reported to Celgene Drug Safety within 24 hours of the Investigator's knowledge of the event by facsimile, or other appropriate method, using the SAE Report Form, or approved equivalent form.

12.1.1 Adverse Event Characteristics and Related Attribututions

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov)
- **Attribution** of the AE:
    - Definite – The AE *is clearly related* to the study treatment.
    - Probable – The AE *is likely related* to the study treatment.
    - Possible – The AE *may be related* to the study treatment.
    - Unlikely – The AE *is doubtfully related* to the study treatment.
    - Unrelated – The AE *is clearly NOT related* to the study treatment.

12.1.2 Recording of Adverse Events

All adverse events will be recorded on a patient specific adverse event log. The AE log will be maintained by the research staff and kept in the patient's research chart.

12.1.3 Reporting of AE to WCM IRB

The participating investigator will report all adverse events and serious adverse events to the Principal Investigator and to the IRB according to the local IRB's policies and procedures in reporting adverse events. In the event of a multi-center study, the Principal Investigator will report adverse events and serious adverse events from all participating sites to the WCM IRB according to the IRB's policies and procedures in reporting adverse events.

12.2 Definition of SAE

A serious adverse event (SAE) is any AE occurring at any dose that:

- Results in death;
- Is life-threatening (i.e., in the opinion of the Investigator, the subject is at immediate risk of death from the AE);
- Requires inpatient hospitalization or prolongation of existing hospitalization (hospitalization is defined as an inpatient admission, regardless of length of stay);
- Results in persistent or significant disability/incapacity (a substantial disruption of the subject's ability to conduct normal life functions);
- Is a congenital anomaly/birth defect;
- Constitutes an important medical event

Important medical events are defined as those occurrences that may not be immediately life threatening or result in death, hospitalization, or disability, but may jeopardize the subject or require medical or surgical intervention to prevent one of the other outcomes listed above. Medical and scientific judgment should be exercised in deciding whether such an AE should be considered serious.

Events not considered to be SAEs are hospitalizations for:

- A standard procedure for protocol therapy administration. However, hospitalization or prolonged hospitalization for a complication of therapy administration will be reported as an SAE.
- Routine treatment or monitoring of the studied indication not associated with any deterioration in condition. The administration of blood or platelet transfusion as routine treatment of studied Indication. However, hospitalization or prolonged hospitalization for a complication of such transfusion remains a reportable SAE.
- A procedure for protocol/disease-related investigations (e.g., surgery, scans, endoscopy, sampling for laboratory tests, bone marrow sampling). However, hospitalization or prolonged hospitalization for a complication of such procedures remains a reportable SAE.
- Hospitalization or prolongation of hospitalization for technical, practical, or social reasons, in absence of an AE.

- A procedure that is planned (i.e., planned prior to starting of treatment on study); must be documented in the source document and the CRF. Hospitalization or prolonged hospitalization for a complication remains a reportable SAE.
- An elective treatment of or an elective procedure for a pre-existing condition unrelated to the studied indication.
- Emergency outpatient treatment or observation that does not result in admission, unless fulfilling other seriousness criteria above. If an AE is considered serious, both the AE page/screen of the CRF and the SAE Report Form must be completed.

The following event will NOT be considered SAE:

- Leukopenia and lymphopenia of any grade as these are expected pharmacodynamic outcomes of study treatment.
- Grade 3 or 4 neutropenia that is not accompanied by fever ≥ 100.4°F [38°C]) and improves to Grade ≤ 2 by Day 1 of the next cycle
- Grade 3 thrombocytopenia that does not result in bleeding and improves to Grade ≤ 2 by Day 1 of the next cycle
- Grade 3 or 4 anemia
- Grade 3 nausea or vomiting ≤ 7 days (in the absence of premedication or that can be managed with oral or IV anti-emetics)

12.2.1 Reporting of SAE to IRB

All SAEs occurring on this study will be reported to the IRB according to the IRB policy. The IRB requires immediate reporting of all unexpected and study-related (definite or probable) adverse events. The following procedure will be followed for reporting SAE to the IRB:

- Complete the SAE Cover Sheet (See Appendix B)
- If the event is unexpected AND definitely or probably related to the study, complete the IRB Unexpected, Study-related Adverse Events, Incidents, and Information Reporting Form. This form should be submitted within 24 hours of investigator notification of the event.
- If the event is expected OR possibly or unrelated to the study, only the SAE Cover Sheet must be completed. These events will be reported to the IRB at the time of continuing renewal on the Adverse Event & IND Safety Reporting Cumulative Table.

