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THE UNIVERSITY OF TEXAS
M.D. ANDERSON CANCER CENTER
DIVISION OF CANCER MEDICINE
DEPARTMENT OF LYMPHOMA AND MYELOMA

Smart Start:
A Phase II Study of Rituximab, Lenalidomide, and Ibrutinib Combined With Chemotherapy For Patients With High Risk Diffuse Large B-Cell Lymphoma

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1 Objectives and Hypotheses

1.1 Objectives:

1.1.1 Primary Endpoint 1: To determine the overall response rate at the end of 2 cycles of therapy with rituximab, lenalidomide, and ibrutinib in patients with high risk newly diagnosed non-GCB DLBCL

1.1.2 Primary Endpoint 2: To determine the complete response rate at the end of 6 cycles of therapy with rituximab, lenalidomide, and ibrutinib combined with chemotherapy (CHOP or EPOCH) in patients with high risk newly diagnosed non-GCB DLBCL

1.1.3 Secondary Endpoint 1: To determine the overall response rate, landmark survival outcomes (progression free and overall survival), and safety of lenalidomide and ibrutinib with chemotherapy (CHOP or EPOCH) in patients with high risk newly diagnosed non-GCB DLBCL.

1.1.4 Secondary Endpoint 2: To evaluate descriptively the complete response rate in RLI-CHOP and in RLI-EPOCH.

1.1.5 Exploratory objectives: To evaluate the baseline and therapy induced changes in the profile of mutations, gene expression, minimal residual disease clonotype levels, immune cell subsets, and tumor protein expression in tumor biopsy and blood samples in patients with high risk newly diagnosed non-GCB DLBCL.

1.2 Hypotheses:

1.2.1 The combination of rituximab, lenalidomide, and ibrutinib alone will show a high overall response rate in newly diagnosed non-GCB DLBCL, higher than single-agent ibrutinib, lenalidomide, or rituximab ORR in patients with relapsed DLBCL

1.2.2 Response-associated characteristics will be identified from analysis of biopsy material and peripheral blood from baseline and on-therapy time points, for future validation and potential patient selection.

2 Background

2.1 Diffuse large B-cell lymphoma:

Diffuse large B-cell lymphoma (DLBCL), the most common lymphoid malignancy with ~30,000 new cases in the US annually, is uniformly treated with a combination (CHOP) which remains essentially unchanged over the past 30+ years.(1-3) Knowledge of DLBCL biology has made significant advances, including the definition of two distinct subtypes with unique gene expression programs,(4-6) genomic abnormalities,(7) microRNA profiles,(8-10) signaling pathways,(11-13) and response to targeted therapies.(14, 15)

In 1976, McKelvey et al demonstrated a 67% complete response (CR) rate and ~70% 1-year overall survival (OS) in “diffuse lymphoma” with CHOP chemotherapy.(1) Multiple attempts to improve upon the CHOP regimen have yielded disappointing results, including the American Intergroup Trial which evaluated three more aggressive regimens (m-BACOD, ProMACE-CytaBOM, and MACOP-B) versus CHOP.(16) The trial found that the four regimens were essentially equivalent in efficacy, with CHOP achieving a 54% 3-year disease-free survival (DFS). The CHOP regimen had moderately lower toxicity rates than the other regimens, and has thus remained the standard of care.

In 1998, rituximab, a chimeric immunoglobulin G1 monoclonal antibody targeting surface CD20, was reported to have efficacy in relapsing or refractory aggressive lymphomas. Coiffier et al. reported a 37% overall response rate (ORR) with single-agent rituximab, but the duration of clinical benefit was brief.(17) With significant activity in relapsed or refractory patients, rituximab was moved to clinical trials in frontline therapy. In a phase II clinical trial of rituximab plus CHOP (R-CHOP), published in 2001, Vose et al. reported an ORR of 94% in untreated DLBCL patients, including 15 of 16 patients with an International Prognostic Index (IPI) score of 2 or higher.(18)

The IPI is a clinical prognostic system created from pre-treatment factors from patients with DLBCL treated with CHOP, including age, stage, performance status, number of extranodal sites, and lactate dehydrogenase.(19) Despite the fact that the IPI does not directly account for the biology of DLBCL, it has yet to be supplanted as a clinically relevant prognostic tool. In the era of R-CHOP, the IPI has been revisited to determine if it remains relevant. The Revised IPI demonstrates that patients with 3 or greater adverse clinical predictors achieve poor outcomes, with a 4 year progression free survival (PFS) and OS of 53 and 55%, respectively (Appendix B).(20) The striking similarity between PFS and OS for this group implies that of the 47% of patients who have progressed in the first 4 years, less than 10% were still

alive 4 years after initial therapy. This speaks to the need to improve therapy for patients with relapsed DLBCL, but perhaps an even greater need to improve frontline therapy to prevent relapse for patients with high-risk DLBCL.

2.2 Standard Treatment of DLBCL, R-CHOP

DLBCL is a systemic disease and requires treatment at the time of diagnosis with systemic immunochemotherapy. The standard therapy of DLBCL is R-CHOP based on a consecutive series of clinical trials as detailed in section 2.1. The therapy of DLBCL has not been influenced to date by our rapidly increasing knowledge of the disease biology.(3, 21) Patients with localized disease (either stage I or contiguous stage II) may be treated with either standard R-CHOP x 6 cycles, or R-CHOP x 3 cycles followed by involved field radiotherapy, based upon a cooperative group study evaluating CHOP x 8 vs CHOP x 3 with radiation.(22) However, patients with high IPI or elevated Ki-67 are often considered to have increased chance of relapsing outside a radiation field, and thus may be offered R-CHOP x 6 cycles and involved field radiotherapy. For patients not appropriate for local therapy approaches (Stage II non-contiguous, or Stage III/IV), R-CHOP x 6 remains the standard approach. There is an ongoing randomized phase III [NCT00118209] clinical trial comparing the CHOP-variant regimen R-EPOCH against R-CHOP for newly diagnosed patients with DLBCL. The preliminary results show no difference of EFS between the two regimens and will be presented at the American Society of Hematology (ASH) conference of 2016.

2.3 Dose Adjusted Rituximab EPOCH

R-EPOCH (etoposide, prednisone vincristine, cyclophosphamide, doxorubicin) is a CHOP-like regimen which employs infusional chemotherapy. The schedule for DA-EPOCH includes infusional doxorubicin, etoposide, and vincristine over 4 days, followed by cyclophosphamide on day 5. The doses of these four chemotherapy drugs are typically adjusted based upon hematologic values, essentially a pharmacodynamics biomarker. DA-EPOCH was designed to improve the therapeutic index of chemotherapy by taking advantage of increased sensitivity of highly proliferative tumors to prolonged exposure to low concentrations of chemotherapy. A prospective multi-institutional study of R-DA-EPOCH in 50 patients with previously untreated large B-cell lymphomas showed that highly proliferative tumors were sensitive to treatment, unlike CHOP-based treatments.(23) In previously untreated DLBCL, EPOCH (without rituximab) showed a complete response rate of 92%, and 70% of patients remained free of progression at the median follow up of 62 months.(23) Subsequent clinical trials have found that response to R-DA-EPOCH (DA, dose adjusted) may be different in certain subsets of DLBCL.(24) A randomized phase III trial comparing R-CHOP with R-DA-EPOCH in untreated DLBCL patients

has recently completed accrual, and the highly anticipated results are expected in 2015. This trial will include evaluation of the above-mentioned subsets to determine if there is truly a differential response.

