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**Study Title**

**Prospective, Multi-Center Phase I/II Trial of Lenalidomide and Dose-Adjusted  
EPOCH-R in MYC-associated B-cell Lymphomas**

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This is a multi-institutional study being conducted by institutional members of the Personalized Cancer Care Consortium (PCCC), as well as additional sites.

**Protocol History**

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06/16/2014	Modified submission
12/11/2014	Amended inclusion criteria
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06/15/2016	Clarification on study entry requirements and treatment during consolidation. Closure of Phase I portion of study and opening of Phase II portion.
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10/23/2017	Reformatting of schema in Appendix B
10/30/2018	Clarified inclusion criteria, timing requirements of study assessments, and how to attribute adverse events.
5/28/2019	Clarified eligibility criteria, PJP and HSV prophylaxis requirements, and dose modifications for lenalidomide.

<b>TABLE OF CONTENT</b>	<b>Page</b>
<b>1.0 INTRODUCTION</b>	<b>4</b>
1.1 Rationale for lenalidomide dosing	8
1.2 Lenalidomide Background	9
<b>2.0 OBJECTIVES</b>	<b>11</b>
2.1 Primary Objectives	11
2.2 Secondary Objectives	12
<b>3.0 STUDY DESIGN</b>	<b>12</b>
<b>4.0 STUDY POPULATION</b>	<b>13</b>
4.1 Number of Subjects	13
4.2 Inclusion Criteria	13
4.3 Exclusion Criteria	14
<b>5.0 REGISTRATION PROCEDURES</b>	<b>15</b>
5.1 General Guidelines	15
5.2 Registration Process	16
<b>6.0 TREATMENT PLAN</b>	<b>17</b>
6.1 Induction Phase	17
6.2 CNS Prophylaxis	18
6.3 Dose-Adjustment Paradigm	18
6.4 Consolidation and Maintenance Phase	19
<b>7.0 DOSE MODIFICATION / TOXICITY MANAGEMENT</b>	<b>19</b>
7.1 EPOCH-R Dose Modifications	20
7.2 Lenalidomide Dose Modifications	20
<b>8.0 CRITERIA FOR SUBJECT DISCONTINUATION</b>	<b>21</b>
8.1 Lenalidomide Specific Criteria	21
8.2 General Criteria	21
<b>9.0 CRITERIA FOR STUDY DISCONTINUATION</b>	<b>21</b>
9.1 Study Subject Replacement	22
<b>10.0 CLINICAL AND LABORATORY EVALUATIONS</b>	<b>22</b>
10.1 Pre-Treatment Evaluations	22
10.2 Evaluations During Treatment	23
10.3 Post-Treatment Evaluations	24
10.4 Evaluations During Maintenance Treatment	24
10.5 Follow-up Evaluations	24
10.6 Correlative Studies	25
<b>11.0 REPORTING OF ADVERSE EVENTS(AE)</b>	<b>26</b>
11.1 Adverse Event (AE)	26
11.2 Serious Adverse Event (SAE)	26
11.3 Unexpected Events	27
11.4 Routine AE Reporting Requirements	27
11.5 SAE Reporting to the Coordinating Center (CC)	27
11.6 Serious and Unexpected AE Reporting by the CC	28
11.7 Serious Adverse Event Reporting to Celgene	28
11.8 Abnormal Laboratory Values	29

11.9 Second Primary Malignancies	30
11.10 Pregnancies	30
11.12 Male Subjects	31
11.13 Expedited Reporting by Investigator to Celgene	31
11.14 Report of Adverse Event to Institutional Review Board (IRB)	32
11.15 Investigator Reporting to the FDA	32
<b>12.0 DATA REPORTING</b>	32
<b>13.0 STUDY MANAGEMENT AND REGULATORY AFFAIRS</b>	33
13.1 Multicenter Guidelines	33
13.2 IRB Approval and Consent	33
13.3 Required Documentation	33
13.4 Data and Safety Monitoring	34
13.5 Auditing	35
13.6 Amendments to the Protocol	35
13.7 Annual IRB Renewals, Continuing Review and Final Reports	36
13.8 Record Retention	36
13.9 Obligations of Study Site Investigators	37
<b>14.0 EVALUATION OF RESPONSE AND SAFETY</b>	37
<b>15.0 STATISTICAL CONSIDERATIONS</b>	38
15.1 Primary Outcome Measures	38
15.2 Secondary Outcome Measures	38
15.3 Safety Outcome Measures	38
15.4 Statistical Methods and Sample Size	38
<b>REFERENCES/BIBLIOGRAPHY</b>	41
<b>APPENDICES</b>	
Appendix A: Study Flowchart	
Appendix B: Study Schema	
Appendix C: Current NCI Common Terminology Criteria for Adverse Events v 4.0 (CTCAE)	
Appendix D: MULTICENTER GUIDELINES	
Appendix E: DA-EPOCH-R detailed schedule and dose modification	
Appendix F: Other Study Drug(s) Background, including Safety Profile	

## 1.0 INTRODUCTION

Non-Hodgkin Lymphoma (NHL) is a malignancy that involves the lymphoid and hematopoietic systems with an expected incidence in the United States (US) of approximately 66,000 cases in 2012 and 25,000 deaths.<sup>1</sup> NHL is divided into several histologic subtypes that continue to be refined as better understanding of the molecular basis of lymphomagenesis continues to evolve.<sup>2</sup> Treatment approaches vary between observation, immunotherapy, chemoimmunotherapy, and stem cell transplantation. These choices of therapy largely depend on the histologic subtype, stage of the disease, goals of care, performance status, and the age of the patient.

Diffuse large B-cell lymphoma (DLBCL) comprises 25-30% of all NHL cases representing the most commonly diagnosed lymphoid malignancy in the US. DLBCL is a potentially curable entity but the likelihood of cure depends on the stage of disease and variable clinical and molecular prognostic factors that predict long-term outcomes.<sup>3,4</sup> For decades, CHOP multi-agent chemotherapy (cyclophosphamide, oncovoin, Adriamycin, and prednisone) has been the backbone therapy for DLBCL standing the rigorous randomized studies that compared that regimen with other second and third generation programs such as m-BACOD, MACOP-B, and ProMACE-CytaBOM.<sup>5</sup> However, the past decade has witnessed improvement in overall survival (OS) for DLBCL patients when rituximab, a chimeric monoclonal anti-CD20 antibody, was added to CHOP chemotherapy.<sup>6,7</sup> The R-CHOP chemoimmunotherapy program has become the standard front-line treatment for all patients with DLBCL<sup>8</sup> but despite this improvement, almost one third of patients fail this curative therapy and ultimately succumb to their disease.<sup>9</sup> Predicting the subset of patients with the high possibility of treatment failure has become a priority in lymphoma research as this allows for selecting better and more suitable therapies that have higher chances of long term durable remissions.

The International Prognostic index (IPI) has historically been a reproducible prognostic guide in patients who have received CHOP alone or with rituximab.<sup>3,10</sup> This index divides patients into various risk categories that differ in their complete remissions (CRs) and overall survival (OS). While the IPI has been a clinically-based model that relies heavily on stage, performance status, and LDH, the more sophisticated gene expression profiling (GEP) studies have demonstrated that DLBCL can be divided into three main categories irrespective of the IPI.<sup>4,11</sup> GEP analyses divide DLBCL based on the cell of origin into germinal center B-cell (GCB), non-germinal center or the activated B-cell (ABC), and primary mediastinal B-cell lymphoma types. These 3 subtypes differ in outcomes even when similar regimens such as R-CHOP are delivered. In all studies, patients with ABC-DLBCL had inferior OS compared with other subtypes. This finding

led to designing clinical trials targeting signaling pathways known to be active in the ABC type. To that end, bortezomib a known NF-Kappa-B pathway inhibitor was added to R-CHOP in a phase II study of patients with DLBCL and mantle cell lymphoma, showing similar responses and survival in ABC and GCB subtypes of treated DLBCL patients.<sup>12</sup> Based on further understanding that NF-kappa-B is an active pathway in the ABC subtype of lymphoma, a randomized study comparing R-CHOP alone or with bortezomib has recently been concluded and its results are expected shortly.

Another high-risk molecular feature in DLBCL has been the presence of abnormalities in the C-myc proto-oncogene signature.<sup>13,14</sup> The human C-myc oncogene is responsible for malignant transformation of several types of lymphomas, and is the *sine qua non* mutation associated with Burkitt Lymphoma (BL).<sup>15,16</sup> However, evidence of C-myc mutation or up-regulation is also found in about ~15-20% of DLBCL and in a recently-recognized provisional diagnostic category termed *B-cell lymphoma, unclassifiable, with features intermediate between Diffuse Large B-cell and Burkitt Lymphoma* (BCLU).<sup>2</sup> Alterations in C-myc may be detected either via cytogenetics (including regular karyotype analysis or fluorescent in-situ hybridization (FISH) for the chromosomal rearrangement, breaks or gain of copy number) or by immunohistochemistry (IHC) for C-myc.<sup>17,18</sup> While the finding of breaks or translocation by FISH is universally recognized as evidence of clinically meaningful activation of this oncogene, the significance of gain of copy number, and of IHC positivity, is less certain.<sup>19</sup> When C-myc abnormalities coincide with other adverse prognostic markers, a new genre of lymphomas, defined more by biologic features than by histologic features, emerge. These lymphomas, which classically include C-myc along with BCL-2 abnormalities, have been dubbed “double hit” lymphomas (DHL), and are an emerging therapeutic challenge.<sup>20,21</sup> Importantly, DHL are not restricted to any one histologic subtype, and can be DLBCL, BCLU, follicular lymphoma (FL; particularly in transformed cases), and mantle cell lymphoma (MCL), among others.

There are no prospective data that defines the optimal approach for C-myc associated lymphoid malignancies. In an attempt to analyze characteristics of patients diagnosed with C-myc lymphoma, Savage and colleagues noted no statistically significant differences in median age, gender, performance status, LDH, IPI score, or BCL-2 protein expression, or cell-of-origin between DLBCL patients who had or lacked the C-myc rearrangement.<sup>22</sup> In contrast, a Japanese study of 252 DLBCL found that the 28 (11%) patients with 8q24/C-myc aberrations were more likely to have a poor performance status (PS), increased LDH, and increased bone marrow involvement at presentation.<sup>13</sup> Given that the cell of origin has been associated with differential survival outcome in DLBCL patients, understanding the impact of C-myc on GCB and ABC subtypes is critical. Hu et al showed recently that C-myc translocation when associated

with another mutation (BCL-2 or BCL-6) has more prognostic implication than the cell of origin.<sup>23</sup>

Despite variability in the IPI scores and cell of origin phenotype, DHL patients have consistently shown inferior outcomes compared with other DLBCL patients when treated with R-CHOP or similar regimens.<sup>24,25</sup> Both C-myc aberrancy and DHL phenotype, whether by FISH or IHC, correlate with high IPI score. Moreover, salvage chemoimmunotherapy followed by high-dose chemotherapy and autologous stem cell transplantation (HDT-ASCT) produces inferior CR rates, PFS, and OS in patients with DLBCL with C-myc rearrangements, irrespective of presence or absence of DHL phenotype, as compared to those with DLBCL without C-myc rearrangement (2-year OS less than 30%).<sup>26</sup> Given the above, identifying an effective regimen for C-myc associated lymphomas is of critical importance.

In an effort to improve on the outcomes achieved with R-CHOP chemoimmunotherapy, the dose-adjusted (DA) EPOCH-R regimen was developed based on in vitro pharmacodynamics principles to help overcome drug resistance.<sup>27</sup> In this regimen, doxorubicin, vincristine, and etoposide are administered as a 96-hour continuous infusion, and cyclophosphamide and prednisone are administered on a bolus schedule. Rituximab is administered as per standard infusion protocol. The rationale for the administration schedule derived from the laboratory observation that human tumor cell lines, including those with a multi-drug resistance phenotype, are more sensitive to cytotoxic natural products given for prolonged periods at low concentrations than to the same agents given for brief periods at higher concentrations. EPOCH was initially developed and tested in 131 patients with relapsed or refractory NHL.<sup>28</sup> The response rate in these heavily pre-treated patients was 74% with 24% of patients achieving CR. In the front-line setting, Wilson et al adjusted the doses of this regimen based on the nadir counts after each cycle.<sup>29</sup>

The doses of doxorubicin, etoposide and cyclophosphamide were escalated 20% on every cycle in which the nadir absolute neutrophil count (ANC) exceeded 500/ $\mu$ L, or reduced 20% if the ANC was less than 500/ $\mu$ L for more than 2 CBC measurements (CBC obtained twice weekly only) or the platelet nadir was < 25,000/ $\mu$ L. The rationale for dose adjustment in each patient was based on the fact that dose intensity has been associated with improved outcome in aggressive lymphomas and that small changes in steady state concentrations for infused agents could significantly affect efficacy. Fifty patients with untreated de novo DLBCL were enrolled. Patients had an IPI distribution of 56% low and 44% high risk disease. CRs were obtained in 45 patients (92%) and partial responses (PRs) in 4 patients. There was no difference in CR rate among the IPI risk groups with 19 of 22 high risk and 26 of 27 low risk patients achieving CR. With a

median follow-up of 62 months, the actuarial progression-free survival (PFS) was 70% and OS was 73%. The regimen was well tolerated with an 8% incidence of fever and neutropenia. In further analyses on DLBCL patients treated with DA-EPOCH with rituximab (R), the regimen appeared to benefit both GCB and ABC subtypes although there was a marginal benefit favoring the GCB subtype.<sup>30</sup>

The favorable outcomes noted using DA-EPOCH-R regimen led to a prospective phase III study comparing this program to the standard R-CHOP regimen. This intergroup study was recently closed to accrual and results are forthcoming. Importantly, several retrospective studies have supported that DA-EPOCH-R might have a superior outcome in C-myc lymphomas when compared to historical controls. Abramson et al reported on 34 patients with DHL by FISH noting that median OS was 34 months in those treated with DA-EPOCH-R versus 8 months in others who received R-CHOP.<sup>31</sup> Gandhi et al reported on a 106 patients with DHL by FISH noting that DA-EPOCH-R achieved higher CR rates compared with other used programs. The numbers were too small in this study to evaluate the role of stem cell transplantation.

Lenalidomide is an immunomodulatory agent with anti-angiogenic properties that is currently approved for the treatment of multiple myeloma, myelodysplasia, and mantle cell lymphoma.<sup>32</sup> While these antiangiogenic and immunomodulatory effects for lenalidomide are well known, the precise mechanisms of action remain unknown.<sup>33</sup> In general, its effects include inhibition of regulatory T-cells, co-stimulation of other T cell subsets, VEGF inhibition, Akt inhibition, inhibition of cell cycle regulatory proteins and down-regulation of a variety of cytokines including IL-6 and TNF.<sup>34,35</sup> Phase I trials with lenalidomide were prompted by preclinical data suggesting anti-tumor effects with doses up to 50 mg daily being evaluated in both hematologic and solid tumor populations.<sup>36</sup> Lenalidomide has less myelosuppression when a 7-day break is introduced, and the most common schedule selected for further development is 25 mg daily on Days 1-21, followed by a 7-day rest period.<sup>37,38</sup> The vast majority of side effects is mild, and includes rash, pruritus, diarrhea, and fatigue. Grade 3 and 4 toxicities observed in these trials include neutropenia and thrombocytopenia in approximately 10% of patients. Importantly, severe constipation, neuropathy and somnolence that characterize thalidomide effects were not seen.

There are several trials investigating lenalidomide monotherapy in patients with relapsed lymphomas. Wiernik and colleagues recently published a final analysis of lenalidomide 25 mg daily on Days 1-21 repeated every 28 days in 49 patients with relapsed aggressive lymphomas.<sup>39</sup> Approximately half of patients had DLBCL, with the remaining patients comprised of grade 3 FL, MCL, and transformed FL. The overall response rate (ORR) was 35%, with a median duration of response 6.2 months and

median PFS 4.0 months. This was a heavily pretreated population of patients, with a median of 4 prior regimens, and 30% of patients having failed a prior autologous stem cell transplant. Witzig and colleagues reported on the same schedule of lenalidomide in patients with heavily pretreated relapsed indolent lymphomas.<sup>40</sup> Importantly, 50% of enrolled patients were refractory to their last treatment and all had received prior rituximab. In this study, the ORR was 23% in all patients, and 27% in relapsed FL patients. What is interesting, however, is that although the median PFS was 4.4 months, the median duration of response for responding patients was not reached at the time of that report and exceeded 16.5 months.

Importantly, Hernandez-Ilizaliturri et al retrospectively evaluated clinical outcomes of patients with GCB versus ABC DLBCL treated with salvage lenalidomide.<sup>41</sup> Forty patients (ABC type in 17) with relapsed/refractory DLBCL who received a median of 4 prior therapies were included. The subgroups were similar in terms of stage, international prognostic index score, prior number of treatments, and rituximab resistance. A significant difference in clinical response to lenalidomide was observed in ABC versus GCB patients. ORR was 52.9% versus 8.7% ( $P = .006$ ); CRs were 23.5% versus 4.3%. Median PFS was 6.2 versus 1.7 months ( $P = .004$ ), although no difference in OS was observed. While lenalidomide appears to exert enhanced activity in the ABC subset of DLBCL patients, it also inhibits the NF-kappa-B pathway that can enhance the activity of the translocated C-myc gene in Burkitt's lymphoma.<sup>42</sup> This might suggest that lenalidomide could have activity in lymphoid malignancies that are C-myc driven.

The documented experience with the DA-EPOCH-R regimen coupled with retrospective analyses and few small prospective studies supporting the activity of this program in C-myc associated lymphomas and specifically DHL makes it the ideal backbone for the incorporation of novel agents. Lenalidomide appears to have antineoplastic and molecular properties that support further investigation in these difficult to treat lymphomas. Accordingly, we initiated this phase I/II DA-EPOCH-R study to will evaluate the feasibility, response, and PFS of DA-EPOCH-R plus lenalidomide in DHL lymphomas.

## **1.1 Rationale for Lenalidomide Dosing**

On the basis of the activity of lenalidomide in relapsed lymphomas including mantle cell lymphoma, this agent was added to rituximab (lenalidomide 20 mg/day, days 1-21/28, plus rituximab 375 mg/m<sup>2</sup> weekly in cycle 1) to examine patients with relapsed/refractory aggressive NHL (mainly DLBCL) (wang reference below). ORR was 33%, with a median DOR, PFS, and OS of 10.2, 3.7, and 10.7 months, respectively. Although this R2 treatment led to a comparable ORR to that shown with lenalidomide

alone, the CR rate was elevated with the combination. In elderly patients (age  $\geq$  65 years), the R2 combination (lenalidomide 20 mg/day, days 1-21/28, plus rituximab 375 mg/m<sup>2</sup> on days 1 and 21 for 4 cycles) was given along with lenalidomide maintenance in patients with at least stable disease (zinzani below). Following induction, patients receiving R2 showed a 35% ORR and 30% CR; 8 of 10 patients in maintenance achieved CR and with a median 32-month DOR.