[redacted]

12.2.2 Reporting of SAE to FDA

Serious adverse events (SAEs) that are **unlisted/unexpected, and at least possibly associated to the drug,** and that have not previously been reported in the Investigators brochure, or reference safety information document should be reported promptly to the Food and Drug Administration

(FDA) by telephone or by fax. Fatal or life threatening SAEs that meet the criteria for reporting to the FDA must be reported to the FDA within 7 calendar days after awareness of the event. All other SAEs that meet the criteria for reporting to the FDA must be reported to the FDA within 15 calendar days after awareness of the event. A clear description of the suspected reaction should be provided along with an assessment as to whether the event is drug or disease related. For multicenter trial, all participating study sites should NOT report SAEs to the FDA. Rather, participating sites should report SAEs to Celgene and the primary study site, and the primary site will be responsible for reporting to FDA.

If an SAE occurs on this study, the event will be filed on a MedWatch 3500A form with the FDA. MedWatch 3500A (Mandatory Reporting) form is available at http://www.fda.gov/medwatch/getforms.html

In the United States, all suspected unexpected serious adverse reactions (SUSARs) will be reported in an expedited manner in accordance with 21 CFR 312.32.

Adverse event updates/IND safety reports
Celgene shall notify the Investigator via an IND Safety Report of the following information:

- Any AE suspected of being related to with the use of drug in this study or in other studies that is both serious and unexpected.
- Any finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.

The Investigator shall notify his/her IRB/EC promptly of these new serious and unexpected AE(s) or *significant risks to subjects.* The investigator must keep copies of all pertinent safety information on file, including correspondence with Celgene and the IRB/EC. All pregnancies or suspected pregnancies occurring in either a female subject or partner of a male subject are immediately reportable events.

Pregnancies
Pregnancies and suspected pregnancies (including elevated βhCG or positive pregnancy test in a female subject of reproductive potential, regardless of disease state) occurring while the subject is on IP, or within 28 days of the subject's last dose of IP, are considered immediately reportable events. IP is to be discontinued immediately. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Celgene Drug Safety immediately by email, phone or facsimile, or other appropriate method, using the Pregnancy Initial Report Form, or approved equivalent form. The female subject should be referred to an obstetrician-gynecologist,

(preferably one with reproductive toxicity experience) or another appropriate healthcare professional for further evaluation.

The Investigator will follow the female subject until completion of the pregnancy outcome and up to 1 year to monitor the baby, and must notify Celgene Drug Safety immediately about the outcome of the pregnancy (either normal or abnormal outcome) using the Pregnancy Follow-up Report Form and Infant Follow-Up Form, or approved equivalent form.

If the outcome of the pregnancy was abnormal (e.g., spontaneous or therapeutic abortion, STILLBIRTH, NEONATAL DEATH, OR CONGENITAL ANOMALY), the Investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE to Celgene Drug Safety immediately by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 28 days that the Investigator suspects is related to the in utero exposure to the IP should also be reported to Celgene Drug Safety immediately by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

Male Subjects
If a female partner of a male subject taking investigational product becomes pregnant, the male subject taking IP should notify the Investigator immediately, and the pregnant female partner should be advised to call their healthcare provider immediately. Male patients treated with azacitidine and CC-486 are advised to continue complete abstinence or condom use during treatment and 28 days after stopping treatment.

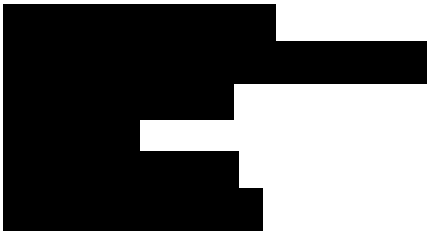
12.2.3 Reporting of SAE to Celgene

Serious adverse events (SAE) are defined above. The investigator must inform Celgene in writing using a Celgene SAE form or MEDWATCH 3500A form of any SAE within 24 hours of being aware of the event. The written report must be completed and supplied to Celgene by facsimile within 24 hours/1 business day. The initial report must be as complete as possible, including an assessment of the causal relationship between the event and the investigational product(s), if available. Information not available at the time of the initial report (e.g., an end date for the adverse event or laboratory values received after the report) must be documented on a follow-up report. A final report to document resolution of the SAE is required. [redacted] A copy of the fax transmission confirmation of the SAE report to Celgene should be attached to the SAE and retained with the patient records.