2.4 Cell of Origin subtypes:

In 2000, Dr. Louis Staudt et al described DLBCL as at least two unique subtypes, defined by their putative cell of origin. These subtypes, known as the activated B-cell (ABC) and germinal center B-cell (GCB) subtypes, are known to be as different from each other as acute myeloid and lymphoid leukemias.(25) The ABC DLBCL subtype is occasionally referred to as “non-GCB DLBCL”, a historical term that originates from the concept that all DLBCL were presumed to originate from the germinal center. The currently available CLIA certified and clinically utilized methods of assigning cell of origin are largely immunohistochemically (IHC) based, which result in assignment into GCB and “non-GCB”, which is largely equivalent to the ABC subtype.(26) For the remainder of this protocol, the terms “ABC DLBCL” and “non-GCB DLBCL” will be considered interchangeable unless otherwise specified. The most prevalently utilized method is that of Hans et al (2004) in which samples are analyzed for expression levels of CD10, Bcl-6, and MUM1.

Among the prominent differences are the utilization of B-cell-receptor, MyD88, and NF-kappaB signaling pathways combined with PRDM1 disruption in ABC-DLBCL. GCB-DLBCL has frequent alterations in epigenetic regulators EZH2, CREBBP, and EP300.(11, 12, 27-30) These differences have subsequently been confirmed to have significant clinical relevance, with R-CHOP achieving 5-year OS rates in activated B-cell (ABC) and germinal center B-cell subtypes (GCB) DLBCL of ~50% and ~70%, respectively.(21)

A phase II study using bortezomib, a proteasome inhibitor, in relapsed DLBCL patients confirmed the pathway-based prediction of efficacy restricted to ABC patients, when used in combination with a standard multi-drug regimen.(14) In addition, a recent phase I/II trial demonstrated that rituximab plus lenalidomide, an immunomodulatory agent, is dramatically more effective vs. the ABC subtype.(31) In previous trials, R-DA-EPOCH has shown excellent outcomes in GCB DLBCL, although ABC DLBCL remains poorly treated with ~4/10 patient suffering relapse in < 24 months (Figure 1).

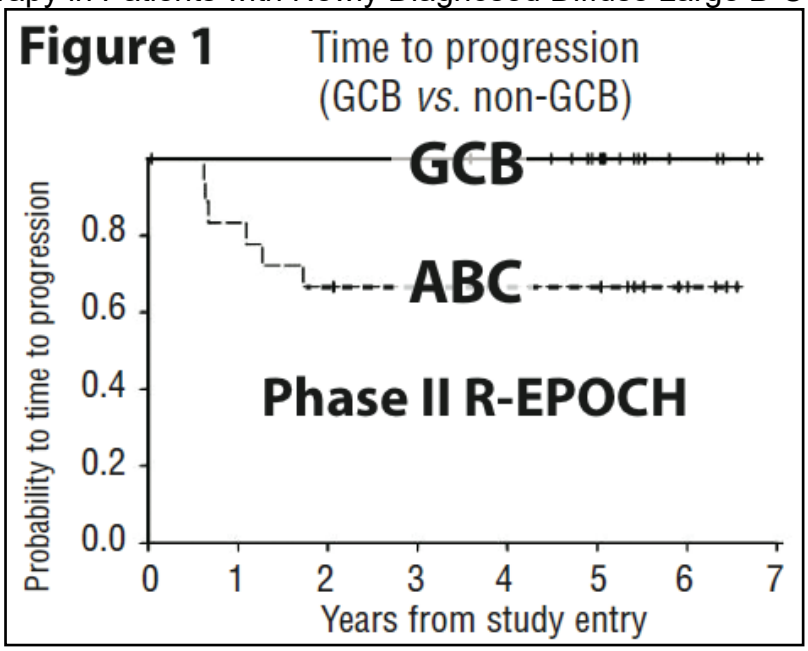


Figure 1. ABC (non-GCB analog) vs GCB DLBCL subtypes time to progression when treated with dose adjusted R-EPOCH (adapted from (24)).

2.5 PET/CT Scans in lymphoma

PET/CT scans are used in NHL to evaluate residual masses detected on CT after completion of chemotherapy, with the negative predictive values for outcome of 80% to 100%.(32, 33) Results from a PET scan after one cycle of chemotherapy were essentially equivalent to results from a PET scan obtained at the completion of chemotherapy in predicting PFS in NHL and HD.(34)

Moskowitz et al evaluated the predictive value of an FDG PET in patients with high risk untreated DLBCL after 3 cycles of conventional chemotherapy.(35) Of the 38 patients with a positive interim FDG PET, only 5 (13%) had biopsy-confirmed persistent disease. Interestingly, the patients with positive interim FDG PET and negative biopsy had no significant difference in long-term outcomes from patients with negative interim FDG PET ($p=0.27$). As a result of this important trial, the positive predictive value of an interim FDG PET is considered low enough that a biopsy for confirmation is mandatory prior to altering the treatment plan. Essentially, interim FDG PET scans have an excellent negative predictive value, however the positive predictive value is not clinically viable.

2.6 Non-imaging based disease monitoring

A novel technology (LymphoSIGHT, Sequenta) has been shown to allow a detection of a tumor-specific clonotype (DoC) in blood and to correlate with therapeutic response and identification of relapse prior to imaging findings.(36-38) This novel technology amplifies the immunoglobulin (Ig) gene segments from tumor biopsy DNA, which can allow detection of a tumor-specific clonotype (DoC) in blood, and to

correlate with therapeutic response and identification of relapse prior to imaging findings.(39)

Genomic DNA from tumor is isolated using standard kits from Qiagen, and is subsequently amplified using locus-specific primer sets for all known alleles of germline immunoglobulin heavy chain (IgH) and T-cell receptor (TCR) sequences.(36) The tumor-specific sequences identified at diagnosis are then used as a target to assess the presence of tumor-specific clonotype in follow-up samples. For quantitation, multiple sequencing reads (~10X coverage) are generated for each rearranged B cell in the reaction.

To determine the absolute measure of the tumor-specific clonotype present in the follow-up sample, a known quantity of reference IgH sequence is added into the reaction and the associated sequencing reads are counted. The resulting number of reference IgH reads per sequence are then applied to the tumor-specific clonotype reads to obtain an absolute measure of the total tumor-specific clonotype in the reaction.

The tumor-specific clonotype reads and the absolute number of total leukoctyes in the reaction metrics can be combined to calculate a final tumor-specific clonotype measurement, which is the number of tumor-specific clonotype reads divided by the total leukocytes in the sample.

In addition to LymphoSIGHT, recent advances in detection of circulating tumor DNA (ctDNA) have allowed for the possibility of “liquid biopsies”.(40) The detection of ctDNA is related to the release of DNA by apoptotic/necrotic cells, and potentially by spontaneous release for unclear reasons. Various methods have been employed to detect ctDNA, including the cancer personalized profiling by deep sequencing (CAPP-Seq).(41) The creation of CAPP-Seq was initially piloted in samples from patients with lung cancer by creation of a multiphase bioinformatics approach to create a ‘selector’, consisting of biotinylated DNA oligonucleotides that target recurrently mutated gene regions. This approach identified a median 4 single nucleotide variations per patient with lung cancer, without modification of the selector for genomic aberrations found in any given individual patient’s tumor. Thus, this approach has the advantage of being “off the shelf”, meaning that it is broadly applicable.