Because R-CHOP has been used as a standard first-line therapy in DLBCL, it was rational to investigate the possible enhancement of its activity when lenalidomide was added in (i.e., R2-CHOP). Multiple phase II studies showed that not only was R2-CHOP active without increased toxicity, but that it could in part overcome the negative prognostic impact of the non-GCB phenotype. As has been seen with other combination studies, multiple dosing schema for lenalidomide have been identified in both FL and DLBCL with standard R-CHOP21, including lenalidomide 25 mg/day on days 1-14 in FL patients, (both Tilly's references below), and 25 mg on days 1-10 (the JCO 2015 reference below) and 15 mg/day on days 1-14 in DLBCL patients (Vitolo below). Efficacy outcomes showed very high ORR (92%-98%) and CR/CRu (74%-86%) rates, with similar 24-month PFS and OS in both non-GCB and GCB-type DLBCL patients.

## **1.2 Lenalidomide Background**

As discussed above, lenalidomide is a proprietary IMiD® compound of Celgene Corporation. IMiD® compounds have both immunomodulatory and anti-angiogenic properties which could confer antitumor and anti-metastatic effects. Lenalidomide has been demonstrated to possess anti-angiogenic activity through inhibition of bFGF, VEGF and TNF-alpha induced endothelial cell migration, due at least in part to inhibition of Akt phosphorylation response to bFGF.<sup>33</sup> In addition, lenalidomide has a variety of immunomodulatory effects. Lenalidomide stimulates T cell proliferation, and the production of IL-2, IL-10 and IFN-gamma, inhibits IL-1 beta and IL-6 and modulates IL-12 production. Up-regulation of T cell derived IL-2 production is achieved at least in part through increased AP-1 activity.<sup>34</sup>

### **1.2.1 Safety Profile**

#### *Embryo-Fetal Toxicity*

The drug is not to be used during pregnancy. Lenalidomide caused limb abnormalities in a developmental monkey study. If lenalidomide is used during pregnancy, it may cause birth defects or embryo-fetal death. Females of reproductive potential must use 2 forms of contraception or continuously abstain from heterosexual sex during and for 4 weeks after lenalidomide treatment.

### *Hematologic Toxicity (Neutropenia and Thrombocytopenia)*

Lenalidomide can cause significant neutropenia and thrombocytopenia. Eighty percent of patients with del 5q myelodysplastic syndrome (MDS) had to have a dose delay/reduction during the major study. Thirty-four percent of patients had to have a second dose delay/reduction. Grade 3 or 4 hematologic toxicity was seen in 80% of patients enrolled in the study. Patients on therapy for del 5q MDS should have their complete blood counts monitored weekly for the first 8 weeks of therapy and at least monthly thereafter. Patients may require dose interruption and/or reduction. Patients may require use of blood product support and/or growth factors.

### *Venous Thromboembolism:*

Lenalidomide has demonstrated a significantly increased risk of deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients with multiple myeloma (MM) who were treated with lenalidomide and dexamethasone therapy. Patients and physicians are advised to be observant for the signs and symptoms of thromboembolism. Patients should be instructed to seek medical care if they develop symptoms such as shortness of breath, chest pain, or arm or leg swelling. It is not known whether prophylactic anticoagulation or antiplatelet therapy prescribed in conjunction with lenalidomide may lessen the potential for venous thromboembolism. The decision to take prophylactic measures should be done carefully after an assessment of an individual patient's underlying risk factors.

### *Allergic Reactions*

Angioedema and serious dermatologic reactions including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported. These events can be fatal. Patients with a prior history of Grade 4 rash associated with thalidomide treatment should not receive lenalidomide. Lenalidomide interruption or discontinuation should be considered for Grade 2-3 skin rash. Lenalidomide must be discontinued for angioedema, Grade 4 rash, exfoliative or bullous rash, or if SJS or TEN is suspected and should not be resumed following discontinuation for these reactions. Lenalidomide capsules contain lactose. Risk-benefit of lenalidomide treatment should be evaluated in patients with lactose intolerance.

### *Tumor Lysis Syndrome*

Fatal instances of tumor lysis syndrome (TLS) have been reported during treatment with lenalidomide. The patients at risk of TLS are those with high tumor burden prior to treatment. These patients should be monitored closely and appropriate precautions taken.

### *Tumor Flare Reaction*

Tumor flare reaction (TFR) occurred during investigational use of lenalidomide for chronic lymphocytic leukemia (CLL) and lymphoma, and is characterized by tender lymph node swelling, low-grade fever, pain and rash. Treatment of CLL with lenalidomide outside of a well-monitored clinical trial is discouraged. Monitoring and evaluation for TFR is recommended in patients with MCL and other lymphomas. Tumor flare may mimic the progression of disease (PD). In patients with Grade 3 or 4 TFR, it is recommended to withhold treatment with lenalidomide until TFR resolves to  $\leq$  Grade 1. In the MCL trial, approximately 10% of subjects experienced TFR; all reports were Grade 1 or 2 in severity. All of the events occurred in cycle 1 and one patient developed TFR again in cycle 11. Lenalidomide may be continued in patients with Grade 1 and 2 TFR without interruption or modification, at the physician's discretion. Patients with Grade 1 or 2 TFR may also be treated with corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs) and/or narcotic analgesics for management of TFR symptoms. Patients with Grade 3 or 4 TFR may be treated for management of symptoms per the guidance for treatment of Grade 1 and 2 TFR.

### *Hepatotoxicity*

Hepatic failure, including fatal cases, has occurred in patients treated with lenalidomide in combination with dexamethasone. The mechanism of drug-induced hepatotoxicity is unknown. Pre-existing viral liver disease, elevated baseline liver enzymes, and concomitant medications may be risk factors. Monitor liver enzymes periodically. Stopping lenalidomide upon elevation of liver enzymes is recommended. After return to baseline values, treatment at a lower dose may be considered.

### *Second Primary Malignancies*

Patients with myeloma treated with lenalidomide in studies including melphalan and stem cell transplantation had a higher incidence of second primary malignancies, particularly acute myelogenous leukemia (AML) and Hodgkin lymphoma (HL), compared to patients in the control arms who received similar therapy but did not receive lenalidomide. Monitor patients for the development of second malignancies. Take into account both the potential benefit of lenalidomide and the risk of second primary malignancies when considering treatment with lenalidomide.

## **2.0 OBJECTIVES**

### **2.1 Primary objectives**

The primary objective of the phase I portion of the study is to determine the maximum tolerated dose (MTD) of lenalidomide when added to DA-EPOCH-R in patients with DHL lymphomas.

The primary objective of the phase II portion of the study is to determine the 1- and 2-year PFS of DA-EPOCH-R in subjects with DHL lymphomas.

## 2.2 Secondary objectives

- Determine the overall response rate, complete response, and duration of response
- Measure the Quality of Life (QOL) using standardized scale;
- Assess the toxicity profile using version 4.0 of the NCI-CTCAE criteria
- Evaluate the OS at 1 and 2 years

## 3.0 STUDY DESIGN

This is a multi-center single arm phase I/II study with DA-EPOCH-R plus lenalidomide in DHL non-Burkitt non-Hodgkin lymphomas. In the phase 1 portion of the study, a standard 3+3 dose escalation schema will be followed in order to establish the safest dose for this combination schedule. Lenalidomide will be taken orally on days 1-14 of every 21 day cycle. The initial dose of lenalidomide will be 10 mg and the dose will be escalated to a maximum dose of 25 mg unless the MTD is established during an earlier dosing schedule. NOTE: Phase I of the clinical trial was completed and published (Cancer. 2019 Jun 1;125(11):1830-1836. doi: 10.1002/cncr.31877 PMID: 30707764). The recommended phase II starting dose of lenalidomide is 15mg/d on Days 1-41, repeated every 21 days.

Three subjects will be accrued to the first cohort (10 mg of lenalidomide). If 0 of 3 subjects experience a dose limiting toxicity (DLT), then the dose will be escalated and a subsequent cohort of 3 subjects will be enrolled at the next highest dose level of lenalidomide. If 1 of 3 subjects experiences a DLT, then 3 additional subjects will be enrolled at that same dose level and if no further DLTs are observed then the dose will be escalated. If 2 or more DLTs occur at any dose level, then the MTD will have been exceeded. A minimum of 6 subjects will be treated at the MTD, which will be the recommended dose of lenalidomide in the phase II portion, before proceeding to the next phase. Please refer to Table 1-1 and Appendix F for the complete lenalidomide dose escalation schedule.

**Table 1-1 Lenalidomide Dose Escalation Schedule**

Dose Level	Lenalidomide Dose ( <i>days 1-14, q21 days</i> )
Dose Level -1	5mg
Dose Level 1 (starting dose level)	10mg
Dose Level 2	15mg
Dose Level 3	20mg
Dose Level 4	25mg

A DLT is defined as any non-hematologic grade 4 toxicity (based on the CTCAE version-4.0) and/or any recurrent grade 3 non-hematologic toxicity despite optimal medical management that occurs in Cycle 1 ONLY (a cycle equals 21 days). During the lenalidomide dose escalation portion of the study, a hematologic toxicity will not count as a DLT since this regimen is being adjusted based on nadir counts.

Subjects can be treated for a maximum of 6 induction cycles provided they continue to demonstrate a response. After completion of induction therapy, subjects who are transplantation-eligible, can proceed to transplant and will be taken off study. Subjects who receive a transplant will be followed for survival, please refer to Section 10.5 for follow-up requirements. Those subjects who do not move forward with transplant will proceed to maintenance therapy with lenalidomide. During maintenance therapy subjects will take 10mg of lenalidomide on days 1-14 of every 21 day cycle. Subjects can receive up to 12 cycles of maintenance therapy, which will be followed by observation and surveillance as defined in Section 10.4.

#### **4.0 STUDY POPULATION**

##### **4.1 Number of Subjects**

55 subjects with either *MYC* and *BCL2* rearranged or *MYC* and *BCL2* overexpressing non-Burkitt non-Hodgkin lymphomas who meet eligibility criteria and have none of the exclusion criteria will be enrolled into this study.

##### **4.2 Inclusion Criteria**

Subjects must fulfill ALL of the following criteria:

1. B-cell lymphoma stage 2-4 with comprehensive immunohistochemistry (IHC) panel establishing lineage (CD20, CD3) and cell of origin (CD10, BCL6 and MUM1) in addition to proliferative/prognostic markers (Ki-67, C-myc and BCL2). DHL will be identified using cytogenetics and/or immunohistochemistry as detailed in section 4.1.2 below.
2. To define DHL, patients must have evidence of C-myc [defined as: Cytogenetic evidence (FISH or karyotype) of C-myc breaks (Increased copy number in itself is not considered positivity for C-myc) OR Positive IHC defined as  $\geq 40\%$  of the lymphoma cells staining for MYC] PLUS either:
  - a) Breaks in *BCL-2* via cytogenetic studies or
  - b) BCL-2 immunopositivity in  $\geq 70\%$  of lymphoma cells during phase I portion of the trial and  $\geq 50\%$  of lymphoma cells during the phase II portion of the trial.
3. At the investigator's discretion and for subjects who are unstable, one cycle of an anthracycline based chemotherapy in the phase II portion of the trial is allowed

prior to enrollment, but no more than one cycle. For purposes of this trial, prednisone or other corticosteroids used for non-lymphomatous conditions will be allowed. In addition, a prior/recent short course ( $\leq 2$  weeks) of steroids for symptom relief of lymphoma-related symptoms will be allowed.

4. AST and ALT  $\leq 3$  x upper limit of normal (ULN), and total bilirubin  $\leq 1.5$  x ULN (with exception of patients with Gilbert's syndrome, asymptomatic gallstones, liver involvement with NHL or stable chronic liver disease per investigator assessment).
5. Patients must have adequate renal function by virtue of GFR  $\geq 50$  ml/minute using Cockcroft-Gault formula.
6. Patients must have adequate bone marrow function (platelets  $\geq 100,000$  and ANC  $\geq 1,200$ ). Patients with bone marrow involvement are allowed at the investigator's discretion regardless of cytopenias.
7. ECOG PS 0-2.
8. Age  $\geq 18$  years.
9. All study participants must be registered into the mandatory lenalidomide REMS® program, and be willing and able to comply with the requirements of the REMS® program.
10. Females of reproductive potential must adhere to the scheduled pregnancy testing as required in the lenalidomide REMS® program. (Please see study schema for further details)
11. Able to take aspirin (81 or 325 mg) daily as prophylactic anticoagulation (patients intolerant to ASA may use warfarin or low molecular weight heparin or alternative anti-platelet agents).
12. Ability to read, understand, and sign a written informed consent approved by each institutional IRB. Alternatively, patients with legal guardians who can read, understand, and sign written informed consent may also enroll.

#### **4.3 Exclusion Criteria**

1. Prior therapy for lymphoma
2. Known CNS involvement
3. Known HIV positive status
4. Pregnant females
5. Burkitt and/or precursor lymphoblastic leukemia/lymphoma.
6. Prior pomalidomide exposure
7. Known hypersensitivity to lenalidomide or thalidomide
8. The development of erythema nodosum if characterized by a desquamating rash while taking thalidomide or similar drugs.

9. Subjects who have currently active hepatic or biliary disease (with exception of patients with Gilbert's syndrome, asymptomatic gallstones, liver involvement with NHL or stable chronic liver disease per investigator assessment).
10. Treatment with any known non-marketed drug substance or experimental therapy within 4 weeks prior to enrollment, or currently participating in any other interventional clinical study for NHL or any other illness (except observational, prevention, and/or registry trials).
11. Prior radiation or chemotherapy exposure inclusive of low dose chemotherapy such as methotrexate for autoimmune conditions.
12. No current malignancy. Subjects with a prior malignancy are allowed if their physician believes they were treated with curative intent and they have a less than 10% risk of recurrence. Subjects with a history of completely resected non-melanoma skin cancer, or successfully treated in situ carcinoma (any site) are eligible. Women with a history of cervical cancers are also allowed.
13. Chronic or current active infectious disease requiring systemic antibiotics, antifungal, or antiviral treatment such as, but not limited to, chronic renal infection, chronic chest infection with bronchiectasis, tuberculosis and active Hepatitis C.
14. History of significant cerebrovascular disease in the past 3 months or ongoing event with active symptoms or sequelae.
15. Positive serology for Hepatitis B (HB) defined as a positive test for HBsAg. In addition, if negative for HBsAg but HBcAb positive (regardless of HBsAb status), a HB DNA test will be performed and if positive, the subject will be excluded if unable to tolerate and/or receive anti-Hepatitis-B therapy. Positive serology because of prior vaccination is allowed.
16. Positive serology for hepatitis C (HC) defined as a positive test for HCAb.
16. Inability to comply with study or follow-up testing and procedures.

## **5.0 REGISTRATION PROCEDURES**

### **5.1 General Guidelines**

Prior to registration and any study-specific evaluations being performed, all patients must provide written informed consent for the study. It is recommended that prior to presenting the informed consent form to a potential patient you obtain confirmation of slot availability from with the University of Chicago Study Coordinator via email [PhaseIICRA@medicine.bsd.uchicago.edu](mailto:PhaseIICRA@medicine.bsd.uchicago.edu) or via phone (773) 702-9885. Subjects must meet all of the eligibility requirements listed in Section 4.0 to participate in the study and must be registered on study centrally with the University of Chicago Study Coordinator. All required material to document the subject's eligibility must be submitted at least 48

hours prior to the planned commencement of study treatment to the University of Chicago Study Coordinator in order to allow for sufficient time to confirm eligibility. Details of the registration process are detailed in Section 5.2.

## **5.2 Registration Process**

Upon confirmation that the subject meets all of the selection criteria listed in Section 4.0, please contact the University of Chicago Study Coordinator via email [PhaseIIICRA@medicine.bsd.uchicago.edu](mailto:PhaseIIICRA@medicine.bsd.uchicago.edu) or via phone (773) 702-9885 to begin the registration process. Reservations for potential subjects will only be held for subjects who have signed the informed consent document for this study.

The following information will need to be provided at time of registration:

1. Provider of information' name
2. Study # and institution name
3. Treating physician's name
4. Subject's name and hospital ID number
5. Subject's zip code of residence
6. Race, gender, and date of birth of subject
7. Diagnosis and date of initial diagnosis
8. Planned study treatment study date

Additionally, all required materials needed to document the subject's eligibility must be submitted to the University of Chicago Study Coordinator at least 48 hours prior commencement of study treatment. The required materials that need to be submitted are the eligibility checklist, source documentation, and the signed informed consent form. The University of Chicago Study Coordinator will also need to verify the affiliate institute has received IRB approval for the correct version of the protocol/consent and has an annual update on file, if appropriate.

Source documentation should include copies of all original documents that support each inclusion/exclusion criteria. The eligibility checklist does not serve as source documentation but rather as a checklist that original source documentation exists for each criterion.

The University of Chicago Study Coordinator will review all provided information and documentation to ensure the potential subject is eligible to start treatment. If there are questions about eligibility, the University of Chicago Study Coordinator will discuss it with the Principal Investigator (PI). The PI may clarify, but not overturn, eligibility criteria.

Affiliate sites must confirm registration of the subject by obtaining a subject study ID number and the lenalidomide dose level from the University of Chicago Study Coordinator via phone, fax or email. Following registration, subjects must begin protocol treatment within 14 business days. Issues that would cause treatment delays should be discussed with the PI. If a subject does not receive protocol therapy following 14 days of registration, the subject's registration on the study will be canceled. The University of Chicago Study Coordinator should be notified of cancellations as soon as possible.

Please note the date the subject receives treatment for the first time will be considered the subject's "On Study Date." Subjects that sign consent and do not go "On Study" will be recorded in the database with the date they signed consent and the reason for not going "On Study" (e.g., ineligible, screen failure or withdrawn consent).

## **6.0 TREATMENT PLAN**

The phase I portion of the study has been completed and the maximum tolerated dose of lenalidomide has been identified as 15mg. During the phase II portion of the study all subjects will be treated with 15mg of lenalidomide during induction and 10mg of lenalidomide during maintenance daily on days 1 through 14 of a 21 day cycle. All subjects will receive the same dose of DA-EPOCH-R as outlined in Section 6.1 no matter what portion of the study they are enrolled into. Aside from the lenalidomide and the prednisone, all other agents used in this protocol are administered intravenously.