All participating study sites must report SAEs to Celgene as described and within 24 hours of awareness. Participating sites should also report SAEs to the primary study site.

12.3 IND Annual Reports

If the FDA has granted an IND number, it is a requirement of 21 CFR 312.33, that an annual report is provided to the FDA within 60-days of the IND anniversary date. 21 CRF 312.33 provides the data elements that are to be submitted in the report. The Annual Report should be filed in the study's Regulatory Binder, and a copy provided to Celgene Corporation as a supporter of this study as follows.



12.4 AE/SAE Follow Up

All SAEs and AEs reported during this study will be followed until resolution or until the investigator confirms that the AE/SAE has stabilized and no more follow-up is required. This requirement indicates that follow-up may be required for some events after the patient discontinues participation from the study.

13. DATA AND SAFETY MONITORING PLAN (DSMP)

This is a multi-institution study. The data and safety monitoring for this study will be overseen by the Weill Cornell IRB as well as the principal investigators from each site. The study will be reviewed by the Weill Cornell Medical College Data and Safety Monitoring Board (DSMB) as an independent means of data and safety monitoring. Enrollment information, adverse event and safety information, protocol changes, and other interim data will be evaluated by the DSMB on a semi-annual basis. After each evaluation, the Board will provide the principal investigator with recommendations for protocol modification, continuation, or termination.

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Appendix A: Cockcroft-Gault estimation of CrCl

Cockcroft-Gault estimation of creatinine clearance (CrCl):
(Cockcroft, 1976; Luke 1990)

$$\text{CrCl (mL/min) (\textbf{Males}) } = \frac{(140 - \text{age}) \times (\text{weight, kg})}{72 \times (\text{serum creatinine, mg/dL})}$$

$$\text{CrCl (mL/min) (\textbf{Females}) } = \frac{(140 - \text{age}) \times (\text{weight, kg})}{72 \times (\text{serum creatinine, mg/dL})} \times 0.85$$

Appendix B: International Prognostic Index (IPI) Score

One point is assigned for each of the following risk factors:

- Age greater than 60 years
- Stage III or IV disease
- Elevated serum LDH
- Eastern Cooperative Oncology Group performance status of 2, 3, or 4
- More than 1 extranodal site

IPI Score	Risk Group
0 - 1	Low risk
2	Low-intermediate risk
3	High-intermediate risk
4 - 5	High risk

Source: A Predictive Model for Aggressive Non-Hodgkin's Lymphoma. The International Non-Hodgkin's Lymphoma Prognostic Factor Project. New England Journal of Medicine 1993;329:987-94

Appendix C: Performance Status Criteria

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

Appendix D: New York Heart Association (NYHA) Classification for Congestive Heart Failure

Functional Capacity	Objective Assessment
Class I. Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	**A.** No objective evidence of cardiovascular disease.
Class II. Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	**B.** Objective evidence of minimal cardiovascular disease.
Class III. Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.	**C.** Objective evidence of moderately severe cardiovascular disease.
Class IV. Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	**D.** Objective evidence of severe cardiovascular disease.

Source: The Criteria Committee of the New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th ed. Boston, Mass: Little, Brown & Co; 1994:253-256.