2.7 Targeted Therapy Opportunities in the ABC DLBCL subtype:

ABC DLBCL requires constitutive activity of the targetable B-cell receptor and NF-κB pathways for survival. Recent work has demonstrated the subtype-selective activity of lenalidomide in ABC DLBCL comes from inhibition of the expression of the

survival-critical transcription factors IRF4 and SPIB, which are not essential for other lymphoma subtypes (Figure 2, adapted from (42)). Confirmation of these data come from multiple clinical trials which demonstrate either significant single agent activity of lenalidomide in ABC DLBCL (ORR 53%)(15, 43) or equivalent activity in ABC and GCB DLBCL of the well tolerated combination of R-CHOP + lenalidomide (ORR ~90%, CR ~90%).(44-46)

Not surprisingly due to the reliance on BCR signaling, the same pattern of an impressive response rate in ABC DLBCL has been seen for ibrutinib, the first in class BTK inhibitor. The Phase I trial found an ORR of 22% in relapsed refractory DLBCL patients, but 40% in the non-GCB (similar to ABC) subtype achieved response.(47) The phase Ib trial of ibrutinib with RCHOP showed an ORR of 100% in patients with untreated B-cell lymphomas.(48) Additional data detailed in Section 2.11 provide strong pre-clinical rationale for the combination of lenalidomide with ibrutinib (Figure 2, adapted from (42). Importantly, the three trials which have added lenalidomide to R-CHOP and the single trial which added ibrutinib to R-CHOP in DLBCL have found no synergistic toxicity. Investigators were able to dose escalate lenalidomide and ibrutinib to clinically active dose levels without adding toxicity beyond what is expected from R-CHOP alone.

Together, these data strongly suggest that lenalidomide and ibrutinib 1) have a strong rationale for use in non-GCB (ABC) DLBCL based on pre-clinical and clinical data, and 2) have been well tolerated when combined with standard immuno-chemotherapy. Randomized registration trials comparing R-CHOP with both R-CHOP + lenalidomide and with R-CHOP + ibrutinib are ongoing.

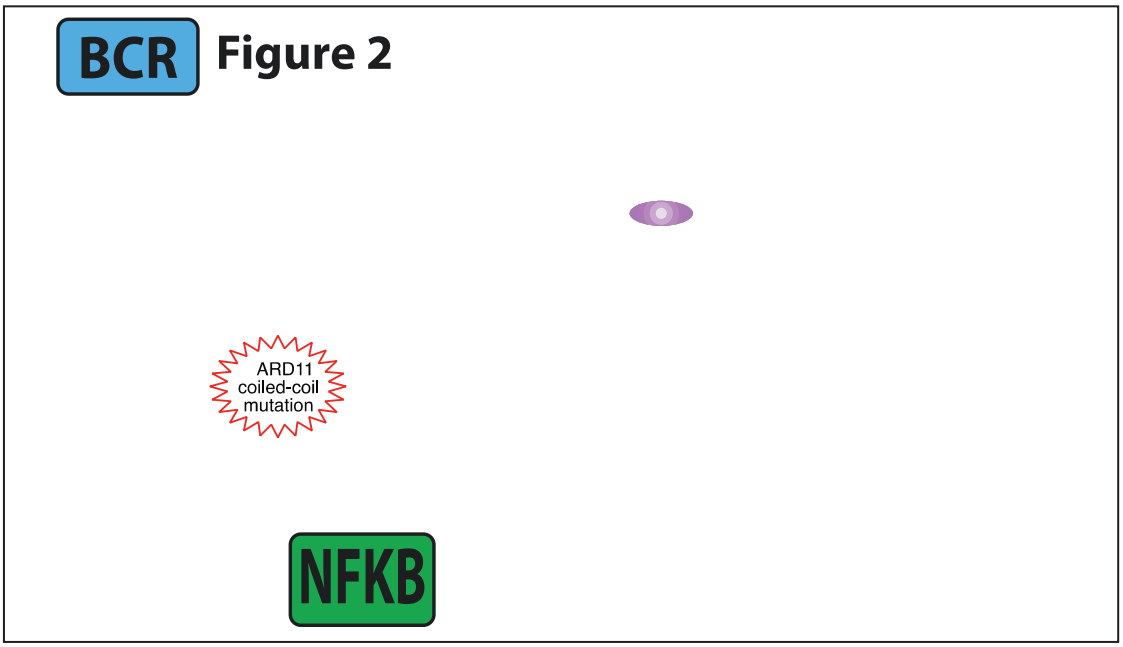


Figure 2. Lenalidomide and the BCR and TLR pathways in ABC DLBCL

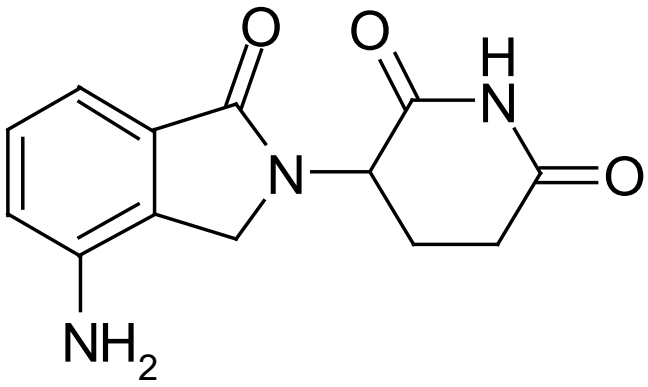
2.8 Lenalidomide

REVLIMID® (lenalidomide), a thalidomide analogue, is an immunomodulatory agent with anti-angiogenic properties. Lenalidomide is indicated for the treatment of patients with transfusion-dependent anemia due to low- or Intermediate-1-risk myelodysplastic syndromes associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities. Revlimid® is also approved in combination with dexamethasone for the treatment of patients with multiple myeloma that have received at least one prior therapy.

Lenalidomide, an oral agent, is a thalidomide derivative that belongs to a new class of agents known as immunomodulatory drugs (IMiDs). Lenalidomide has clinical activity in non-Hodgkin's lymphoma (NHL) and has been shown to possess several immunomodulatory properties. In addition to its known effect on various cytokines, lenalidomide may affect the immune cellular component of the tumor microenvironment. Potential effects include inducing lymphocyte proliferation, increasing the production of IL-2/INF-g by effector cells and angiogenesis inhibition.

The chemical name is 3-(4-amino-1-oxo 1,3-dihydro -2H-isoindol-2-yl) piperidine-2, 6-dione and it has the following chemical structure:

Figure 3 Chemical Structure of Lenalidomide



The empirical formula for lenalidomide is C13H13N3O3, and the gram molecular weight is 259.3. Lenalidomide is an off-white to pale-yellow solid powder. It is soluble in organic solvent/water mixtures, and buffered aqueous solvents. Lenalidomide is more soluble in organic solvents and low pH solutions. Solubility was significantly lower in less acidic buffers, ranging from about 0.4 to 0.5 mg/ml. Lenalidomide has an asymmetric carbon atom and can exist as the optically active forms S(-) and R(+), and is produced as a racemic mixture with a net optical rotation of zero.