### **6.1 Induction phase**

During induction a treatment cycle is equal to 21 days (3 weeks) and subjects can receive a maximum of 6 cycles of treatment.

Lenalidomide will be given orally on days 1-14 of every cycle at a dose of 15mg. Lenalidomide (Revlimid®) will be provided to research subjects for the duration of their participation in this trial at no charge to them or their insurance providers. Lenalidomide will be provided in accordance with the Celgene Corporation's lenalidomide REMS® program. Per standard lenalidomide REMS® program requirements, all physicians who prescribe lenalidomide for research subjects enrolled into this trial, and all research subjects enrolled into this trial, must be registered in, and must comply with, all requirements of the lenalidomide REMS® program. Only enough lenalidomide for one cycle of therapy will be supplied to the subject each cycle.

The rest of the DA-EPOCH-R chemotherapy regimen is outlined below and will be administered as previously described in the standard fashion: *Wilson WH et al. Dose-*

*adjusted EPOCH chemotherapy for untreated large B-cell lymphomas: a pharmacodynamic approach with high efficacy. Blood 2002; 99:2685.*

- Etoposide (VP-16) 50 mg/m<sup>2</sup>/d civi days days 1-4 (continuous infusion)
- Prednisone 60 mg/m<sup>2</sup>/BID po days 1-5
- Vincristine 0.4 mg/m<sup>2</sup>/d civi days 1-4 (continuous infusion)
- Doxorubicin (Adriamycin) 10 mg/m<sup>2</sup>/d civi days 1-4 (continuous infusion)
- Cyclophosphamide (Cytosan) 750 mg/m<sup>2</sup> IV over 15 min day 5
- Rituximab 375 mg/m<sup>2</sup> on day 1 every 21-days (per standard institutional guidelines)
- Physicians can use their preference for PJP and HSV prophylaxis. Antifungal and other anti-bacterial prophylaxis is not required per protocol and is up to physician's discretion. Growth factor support is required, but specific medication is at the discretion of the physician.
  - Recommended: Filgrastim (Neupogen) 5 mcg/kg sc qd beginning on d6 till ANC > 5,000/uL or Neulasta on days 1 or 2 or 3 after finishing chemotherapy

## **6. 2 CNS Prophylaxis**

If clinically indicated, subjects who are deemed appropriate for central nervous system (CNS) prophylaxis by their treating physician will receive a dose of intrathecal methotrexate between 12 to 15mg with each cycle of chemotherapy. Exact dose of intrathecal methotrexate will be left to the investigator's discretion.

## **6.3 Dose- Adjustment Paradigm**

Dose-adjustment paradigm is based on twice weekly CBC with differential laboratory reports. The dose adjustment rules apply to the starting doses of Etoposide (VP-16), Doxorubicin (Adriamycin) and Cyclophosphamide (Cytosan) noted above.

- If nadir ANC > 500/uL, 20% increase in Etoposide (VP-16), Doxorubicin (Adriamycin) and Cyclophosphamide (Cytosan) above last cycle
- If nadir ANC < 500/uL on 1 or 2 measurements, same doses as last cycle
- If nadir ANC < 500/uL on at least 3 measurements, or nadir platelet < 25,000/uL on 1 measurement, 20% decrease in Etoposide (VP-16), Doxorubicin (Adriamycin) and Cyclophosphamide (Cytosan) below last cycle

See appendix at the end of the protocol for a detailed description of dose modifications based on nadir counts (Appendix E).

The intended treatment plan is for subjects to receive 6 cycles of induction treatment

with lenalidomide and DA-EPOCH-R before moving on to transplant or consolidation. If a subject has completed at least 4 cycles of induction treatment and is either unwilling or unable to tolerate further therapy with DA-EPOCH-R and lenalidomide, the treating physician may choose to complete a PET Scan to assess the subject's response to treatment. If the subject is found to be in a complete remission, the subject may proceed to transplant or consolidation or maintenance as per the treating physician's discretion.

#### **6.4 Consolidation & maintenance phase**

Subjects who are transplantation (HSCT)-eligible will receive the BEAM-conditioning program, followed by auto-HSCT, and then will be observed. HSCT will be done if deemed appropriate by the treating physician.

Subjects who do not undergo HSCT and are currently in first remission should receive maintenance therapy with lenalidomide. During maintenance therapy subjects will take 10mg of lenalidomide on days 1-14 of every 21 day cycle. Subjects can receive up to 12 cycles of maintenance therapy, which will be followed by observation and surveillance as defined in Section 10.5. Maintenance treatment with lenalidomide should be started within 4 weeks of the PET Scan performed at end of treatment and within 8 weeks of their last dose of chemotherapy.

#### **7.0 DOSE MODIFICATION/TOXICITY MANAGEMENT**

Subjects enrolled in this study will be evaluated clinically and with standard laboratory tests before and during their participation in this study. Safety evaluations will consist of medical interviews, recording of adverse events, physical examinations, blood pressure, and laboratory measurements. Subjects will be evaluated for adverse events (all grades), serious adverse events, and adverse events requiring study drug interruption or discontinuation at each study visit for the duration of their participation in the study.

During the lenalidomide dose escalation portion of the study, hematologic toxicity will not count as a DLT since this regimen is being adjusted based on nadir counts. As mentioned previously, DLTs will be defined as any non-hematologic grade 4 toxicity (based on the CTCAE version 4.0) and/or any recurrent grade 3 non-hematologic toxicity despite optimal medical management occurring in cycle 1 of therapy. The remaining chemotherapeutic agents will stay at the same doses regardless of any hematologic toxicity.

## 7.1 EPOCH-R Dose Modifications

Dose modifications for non-hematologic toxicities are as follows:

- For grades 1 and/or 2 non-hematologic toxicity, all drugs are to continue while maximum supportive care measures are being implemented.
- For grade 3 and 4 non-hematologic toxicity, the regimen will be delayed until toxicities are resolved to grade 2 or less. Upon resumption, doses of the chemotherapeutic agents will be decreased by 25% (except for rituximab and prednisone).

## 7.2 Lenalidomide Dose Modifications

During the phase II portion of the study, dose delays/modifications for lenalidomide are allowed as outlined below. During induction treatment, lenalidomide can be dose reduced to dose level -1, 10mg, and dose level -2, 5mg. During maintenance, lenalidomide can be reduced from 10mg to 5mg. There are no lenalidomide dose modifications allowed below 5mg.

Subjects who are not able to tolerate lenalidomide during induction treatment due to cytopenias or toxicity can omit the lenalidomide from further induction cycles. If the subject's counts recover in the allotted time to start maintenance treatment the subject may be re-evaluated for participation in maintenance treatment with lenalidomide. Prior approval from the overall study PI must be obtained.

### Neutropenia

- For  $\geq$  grade 3 neutropenia despite maximum supportive care on day 1 of a cycle, hold lenalidomide, and monitor CBC weekly. Resume therapy at next lower dose level when neutropenia resolves to  $\leq$  grade 2. Hence, for neutropenia occurring on day 1 of a cycle, the cycle may be delayed.
- For  $\geq$  grade 3 neutropenia despite maximum supportive care during a cycle, hold lenalidomide and monitor CBC weekly. Resume therapy at next lower dose level when neutropenia resolves to  $\leq$  grade 2.
- If treatment is delayed for more than 6 weeks, discontinue all protocol therapy and remove patient from study.

### Thrombocytopenia

- For  $\geq$  grade 3 thrombocytopenia despite maximum supportive care on day 1 of a cycle, hold lenalidomide and monitor CBC weekly. Resume therapy at the next lower dose level for the next cycle when thrombocytopenia resolves to  $\leq$  grade 2.
- For  $\geq$  grade 3 thrombocytopenia despite maximum supportive care during a cycle, hold lenalidomide for remainder of the cycle. Resume therapy at the next lower dose level for the next cycle, provided thrombocytopenia has resolved to  $\leq$  grade 2.
- If treatment is delayed for more than 6 weeks, discontinue all protocol therapy and remove patient from study.

## Anemia

- In the instance of **drug-related** anemia based on hemoglobin despite maximum supportive care on day 1 that has worsened by one or more grade levels from previous cycle, reduce lenalidomide by one dose level.
- In the instance of **drug-related** grade 4 hemoglobin at any time during a cycle, discontinue lenalidomide.
- Epoetin may be used to treat drug-related anemia. If epoetin is used, patients should receive either prophylactic aspirin or low molecular weight heparin unless contraindicated.

## Dermatologic Toxicity

In the instance of any grade desquamating rash, lenalidomide must be stopped. In the instance of grade 3 non-desquamating rash despite maximum supportive care, the rash must resolve to grade 1 or less prior to restarting lenalidomide. Lenalidomide should be restarted 5mg less than prior dose.

## Other Non-Hematologic Toxicity

In the instance of a **related** grade 3 or higher other non-hematologic toxicity, hold lenalidomide, notify the study Principal Investigator, and monitor toxicity at least weekly. If toxicity resolves to  $\leq$  grade 2, then resume lenalidomide at next lower dose level.

## 8.0 **CRITERIA FOR SUBJECT DISCONTINUATION**

### 8.1 **Lenalidomide-Specific Criteria**

Subjects who have a severe or life-threatening anaphylaxis or hypersensitivity reaction should be discontinued from the study.

### 8.2 **General Criteria**

Subjects who meet the following criteria should be discontinued from the study:

- inability of subject to comply with study requirements
- determination by the investigator that it is no longer safe for the subject to continue therapy

## 9.0 **CRITERIA FOR STUDY DISCONTINUATION**

Subjects will discontinue treatment after completion per the specified protocol. Subjects can be taken off treatment before completion if they progress while on treatment, develop unacceptable toxicity that precludes treatment resumption, withdraw voluntarily, or deemed best to be taken off treatment per their treating physician. Subjects will

continue to be followed until study completion, subject withdrawal or per investigator discretion.

## **9.1 Study Subject Replacement**

In the phase I portion of the study, a subject will need to complete the prescribed treatment plan in cycle 1 in order to be included in the DLT assessment. If a subject does not complete cycle 1 of induction treatment, the subject will be replaced. In the phase II portion of the study, a subject must complete 6 cycles of induction treatment to be included in the determination of the 1- and 2-year PFS of DA-EPOCH-R in subjects with DHL lymphoma.

## **10.0 CLINICAL AND LABORATORY EVALUATIONS**

### **10.1 Pre-Treatment Evaluations**

The following evaluations must be performed within four weeks prior to the date induction treatment on this study is initiated:

- Medical history and documentation of the rationale for treatment of the subject's disease on this study
- Physical examination, including vital signs, blood pressure, performance status (ECOG), height, weight, BSA, and BMI
- Laboratory evaluations:
  - CBC with differential
  - Comprehensive Metabolic Panel (CMP)
  - LDH
  - uric acid
  - beta-2-microglobulins
  - quantitative immunoglobulins
- Hepatitis B and C serology
- HIV serology
- Tumor assessments: CT scans of the chest, abdomen, and pelvis with IV and oral contrast (unless contraindicated).
- PET scan
- If indicated by the treating physician, a lumbar puncture can be done to screen for central nervous system (CNS) involvement with disease
- Bone marrow biopsy and aspirate to be completed to assess if there is disease involvement.
- MUGA and/or ECHO with documentation of the left ventricular ejection fraction
- Quality of Life Questionnaire (QOL)
- Documentation of C-myc and BCL-2 positivity by FISH/karyotype documenting breaks and/or IHC positivity based on the cutoffs defined in inclusion criteria # 2

for both markers. It is acceptable for the documentation to be outside the 28 day screening window.

- Pregnancy test for women of child bearing age (please refer to the study schema for details)
- Blood draw for correlative studies
- Fresh or archival tumor sample collection for correlative studies

If a subject received one cycle of induction treatment prior to the initiation of study treatment, the following assessments do not need to be repeated if they were previously completed within 4 weeks of the initiation of induction treatment:

- Hepatitis B and C serology
- HIV serology
- Tumor assessments: CT scans of the chest, abdomen, and pelvis with IV and oral contrast (unless contraindicated).
- PET scan
- MUGA and/or ECHO with documentation of the left ventricular ejection fraction
- Bone marrow biopsy and aspirate to be completed to assess if there is disease involvement.
- Lumbar puncture can be done to screen for central nervous system (CNS) involvement with disease, if deemed necessary by treating physician

## **10.2 Evaluations during Induction Treatment**

Unless otherwise specified, the following evaluations are done on day 1 of each induction treatment cycle plus or minus 3 days:

- Physical examination, including vital signs, blood pressure, performance status, weight, BSA and BMI
- Laboratory evaluations: CBC, CMP, LDH, beta-2 microglobulin, and quantitative immunoglobulins to be measured every cycle up to 5 days prior to treatment. Results must be available prior to the initiation of treatment with the exception of LDH, quantitative immunoglobulins and beta-2 microglobulin.
  - Bi-weekly CBC with differential to be obtain for nadir count observation
- CT scan of known areas of disease involvement to be performed after the completion of cycle 3. The CT scan can be performed up to 1 week prior to the start of the next cycle.
- QOL to be completed on day 1 of cycle 4
- Blood draw for correlative studies to be completed on day 1 of cycle 4

### **10.3 Post Induction Treatment Evaluations**

Unless otherwise specified, the following evaluations must be performed within 4 weeks after the completion of the last induction treatment cycle.

- Physical examination, including vital signs, blood pressure, performance status, weight, BSA and BMI
- Laboratory evaluations: CBC, CMP, LDH, Beta-2-microglobulin, and quantitative immunoglobulins
- Blood draw for correlative studies
- Bone marrow biopsy and aspirate in those individuals who had known marrow involvement before study initiation at the end of treatment
- CT scans of chest, abdomen, and pelvis
- PET-CT scan
- MUGA or ECHO with documentation of the left ventricular ejection fraction
- QOL

### **10.4 Evaluations during Maintenance Treatment**

If a subject is continuing on with maintenance treatment, the evaluations listed below are strongly encouraged to be completed on day 1 of each maintenance treatment cycle plus or minus 3 days unless otherwise specified. At a minimum the evaluations must be completed every other cycle:

- Physical examination, including vital signs, blood pressure, performance status, weight, BSA and BMI
- Laboratory evaluations: CBC, CMP, LDH to be measured every cycle up to 5 days prior to treatment. Results must be available prior to the initiation of treatment with the exception of LDH.

Please note that for subjects receiving maintenance therapy the first-year follow-up evaluations described in Section 10.5 must also be completed and can be done in conjunction with a maintenance day 1 cycle visit.

### **10.5 Follow -up Evaluations**

Subjects will be followed from the date of induction treatment completion until 2 years, date of removal from study, or date of death, whichever occurs first. For subjects who will receive maintenance therapy the follow-up evaluations can be done in conjunction with a day 1 maintenance cycle visit. Subjects removed from this study for unacceptable adverse event(s) will be followed until date of disease progression or death, whichever occurs first. Additionally, the unacceptable adverse event(s) should be followed until

resolution or stabilization of the adverse event. After two years, subjects should be followed as clinically indicated based on the physician's discretion.

Unless otherwise specified, the following evaluations must be performed every 3 months for 2 years ( $\pm$  1 week) following induction treatment completion. Physical examination, including vital signs, blood pressure, performance status, weight, BSA and BMI

- Laboratory evaluations: CBC, CMP, LDH, Beta-2-microglobulin, and quantitative immunoglobulins
- CT scans of chest, abdomen, and pelvis every 6 months
- PET-CT scan as clinically indicated
- Subjects who are carriers of hepatitis B at the time of discontinuation from study treatment will need to be followed for clinical and laboratory signs of active HBV infection of hepatitis. Hepatitis serology should be drawn every 3 months for the first 12 months after discontinuation from study.

## **10.6 Correlative Studies**

The current clinical trial budget only covers costs associated with the collection, processing, and storage of the specimens collected for the purposes of future correlative studies. Additional funding will be sought via the University of Chicago Cancer Center, Clinical & Translational Science Awards (CTSA) grant, or other funding agencies to secure funds for the analysis of the specimens. Such a follow-up proposal will contain the detailed methodology. Until funding is secured the processed collected specimens will be stored in within Human Tissue Resource Center at the University of Chicago.

The future correlative studies will be centered around (1) evaluating markers of response to the lenalidomide and EPOCH-R regimen, and (2) to assess pretreatment B-cell lymphoma characteristics. The selected collection time points will allow us to analyze baseline characteristics of the disease and see how the disease changes over the course of the subject's treatment course. Pre-treatment biomarker may be correlated with clinical responses to lenalidomide and EPOCH-R treatment in order to detect biomarkers that are predictive of clinical responsive subject populations. Future analysis of the collected specimens may include assays centered on immunology, proteomics, gene expression, and genetic variants.

The correlative studies will include blood specimens and primary tumor samples. The blood draw for correlative studies will occur at baseline, day 1 of cycle 4, and at the end of treatment visit. Each blood collection will consist of:

- 8 mL of blood for PBMC isolation
- 16 to 20 mL of blood for plasma biomarkers & DNA isolation
- 6 mL of blood for serum

If archival tissue from a tumor biopsy completed prior to treatment is available, 10 to 20 unstained slides should be obtained and sent to the University of Chicago Study Coordinator. Please refer to the Laboratory Manual for further details on the collection, handling, processing, and shipment of blood and tissue specimens.

## **11.0 REPORTING OF ADVERSE EVENTS**

### **11.1 Adverse Event Definition**

An adverse event is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with the treatment. An adverse event can be any unfavorable and unintended sign (including a laboratory finding), symptom or disease temporally associated with the use of a medicinal investigational product, whether or not related to the medicinal investigational product.

At each evaluation subjects should be interviewed in a non-directed manner to elicit potential adverse reactions from the subject. The occurrence of an adverse event will be based on changes in the subject's physical examination, laboratory results, and/or signs and symptoms, and review of the subject's own record of adverse events. Each adverse event that is recorded and its relationship to lenalidomide and chemoimmunotherapy (EPOCH-R) regimen documented.

Adverse events will be followed until resolution while the subject remains on-study. Adverse events will be collected from the time of signing the informed consent until 30 days after the last dose of lenalidomide. Once the subject is removed from study, events thought to be related to the study medication will be followed until resolution or stabilization of the adverse event, or until the subject starts a new treatment regimen, or death, whichever comes first.

### **11.2 Serious Adverse Event Definition**

An adverse event is considered serious if it results in **ANY** of the following outcomes:

- 1) Death
- 2) Life-threatening (e.g. places subject at immediate risk of death, this does not include events that might have caused death if they occurred a greater severity)

- 3) Results in in subject hospitalization or prolongation of existing hospitalization for  $\geq 24$  hours
- 4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- 5) A congenital anomaly/birth defect.

Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, the event may jeopardize the subject and/or may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

### **11.3 Unexpected Events**

Unexpected events are those not listed at the observed specificity or severity in the protocol, informed consent, investigator brochure, or FDA-approved package insert. An event is considered unexpected if it is listed as occurring within the class of drugs or otherwise expected from the drug's pharmacological properties but which has not been previously observed with this specific investigational agent.

### **11.4 Routine Adverse Event Reporting Requirements**

All Adverse Events (AEs) must be reported in routine study data submissions. AEs that meet SAE reporting criteria must also be reported via the Serious Event Reporting Form in eVelos.

### **11.5 Serious Adverse Event Reporting to the Coordinating Center**

The University of Chicago Comprehensive Cancer Center (UC CCC) protocol number, the Celgene assigned protocol number, and the protocol-specific subject ID assigned during trial registration should be noted on all reporting forms.

All serious adverse events (SAEs) occurring on this study require expedited reporting to the UC CCC) Clinical Trials Office (CCTO). The responsible Research Nurse or other designated individual at the treating site should report the SAE to the Study Lead Principal Investigator, the University of Chicago Study Coordinator, and the CCTO by the end of the business day when s/he becomes aware of the event. Events occurring after business hours should be reported to the CCTO by 12pm (noon) the next business day. Reports should be made using the 'Serious Event Report' Form. Please send via fax or scan and send via email (preferred) to the following:

## Phase II General

Phone – 773-702-7716

Fax – 773-702-4889

Email-[PhaseIICRA@medicine.bsd.uchicago.edu](mailto:PhaseIICRA@medicine.bsd.uchicago.edu) and [gaccto@bsd.uchicago.edu](mailto:gaccto@bsd.uchicago.edu)

### **11.6 Serious & Unexpected Adverse Event reporting by the Coordinating Center**

The designated UC CCC Regulatory Manager will notify all participating sites of all unexpected and serious adverse reactions that occur on this clinical trial and which are reported to the UC Institutional Review Board (IRB).

### **11.7 Serious Adverse Event Reporting to Celgene**

All SAEs must be reported to Celgene Drug Safety by the responsible University of Chicago Study Coordinator or other designated individual at the lead coordinating site within 24 hours of the Study Lead Investigator's knowledge of the event by facsimile, or other appropriate method, using the SAE Report Form, or approved equivalent form. For each SAE, the Investigator will provide information on severity, start and stop dates, relationship to investigational product (IP), action taken regarding IP, and outcome.

#### **Severity / Intensity**

For both AEs and SAEs, the investigator must assess the severity / intensity of the event. The term "severe" is often used to describe the intensity of a specific event (as in mild, moderate or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This criterion is not the same as "serious" which is based on subject/event outcome or action criteria associated with events that pose a threat to a subject's life or functioning. Seriousness, not severity, serves as a guide for defining regulatory obligations.

#### **Causality**

The Investigator must determine the relationship between the administration of IP and the occurrence of an AE/SAE as Not Suspected or Suspected as defined below:

- Not suspected: Means a causal relationship of the adverse event to IP administration is unlikely or remote, or other medications, therapeutic interventions, or underlying conditions provide a sufficient explanation for the observed event.
- Suspected: Means there is a reasonable possibility that the administration of IP caused the adverse event. 'Reasonable possibility' means there is

evidence to suggest a causal relationship between the IP and the adverse event.

Causality should be assessed and provided for every AE/SAE based on currently available information. Causality is to be reassessed and provided as additional information becomes available.

If an event is assessed as suspected of being related to a comparator, ancillary or additional IP that has not been manufactured or provided by Celgene, please provide the name of the manufacturer when reporting the event.

### **Duration**

For both AEs and SAEs, the Investigator will provide a record of the start and stop dates of the event.

### **Action Taken**

The Investigator will report the action taken with IP as a result of an AE or SAE, as applicable (e.g., discontinuation, interruption, or reduction of IP, as appropriate) and report if concomitant and/or additional treatments were given for the event.

### **Outcome**

All SAEs that have not resolved upon discontinuation of the subject's participation in the study must be followed until recovered, recovered with sequelae, not recovered or death (due to the SAE).

## **11.8 Abnormal Laboratory Values**

An abnormal laboratory value is considered to be an AE if the abnormality:

- Results in discontinuation from the study;
- Requires treatment, modification/ interruption of IP dose, or any other therapeutic intervention;
- Or is judged to be of significant clinical importance.

Regardless of severity grade, only laboratory abnormalities that fulfill a seriousness criterion need to be documented as a serious adverse event. If a laboratory abnormality is one component of a diagnosis or syndrome, then only the diagnosis or syndrome should be recorded on the AE page/screen of the CRF. If the abnormality was not a part of a diagnosis or syndrome, then the laboratory abnormality should be recorded as the AE. If possible, the laboratory abnormality should be recorded as a medical term and

not simply as an abnormal laboratory result (e.g., record thrombocytopenia rather than decreased platelets).

### **11.9 Second Primary Malignancies**

Second Primary Malignancies (SPMs) are considered events of interest and should be included as part of the assessment of adverse events throughout the course of the study. Investigators are to report any second primary malignancies as serious adverse events regardless of causal relationship to lenalidomide, occurring at any time for the duration of the study. For all subjects who develop second primary malignancies, sites will be required to submit all diagnostic reports (e.g. pathology, cytogenetics, flow cytometry results) from the indication diagnostic confirmation samples submitted at screening and all reports for the tumor samples from the SPM diagnosis. For SPMs diagnosed at another institution (outside the investigational site), sites are to make every effort to obtain these reports for the SPM confirmation.

### **11.10 Pregnancies**

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female subject occurring while the subject is on lenalidomide, or within 28 days of the subject's last dose of lenalidomide, are considered immediately reportable events in which case, lenalidomide is to be discontinued immediately. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Celgene Drug Safety immediately by facsimile or email using the Pregnancy Initial Report Form. The female subject should be referred to an obstetrician-gynecologist, preferably one experienced in reproductive toxicity for further evaluation and counseling.

The Investigator will follow the female subject until completion of the pregnancy, 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. If the outcome of the pregnancy was abnormal (e.g., spontaneous or therapeutic abortion), the Investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE to 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.

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.

### **11.12 Male Subjects**

If a female partner of a male subject taking investigational product becomes pregnant, the male subject taking lenalidomide should notify the Investigator, and the pregnant female partner should be advised to call their healthcare provider immediately.

#### **Celgene Drug Safety Contact Information:**

Celgene Corporation  
Global Drug Safety and Risk Management  
Connell Corporate Park  
300 Connell Dr. Suite 6000  
Berkeley Heights, NJ 07922  
Fax: (908) 673-9115  
E-mail: [drugsafety@celgene.com](mailto:drugsafety@celgene.com)

All adverse experience reports must include the subject number, age, sex, weight, severity of reaction (e.g. mild, moderate, severe), relationship to drug (e.g. probably related, unknown relationship, definitely not related), date and time of administration of test medications and all concomitant medications, and medical treatment provided. The investigator is responsible for evaluating all adverse events to determine whether criteria for "serious" and as defined above are present. The investigator is responsible for reporting adverse events to Celgene as described below.

### **11.13 Expedited Reporting by Investigator to Celgene**

SAEs 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). 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. The Celgene tracking number (RV-CL-NHLMIXED-PI-003856) and the institutional protocol number should be included on SAE reports (or on the fax cover letter) sent to Celgene. A copy of the fax transmission confirmation of the SAE report to Celgene should be attached to the SAE and retained with the subject records.

Since this is a multicenter trial, all SAEs must be reported to Celgene as described and within 24 hours of awareness. Participating sites should first report all SAEs to the University of Chicago.

#### **11.14 Report of Adverse Events to the Institutional Review Board**

The principal Investigator is required to notify his/her (IRB of a serious adverse event according to institutional policy.

#### **11.15 Investigator Reporting to the 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 Celgene and the University of Chicago. The University of Chicago, as lead study site, will determine if additional reporting is required.

### **12.0 DATA REPORTING**

Data reporting will be performed utilizing the eVelos electronic data capture system. The University of Chicago Study Coordinator will provide you with the applicable user registration information.

All required data must be recorded in the eVelos database at the completion of each cycle. AEs are to be entered in real time. SAEs are to be entered on the Serious Event Form within 24 hours of the site's knowledge of the event and sent via fax or scanned and sent via email to the University of Chicago (see section 11.5). All case report forms must be completed by designated study personnel. Each screened (consented) subject should be entered into eVelos within 48 hours of enrollment approval.

In addition to direct data entry, supporting source documentation submission to the University of Chicago Study Coordinator is required. Source documentation includes original documents, data, and records (e.g., medical records, raw data collection forms, pharmacy dispensing records, recorded data from automated instruments, laboratory data) that are relevant to the clinical trial. Each site will prepare and maintain adequate and accurate source documents. These documents are designed to record all observations and other pertinent data for each subject enrolled in this clinical trial. Source records must be adequate to reconstruct all data transcribed onto the case report form.

## **13.0 STUDY MANAGEMENT**

### **13.1 Multicenter Guidelines**

The specific responsibilities of the Principal Investigator and the Coordinating Center are presented in Appendix C. Clinical studies coordinated by The University of Chicago must be conducted in accordance with the ethical principles that are consistent with Good Clinical Practices (GCP) and in compliance with other applicable regulatory requirements. The Study Lead PI/Coordinating Center is responsible for distributing all official protocols, amendments, and Safety Reports to all participating institutions for submission to their individual IRBs for action as required.

### **13.2 Institutional Review Board Approval and Consent**

Unless otherwise specified, each participating institution must obtain its own IRB approval. It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB should approve the consent form and protocol.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki. Before recruitment and enrollment onto this study, the patient will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the patient and the investigator is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing an IRB approved consent form.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the patient and by the person who conducted the informed consent discussion.

### **13.3 Required Documentation**

Prior to the selection of a study site that is not a full member of the Personalized Cancer Care Consortium, the audit and trial oversight processes for the site must be reviewed and approved by the UC CCC Clinical Research Advisory Committee

Before the study can be initiated at any site, the following documentation must be provided to the CCTO at the University of Chicago Comprehensive Cancer Center:

- A copy of the official IRB approval letter for the protocol and informed consent
- IRB membership list
- CVs and medical licensure for the principal investigator and any sub-investigators who will be involved in the study
- CAP and CLIA Laboratory certification numbers and institution lab normal values
- Investigational drug accountability standard operating procedures
- Additionally, before the study can be initiated at any site, the required executed research contract/subcontract must be on file with the University of Chicago.

### **13.4 Data and Safety Monitoring**

This study will be remotely monitored by the designated University of Chicago Clinical Research Associate (CRA) in accordance with the University of Chicago, Section of Hematology/Oncology standard operating procedure titled Monitoring of Multi-Institutional Investigator Initiated Clinical Trials.

Prior to subject recruitment, and unless otherwise specified, a participating site will undergo a Site Initiation Teleconference to be conducted by the designated University of Chicago research team. The site's principal investigator and his or her study staff must attend the site initiation meeting.

Monitoring will be conducted to verify the following:

- Adherence to the protocol
- Completeness and accuracy of study data and samples collected
- Compliance with regulations
- Submission of required source documents

Participating sites will also undergo a site close-out teleconference upon completion, termination or cancellation of a study to ensure fulfillment of study obligations during the conduct of the study, and to ensure that the site Investigator is aware of his/her ongoing responsibilities.

Unless otherwise specified, this protocol will undergo weekly review at the multi-institutional data and safety monitoring teleconference as per procedures specified by the UC CCC NCI-approved Data and Safety Monitoring Plan.

The conference will review:

- Enrollment rate relative to expectations, characteristics of participants

- Safety of study participants (SAE & AE reporting)
- Adherence to protocol (protocol deviations)
- Completeness, validity and integrity of study data
- Retention of study participants

Protocol deviations are to be documented using the Protocol Deviation Form in the eVelos clinical trial management system. Deviations that are considered major because they impact subject safety or alter the risk/benefit ratio, compromise the integrity of the study data, and/or affect subjects' willingness to participate in the study must be reported into the eVelos system within 7 days.

### **13.5 Auditing**

In addition to the clinical monitoring procedures, the CCTO will perform routine Quality Assurance Audits of investigator-initiated clinical trials as described in the NCI-approved UC CCC DSM Plan. Audits provide assurance that trials are conducted and study data are collected, documented and reported in compliance with the protocol. Further, they ensure that study data are collected, documented and reported in compliance with GCP guidelines and regulatory requirements by performing annual quality assurance audits. The CCTO will review subjects enrolled at the University of Chicago and at institutions who are formal members of the Personalized Cancer Care Consortium (PCCC) in accordance with audit procedures specified in the Data and Safety Monitoring plan.

Auditing procedures for participating sites that are not full members of the PCCC must be specified and approved by the UC CCC Clinical Research Advisory Committee prior to site approval to participate in the study. In general, for sites that are not full members of the PCCC, auditing responsibility will be delegated to the participating center, with the annual audit report forwarded to the University of Chicago for review.

A regulatory authority (e.g. FDA) may also wish to conduct an inspection of the study, during its conduct or even after its completion. If an inspection has been requested by a regulatory authority, the site investigator must immediately inform the University of Chicago Cancer Clinical Trials Office and Regulatory Manager that such a request has been made

### **13.6 Amendments to the Protocol**

All modifications to the protocol, consent form, and/or questionnaires will be submitted to the University of Chicago IRB for review and approval. A list of the proposed modifications or amendments to the protocol and/or an explanation of the need of these

modifications will be submitted, along with a revised protocol incorporating the modifications. Only the Study Lead PI can authorize any modifications, amendments, or termination of the protocol. Once a protocol amendment has been approved by the University of Chicago IRB, the Regulatory Manager will send the amended protocol and consent form (if applicable) to the affiliate institutions electronically.

Upon receipt of the packet the affiliate institution is expected to do the following:

- The affiliate site must reply to the email from the Regulatory Manager indicating that the amendment was received by the institution and that it will be submitted to the local IRB.
- The amendment should be submitted to the affiliate institution's IRB as soon as possible after receipt. The amendment must be IRB approved by the institution within 3 months from the date that it was received.
- The University of Chicago version date and/or amendment number must appear on the affiliate consent form and on the affiliate IRB approval letter. The version dates can be found on the footer of every page of the protocol and consent form. The amendment number can be found on the University of Chicago IRB amendment approval letter that is sent with the protocol/amendment mailing.
- The IRB approval for the amendment and the amended consent form (if amended consent is necessary) for the affiliate institution must be sent to the designated UC Regulatory Manager as soon as it is received.

### **13.7 Annual IRB Renewals, Continuing Review and Final Reports**

The annual IRB renewal approvals for participating institutions should be forwarded promptly to the Regulatory Manager. If the institution's IRB requires a new version of the consent form with the annual renewal, the consent form should be included with the renewal letter.

### **13.8 Record Retention**

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

Study documentation includes all CRFs, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms). Additionally, all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study should also be maintained.

### **13.9 Obligations of Study Site Investigators**

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

The Study Site Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected and entered into the CRFs. Periodically, monitoring visits or audits will be conducted and he/she must provide access to original records to permit verification of proper entry of data.

### **14.0 EVALUATION OF RESPONSE AND SAFETY**

- 1- Response evaluation will take place after the completion of induction treatment cycles 3 and 6 using CT and/or PET as per the investigator's discretion. Response will be assessed as mentioned above using Cheson et al.<sup>43</sup> Subjects will be given either: CR, PR, SD, or PD.
- 2- PET scan is mandatory at baseline (prior to cycle 1) and at completion of induction therapy for each subject
- 3- Bone marrow biopsy is to be done at end of therapy to document complete response if initial bone marrow showed disease involvement.

Once subjects enter the follow up phase of the study, they will be seen every 3 months for laboratory assessment including LDH, CBC, CMP, and immunoglobulin levels. Imaging studies using CT-Scans of the chest, abdomen, and pelvis will be done every 6 months for two years following the completion of induction treatment and then at the physician's discretion.

Duration of response is calculated as the duration from detecting any objective response until progression or death from any cause. Duration of CR is calculated as time from first CR documentation until progression or death. PFS is calculated from date of study entry (first treatment date) until progression, secondary malignancy, or death from any cause. OS is calculated from study entry until death from any cause.

## **15.0 STATISTICAL ANALYSIS**

### **15.1 Primary Outcome Measures**

The primary endpoint, PFS, will be defined as the time elapsed between treatment initiation and tumor progression or death from any cause (whichever occurs first), with censoring of subjects who are lost to follow up. Subjects will not be censored if/when proceeding to HSCT. Subjects who do not receive 6 cycles of induction treatment will not be included in the primary endpoint analysis.

### **15.2 Secondary Outcome Measures**

Secondary end points include studying the feasibility of combining lenalidomide with DA-EPOCH-R during the phase I portion of the study as described above as well as calculating the overall response rate defined as the sum of PR and CR by CT of PET/CT and/or resolution of marrow-only involvement (if originally involved). Anti-tumor activity will be calculated as the sum of SD, PR, and CR. Assessing response will be according to the Revised Response Criteria for Malignant Lymphoma.<sup>43</sup> Assessment of response will be after cycles 3 and 6. Duration of response will be defined as the time elapsed between initial documented PR or CR and first progression event.

### **15.3 Safety Outcome Measures**

The secondary endpoint of safety will be defined as the occurrence of all grades of toxicity (using CTCAE v 4.0), experienced during study treatment (up to 21 days from last treatment). The occurrence and severity of each event will be recorded.

### **15.4 Statistical Methods and Sample Size**

In the phase I portion of this trial, our primary objective is to determine the safety, tolerability, and feasibility of adding lenalidomide to the DA-EPOCH-R regimen as a front-line therapy in subjects with DHL lymphomas. We will utilize a standard “3+3” design starting at a dose level of 10 mg of lenalidomide. Three patients will be accrued to the first cohort (10 mg of lenalidomide). If 0 of 3 subjects experience a DLT, then the

dose will be escalated and the subsequent cohort of 3 subjects will be enrolled at a dose level of 15 mg of lenalidomide. DLT is defined above within the body of the protocol (sections 3.0 and 7.0) and is assessed during cycle # 1 only. If 1 of 3 subjects experiences a DLT, then 3 additional subjects will be enrolled at that same dose level and if no further DLTs are observed then the dose will be escalated. If 2 or more DLTs occur at any dose level, then the MTD will have been exceeded. A minimum of 6 subjects will be treated at the MTD, which is the recommended dose of lenalidomide in the phase II portion, before proceeding to the next phase.