Appendix E: Deauville Criteria for PET Scan Interpretation

Interpretation

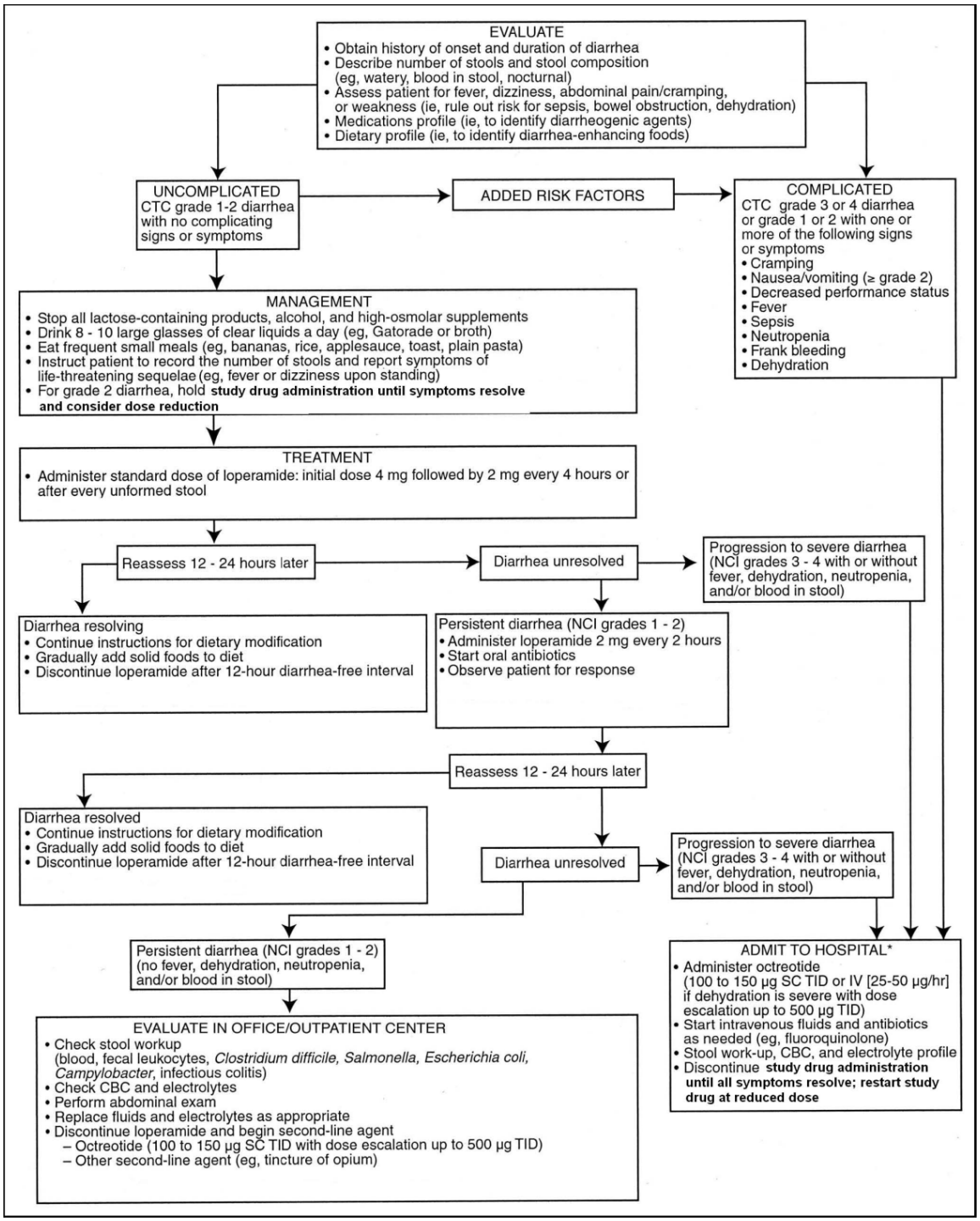
- A visual analysis using the 5-point scale should be applied
- The preferable reference scale should be the mediastinum and the liver

Scoring per the five point scale

1. No uptake
2. Uptake ≤ mediastinum
3. Uptake > mediastinum but ≤ liver
4. Uptake moderately increased compared to the liver at any site.
5. Uptake markedly increased compared to the liver at any site and/or new sites of disease.

Appendix F: Recommendations for Management of Treatment-Induced Diarrhea

The following published guidelines were modified in order to be consistent with the clinical study protocol.



Source: Benson, AB, Ajani JA, Catalano RB, Engelking C, Kornblau SM, Martenson JA Jr, et al: Recommended guidelines for the treatment of cancer treatment-induced diarrhea. J Clin Oncol Jul 15;22(14):2918-26, 2004.

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