2.8.1 Clinical Pharmacology:

Mechanism of Action:

The mechanism of action of lenalidomide remains to be fully characterized. Lenalidomide possesses immunomodulatory and antiangiogenic properties. Lenalidomide inhibited the secretion of pro-inflammatory cytokines and increased the secretion of anti-inflammatory cytokines from peripheral blood mononuclear cells. Lenalidomide inhibited cell proliferation with varying effectiveness (IC50s) in some but not all cell lines. Of cell lines tested, lenalidomide was effective in inhibiting growth of Namalwa cells (a human B cell lymphoma cell line with a deletion of one chromosome 5) but was much less effective in inhibiting growth of KG-1 cells (human myeloblastic cell line, also with a deletion of one chromosome 5) and other cell lines without chromosome 5 deletions. Lenalidomide inhibited the expression of cyclooxygenase-2 (COX-2) but not COX-1 in vitro.

Pharmacokinetics and Drug Metabolism

Absorption:

Lenalidomide, in healthy volunteers, is rapidly absorbed following oral administration with maximum plasma concentrations occurring between 0.625 and 1.5 hours post-dose. Co administration with food does not alter the extent of absorption (AUC) but does reduce the maximal plasma concentration (Cmax) by 36%. The pharmacokinetic disposition of lenalidomide is linear. Cmax and AUC increase

proportionately with increases in dose. Multiple dosing at the recommended dose-regimen does not result in drug accumulation.

Pharmacokinetic analyses were performed on 15 multiple myeloma patients treated in the phase I studies. Absorption was found to be rapid on both Day 1 and Day 28 with time to maximum blood levels ranging from 0.7 to 2.0 hours at all dose levels (5mg, 10mg, 25mg, and 50mg). No plasma accumulation was observed with multiple daily dosing. Plasma lenalidomide declined in a monophasic manner with elimination half-life ranging from 2.8 to 6.1 hours on both Day 1 and 28 at all 4 doses. Peak and overall plasma concentrations were dose proportional over the dosing range of 5mg to 50mg (5). Exposure (AUC) in multiple myeloma patients is 57% higher than in healthy male volunteers.

Metabolism and Excretion

The metabolic profile of lenalidomide in humans has not been studied. In healthy volunteers, approximately two-thirds of lenalidomide is eliminated unchanged through urinary excretion. The process exceeds the glomerular filtration rate and therefore is partially or entirely active. Half life of elimination is approximately 3 hours.

Lenalidomide is available in 5 mg and 10 mg capsules for oral administration. Each capsule contains lenalidomide as the active ingredient and the following inactive ingredients: lactose anhydrous, microcrystalline cellulose, croscarmellose sodium, and magnesium stearate. The 5 mg capsule shell contains gelatin, titanium dioxide and black ink. The 10 mg capsule shell contains gelatin, FD&C blue #2, yellow iron oxide, titanium dioxide and black ink.

2.8.2 Lenalidomide in NHL

Lenalidomide induced growth arrest and apoptosis of lymphoma cell lines as well as enhancing NK-cell–mediated antibody-dependent cellular cytotoxicity (ADCC) of rituximab. (Wu et al 2006) In addition, using a lymphoma xenograft mouse model (Hernandez-Ilizaliturri et al 2005) demonstrated that IMiD molecules enhanced the antitumor activity of rituximab, resulting in improved survival of tumor-bearing animals.

2.8.3 Lenalidomide in Aggressive NHL

Wiernik et al reported preliminary results of lenalidomide monotherapy in patients with relapsed or refractory non-Hodgkin's lymphoma. Lenalidomide (25 mg/d) was administered on days 1 to 21 of a 28-day cycle and continued for 52 weeks as tolerated or until disease progression. Patients with various aggressive histologic subtypes (including diffuse large B-cell, follicular center cell, mantle cell, and

transformed NHL) were enrolled. Forty-one of the 50 patients were assessable for response. Clinical responses were observed in all lymphoma subtypes. The ORR was 34% (n = 14) including five patients with CR unconfirmed (CRu), with a median progression-free survival in patients achieving a CRu of more than 239 (> 191 to > 373 days) days. (Witzig et al 2007) An ongoing multicenter clinical trial is further investigating clinical efficacy of single agent lenalidomide in patients with aggressive NHL.

Kaufman et al first reported the clinical efficacy of thalidomide combined with rituximab in patients with relapsed/refractory mantle-cell lymphoma (MCL). The ORR and CR rate in this study was 81% and 31%, respectively with a median progression-free survival of 20.4 months. (Kaufman et al 2004) On the basis of these findings, a phase I clinical trial of lenalidomide (5 to 25 mg) in combination with rituximab was initiated for MCL. The MTD was 20 mg/d, 21 of 28 days. The DLT was prolonged neutropenia. Thirteen of 15 patients were assessable and had a median of three (range 1-4) prior therapies. Although there were no responses in the 10- and 15-mg dose cohorts, five of six patients in the 20-mg cohort responded including a complete response. (Wang et al 2007) On the basis of the important single-agent activity of lenalidomide and bortezomib in MCL, CALGB is currently conducting a phase II trial of the combination of the two agents in patients with relapsed or refractory MCL.

2.8.4 Clinical trials evaluating lenalidomide combined with R-CHOP in DLBCL

Investigators from the Mayo Clinic conducted a phase II clinical trial which evaluated lenalidomide 25mg orally daily along with full dose R-CHOP (R2CHOP) in patients with previously untreated stage II – IV, CD20+ DLBCL. Lenalidomide was administered on days 1 – 10 of a 21 day cycle for a total of 6 cycles of therapy.(49) All patients received a pegfilgrastim 6 mg subcutaneously on day 2 and low-dose aspirin 81 mg per day prophylaxis throughout, unless they were on therapeutic dose warfarin or low molecular weight heparin for intercurrent conditions. The treatment continued for a maximum of six cycles or until disease progression. Tumor lysis prophylaxis, antiemetics, and supportive care were standard of care and at the discretion of the treating physician. In the 60 evaluable patients, 59 patients achieved a response to therapy (98%) with 48 achieving a complete response (80%). The median duration of response was not reached in the manuscript, with a median follow up of surviving patients of 23.5 months. The progression free survival was 70% at 12 months and 59% at 24 months, and the overall survival was 90% at 12 months and 78% at 24 months. There was no difference identified between the cell of origin subtypes in the 2 year progression free survival or 2 year overall survival. However, the investigators compared the patients treated with R2CHOP with a matched historical cohort of patients treated with RCHOP and found that the

non-GCB subtype achieved superior outcomes with R2CHOP. The 2 year progression free survival in non-GCB patients treated with R2CHOP was 60% vs. 28% in non-GCB patients treated with RCHOP. The 2 year overall survival in non-GCB patients treated with R2CHOP was 83% vs. 46% in non-GCB patients treated with RCHOP ($p<0.001$).