In the phase II portion of the study, our primary end point is to assess PFS at 1 and 2 years from enrollment. We believe that the combination of DA-EPOCH-RR would warrant further validation if we could improve one-year PFS by approximately 20%, to a rate of 60%. We propose an Optimal Two-Stage Design to test the null hypothesis that  $P \leq 0.40$  versus the alternative that  $P \geq 0.60$ , where P represents one-year PFS. We propose error probability limits of  $\alpha=0.05$  and  $\beta=0.20$ . The Optimal Two-Stage Design provides for early stopping of the trial if there is sufficient indication of futility. Under these conditions, if seven or fewer of the first 16 subjects are alive and progression-free at one year, the trial will be terminated, and DA-EPOCH-RR will be considered to have no greater efficacy than previously reported treatment regimens. However, if 8 or more subjects are alive and progression-free, the trial will proceed, to a total enrollment of 46 subjects. If the number of subjects that are progression-free at this point is less than or equal to 23, the combination will not be considered superior to previously reported regimens.

Although interim analysis for futility is planned, enrollment will not stop at any time unless it is evident that seven or fewer of the first 16 evaluable for one-year progression-free survival (PFS) will not achieve this outcome (i.e., we will not stop enrollment after the first 16 subjects are enrolled in order to wait for one-year PFS data for that population).

The sample size of 46 subjects that will be evaluated for primary efficacy endpoint of one-year PFS will be defined as those having DHL by IHC criteria (i.e., MYC+ $\geq$ 40% AND BCL2+ $\geq$  70%). An additional total of nine subjects (for a total of 55) will be permitted to enroll, so long as they otherwise meet the inclusion/exclusion criteria as specified by this protocol. The rationale for the additional 9 allowed subjects to be enrolled is to account for screen failures and subjects who might withdraw consents or are taken off study. Those subjects that do not begin protocol-specified treatment for any reason may be removed from the trial and replaced with additional subject(s) in order to satisfy total enrollment as specified.

We recognize that HSCT (either autologous or allogeneic) may be employed at the choice of the treating physician, and that this might complicate the interpretation of efficacy results. However, recent reports indicate that HSCT in first CR is still seldom used, and we are lacking data indicative of a clear benefit for such a strategy. The ultimate decision regarding HSCT in first remission will be at the discretion of the treating physician, and would propose an exploratory analysis in which such subjects are audited (either at time of enrollment or at time of transplant) to evaluate whether HSCT seems to benefit these subjects. Subjects who undergo HSCT will be censored when evaluating progression but will also be evaluated separately to document progression after HSCT as subjects will be followed for 48 months from the date of study treatment completion.

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## APPENDIX A: STUDY FLOW CHART/SCHEMA

	Screening*	Day 1 of each Induction Cycle	End of Induction Treatment Visit	Day 1 of each Maintenance Cycle <sup>9</sup>	Follow-up
Window	Within 4 weeks	(± 3 days)	Within 4 weeks of last induction treatment	(± 3 days)	Every 3 months for 2 years post induction completion
Physical exam, vital signs, height, weight, performance status, BMI, BSA	x	x <sup>1</sup>	x	x	x
CBC, CMP, LDH	x	x <sup>2</sup>		x	
Quantitative immunoglobulins (IgG, IgM, IgA), beta-2-microglobulin	x	x <sup>2</sup>			x
Uric Acid, Hepatitis B and C, HIV	x				
Quality of life assessment using FACT-L (QOL)	x	x <sup>6</sup>	x		
Documentation of C-myc and BCL 2positivity	x				
MUGA or ECHO	x		x		
CT scan of chest, abdomen, and pelvis	x	x <sup>6</sup>	x		x <sup>10</sup>
Bone marrow biopsy and aspirate	x		x <sup>7</sup>		
PET-CT scans	x		x		x <sup>8</sup>
Pregnancy testing <sup>3</sup>	x				
Follow carriers of hepatitis B for active HBV infection or signs of hepatitis			x		x
Lumbar puncture and intrathecal-MTX		x <sup>4</sup>			
Blood draw for correlative studies	x <sup>5</sup>	x <sup>6</sup>	x		

<sup>1</sup> Does not need to be repeated for C1D1 if screening visit is done within 7 days of starting treatment

<sup>2</sup> Labs can be drawn up to 5 days prior to treatment. Results must be available prior to treatment except for LDH.

<sup>3</sup> Pregnancy test requirements for females of Reproductive Potential: Obtain a negative pregnancy test 10 to 14 days prior to writing an initial prescription for lenalidomide and again within 24 hours prior to writing an initial prescription for lenalidomide even if continuous abstinence is the chosen method of birth control. The pregnancy test must be sensitive to at least 50 mIU/mL. Pregnancy testing should occur weekly during the first 4 weeks of use. Pregnancy testing should be repeated every 4 weeks if patient has regular menses or is amenorrheic, or every 2 weeks if irregular menses. If a patient misses her period or if there is any abnormality in menstrual bleeding, lenalidomide should be discontinued immediately. Obtain a pregnancy test and counsel the patient. If pregnancy does occur during treatment, lenalidomide must be immediately discontinued

<sup>4</sup> If clinically indicated, intrathecal therapy can be done between days 1-5 of each cycle of chemotherapy. 12 to 15 mg of intrathecal methotrexate will be used for any patient receiving intrathecal therapy, but the exact dose will be left to the investigator's discretion.

<sup>5</sup> Blood draw for correlative studies may be drawn prior to study treatment on day 1.

<sup>6</sup> Assessment should only be completed on day 1 of cycle 4.

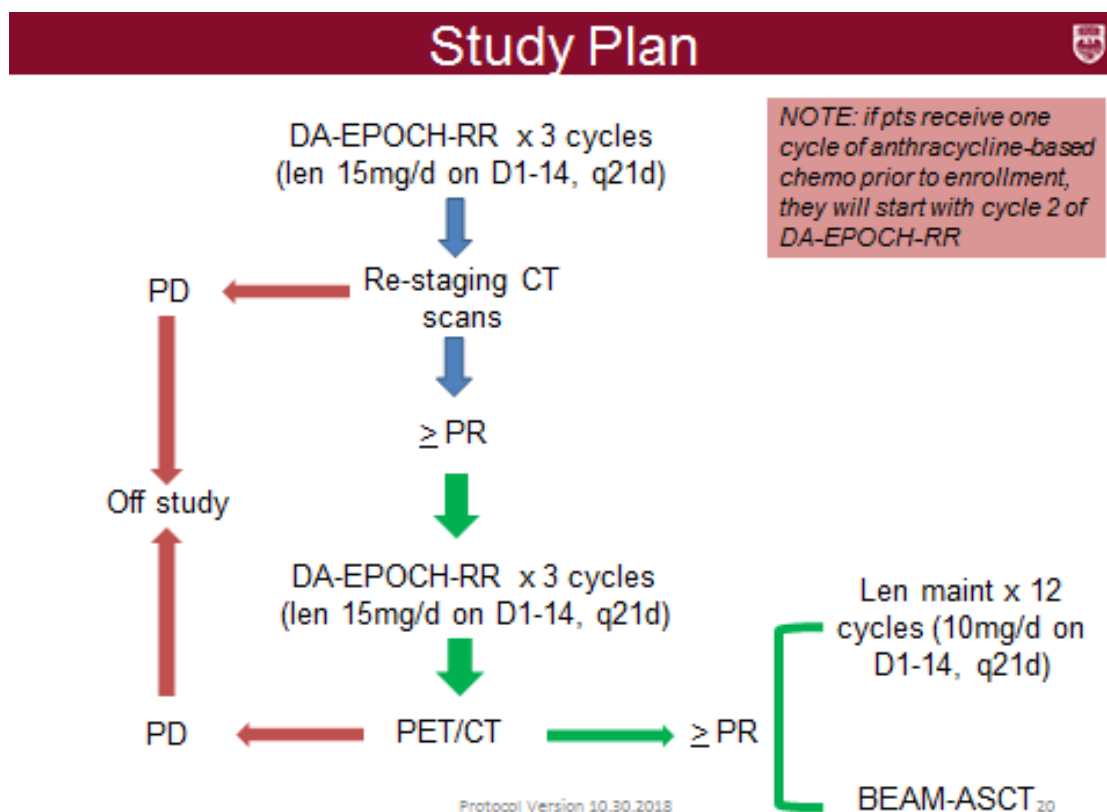
<sup>7</sup> Assessment should only be completed if marrow involvement was present at baseline.

<sup>8</sup> Assessment should only be completed as clinically indicated.

<sup>9</sup> Subjects will also need to adhere to the year one follow-up schedule. Follow-up assessments can be completed in conjunction with a maintenance day 1 cycle visit. It is encouraged for patients to have evaluations done at the start of every cycle, but at a minimum must be completed every other cycle.

<sup>10</sup> CT-scan of chest, abdomen, and pelvis should be completed every 6 month during follow-up.

## APPENDIX B: STUDY SCHEMA



## **APPENDIX C: CURRENT NCI COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS (CTCAE)**

*[Please refer to the following web link:]*

**[http://ctep.cancer.gov/protocolDevelopment/electronic\\_applications/ctc.htm](http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm)**

## **APPENDIX D: MULTICENTER GUIDELINES**

### **Responsibility of the Study Lead PI**

- The Study Lead PI will be the single liaison with regulatory and data management staff, outside sponsor/s, FDA, and funding agencies. The Study Lead PI is responsible for the coordination, development, submission, and approval of the protocol as well as its subsequent amendments. The protocol must not be rewritten or modified by anyone other than the Study Lead PI. There will be only one version of the protocol, and each participating institution will use that document. The Study Lead PI is responsible for assuring that all participating institutions are using the correct version of the protocol.
- The Study Lead PI is responsible for the overall conduct of the study at all participating institutions and for monitoring its progress. All reporting requirements are the responsibility of the Study Lead PI.
- The Study Lead PI is responsible for the timely review of Adverse Events (AE) to assure safety of the patients.
- The Study Lead PI will be responsible for the review of and timely submission of data for study analysis.

### **Responsibilities of the Coordinating Center**

- The Coordinating Center is responsible for maintaining copies of IRB approvals from each participating site.
- The Coordinating Center is responsible for central patient registration. The Coordinating Center is responsible for assuring that IRB approval has been obtained at each participating site prior to the first subject registration from that site.
- The Coordinating Center is responsible for the preparation of all submitted data for review by the Study Lead PI.
- The Coordinating Center will maintain documentation of AE reports. The Coordinating Center will submit AE reports to the Study Lead PI for timely review.

## APPENDIX E: DA-EPOCH-R Dose Modifications and Levels

### (DA-EPOCH-R) Dose Modifications

#### Hematologic Toxicity

Delay cycle by up to 2 weeks if ANC < 1000/ $\mu$ L or platelets < 100,000/ $\mu$ L. Filgrastim may be used for several days to increase ANC. If no recovery after 2 weeks, contact the PI for guidance.

Doses for doxorubicin, etoposide and cyclophosphamide will be based on measurements of the previous cycle ANC or platelet nadir whichever is lower (**i.e., twice weekly starting 3-4 days after completion of chemotherapy**).

If ANC $\geq$ 500/ $\mu$ L on all measurements:	<input type="checkbox"/> one dose level*
If ANC < 500/ $\mu$ L on 1 or 2 measurements (3-4 days apart):	maintain dose level
If ANC < 500/ $\mu$ L $\geq$ 3 measurements (3-4 days apart):	<input type="checkbox"/> one dose level**
<b>OR</b>	
If platelet < 25,000/ $\mu$ L on $\geq$ 1 measurement:	<input type="checkbox"/> one dose level

\* to a maximum of Dose Level 7.

\*\* to a minimum of Dose Level -2. During induction recurrence of a toxicity requiring a dose modification below Dose Level -2 will require the lenalidomide to be omitted for remaining treatment cycles. If the subject's counts recover in the allotted time to start maintenance treatment the subject may be re-evaluated for participation in maintenance treatment with lenalidomide. Prior approval from the overall study PI must be obtained. During maintenance recurrence of a toxicity requiring a dose reduction below Dose Level -2 will result in removal of patient from protocol therapy.

### DA-EPOCH Dose Levels

Dose adjustments for hematologic toxicity apply only to etoposide, doxorubicin and cyclophosphamide. Only cyclophosphamide is reduced in Dose Levels -1 through -3.

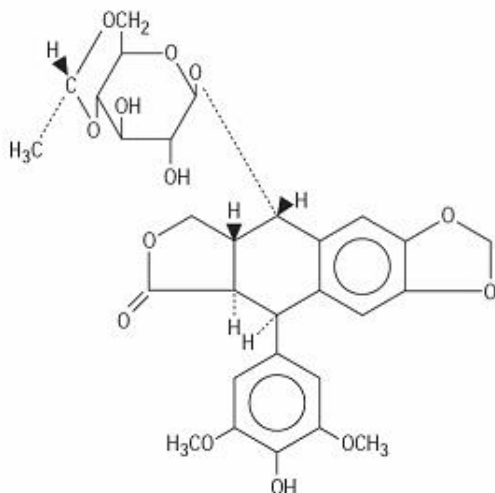
Adjusted agents	Dose Levels									
	-3	-2	-1	1	2	3	4	5	6	7
Doxorubicin (mg/m <sup>2</sup> /day)	10	10	10	<b>10</b>	12	14.4	17.3	20.7	24.8	29.8
Etoposide (mg/m <sup>2</sup> /day)	50	50	50	<b>50</b>	60	72	86.4	103.7	124.4	149.3
Cyclophosphamide (mg/m <sup>2</sup> )	384	480	600	<b>750</b>	900	1080	1296	1555	1866	2239
<b>Non-adjusted agents</b>										
Rituximab (mg/m <sup>2</sup> )	375	375	375	<b>375</b>	375	375	375	375	375	375
Vincristine (mg/m <sup>2</sup> /day) (No Cap)	0.4	0.4	0.4	<b>0.4</b>	0.4	0.4	0.4	0.4	0.4	0.4
Prednisone (mg/m <sup>2</sup> BID)	60	60	60	<b>60</b>	60	60	60	60	60	60

## APPENDIX F: Other Study Drug(s) Background, including Safety Profile

### Etoposide

Etoposide (also commonly known as VP-16) is a semisynthetic derivative of podophyllotoxin used in the treatment of certain neoplastic diseases. It is 4'-demethylepipodophyllotoxin 9-[4,6-O-(R)-ethylidene- $\beta$ -D-glucopyranoside]. It is very soluble in methanol and chloroform, slightly soluble in ethanol and sparingly soluble in water and ether. It is made more miscible with water by means of organic solvents. It has a molecular weight of 588.58 and a molecular formula of C<sub>29</sub>H<sub>32</sub>O<sub>13</sub>. Etoposide Injection USP is available for intravenous use as 20 mg/mL solution in 100 mg (5 mL), 500 mg (25 mL), and 1 g (50 mL) sterile, multiple-dose vials. The pH of the clear, nearly colorless to yellow liquid is 3 to 4. Each mL contains 20 mg etoposide USP, 2 mg citric acid, 30 mg benzyl alcohol, 80 mg modified polysorbate 80/tween 80, 650 mg polyethylene glycol 300, and 30.5 percent (v/v) alcohol.

The structural formula is:



### Clinical Pharmacology

Etoposide has been shown to cause metaphase arrest in chick fibroblasts. Its main effect, however, appears to be at the G<sub>2</sub> portion of the cell cycle in mammalian cells. Two different dose-dependent responses are seen. At high concentrations (10 mcg/mL or more), lysis of cells entering mitosis is observed. At low concentrations (0.3 to 10 mcg/mL), cells are inhibited from entering prophase. It does not interfere with microtubular assembly. The predominant macromolecular effect of etoposide appears to be the induction of DNA strand breaks by an interaction with DNA topoisomerase II or the formation of free radical

### Pharmacokinetics

On intravenous administration, the disposition of etoposide is best described as a biphasic process with a distribution half-life of about 1.5 hours and terminal elimination half-life ranging from 4 to 11 hours. Total body clearance values range from 33 to 48 mL/min or 16 to 36 mL/min/m<sup>2</sup> and, like the terminal elimination half-life, are independent of dose over a range of 100 to 600 mg/m<sup>2</sup>. Over the same dose range, the areas under the plasma concentration vs. time curves (AUC) and the maximum plasma concentration (C<sub>max</sub>) values increase linearly with dose. Etoposide does not accumulate in the plasma following daily administration of 100 mg/m<sup>2</sup> for 4 to 5 days.

The mean volumes of distribution at steady state fall in the range of 18 to 29 liters or 7 to 17 L/m<sup>2</sup>. Etoposide enters the CSF poorly. Although it is detectable in CSF and intracerebral tumors, the concentrations are lower than in extra-cerebral tumors and in plasma. Etoposide concentrations are higher in normal lung than in lung metastases and are similar in primary tumors and normal tissues of the myometrium. In vitro, etoposide is highly protein bound (97%) to human plasma proteins. An inverse relationship between plasma albumin levels and etoposide renal clearance is found in children. In a study determining the effect of other therapeutic agents on the in vitro binding of carbon-14 labeled etoposide to human serum proteins, only phenylbutazone, sodium salicylate, and aspirin displaced protein-bound etoposide at concentrations achieved in vivo.

Etoposide binding ratio correlates directly with serum albumin in patients with cancer and in normal volunteers. The unbound fraction of etoposide significantly correlated with bilirubin in a population of cancer patients. Data have suggested a significant Inverse correlation between serum albumin concentration and free fraction of etoposide.

After intravenous administration of <sup>14</sup>C-etoposide (100 to 124 mg/m<sup>2</sup>), mean recovery of radioactivity in the urine was 56% of the dose at 120 hours, 45% of which was excreted as etoposide: fecal recovery of radioactivity was 44% of the dose at 120 hours.

In children, approximately 55% of the dose is excreted in the urine as etoposide in 24 hours. The mean renal clearance of etoposide is 7 to 10 mL/min/m<sup>2</sup> or about 35% of the total body clearance over a dose range of 80 to 600 mg/m<sup>2</sup>. Etoposide, therefore, is cleared by both renal and non-renal processes, i.e., metabolism and biliary excretion. The effect of renal disease on plasma etoposide clearance is not known.

### Absorption

Biliary excretion of unchanged drug and/or metabolites is an important route of etoposide elimination as fecal recovery of radioactivity is 44% of the intravenous dose. The hydroxy acid metabolite [4'-demethylepipodophyllic acid-9-(4,6-O-(R)-ethylidene- $\beta$ -D-glucopyranoside)], formed by opening of the lactone ring, is found in the urine of adults and children. It is also present in human plasma, presumably as the trans isomer. Glucuronide and/or sulfate conjugates of etoposide are also excreted in human urine. Only 8% or less of an intravenous dose is excreted in the urine as radiolabeled metabolites of  $^{14}\text{C}$ -etoposide. In addition, O-demethylation of the dimethoxyphenol ring occurs through the CYP450 3A4 isoenzyme pathway to produce the corresponding catechol. After intravenous infusion, the  $C_{\text{max}}$  and AUC values exhibit marked intra- and inter-subject variability.

There is no evidence of a first-pass effect for etoposide. For example, no correlation exists between the absolute oral bioavailability of etoposide capsules and non-renal clearance. No evidence exists for any other differences in etoposide metabolism and excretion after administration of oral capsules as compared to intravenous infusion.

In adults, the total body clearance of etoposide is correlated with creatinine clearance, serum albumin concentration, and nonrenal clearance. Patients with impaired renal function receiving etoposide have exhibited reduced total body clearance, increased AUC and a lower volume of distribution at steady state. Use of cisplatin therapy is associated with reduced total body clearance. In children, elevated serum SGPT levels are associated with reduced drug total body clearance. Prior use of cisplatin may also result in a decrease of etoposide total body clearance in children. Although some minor differences in pharmacokinetic parameters between age and gender have been observed, these differences were not considered clinically significant.

### Adverse Reactions

The following data on adverse reactions are based on intravenous administration of etoposide as a single agent, using several different dose schedules for treatment of a wide variety of malignancies.

#### *Hematologic Toxicity*

Myelosuppression is dose-related and dose-limiting, with granulocyte nadirs occurring 7 to 14 days after drug administration and platelet nadirs occurring 9 to 16 days after drug administration. Bone marrow recovery is usually complete by day 20, and no cumulative toxicity has been reported. Fever and infection have

also been reported in patients with neutropenia. Death associated with myelosuppression has been reported.

The occurrence of acute leukemia with or without a preleukemic phase has been reported rarely in patients treated with etoposide in association with other antineoplastic agents.

#### *Gastrointestinal Toxicity*

Nausea and vomiting are the major gastrointestinal toxicities. The severity of such nausea and vomiting is generally mild to moderate with treatment discontinuation required in 1% of patients. Nausea and vomiting can usually be controlled with standard antiemetic therapy. Mild to severe mucositis/esophagitis may occur. Gastrointestinal toxicities are slightly more frequent after oral administration than after intravenous infusion.

#### *Hypotension*

Transient hypotension following rapid intravenous administration has been reported in 1% to 2% of patients. It has not been associated with cardiac toxicity or electrocardiographic changes. No delayed hypotension has been noted. To prevent this rare occurrence, it is recommended that etoposide be administered by slow intravenous infusion over a 30- to 60-minute period. If hypotension occurs, it usually responds to cessation of the infusion administration of fluids or other supportive therapy as appropriate. When restarting the infusion, a slower administration rate should be used.

#### *Allergic Reactions*

Anaphylactic-like reactions characterized by chills, fever, tachycardia, bronchospasm, dyspnea, and/or hypotension have been reported to occur in 0.7% to 2% of patients receiving intravenous etoposide and in less than 1% of the patients treated with oral capsules. These reactions have usually responded promptly to the cessation of the infusion, antihistamines, or volume expanders as appropriate; however, the reactions can be fatal. Hypertension and/or flushing have also been reported. Blood pressure usually normalizes within a few hours after cessation of the infusion. Anaphylactic-like reactions have occurred during the initial infusion of etoposide.

Facial/tongue swelling, coughing, diaphoresis, cyanosis, tightness in throat, laryngospasm, back pain, and/or loss of consciousness have sometimes occurred in association with the above reactions. In addition, an apparent hypersensitivity-associated apnea has been reported rarely.

Rash, urticaria, and/or pruritus have infrequently been reported at recommended doses. At investigational doses, a generalized pruritic erythematous maculopapular rash, consistent with perivascularitis, has been reported.

#### *Skin*

Reversible alopecia, sometimes progressing to total baldness was observed in up to 66% of patients.

#### *Other Toxicities*

The following adverse reactions have been infrequently reported: abdominal pain, aftertaste, constipation, dysphagia, asthenia, fatigue, malaise, somnolence, transient cortical blindness, optic neuritis, interstitial pneumonitis/pulmonary fibrosis, fever, seizure (occasionally associated with allergic reactions), Stevens-Johnson syndrome, and toxic epidermal necrolysis, pigmentation, and a single report of radiation recall dermatitis.

Hepatic toxicity, generally in patients receiving higher doses of the drug than those recommended, has been reported with etoposide. Metabolic acidosis has also been reported in patients receiving higher doses. Reports of extravasation with swelling have been received post marketing. Rarely extravasation has been associated with necrosis and venous induration.

The incidences of adverse reactions in the table that follows are derived from multiple databases from studies in 2,081 patients when etoposide was used either orally or by injection as a single agent.

ADVERSE DRUG EFFECT	PERCENT RANGE OF REPORTED INCIDENCE
Hematologic toxicity	
Leukopenia (less than 1,000 WBC/mm <sup>3</sup> )	3–17
Leukopenia (less than 4,000 WBC/mm <sup>3</sup> )	60–91
Thrombocytopenia (less than 50,000 platelets/mm <sup>3</sup> )	1–20
Thrombocytopenia (less than 100,000 platelets/mm <sup>3</sup> )	22–41
Anemia	0–33
Gastrointestinal toxicity	
Nausea and vomiting	31–43
Abdominal pain	0–2
Anorexia	10–13
Diarrhea	1–13
Stomatitis	1–6

Hepatic	0–3
Alopecia	8–66
Peripheral neurotoxicity	1–2
Hypotension	1–2
Allergic reaction	1–2

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### Overdosage

No proven antidotes have been established for etoposide overdosage.

### Dosage and Administration

Note: Plastic devices made of acrylic or ABS (a polymer composed of acrylonitrile, butadiene, and styrene) has been reported to crack and leak when used with undiluted etoposide injection.

### Etoposide Injection

The usual dose of etoposide Injection in testicular cancer in combination with other approved chemotherapeutic agents ranges from 50 to 100 mg/m<sup>2</sup>/day on days 1 through 5 to 100 mg/m<sup>2</sup>/day on days 1, 3, and 5. In small cell lung cancer, the etoposide Injection dose in combination with other approved chemotherapeutic drugs ranges from 35 mg/m<sup>2</sup>/day for 4 days to 50 mg/m<sup>2</sup>/day for 5 days.

For recommended dosing adjustments in patients with renal impairment. Chemotherapy courses are repeated at 3- to 4-week intervals after adequate recovery from any toxicity. The dosage should be modified to take into account the myelosuppressive effects of other drugs in the combination or the effects of prior x-ray therapy or chemotherapy, which may have compromised bone marrow reserve.

### Administration Precautions

As with other potentially toxic compounds, caution should be exercised in handling and preparing the solution of etoposide. Skin reactions associated with accidental exposure to etoposide may occur. The use of gloves is recommended. If etoposide solution contacts the skin or mucosa, immediately and thoroughly wash the skin with soap and water and flush the mucosa with water.

### Preparation for Intravenous Administration

Etoposide injection must be diluted prior to use with either 5% Dextrose injection, or 0.9% Sodium Chloride injection, to give a final concentration of 0.2 to 0.4 mg/mL. If solutions are prepared at concentrations above 0.4 mg/mL, precipitation may occur. Hypotension following rapid intravenous administration has been reported; hence, it is recommended that the etoposide solution be

administered over a 30- to 60-minute period. A longer duration of administration may be used if the volume of fluid to be infused is a concern. Etoposide should not be given by rapid intravenous injection. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

### Stability

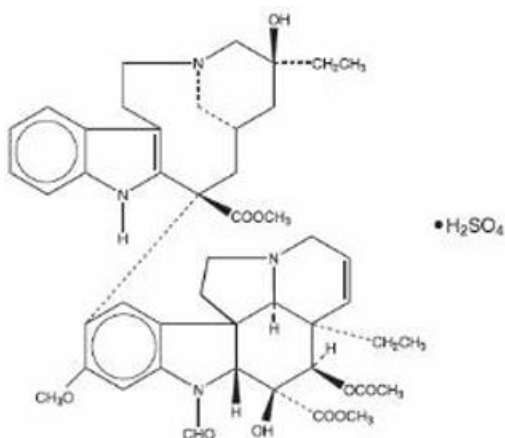
Unopened vials of etoposide injection are stable for 24 months at room temperature (25°C). Vials diluted as recommended to a concentration of 0.2 or 0.4 mg/mL are stable for 96 and 24 hours, respectively, at room temperature (25°C) under normal room fluorescent light in both glass and plastic containers. Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published. There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

## **Vincristine**

### Description

Vincristine Sulfate Injection, USP is the salt of an alkaloid obtained from a common flowering herb, the periwinkle plant (*Vinca rosea* Linn). Originally known as leurocristine, it has also been referred to as LCR and VCR. The molecular formula for Vincristine Sulfate, USP is  $C_{46}H_{56}N_4O_{10} \cdot H_2SO_4$ . It has a molecular weight of 923.04.

The structural formula is as follows:



Vincristine Sulfate, USP is a white to off-white powder. It is soluble in methanol, freely soluble in water, but only slightly soluble in 95% ethanol. In 98% ethanol, Vincristine Sulfate, USP has an ultraviolet spectrum with maxima at 221 nm ( $\epsilon +47,100$ ).

Vincristine sulfate injection, USP is a sterile, preservative-free, single use only solution available for intravenous use in 2 mL (1 mg and 2 mg) vials. Each mL contains 1 mg Vincristine Sulfate, USP, 100 mg mannitol and Water for Injection, USP. Q.S. Sulfuric acid or sodium hydroxide has been added for pH control. The pH of Vincristine Sulfate Injection, USP ranges from 4.0 to 5.0. At the time of manufacture, the air in the containers is replaced by nitrogen.

### Clinical Pharmacology

The mechanisms of action of vincristine sulfate remain under investigation. The mechanism of action of vincristine sulfate has been related to the inhibition of microtubule formation in mitotic spindle, resulting in an arrest of dividing cells at the metaphase stage. Central nervous system leukemia has been reported in patients undergoing otherwise successful therapy with vincristine sulfate. This suggests that vincristine does not penetrate well into the cerebrospinal fluid.

Pharmacokinetic studies in patients with cancer have shown a triphasic serum decay pattern following rapid intravenous injection. The initial, middle and terminal half-lives are 5 minutes, 2.3 hours, and 85 hours respectively; however, the range of the terminal half-life in humans is from 19 to 155 hours. The liver is the major excretory organ in humans and animals. The metabolism of vinca alkaloids have been shown to be mediated by hepatic cytochrome P450 isoenzymes in the CYP 3A subfamily. This metabolic pathway may be impaired in patients with hepatic dysfunction or who are taking concomitant potent inhibitors of these isoenzymes. About 80% of an injected dose of vincristine sulfate appears in the feces and 10% to 20% can be found in the urine. Within 15 to 30 minutes after injection, over 90% of the drug is distributed from the blood into tissue, where it remains tightly, but not irreversibly, bound.

Current principles of cancer chemotherapy involve the simultaneous use of several agents. Generally, each agent used has a unique toxicity and mechanism of action so that therapeutic enhancement occurs without additive toxicity. It is rarely possible to achieve equally good results with single-agent methods of treatment. Thus, vincristine sulfate is often chosen as part of polychemotherapy because of lack of significant bone-marrow suppression (at recommended doses) and of unique clinical toxicity (neuropathy).

### Indication and Usage

Vincristine sulfate injection is indicated in acute leukemia. Vincristine sulfate injection has also been shown to be useful in combination with other oncolytic agents in Hodgkin's disease, non-Hodgkin's malignant lymphomas, rhabdomyosarcoma, neuroblastoma, and Wilms' tumor.

## Precautions

### *General*

Acute uric acid nephropathy, which may occur after the administration of oncolytic agents, has also been reported with vincristine sulfate. In the presence of leukopenia or a complicating infection, administration of the next dose of vincristine sulfate injection warrants careful consideration. If central nervous system leukemia is diagnosed, additional agents may be required, because vincristine does not appear to cross the blood–brain barrier in adequate amounts.

Particular attention should be given to dosage and neurologic side effects if vincristine sulfate injection is administered to patients with preexisting neuromuscular disease and when other drugs with neurotoxic potential are also being used.

Acute shortness of breath and severe bronchospasm have been reported following the administration of vinca alkaloids. These reactions have been encountered most frequently when the vinca alkaloid was used in combination with mitomycin–C and may require aggressive treatment, particularly when there is preexisting pulmonary dysfunction. The onset of these reactions may occur minutes to several hours after the vinca alkaloid is injected and may occur up to 2 weeks following the dose of mitomycin. Progressive dyspnea requiring chronic therapy may occur. Vincristine sulfate should not be readministered.

Care must be taken to avoid contamination of the eye with concentration of vincristine sulfate injection used clinically. If accidental contamination occurs severe irritation (or, if the drug was delivered under pressure, even corneal ulceration) may result. The eye should be washed immediately and thoroughly.

### *Laboratory Tests*

Because dose–limiting clinical toxicity is manifested as neurotoxicity clinical evaluation (e.g., history, physical examination) it is necessary to detect the need for dosage modification. Following administration of vincristine sulfate injection, some individuals may have a fall in the white blood cell count or platelet count, particularly when previous therapy or the disease itself has reduced bone–marrow function. Therefore, a complete blood count should be done before administration of each dose. Acute elevation of serum uric acid may also occur during induction of remission in acute leukemia; thus, such levels should be determined frequently during the first 3 to 4 weeks of treatment or appropriate measures taken to prevent uric acid nephropathy. The laboratory performing these tests should be consulted for its range of normal values.

### *Drug Interactions*

The simultaneous oral or intravenous administration of phenytoin and antineoplastic chemotherapy combinations that included vincristine sulfate has been reported to reduce blood levels of the anticonvulsant and to increase seizure activity. Dosage adjustment should be based on serial blood level monitoring. The contribution of vincristine sulfate to this interaction is not certain. The interaction may result from reduced absorption of phenytoin and an increase in the rate of its metabolism and elimination.

Caution should be exercised in patients concurrently taking drugs known to inhibit drug metabolism by hepatic cytochrome P450 isoenzymes in the CYP 3A subfamily, or in patients with hepatic dysfunction. Concurrent administration of vincristine sulfate with itraconazole (a known inhibitor of the metabolic pathway) has been reported to cause an earlier onset and/or an increased severity of neuromuscular side effects. This interaction is presumed to be related to inhibition of the metabolism of vincristine.

*Carcinogenesis, Mutagenesis, Impairment of Fertility* – Neither in vivo nor in vitro laboratory tests have conclusively demonstrated the mutagenicity of this product. Fertility following treatment with vincristine sulfate alone for malignant disease has not been studied in humans. Clinical reports of both male and female patients who received multiple-agent chemotherapy that included vincristine sulfate indicate that azoospermia and amenorrhea can occur in post-pubertal patients. Recovery occurred many months after completion of chemotherapy in some but not all patients. When the same treatment is administered to pre-pubertal patients, permanent azoospermia and amenorrhea are much less likely.

Patients who received chemotherapy with vincristine sulfate in combination with anti-cancer drugs known to be carcinogenic have developed second malignancies. The contributing role of vincristine sulfate in this development has not been determined. No evidence of carcinogenicity was found following intraperitoneal administration of vincristine sulfate in rats and mice, although this study was limited.

### *Usage in Pregnancy – Pregnancy Category D.*

*Nursing Mothers* – It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions due to vincristine sulfate in nursing infants, a decision should be made either to discontinue nursing or the drug, taking into account the importance of the drug to the mother.

### Adverse Reactions:

Prior to the use of this drug, patients and/or their parents/guardian should be advised of the possibility of untoward symptoms. In general, adverse reactions are reversible and are related to dosage. The most common adverse reaction is hair loss; the most troublesome adverse reactions are neuromuscular in origin.

When single, weekly doses of the drug are employed, the adverse reactions of leukopenia, neurotic pain, and constipation occur but are usually of short duration (ie., less than 7 days). When the dosage is reduced, these reactions may lessen or disappear. The severity of such reactions seems to increase when the calculated amount of drug is given in divided doses.

Other adverse reactions, such as hair loss, sensory loss, paresthesia, difficulty in walking, slapping gait, loss of deep–tendon reflexes, and muscle wasting, may persist for at least as long as therapy is continued. Generalized sensorimotor dysfunction may become progressively more severe with continued treatment. Although most such symptoms usually disappear by about the sixth week after discontinuance of treatment, some neuromuscular difficulties may persist for prolonged periods in some patients. Regrowth of hair may occur while maintenance therapy walking, slapping gait, loss of deep–tendon reflexes, and muscle wasting, may persist for at least as long as therapy is continued.

Generalized sensorimotor dysfunction may become progressively more severe with continued treatment. Although most such symptoms usually disappear by about the sixth week after discontinuance of treatment, some neuromuscular difficulties may persist for prolonged periods in some patients. Regrowth of hair may occur while maintenance therapy continues.

The following adverse reactions have been reported: Hepatic veno-occlusive disease has been reported in patients receiving vincristine, particularly in pediatric patients, as part of standard combination chemotherapy regimens. Some of the patients had fatal outcomes; some who survived had undergone liver transplantation.

### *Hypersensitivity*

Rare cases of allergic–type reactions, such as anaphylaxis, rash and edema, that are temporally related to vincristine therapy have been reported in patients receiving vincristine as a part of multidrug chemotherapy regimens.

### *Gastrointestinal*

Constipation, abdominal cramps, weight loss, nausea, vomiting, oral ulceration, diarrhea, paralytic ileus, intestinal necrosis and/or perforation, and anorexia have

occurred. Constipation may take the form of upper-colon impaction, and, on physical examination, the rectum may be empty. Colicky abdominal pain coupled with an empty rectum may mislead the physician. A flat film of the abdomen is useful in demonstrating this condition. All cases have responded to high enemas and laxatives. A routine prophylactic regimen against constipation is recommended for all patients receiving vincristine sulfate injection.

Paralytic ileus (which mimics the “surgical abdomen”) may occur, particularly in young pediatric patients. The ileus will reverse itself with temporary discontinuance of vincristine sulfate injection and with symptomatic care.

#### *Genitourinary*

Polyuria, dysuria, and urinary retention due to bladder atony have occurred. Other drugs known to cause urinary retention (particularly in the elderly) should, if possible, be discontinued for the first few days following administration of vincristine sulfate injection.

#### *Cardiovascular*

Hypertension and hypotension have occurred. Chemotherapy combinations that have included vincristine sulfate, when given to patients previously treated with mediastinal radiation, have been associated with coronary artery disease and myocardial infarction. Causality has not been established.