Therapy was well tolerated, with only one patient experiencing a toxic death on trial thought related to intestinal perforation due to significant gut involvement with DLBCL responding to therapy. Two patients experienced a grade 4 non-hematologic toxicity (intra-abdominal hemorrhage, thrombosis), and other non-hematologic toxicities were generally grade 2 or less. Although neutropenia was common (Grade 3: 13% and Grade 4: 75%), neutropenic fever was rare at 9%. The dose intensity was excellent, with 87% of cycles administered containing the full lenalidomide dosage.

Investigators from the Fondazione Italiana Linfomi conducted the REAL07 phase II clinical trial which evaluated lenalidomide 15mg orally daily with full dose RCHOP in patients with previously untreated stage II – IV, CD20+ DLBCL or grade 3b FL who were aged 60-80 years. Lenalidomide was administered on days 1 - 14 of a 21 day cycle for a total of 6 cycles of therapy.(50) All patients received prophylaxis for neutropenia with granulocyte colony-stimulating factors, for deep vein thrombosis with low-molecular-weight heparins, and for Pneumocystis jirovecii infection with co-trimoxazole or a pentamidine aerosol. Occult carriers of hepatitis B virus were given lamivudine. In the 49 evaluable patients, 45 achieved a response to therapy (92%); 42 achieved a complete response (86%) and 3 achieved a partial response (6%). At a median follow up of 28 months, the 2 year overall survival was 92% and 2 year progression free survival was 80%. Of the 32 patients with adequate tissue for cell of origin determination, 16 (50%) had GCB and 16 had non-GCB DLBCL. In the GCB patients, 14 (88%) achieved a response, with 13 (81%) achieving a complete response. In the non-GCB patients, 14 (88%) achieved a response, with all achieving a complete response. The 2 year progression free survival was 71% in the patients with GCB DLBCL, and 81% in the patients with non-GCB DLBCL. The 2 year overall survival was 88% in the patients with GCB DLBCL, and 94% in the patients with non-GCB DLBCL.

Therapy was well tolerated, with hematologic toxicities appearing similar to the trial from the Mayo Clinic and no toxic deaths on trial reported. Although neutropenia was common (Grade 3: 14% and Grade 4: 55%), neutropenic fever was rare at 10%. The dose intensity was excellent, with a median dosage of lenalidomide of 94% of the planned dosage for the entire trial.

2.8.5 Adverse events described in prior lenalidomide clinical trials

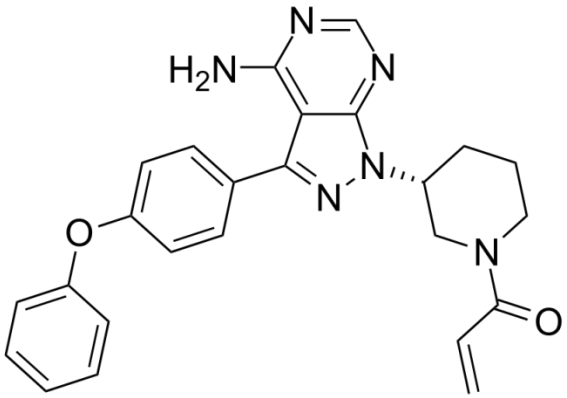
Most frequently reported adverse events during clinical studies with lenalidomide in oncologic and non-oncologic indications, regardless of presumed relationship to study medication include: anemia, neutropenia, thrombocytopenia and pancytopenia, abdominal pain, nausea, vomiting and diarrhea, dehydration, rash, itching, infections, sepsis, pneumonia, UTI, Upper respiratory infection, atrial fibrillation, congestive heart failure, myocardial infarction, chest pain, weakness, hypotension, hypercalcemia, hyperglycemia, back pain, bone pain, generalized pain, dizziness, mental status changes, syncope, renal failure, dyspnea, pleural effusion, pulmonary embolism, deep vein thrombosis, CVA, convulsions, dizziness, spinal cord compression, syncope, disease progression, death not specified and fractures.

Patients with cancer have a higher risk of developing a second new cancer when compared to people without cancer. In clinical studies of newly diagnosed multiple myeloma, a higher number of second cancers were reported in patients treated with lenalidomide as induction therapy (treatment for several cycles to reduce number of cancer cells) and/or bone marrow transplant followed by lenalidomide for a long period of time compared to patients treated with induction therapy and/or bone marrow transplant then placebo (a capsule containing no lenalidomide). Patients should make their doctors aware of their medical history and any concerns they may have regarding their own increased risk of other cancers.

2.9 Ibrutinib

Ibrutinib (PCI-32765; JNJ-54179060) is a first-in-class, potent, orally administered, covalently-binding, small molecule Bruton's tyrosine kinase (BTK) inhibitor currently being co-developed by Janssen Scientific Affairs, LLC, and Pharmacyclics, Inc for the treatment of B-cell malignancies. Ibrutinib (IMBRUVICA™) is approved for small lymphatic lymphoma for approved indications by the U.S. Food and Drug Administration for the treatment of adult patients with mantle cell lymphoma (MCL) who have received at least 1 prior therapy, as well as chronic lymphocytic leukemia (CLL) patients who have received at least one prior therapy or have a deletion of 17p, and Waldenstrom's macroglobulinemia. Ibrutinib and PCI-32765 refer to the same molecule; hereafter, ibrutinib will be used. For additional details, refer to appendix F. Ibrutinib is not approved for large B-cell lymphoma and combination use of products not approved for indication.

Figure 4 Chemical Structure of Ibrutinib



Ibrutinib is 1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d] pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one and has a molecular weight of 440.50 g/mole (anhydrous basis). Ibrutinib is a white to off-white crystalline solid. It has a single chiral center and is the R-enantiomer. The investigational drug product, ibrutinib, is an oral formulation containing micronized ibrutinib.

In vitro studies have shown that ibrutinib binds covalently to a cysteine residue (Cys-481) in the BTK active site, leading to potent and irreversible inhibition of BTK enzymatic activity.(12) In cellular signal transduction assays with a B-cell lymphoma cell line, ibrutinib inhibited autophosphorylation of BTK, phosphorylation of BTK's physiological substrate, phospholipase-C gamma (PLCγ), and phosphorylation of a further downstream kinase, extracellular signal-regulated kinase. Ibrutinib inhibited the proliferation of cell lines derived from DLBCL patients with a median effective concentration of 1 or 2 nM.

2.9.1 Ibrutinib Pharmacokinetics and Drug Metabolism:

In vitro preclinical data show that ibrutinib is metabolized primarily by CYP3A. In healthy volunteers, co-administration of ketoconazole, a strong CYP3A inhibitor, increased Cmax and AUC of ibrutinib by 29- and 24-fold, respectively. The highest ibrutinib dose evaluated in clinical trials was 12.5 mg/kg (actual doses of 840 – 1400 mg) given for 28 days with single dose AUC values of 1445 ± 869 ng · hr/mL which is approximately 50% greater than steady state exposures seen at the highest indicated dose (560 mg). Guidance on concomitant use of ibrutinib with CYP3A inhibitors or inducers is provided in Appendix E and F.

Ibrutinib is absorbed after oral administration with a median Tmax of 1 to 2 hours. Ibrutinib exposure increases with doses up to 840 mg. The steady-state AUC (mean ± standard deviation) observed in patients at 560 mg is 953 ± 705 ng·h/mL and in

patients at 420 mg is 680 ± 517 ng·h/mL. Administration with food increased ibrutinib Cmax and AUC by approximately 2 to 4- and 2-fold, respectively, compared with administration of ibrutinib after overnight fasting.