#### *Neurologic*

Frequently, there is a sequence to the development of neuromuscular side effects. Initially, only sensory impairment and paresthesia may be encountered. With continued treatment, neurotic pain and, later, motor difficulties may occur. There have been no reports of any agent that can reverse the neuromuscular manifestations that may accompany therapy with vincristine sulfate. Loss of deep-tendon reflexes, foot drop, ataxia, and paralysis have been reported with continued administration. Cranial nerve manifestations, such as isolated paresis and/or paralysis of muscles controlled by cranial motor nerves including potentially life-threatening bilateral vocal cord paralysis, may occur in the absence of motor impairment elsewhere; extra-ocular and laryngeal muscles are those most commonly involved. Jaw pain, pharyngeal pain, parotid gland pain, bone pain, back pain, limb pain, and myalgias have been reported; pain in these areas may be severe. Convulsions, frequently with hypertension, have been reported in a few patients receiving vincristine sulfate. Several instances of convulsions followed by coma have been reported in pediatric patients. Transient cortical blindness and optic atrophy with blindness have been reported. Treatment with vinca alkaloids has resulted in both vestibular and auditory damage to the eighth cranial nerve. Manifestations include partial or total

deafness which may be temporary or permanent and difficulties with balance including dizziness, nystagmus, and vertigo. Particular caution is warranted when vincristine is used in combination with other agents known to be ototoxic such as the platinum-containing oncolytics.

### *Endocrine*

Rare occurrences of a syndrome attributable to inappropriate antidiuretic hormone secretion have been observed in patients treated with vincristine sulfate. This syndrome is characterized by high urinary sodium excretion in the presence of hyponatremia; renal or adrenal disease, hypotension, dehydration, azotemia, and clinical edema are absent. With fluid deprivation, improvement occurs in the hyponatremia and in the renal loss of sodium.

### *Hematologic*

Vincristine sulfate injection does not appear to have any constant or significant effect on platelets or red blood cells. Serious bone-marrow depression is usually not a major dose-limiting event. However, anemia, leukopenia, and thrombocytopenia have been reported. Thrombocytopenia, if present when therapy with vincristine sulfate injection is begun, may actually improve before the appearance of bone marrow remission.

### *Skin*

Alopecia and rash have been reported.

### *Other*

Fever and headache have occurred.

### Overdosage

Side effects following the use of vincristine sulfate injection are dose related. In pediatric patients under 13 years of age, death has occurred following doses of vincristine sulfate that were 10 times those recommended for therapy. Severe symptoms may occur in this patient group following dosages of 3 to 4 mg/m<sup>2</sup>. Adults can be expected to experience severe symptoms after single doses of 3 mg/m<sup>2</sup> or more. Therefore, following administration of doses higher than those recommended, patients can be expected to experience exaggerated side effects. Supportive care should include the following: (1) prevention of side effects resulting from the syndrome of inappropriate antidiuretic hormone secretion (preventive treatment would include restriction of fluid intake and perhaps the administration of a diuretic affecting the function of Henle's loop and the distal tubule); (2) administration of anticonvulsants; (3) use of enemas or cathartics to prevent ileus (in some instances, decompression of the gastrointestinal tract may

be necessary); (4) monitoring the cardiovascular system; (5) determining daily blood counts for guidance in transfusion requirements.

Folinic acid has been observed to have a protective effect in normal mice that were administered lethal doses of vincristine sulfate. Isolated case reports suggest that folinic acid may be helpful in treating humans who have received an overdose of vincristine sulfate. It is suggested that 100 mg of folinic acid be administered intravenously every 3 hours for 24 hours and then every 6 hours for at least 48 hours. Theoretically (based on pharmacokinetic data), tissue levels of vincristine sulfate can be expected to remain significantly elevated for at least 72 hours. Treatment with folinic acid does not eliminate the need for the above mentioned supportive measures.

Most of an intravenous dose of vincristine is excreted into the bile after rapid tissue binding. Because only very small amounts of the drug appear in dialysate, hemodialysis is not likely to be helpful in cases of overdosage. An increase in the severity of side effects may be experienced by patients with liver disease that is severe enough to decrease biliary excretion.

Enhanced fecal excretion of parenterally administered vincristine has been demonstrated in dogs pretreated with cholestyramine. There are no published clinical data on the use of cholestyramine as an antidote in humans. There are no published clinical data on the consequences of oral ingestion of vincristine. Should oral ingestion occur, the stomach should be evacuated. Evacuation should be followed by oral administration of activated charcoal and a cathartic. Treatment of patients following intrathecal administration of vincristine sulfate injection has included immediate removal of spinal fluid and flushing with Lactated Ringer's, as well as other solutions and has not prevented ascending paralysis and death.

In one case, progressive paralysis in an adult was arrested by the following treatment initiated immediately after the intrathecal injection:

As much spinal fluid was removed as could be safely done through lumbar access.

The subarachnoid space was flushed with Lactated Ringer's solution infused continuously through a catheter in a cerebral lateral ventricle at the rate of 150 mL/h. The fluid was removed through a lumbar access.

As soon as fresh frozen plasma became available, the fresh frozen plasma, 25 mL, diluted in 1 L of Lactated Ringer's solution was infused through the cerebral

ventricular catheter at the rate of 75 mL/h with removal through the lumbar access. The rate of infusion was adjusted to maintain a protein level in the spinal fluid of 150 mg/dL.

Glutamic acid, 10 g, was given intravenously over 24 hours followed by 500 mg 3 times daily by mouth for 1 month or until neurological dysfunction stabilized. The role of glutamic acid in this treatment is not certain and may not be essential.

#### Dosage and Administration

This preparation is for intravenous use only. Neurotoxicity appears to be dose related. Extreme care must be used in calculating and administering the dose of Vincristine Sulfate Injection, USP since overdosage may have a very serious or fatal outcome. The usual dose of Vincristine Sulfate Injection, USP for pediatric patients is 1.5–2 mg/m<sup>2</sup>. For pediatric patients weighing 10 kg or less, the starting dose should be 0.05 mg/kg, administered once a week. The standard dose of Vincristine Sulfate Injection, USP for adults is 1.4 mg/m<sup>2</sup>. A 50% reduction in the dose of Vincristine Sulfate Injection, USP is recommended for patients having a direct serum bilirubin value above 3 mg/100 mL.

The drug is administered intravenously at weekly intervals. TO REDUCE THE POTENTIAL FOR FATAL MEDICATION ERRORS DUE TO INCORRECT ROUTE OF ADMINISTRATION, VINCRISTINE SULFATE INJECTION SHOULD BE DILUTED IN A FLEXIBLE PLASTIC CONTAINER AND PROMINENTLY LABELED FOR INTRAVENOUS USE ONLY. The concentration of Vincristine Sulfate Injection, USP is 1 mg/mL. Do not add extra fluid to the vial prior to removal of the dose. Withdraw the solution of Vincristine Sulfate Injection, USP into an accurate dry syringe, measuring the dose carefully. Do not add extra fluid to the vial in an attempt to empty it completely.

#### Preparation for flexible plastic container

Vincristine Sulfate Injection, USP when diluted with 0.9% Sodium Chloride Injection in concentrations from 0.0015 mg/mL to 0.08 mg/mL is stable for up to 24 hours when protected from light or 8 hours under normal light at 25°C.

#### Preparation for syringe

Special Dispensing Information: when dispensing vincristine sulfate injection, usp in a syringe, it is imperative that it be packaged in the provided overwrap which bears the following statement: “DO NOT REMOVE COVERING UNTIL MOMENT OF INJECTION. FOR INTRAVENOUS USE ONLY – FATAL IF GIVEN BY OTHER ROUTES”. A syringe containing a specific dose must be labeled, using the auxiliary sticker provided, to state: “FOR INTRAVENOUS USE ONLY – FATAL IF GIVEN BY OTHER ROUTES.”

Caution: It is extremely important that the intravenous needle or catheter be properly positioned before any vincristine is injected. Leakage into surrounding tissue during intravenous administration of Vincristine Sulfate Injection, USP may cause considerable irritation. If extravasation occurs, the injection should be discontinued immediately and any remaining portion of the dose should then be introduced into another vein. Local injection of hyaluronidase and the application of moderate heat to the area of leakage will help disperse the drug and may minimize discomfort and the possibility of cellulitis.

Vincristine Sulfate Injection, USP must be administered via an intact, free-flowing intravenous needle or catheter. Care should be taken that there is no leakage or swelling occurring during administration.

The solution may be injected either directly into a vein or into the tubing of a running intravenous infusion (see Drug Interactions below). Injection of Vincristine Sulfate Injection, USP should be accomplished within 1 minute.

Patients Receiving Radiation Therapy - Vincristine Sulfate Injection, USP should not be given to patients while they are receiving radiation therapy through ports that include the liver. When Vincristine Sulfate Injection, USP is used in combination with L-asparaginase, Vincristine Sulfate Injection, USP should be given 12 to 24 hours before administration of the enzyme in order to minimize toxicity; administering L-asparaginase before Vincristine Sulfate Injection, USP may reduce hepatic clearance of vincristine.

#### Drug Interactions

Vincristine Sulfate Injection, USP should not be diluted in solutions that raise or lower the pH outside the range of 3.5 to 5.5. It should not be mixed with anything other than normal saline or glucose in water. Whenever solution and container permit, parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

#### Handling and Disposal

Procedures for proper handling and disposal of anticancer drugs should be considered.<sup>1</sup>

### **Rituximab**

Rituximab is a genetically engineered, chimeric, murine/human monoclonal antibody directed against the CD20 antigen found on the surface of normal and malignant pre-B and mature B cells. The antibody is an IgG<sub>1</sub>  $\kappa$  immunoglobulin containing murine light-and heavy-chain variable region sequences and human

constant region sequences. Rituximab is composed of two heavy chains of 451 amino acids and two light chains of 213 amino acids (based on cDNA analysis) and has an approximate molecular mass of 145 kD. Rituximab has a binding affinity for the CD20 antigen of ~8.0 nM.

### Safety Profile

No dose-limiting effects were observed in the Phase I/II studies. Reported adverse events including fever, chills, headache, nausea, vomiting, rhinitis, asthenia, and hypotension, occurred primarily during rituximab infusions and typically responded to an interruption of the infusion and resumption at a slower rate.

### *Fatal Infusion Reactions*

Severe and fatal cardiopulmonary events, including angioedema, hypoxia, pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, and cardiogenic shock, have been reported. These severe reactions typically occurred during the first infusion with time to onset of 30-120 minutes.

### *Cardiac Events*

Patients with preexisting cardiac conditions, including arrhythmia and angina, have had recurrences of these cardiac events during rituximab infusions.

### *Tumor Lysis Syndrome*

Tumor lysis syndrome (some cases with fatal outcome) has been reported and is characterized in patients with a high number of circulating malignant cells ( $\geq 25,000/\mu\text{l}$ ) by rapid reduction in tumor volume, renal insufficiency, hyperkalemia, hypocalcemia, hyperuricemia, and hyperphosphatemia.

### *Renal Events*

Rituximab has been associated with severe renal toxicity including acute renal failure requiring dialysis, and in some cases has led to death. Renal toxicity has occurred in patients with high numbers of circulating malignant cells ( $\geq 25,000/\text{mm}^3$ ) or high tumor burden who experience tumor lysis syndrome and in patients administered concomitant cisplatin.

*Mucocutaneous Reactions:* Severe bullous skin reactions, including fatal cases of toxic epidermal necrolysis and paraneoplastic pemphigus, have been reported in patients treated with rituximab. The onset of reaction has varied from 1 to 13 weeks following rituximab exposure.

### *Hematologic Events*

In clinical trials, Grade 3 and 4 cytopenias were reported in 48% of patients treated with rituximab; these include: lymphopenia (40%), neutropenia (6%), leukopenia (4%), anemia (3%), and thrombocytopenia (2%). The median duration of lymphopenia was 14 days (range, 1 to 588 days) and of neutropenia was 13 days (range, 2 to 116 days). A single occurrence of transient aplastic anemia (pure red cell aplasia) and two occurrences of hemolytic anemia following Rituximab therapy were reported. In addition, there have been a limited number of post marketing reports of prolonged pancytopenia, marrow hypoplasia, and late onset neutropenia.

#### *Infectious Events*

Rituxan induced B-cell depletion in 70% to 80% of patients with NHL was associated with decreased serum immunoglobulins in a minority of patients; the lymphopenia lasted a median of 14 days (range, 1-588 days). Infectious events occurred in 31% of patients: 19% of patients had bacterial infections, 10% had viral infections, 1% had fungal infections, and 6% were unknown infections. Serious infectious events (Grade 3 or 4), including sepsis, occurred in 2% of patients.

#### *Hepatitis B Reactivation*

Hepatitis B virus (HBV) reactivation with fulminant hepatitis, hepatic failure, and death has been reported in some patients with hematologic malignancies treated with rituximab. The majority of patients received rituximab in combination with chemotherapy. The median time to the diagnosis of hepatitis was approximately four months after the initiation of rituximab and approximately one month after the last dose.

#### *Other Serious Viral Infections*

The following additional serious viral infections, either new, reactivated or exacerbated, have been identified in clinical studies or post-marketing reports. The majority of patients received Rituxan in combination with chemotherapy or as part of a hematopoietic stem cell transplant. These viral infections included JC virus (progressive multifocal leukoencephalopathy [PML]), cytomegalovirus, herpes simplex virus, parvovirus B19, varicella zoster virus, West Nile virus, and hepatitis C. In some cases, the viral infections occurred up to one year following discontinuation of Rituxan and have resulted in death.

#### *Progressive multifocal leukoencephalopathy (PML)*

PML is a rare disease caused by the reactivation of latent JC virus in the brain. Immunosuppression allows reactivation of the JC virus which causes demyelination and destruction of oligodendrocytes resulting in death or severe disability. Rare cases of PML, some resulting in death, have been reported in

patients with hematologic malignancies who have received rituximab. The majority of these patients had received rituximab in combination with chemotherapy or as part of a hematopoietic stem cell transplant. Cases of PML resulting in death have also been reported following the use of rituximab for the treatment of autoimmune diseases. Most cases of PML were diagnosed within 12 months of their last infusion of rituximab. Physicians should consider PML in any patient presenting with new onset neurologic manifestations. Consultation with a neurologist, brain MRI, and lumbar puncture should be considered as clinically indicated. In patients who develop PML, rituximab should be discontinued and reductions or discontinuation of any concomitant chemotherapy or immunosuppressive therapy should be considered.

#### *Bowel Obstruction and Perforation*

Abdominal pain, bowel obstruction and perforation, in some cases leading to death, were observed in patients receiving Rituxan in combination with chemotherapy for DLBCL. In post-marketing reports, which include both patients with low-grade or follicular NHL and DLBCL, the mean time to onset of symptoms was 6 days (range 1–77) in patients with documented gastrointestinal perforation. Complaints of abdominal pain, especially early in the course of treatment, should prompt a thorough diagnostic evaluation and appropriate treatment.

#### *Immunogenicity*

Patients may develop a human anti-chimeric antibody (HACA) response with rituximab treatment. The clinical significance of this is unclear.

#### *Pregnancy*

B-cell lymphocytopenia generally lasting less than 6 months can occur in infants exposed to rituximab in utero.

#### *Immunization*

Response rates may be reduced with non-live vaccines.

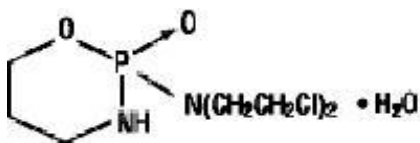
#### *Additional Safety Signals*

The following serious adverse events have been reported to occur in patients following completion of rituximab infusions: arthritis, disorders of blood vessels (vasculitis, serum sickness and lupus-like syndrome), eye disorders (uveitis and optic neuritis), lung disorders including pleuritis and scarring of the lung (bronchiolitis obliterans), that may result in fatal outcomes, and fatal cardiac failure.

## Cyclophosphamide

### Description

Cyclophosphamide for Injection, USP is a sterile white powder containing cyclophosphamide monohydrate. Cyclophosphamide is a synthetic antineoplastic drug chemically related to the nitrogen mustards. Cyclophosphamide is a white crystalline powder with the molecular formula  $C_7H_{15}Cl_2N_2O_2P \cdot H_2O$  and a molecular weight of 279.1. The chemical name for cyclophosphamide is 2-[bis(2-chloroethyl) amino]tetrahydro-2H-1,3,2-oxazaphosphorine 2-oxide monohydrate. Cyclophosphamide is soluble in water, saline, or ethanol and has the following structural formula:



### Clinical Pharmacology

Cyclophosphamide is biotransformed principally in the liver to active alkylating metabolites by a mixed function microsomal oxidase system. These metabolites interfere with the growth of susceptible rapidly proliferating malignant cells. The mechanism of action is thought to involve cross-linking of tumor cell DNA. Cyclophosphamide is well absorbed after oral administration with a bioavailability greater than 75%. The unchanged drug has an elimination half-life of 3 to 12 hours. It is eliminated primarily in the form of metabolites, but from 5 to 25% of the dose is excreted in urine as unchanged drug. Several cytotoxic and non-cytotoxic metabolites have been identified in urine and in plasma. Concentrations of metabolites reach a maximum in plasma 2 to 3 hours after an intravenous dose. Plasma protein binding of unchanged drug is low but some metabolites are bound to an extent greater than 60%. It has not been demonstrated that any single metabolite is responsible for either the therapeutic or toxic effects of cyclophosphamide. Although elevated levels of metabolites of cyclophosphamide have been observed in patients with renal failure, increased clinical toxicity in such patients has not been demonstrated.

### Warnings

#### *Carcinogenesis, Mutagenesis, and Impairment of Fertility*

Second malignancies have developed in some patients treated with cyclophosphamide used alone or in association with other antineoplastic drugs and/or modalities. Most frequently, they have been urinary bladder, myeloproliferative, or lymphoproliferative malignancies. Second malignancies most frequently were detected in patients treated for primary myeloproliferative or lymphoproliferative malignancies or nonmalignant disease in which immune processes are believed to be involved pathologically.

In some cases, the second malignancy developed several years after cyclophosphamide treatment had been discontinued. In a single breast cancer trial utilizing two to four times the standard dose of cyclophosphamide in conjunction with doxorubicin a small number of cases of secondary acute myeloid leukemia occurred within two years of treatment initiation. Urinary bladder malignancies generally have occurred in patients who previously had hemorrhagic cystitis. In patients treated with cyclophosphamide-containing regimens for a variety of solid tumors, isolated case reports of secondary malignancies have been published. One case of carcinoma of the renal pelvis was reported in a patient receiving long-term cyclophosphamide therapy for cerebral vasculitis. The possibility of cyclophosphamide-induced malignancy should be considered in any benefit-to-risk assessment for use of the drug.

Cyclophosphamide can cause fetal harm when administered to a pregnant woman and such abnormalities have been reported following cyclophosphamide therapy in pregnant women. Abnormalities were found in two infants and a six-month old fetus born to women treated with cyclophosphamide. Ectrodactylia was found in two of the three cases. Normal infants have also been born to women treated with cyclophosphamide during pregnancy, including the first trimester. If this drug is used during pregnancy, or if the patient becomes pregnant while taking (receiving) this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant.

Cyclophosphamide interferes with oogenesis and spermatogenesis. It may cause sterility in both sexes. Development of sterility appears to depend on the dose of cyclophosphamide, duration of therapy, and the state of gonadal function at the time of treatment. Cyclophosphamide-induced sterility may be irreversible in some patients.

Amenorrhea associated with decreased estrogen and increased gonadotropin secretion develops in a significant proportion of women treated with cyclophosphamide. Affected patients generally resume regular menses within a few months after cessation of therapy. Girls treated with cyclophosphamide during prepubescence generally develop secondary sexual characteristics normally and have regular menses. Ovarian fibrosis with apparently complete loss of germ cells after prolonged cyclophosphamide treatment in late prepubescence has been reported. Girls treated with cyclophosphamide during prepubescence subsequently have conceived.

Men treated with cyclophosphamide may develop oligospermia or azoospermia associated with increased gonadotropin but normal testosterone secretion. Sexual potency and libido are unimpaired in these patients. Boys treated with cyclophosphamide during prepubescence develop secondary sexual characteristics normally, but may have oligospermia or azoospermia and increased gonadotropin secretion. Some degree of testicular atrophy may occur. Cyclophosphamide-induced azoospermia is reversible in some patients, though the reversibility may not occur for several years after cessation of therapy. Men temporarily rendered sterile by cyclophosphamide have subsequently fathered normal children.

### *Urinary System*

Hemorrhagic cystitis may develop in patients treated with cyclophosphamide. Rarely, this condition can be severe and even fatal. Fibrosis of the urinary bladder, sometimes extensive, also may develop with or without accompanying cystitis. Atypical urinary bladder epithelial cells may appear in the urine. These adverse effects appear to depend on the dose of cyclophosphamide and the duration of therapy. Such bladder injury is thought to be due to cyclophosphamide metabolites excreted in the urine. Forced fluid intake helps to assure an ample output of urine, necessitates frequent voiding, and reduces the time the drug remains in the bladder. This helps to prevent cystitis. Hematuria usually resolves in a few days after cyclophosphamide treatment is stopped, but it may persist. Medical and/or surgical supportive treatment may be required, rarely, to treat protracted cases of severe hemorrhagic cystitis. It is usually necessary to discontinue cyclophosphamide therapy in instances of severe hemorrhagic cystitis.

### *Cardiac Toxicity*

Although a few instances of cardiac dysfunction have been reported following use of recommended doses of cyclophosphamide, no causal relationship has been established. Acute cardiac toxicity has been reported with doses as low as 2.4 g/m<sup>2</sup> to as high as 26 g/m<sup>2</sup>, usually as a portion of an intensive antineoplastic multi-drug regimen or in conjunction with transplantation procedures. In a few instances with high doses of cyclophosphamide, severe, and sometimes fatal, congestive heart failure has occurred after the first cyclophosphamide dose. Histopathologic examination has primarily shown hemorrhagic myocarditis. Hemopericardium has occurred secondary to hemorrhagic myocarditis and myocardial necrosis. Pericarditis has been reported independent of any hemopericardium. No residual cardiac abnormalities, as evidenced by electrocardiogram or echocardiogram appear to be present in patients surviving episodes of apparent cardiac toxicity associated with high

doses of cyclophosphamide. Cyclophosphamide has been reported to potentiate doxorubicin-induced cardiotoxicity.

### *Infections*

Treatment with cyclophosphamide may cause significant suppression of immune responses. Serious, sometimes fatal, infections may develop in severely immunosuppressed patients. Cyclophosphamide treatment may not be indicated, or should be interrupted, or the dose reduced, in patients who have or who develop viral, bacterial, fungal, protozoan, or helminthic infections.

### *Other*

Anaphylactic reactions have been reported; death has also been reported in association with this event. Possible cross-sensitivity with other alkylating agents has been reported.

## Precautions

### *General*

Special attention to the possible development of toxicity should be exercised in patients being treated with cyclophosphamide if any of the following conditions are present: Leukopenia, Thrombocytopenia, Tumor cell infiltration of bone marrow, Previous X-ray therapy, and previous therapy with other cytotoxic agents, impaired hepatic function, and impaired renal function

### *Laboratory Tests*

During treatment, the patient's hematologic profile (particularly neutrophils and platelets) should be monitored regularly to determine the degree of hematopoietic suppression. Urine should also be examined regularly for red cells which may precede hemorrhagic cystitis.

### *Drug Interactions*

The rate of metabolism and the leukopenic activity of cyclophosphamide reportedly are increased by chronic administration of high doses of phenobarbital.

The physician should be alert for possible combined drug actions, desirable or undesirable, involving cyclophosphamide even though cyclophosphamide has been used successfully concurrently with other drugs, including other cytotoxic drugs.

Cyclophosphamide treatment, which causes a marked and persistent inhibition of cholinesterase activity, potentiates the effect of succinylcholine chloride.

If a patient has been treated with cyclophosphamide within 10 days of general anesthesia, the anesthesiologist should be alerted.

### *Adrenalectomy*

Since cyclophosphamide has been reported to be more toxic in adrenalectomized dogs, adjustment of the doses of both replacement steroids and cyclophosphamide may be necessary for the adrenalectomized patient.

### *Wound Healing*

Cyclophosphamide may interfere with normal wound healing.

### *Nursing Mothers*

Cyclophosphamide is excreted in breast milk. Because of the potential for serious adverse reactions and the potential for tumorigenicity shown for cyclophosphamide in humans, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

### *Geriatric Use*

Insufficient data from clinical studies of cyclophosphamide for malignant lymphoma, multiple myeloma, leukemia, mycosis fungoides, neuroblastoma, retinoblastoma, and breast carcinoma are available for patients 65 years of age and older to determine whether they respond differently than younger patients. In two clinical trials in which cyclophosphamide was compared with paclitaxel, each in combination with cisplatin, for the treatment of advanced ovarian carcinoma, 154 (28%) of 552 patients who received cyclophosphamide plus cisplatin were 65 years or older. Subset analyses (<65 versus >65 years) from these trials, published reports of clinical trials of cyclophosphamide-containing regimens in breast cancer and non-Hodgkin's lymphoma, and post marketing experience suggest that elderly patients may be more susceptible to cyclophosphamide toxicities. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range and adjusting as necessary based on patient response.

### Adverse Reactions

Information on adverse reactions associated with the use of cyclophosphamide is arranged according to body system affected or type of reaction. The adverse reactions are listed in order of decreasing incidence.

### *Digestive System*

Nausea and vomiting commonly occur with cyclophosphamide therapy. Anorexia and, less frequently, abdominal discomfort or pain and diarrhea may occur. There are isolated reports of hemorrhagic colitis, oral mucosal ulceration and

jaundice occurring during therapy. These adverse drug effects generally remit when cyclophosphamide treatment is stopped.

### *Skin*

Alopecia occurs commonly in patients treated with cyclophosphamide. The hair can be expected to grow back after treatment with the drug or even during continued drug treatment, though it may be different in texture or color. Skin rash occurs occasionally in patients receiving the drug. Pigmentation of the skin and changes in nails can occur. Very rare reports of Stevens-Johnson syndrome and toxic epidermal necrolysis have been received during post marketing surveillance; due to the nature of spontaneous adverse event reporting, a definitive causal relationship to cyclophosphamide has not been established.

### *Hematopoietic System*

Leukopenia occurs in patients treated with cyclophosphamide, is related to the dose of drug, and can be used as a dosage guide. Leukopenia of less than 2000 cells/mm<sup>3</sup> develops commonly in patients treated with an initial loading dose of the drug, and less frequently in patients maintained on smaller doses. The degree of neutropenia is particularly important because it correlates with a reduction in resistance to infections. Fever without documented infection has been reported in neutropenic patients.

Thrombocytopenia or anemia develops occasionally in patients treated with cyclophosphamide. These hematologic effects usually can be reversed by reducing the drug dose or by interrupting treatment. Recovery from leukopenia usually begins in 7 to 10 days after cessation of therapy.

### *Urinary System*

Cystitis and urinary bladder fibrosis have been observed. Hemorrhagic ureteritis and renal tubular necrosis have been reported to occur in patients treated with cyclophosphamide. Such lesions usually resolve following cessation of therapy.

### *Respiratory System*

Interstitial pneumonitis has been reported as part of the post marketing experience. Interstitial pulmonary fibrosis has been reported in patients receiving high doses of cyclophosphamide over a prolonged period.

### *Other*

Anaphylactic reactions have been reported; death has also been reported in association with this event. Possible cross-sensitivity with other alkylating agents has been reported. SIADH (syndrome of inappropriate ADH secretion) has been

reported with the use of cyclophosphamide. Malaise and asthenia have been reported as part of the post marketing experience.

### Overdosage

No specific antidote for cyclophosphamide is known. Overdosage should be managed with supportive measures, including appropriate treatment for any concurrent infection, myelosuppression, or cardiac toxicity should it occur.

### Dosage and Administration

When used as the only oncolytic drug therapy, the initial course of cyclophosphamide for patients with no hematologic deficiency usually consists of 40 to 50 mg/kg given intravenously in divided doses over a period of 2 to 5 days.

Other intravenous regimens include 10 to 15 mg/kg given every 7 to 10 days or 3 to 5 mg/kg twice weekly.

Oral cyclophosphamide dosing is usually in the range of 1 to 5 mg/kg/day for both initial and maintenance dosing.

Many other regimens of intravenous and oral cyclophosphamide have been reported. Dosages must be adjusted in accord with evidence of antitumor activity and/or leukopenia. The total leukocyte count is a good, objective guide for regulating dosage. Transient decreases in the total white blood cell count to 2000 cells/mm<sup>3</sup> (following short courses) or more persistent reduction to 3000 cells/mm<sup>3</sup> (with continuing therapy) are tolerated without serious risk of infection if there is no marked granulocytopenia. When cyclophosphamide is included in combined cytotoxic regimens, it may be necessary to reduce the dose of cyclophosphamide as well as that of the other drugs. Cyclophosphamide and its metabolites are dialyzable although there are probably quantitative differences depending upon the dialysis system being used. Patients with compromised renal function may show some measurable changes in pharmacokinetic parameters of cyclophosphamide metabolism, but there is no consistent evidence indicating a need for cyclophosphamide dosage modification in patients with renal function impairment.

### Storage

Unopened vials of cyclophosphamide are stable until the date indicated on the package when stored at or below 25°C (77°F)

### Possible Adverse Reactions

Possible adverse reactions include: fluid and electrolyte disturbances, sodium retention, fluid retention, congestive heart failure in susceptible patients,

potassium loss, hypokalemic alkalosis, hypertension, muscle weakness, steroid myopathy, osteoporosis, vertebral compression fractures, aseptic necrosis of femoral and humeral heads, tendon rupture, pathologic fracture of long bones, peptic ulcer with possible subsequent perforation and hemorrhage, perforation of the small and large bowel (particularly in patients with IBD), pancreatitis, abdominal distention, impaired wound healing, thin fragile skin, petechiae and ecchymosis, erythema, increased sweating, convulsions, increased intracranial pressure with papilledema (pseudotumor cerebri) usually after treatment, vertigo, headache, psychic disturbances, menstrual irregularities, development of cushingoid state, secondary adrenocortical and pituitary unresponsiveness, particularly in times of stress, as in trauma, surgery, or illness decreased carbohydrate tolerance, manifestations of latent diabetes mellitus, increased requirements for insulin or oral hypoglycemic agents in diabetics, lip hirsutism, posterior subcapsular cataracts, increased intraocular pressure, glaucoma, exophthalmos negative nitrogen balance due to protein catabolism, myocardial rupture following recent myocardial infarction, anaphylactic or hypersensitivity reactions, thromboembolism, weight gain, increased appetite, nausea, malaise, and hiccups.

## **Doxorubicin**

### Warnings

1. Severe local tissue necrosis will occur if there is extravasation during administration. Doxorubicin must not be given by the intramuscular or subcutaneous route.
2. Myocardial toxicity manifested in its most severe form by potentially fatal congestive heart failure (CHF) may occur either during therapy or months to years after termination of therapy. The probability of developing impaired myocardial function based on a combined index of signs, symptoms and decline in left ventricular ejection fraction (LVEF) is estimated to be 1 to 2% at a total cumulative dose of 300 mg/m<sup>2</sup> of doxorubicin, 3 to 5% at a dose of 400 mg/m<sup>2</sup>, 5 to 8% at 450 mg/m<sup>2</sup> and 6 to 20% at 500 mg/m<sup>2</sup>. The risk of developing CHF increases rapidly with increasing total cumulative doses of doxorubicin in excess of 400 mg/m<sup>2</sup>. Risk factors (active or dormant cardiovascular disease, prior or concomitant radiotherapy to the mediastinal/pericardial area, previous therapy with other anthracyclines or anthracenediones, concomitant use of other cardiotoxic drugs) may increase the risk of cardiac toxicity. Cardiac toxicity with doxorubicin may occur at lower cumulative doses whether or not cardiac risk factors are present. Pediatric patients are at increased risk for developing delayed cardiotoxicity.
3. Secondary AML or MDS has been reported in patients treated with anthracyclines, including doxorubicin. The occurrence of refractory secondary

AML or MDS is more common when anthracyclines are given in combination with DNA-damaging anti-neoplastic agents or radiotherapy, when patients have been heavily pretreated with cytotoxic drugs, or when doses of anthracyclines have been escalated.

4. Dosage should be reduced in patients with impaired hepatic function.
5. Severe myelosuppression may occur.
6. Doxorubicin should be administered only under the supervision of a physician who is experienced in the use of cancer chemotherapeutic agents.

#### Clinical Pharmacology

The cytotoxic effect of doxorubicin on malignant cells and its toxic effects on various organs are thought to be related to nucleotide base intercalation and cell membrane lipid binding activities of doxorubicin. Intercalation inhibits nucleotide replication and action of DNA and RNA polymerases. The interaction of doxorubicin with topoisomerase II to form DNA-cleavable complexes appears to be an important mechanism of doxorubicin cytotoxic activity. Doxorubicin cellular membrane binding may affect a variety of cellular functions. Enzymatic electron reduction of doxorubicin by a variety of oxidases, reductases and dehydrogenases generates highly reactive species including the hydroxyl free radical  $\text{OH}\cdot$ . Free radical formation has been implicated in doxorubicin cardiotoxicity by means of Cu (II) and Fe (III) reduction at the cellular level. Cells treated with doxorubicin have been shown to manifest the characteristic morphologic changes associated with apoptosis or programmed cell death. Doxorubicin-induced apoptosis may be an integral component of the cellular mechanism of action relating to therapeutic effects, toxicities, or both. Animal studies have shown activity in a spectrum of experimental tumors, immunosuppression, carcinogenic properties in rodents, induction of a variety of toxic effects, including delayed and progressive cardiac toxicity, myelosuppression in all species and atrophy of testes in rats and dogs.

#### Indications and Usage

Doxorubicin has been used successfully to produce regression in disseminated neoplastic conditions such as acute lymphoblastic leukemia, acute myeloblastic leukemia, Wilms' tumor, neuroblastoma, soft tissue and bone sarcomas, breast carcinoma, ovarian carcinoma, transitional cell bladder carcinoma, thyroid carcinoma, gastric carcinoma, Hodgkin's disease, malignant lymphoma and bronchogenic carcinoma in which the small cell histologic type is the most responsive compared to other cell types. Doxorubicin is also indicated for use as a component of adjuvant therapy in women with evidence of axillary lymph node involvement following resection of primary breast cancer.

#### Contraindications

Patients should not be treated with doxorubicin if they have any of the following conditions: baseline neutrophil count  $<1500$  cells/  $\text{mm}^3$ ; severe hepatic impairment; recent myocardial infarction; severe myocardial insufficiency; severe arrhythmias; previous treatment with complete cumulative doses of doxorubicin, daunorubicin, idarubicin, and/or other anthracyclines and anthracenediones; or hypersensitivity to doxorubicin, any of its excipients, or other anthracyclines or anthracenediones.

### Dosage and Administration

Care in the administration of doxorubicin will reduce the chance of peri-venous infiltration. It may also decrease the chance of local reactions such as urticaria and erythematous streaking. On intravenous administration of doxorubicin, extravasation may occur with or without an accompanying burning or stinging sensation, even if blood returns well on aspiration of the infusion needle. If any signs or symptoms of extravasation have occurred, the injection or infusion should be immediately terminated and restarted in another vein. If extravasation is suspected, intermittent application of ice to the site for 15 min. q.i.d. x 3 days may be useful. The benefit of local administration of drugs has not been clearly established. Because of the progressive nature of extravasation reactions, close observation and plastic surgery consultation is recommended. Blistering, ulceration and/or persistent pain are indications for wide excision surgery, followed by split-thickness skin grafting. The most commonly used dose schedule when used as a single agent is 60 to 75  $\text{mg}/\text{m}^2$  as a single intravenous injection administered at 21-day intervals. The lower dosage should be given to patients with inadequate marrow reserves due to old age, or prior therapy, or neoplastic marrow infiltration. Doxorubicin has been used concurrently with other approved chemotherapeutic agents. Evidence is available that in some types of neoplastic disease combination chemotherapy is superior to single agents. The benefits and risks of such therapy continue to be elucidated. When used in combination with other chemotherapy drugs, the most commonly used dosage of doxorubicin is 40 to 60  $\text{mg}/\text{m}^2$  given as a single intravenous injection every 21 to 28 days.

### Reconstitution

After adding the diluent, the vial should be shaken and the contents allowed dissolving. The reconstituted solution is stable for 7 days at room temperature and under normal room light (100 foot-candles) and 15 days under refrigeration ( $2^\circ$  to  $8^\circ\text{C}$ ). It should be protected from exposure to sunlight. Discard any unused solution from the 10 mg, 20 mg and 50 mg single dose vials. Unused solutions of the multiple dose vial remaining beyond the recommended storage times should be discarded.

Doxorubicin Hydrochloride Injection, USP is a sterile parenteral, isotonic, available in 5 mL (10 mg), 10 mL (20 mg), 25 mL (50 mg), and 37.5 mL (75 mg) single dose vials and a 100 mL (200 mg) multidose vial. Each mL contains doxorubicin HCl and the following inactive ingredients: sodium chloride 0.9% and water for injection q.s. Hydrochloric acid is used to adjust the pH to a target pH of 3.0.