Reversible binding of ibrutinib to human plasma protein in vitro was 97.3% with no concentration dependence in the range of 50 to 1000 ng/mL. The volume of distribution at steady state (Vd,ss) was 683 L, and the apparent volume of distribution at steady state (Vd,ss/F) was approximately 10000 L.

Metabolism is the main route of elimination for ibrutinib. It is metabolized to several metabolites primarily by cytochrome P450, CYP3A, and to a minor extent by CYP2D6. The active metabolite, PCI-45227, is a dihydrodiol metabolite with inhibitory activity towards BTK approximately 15 times lower than that of ibrutinib.

Ibrutinib is metabolized in the liver. In a hepatic impairment trial, a single dose of 140 mg of ibrutinib was administered in non-cancer subjects. Ibrutinib AUC increased 2.7-, 8.2- and 9.8-fold, respectively, in subjects with mild (n=6), moderate (n=10) and severe (n=8) hepatic impairment relative to subjects with normal liver function. Ibrutinib Cmax increased 5.2-, 8.8- and 7.0-fold, respectively, in subjects with mild, moderate and severe hepatic impairment relative to subjects with normal liver function.

2.9.2 Pharmacodynamics of Ibrutinib

In patients with recurrent B-cell lymphoma > 90% occupancy of the BTK active site in peripheral blood mononuclear cells was observed up to 24 hours after ibrutinib doses of ≥ 2.5 mg/kg/day (≥ 175 mg/day for average weight of 70 kg).

2.9.3 Clinical Efficacy of Ibrutinib in Diffuse Large B-cell Lymphoma

Efficacy results from Studies PCYC-04753 and PCYC-1106-CA demonstrate that ibrutinib has robust activity as a single agent in subjects with relapsed or refractory DLBCL, with possible lower response rates in subjects with the GCB subtype.

2.9.3.1 Study PCYC-04753

This is a completed, Phase 1, multicenter, open-label, dose escalation study in 66 subjects with recurrent NHL. The objectives included studying the safety profile of ibrutinib, identifying the maximum tolerated dose (MTD) and optimal dosing schedule, and characterizing efficacy, pharmacokinetics, and pharmacodynamics. A minimum of 6 subjects per cohort received 1 of 5 escalating dose levels of ibrutinib between 1.25 and 12.5 mg/kg for 28 consecutive days in a 35-day cycle, with the

objective of escalating 3 dose levels above that which achieved full BTK occupancy based on the fluorescent probe assay. Two additional cohorts received a continuous ibrutinib dose of 8.3 mg/kg without a 7-day rest and a fixed continuous dose of 560 mg/day.

Full BTK occupancy was achieved with doses at ≥2.5 mg/kg/day; consequently, per protocol, 12.5 mg/kg/day was the highest dose cohort evaluated. There were 2 dose-limiting toxicities (DLTs) (Grade 2 neutropenia [2.5 mg/kg/day] and Grade 3 hypersensitivity [8.3 mg/kg/day]); these events occurred in different dose cohorts, with neither in the highest-dose nor a continuous dosing cohort. The MTD of ibrutinib in subjects with B-cell malignancies was not established in this study.

Five of 15 subjects with DLBCL (33%) achieved objective responses, 2 CRs and 3 partial responses (PRs). The median time on treatment was 8 weeks (range: 2 to 98 weeks). Median PFS was 2.5 months (range: 0.7 to 4.6 months) and the median follow-up time was 3.5 months (range: 0.8 to 22.5 months).

2.9.3.2 Study PCYC-1106-CA

This is a Phase 2, multicenter, open-label, single-arm study in subjects with relapsed or refractory DLBCL. Subjects are enrolled and retrospectively assigned to 1 of 2 cohorts by subtype: ABC versus GCB as per central GEP. All subjects have received a continuous fixed dose of ibrutinib 560 mg/day. The objectives include studying the efficacy of ibrutinib in DLBCL and the safety of this dosing regimen. The study has completed enrollment. Seventy subjects were enrolled with a median age of 63 years (range: 28 to 92 years) and a median of 3 prior systemic therapies (range: 1 to 7).

Median time from diagnosis was 19 months. In a subset of samples, a comparison of the central IHC by Hans algorithm to the GEP algorithm that was used in this Phase 2 clinical study (ie, Sensation algorithm; 200 genes) was performed (unpublished data on file).55 Non-GCB by central IHC, blinded to the GEP assignment and clinical data, had a 92% concordance (12/13) with GEP. For the 60 response evaluable subjects, the overall response rate (ORR) was 21.7% (13/60 subjects). Median PFS was 1.64 months (Table 3).55 In the ABC subtype, ORR was 40% (10/25 subjects; 95% confidence interval [CI]: 21% to 61%), CR 8% (2/25 subjects), and PR 32% (8/25 subjects). Only 1 PR (1/19 subjects; 5.3%) was observed in the GCB subtype and none in unclassifiable cases. Thus, while the 2 subgroups were clinically not well balanced, ibrutinib showed less activity in the GCB DLBCL subtype (p=0.0126, Fisher’s exact test).

Table 1 Study PCYC-1106-CA Efficacy Results

	ABC Subtype N = 29	GCB Subtype N = 20	Unclassifiable[A] N = 16	Unknown[B] N = 5	Total N = 70
Evaluable for Response	25	19	13	3	60
ORR (CR + PR)	10 (40%)	1 (5.3%)	0	2 (66.7%)	13 (21.7%)
CR	2 (8%)	0	0	1 (33.3%)	3 (5%)
PR	8 (32%)	1 (5.3)	0	1 (33.3%)	10 (16.7%)
PFS (months)	2.5	1.28	0.95	NR	1.64

ABC=activated B-like DLBCL; CR=complete response, GCB=germinal center B-cell; NR=not reached; ORR=overall response rate; PFS=progression-free survival; PP=per-protocol population; PR=partial response

A Gene expression profiling performed, but not assignable to ABC or GCB subtypes.

B Gene expression profiling not yet performed or tissue not available

A post hoc analysis of pooled data from the DLBCL expansion cohort of Study PCYC-04753 and Study PCYC-1106-CA was conducted. The effect of a prior response to chemotherapy on subsequent response to ibrutinib was assessed for all subjects with DLBCL and for subjects in the ABC DLBCL and non-ABC DLBCL subsets. More subjects in the ABC DLBCL subset who were chemo-sensitive had a response (11/14 subjects, 78.6%) compared with the chemo-sensitive non-ABC DLBCL subset (4/16 subjects, 25.0%). Fewer subjects with ABC DLBCL who were chemo-refractory (defined as failure to achieve a response to the last prior chemotherapy regimen) had a response (4/25 subjects, 16%), but the response was still favorable as compared with the chemo-refractory non-ABC DLBCL subset (0/25

subjects, 0%). Based on these results, ibrutinib appears to be more active in subjects with chemo-sensitive DLBCL. Therefore use of ibrutinib in earlier lines of therapy and in the non-GCB subtype of DLBCL may have the greatest clinical effect.

2.9.3.3 Study PCI-32765DBL1002

This is a multicenter, dose-escalation and expansion study in subjects with newly diagnosed CD20-positive B-cell NHL including DLBCL, follicular lymphoma, and MCL. Thirty-three subjects have been enrolled in this study of whom 24 subjects have DLBCL; 18 subjects with newly diagnosed DLBCL were treated at the recommended Phase 2 dose (ibrutinib 560 mg daily) in combination with R-CHOP.

In the dose-escalation phase of this study, subjects were assigned to cohorts of increasing oral daily doses of ibrutinib 280 mg (n=7), 420 mg (n=4), and 560 mg (n=6) administered in combination with R-CHOP. A Study Evaluation Team (SET) reviewed all available data upon completion of the first cycle for all subjects at each dose cohort to determine DLTs. After the recommended Phase 2 dose was determined (560 mg), 16 subjects with newly diagnosed DLBCL were enrolled into the expansion cohort. Subjects are allowed to continue to receive ibrutinib and R-CHOP up to a maximum of 6 cycles.

In patients who received ≥1 dose of ibrutinib and R-CHOP (n = 32), 15 (46·9%) patients received full doses of R-CHOP. Single-dose reductions of vincristine (11/32; 34·4% of patients) were most frequently reported, and one patient each (3%) had one or two dose reductions of cyclophosphamide, doxorubicin, or prednisone. Additionally, four patients had a single ibrutinib dose withheld once.

In the 32 evaluable patients, the ORR was 93.8%, and for individual ibrutinib doses of 280 mg, 420 mg, and 560 mg, the ORR was 85.7%, 100.0%, and 95.2%, respectively. The complete response rate for the patients who received ≥1 dose of ibrutinib + R-CHOP (n = 32) was 71.9%. Among the DLBCL patients (n = 23), the ORR was 95.7%. Of these 23 patients, 18 were treated at the recommended phase II dose of 560mg and all responded. The complete response rate at 560mg in DLBCL patients was 15/18 (83.3%), and the partial response rate was 3/18 (16.7%).

Among the DLBCL patients, 13 had cell of origin subtype determined, of which 11 were evaluable; Seven with GCB subtype and four with non-GCB. The ORR for these 13 patients was 100.0%, regardless of subtype. Five patients with GCB subtype achieved a complete response (71.4%) and two had a partial response. All four patients with confirmed non-GCB subtype achieved a complete response.

The pharmacokinetics of vincristine were evaluated and determined to not be impacted by co-administration of ibrutinib. In addition, the pharmacokinetics of

ibrutinib were also evaluated and appeared not to be affected by the presence of the other components of R-CHOP.

2.9.4 Adverse events described in prior ibrutinib clinical trials

There are reports of hemorrhagic events in subjects treated with ibrutinib, both with or without thrombocytopenia in both monotherapy and combination clinical studies. The majority of these hemorrhagic adverse events were of Grade 1 or 2 in severity; those included contusion, epistaxis, and petechiae. Hemorrhagic events of Grade 3 or higher, including central nervous system hemorrhage of any grade severity, occurred in 3.4% (17/506) of subjects treated in monotherapy studies and in 3.1% (4/130) of subjects treated in combination therapy studies; none were reported in the healthy volunteer studies (N=100). In the extension study, PCYC-1103-CA, 2 additional Grade 3 events associated with bleeding were reported ('gastrointestinal haemorrhage' and 'haematotympanum'). Details of these events are provided in the Appendix F, Section 5 Warnings and Precautions.

It is not clear whether or not these events are attributable to ibrutinib. However, it is possible that treatment with ibrutinib could increase the risk of bruising or bleeding. Subjects in the current study will be monitored closely for hemorrhagic adverse events.

Other malignant diseases have been observed in subjects who have been treated with ibrutinib, including skin cancers, adenocarcinomas, and other hematologic malignancies. It is not clear whether or not these events are attributable to ibrutinib. Subjects in the current study will be monitored for other malignancies.

Mild to moderate rashes have been observed with ibrutinib alone or in combination with other drugs. A single case of Stevens-Johnson Syndrome (SJS) was reported in a male subject with CLL treated with ibrutinib 420 mg/day. The subject was also receiving multiple concomitant medications known to be associated with SJS. Subjects should be monitored closely for signs and symptoms suggestive of SJS. Hypersensitivity reactions including anaphylactic shock (fatal), urticaria, and angioedema have been reported.

In non-randomized clinical trials, infections (including sepsis, bacterial, viral, or fungal infections) were observed in subjects with MCL (≥ Grade 3; 25.2%) and CLL/SLL (≥ Grade 3; 37.6%). Some of these infections have been associated with hospitalization and death. Subjects should be monitored for fever and infections and appropriate anti-infective therapy should be instituted as indicated.

2.10 Background drug information of R-DA-EPOCH and R-CHOP

2.10.1 Information on the drugs which are included in R-DA-EPOCH (rituximab, etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin) and in R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone) are included in Appendix A.

2.11 Overall Rationale for the Study

DLBCL is the most common lymphoid malignancy, with ~30,000 new cases in the US annually. CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) was first reported as therapy for DLBCL in 1976, when its molecular pathobiology was virtually unknown, and has changed only with the addition of the anti-CD20 antibody rituximab (R).(1, 25) DLBCL is now known to be molecularly heterogeneous, largely by the cell-of-origin (COO) distinction between germinal center B-cell (GCB) and activated B-cell (ABC) subtypes.(4, 6, 7) Multiple vulnerabilities of each COO subtype are known, and corresponding inhibitors are now in clinical trials, but subtyping is essentially ignored in DLBCL standard-of-care (SOC) therapy.(21, 51) Aside from R, there is no obvious mechanistic specificity of RCHOP for either COO subtype, but it remains the frontline SOC therapy despite advances in knowledge of DLBCL biology, development of targeted agents, and tools for molecular diagnosis.(21, 52) Justification for this disconnect is largely due to the relative efficacy of RCHOP, which achieves 5-year overall survival (OS) rates of ~50% and ~70% in ABC and GCB subtypes, respectively, but with significant toxicity.(5, 53) Infusional etoposide (E) in R-DA-EPOCH may incrementally improve frontline DLBCL SOC efficacy, including in high-risk disease,(24, 54) but it further adds to toxicity and perpetuates the practice of non-targeted, one-size-fits-all frontline SOC therapy for DLBCL.

The abysmal cure rate (~10%) for the 10,000 patients with DLBCL who relapse each year in the US, and long-term complications of frontline DLBCL SOC, mandate that we improve frontline therapy with novel agents against DLBCL-critical aberrancies.(20, 55, 56) However, improving frontline DLBCL therapy poses a particular challenge for the academic oncologist: how to develop new novel therapies without denying potentially curative SOC therapy.(52) The standard “SOC+X” approach, in which X is a drug with single agent efficacy in relapsed DLBCL patients, has drawbacks including: 1) how to measure what X adds to an already-effective SOC therapy; 2) how to avoid potential antagonism between X, which may be highly effective alone, and SOC agents; and 3) how to test more than one novel agent simultaneously.

Gene expression profiling (GEP) shows that the ABC DLBCL subtype has constitutive similarities to normal B cells activated by acute ligation of their B-cell receptor (BCR). Among those similarities are high activity of the canonical NF-kB

pathway,(11, 57, 58) required for survival of ABC DLBCL (**Figure 2**).(27) CARD11, required for NF-κB activation by BCR signaling, has gain-of-function mutations (GOFM) in 10% of ABC DLBCL that can activate NF-κB independent of BCR signaling. In ABC DLBCL with wild type (WT) CARD11, mutations in the ITAM domain of the BCR subunits CD79A and CD79B, found in 24% of ABC DLBCL tumors, contribute to NF-κB activation by "chronic active BCR signaling".(12) Inhibition of Bruton's tyrosine kinase (BTK), a BCR signaling pathway mediator, is specifically toxic to CARD11-WT ABC DLBCL cell lines. NF-κB activation in ABC DLBCL is further driven by a specific GOFM in MYD88, found in 30% of tumors, resulting in toll-like receptor (TLR) signaling.(28) In addition to pro-survival factors, MYD88 GOFM paradoxically drive production of interferon-β (INF-β), which would be toxic to ABC DLBCL if not suppressed by interferon regulatory factor 4 (IRF4 or MUM1), an NF-κB-driven hallmark of ABC DLBCL. In addition to INF-β suppression, IRF4 further activates CARD11 to amplify NF-κB signaling.(42, 59)

Lenalidomide partially reduces IRF4 expression in ABC DLBCL cell lines, producing a synthetically lethal type I interferon response.(42) Ibrutinib has significant activity against ABC DLBCL cell lines with chronic active BCR signaling.(12) When ibrutinib is combined with lenalidomide, IRF4 expression is completely suppressed, resulting in profound synergy in ABC DLBCL cell lines.(42)

In addition to affecting lymphoma cells directly, lenalidomide and ibrutinib both modulate immune responses. In MM, CLL, and follicular lymphoma (FL), lenalidomide reverses immunosuppression of T cells by tumor cells.(60-62) Lenalidomide increases expression of T cell co-stimulatory molecules, T cell activating cytokines, and the number of cytotoxic T cells in MM patient samples. In indolent lymphomas including FL, we found that R-lenalidomide activated many different immune cell subsets, including T and natural killer cells, and enhanced tumor infiltration of CD8+ T cells.(63, 64) In addition to its irreversible BTK inhibition, ibrutinib also inhibits IL2-inducible kinase (ITK), which drives a shift towards an antitumor Th1-dominant response, and reduces a tumor-promoting Th2 response.(65) In unpublished GEP studies, our group has also found that ibrutinib reduces expression of co-inhibitory receptors, most likely by T cells, in the blood of CLL patients. The relationship of these data to therapeutic immunomodulation in DLBCL is unknown; however, loss or aberrant expression of β2M and CD58, critical for tumor immuno-surveillance by T cells, is common in DLBCL and may correlate with immune-mediated response.(66)

Clinical studies of lenalidomide and ibrutinib in ABC DLBCL: Lenalidomide and ibrutinib have both shown promising efficacy and tolerability as single agents and in

Table 2.
Clinical Trials of Lenalidomide and Ibrutinib in DLBCL

	Relapse, Single agent				Frontline, With RCHOP			
	DLBCL		ABC DLBCL		DLBCL		ABC DLBCL	
	ORR	CR	ORR	CR	ORR	CR	ORR	CR
LEN	28%	15%	**53%**	29%	98%	**80%**	88%	**88%**
IBR	22%	5%	**40%**	8%	100%	**83%**	100%	**100%**

ORR: overall response rate, CR: Complete Response, Len: lenalidomide, Ibr: Ibrutinib. Frontline = Low and High Risk

combination with chemotherapy in relapsed and frontline DLBCL, with increased activity in the ABC subtype (**Table 2**,(15, 47-50)). In phase I trials in combination with RCHOP, both drugs were escalated to their single-agent maximum tolerated doses (MTD) without increased toxicity, and both lenalidomide and ibrutinib are now being evaluated in separate "RCHOP+X" trials against placebo aiming for FDA approval in ABC DLBCL. Despite a strong pre-clinical rationale for use of these promising agents, no trial has examined this combination in untreated ABC DLBCL patients prior to the current proposal.

In relapsed ABC DLBCL, mutations (M) in BCR and MYD88 pathway mediators correlate with clinical responses to ibrutinib (**Table 3,** (67)). Patients with CARD11-M (distal to BTK from BCR) had no response to ibrutinib in a phase II trial, matching ABC DLBCL cell line-based predictions,(12) suggesting the need to target downstream NF-κB drivers.(47, 67) In CLL, BTK and PLCγ2 mutations result in acquired resistance to ibrutinib, though their relevance in DLBCL is unknown.(68) Resistance to lenalidomide in DLBCL is not well characterized, but in MM, which shares many GEP features with ABC DLBCL, it can be driven by activation of the Wnt/β-catenin signaling pathway.(69)

Table 3 Ibrutinib Responses vs Mutations

		MYD88	
		WT	M
CD79B	WT	**34%** (10/29)	**0%** (0/5)
	M	**71%** (5/7)	**80%** (4/5)
CARD11	M	**0%** (0/4)	

Based upon the above data, the below phase Ib/II clinical trial of rituximab,

lenalidomide, and ibrutinib (RLI), combined with CHOP or EPOCH in patients with untreated DLBCL will be conducted. The phase II trial will start with RLI alone **prior to the use of chemotherapy** ("Smart Start") for ≤2 cycles, followed by RLI with CHOP or DA-EPOCH. The "Smart Start" portion will be restricted to ABC DLBCL due to the compelling evidence from our group and others that RLI efficacy is expected to have subtype specificity.

DLBCL is clinically aggressive, but most frontline patients do not require immediate cytoreduction, and thus the Smart Start trial is feasible. The effect of innovative non-cytotoxic RLI alone can be assessed on primary tumor cells in vivo, not only because it will not be given with confounding chemotherapy, but also because its efficacy may be greater without the immuno-suppressive effects of chemotherapy. The Smart Start trial, a first in frontline DLBCL therapy, will allow correlation of the efficacy of RLI alone with baseline and RLI-mediated features of the tumor and immune system, which may identify factors that could be used to understand and predict responses to RLI in future trials. New therapeutic approaches are measured by their efficacy, but also by their toxicity, A recent phase II trial showed that R-lenalidomide had efficacy comparable to historical RCHOP controls as frontline therapy for FL, but with less toxicity.(64) While complete avoidance of cytotoxic therapy for DLBCL is not currently an option, the current trial will take a necessary first step toward that as a future possibility, at least for some identifiable patients.

The Smart Start trial will demonstrate that novel drugs can be tested in the frontline setting, where they have the greatest chance of efficacy,(70) without denying access to the curative potential of SOC therapy. This trial may result in a needed paradigm shift in DLBCL therapy: 1) providing support for future trials comparing targeted therapy combinations vs. chemotherapy; 2) establishing RLI as a potential backbone for testing future combinations with additional targeted agents, possibly in an adaptively randomized context; and 3) stratifying treatment according to toxicity concerns or a high likelihood of a response to RLI therapy.

3 Study Design and Rationale

3.1 Study Design:

This will be a single-center, open label, phase II clinical trial to determine the efficacy and safety of rituximab, lenalidomide, ibrutinib, and chemotherapy (R-CHOP or R-DA-EPOCH) in patients with newly diagnosed high risk DLBCL. The treating physicians will have discretion to choose either R-CHOP of R-DA-EPOCH as backbone chemotherapy, in keeping with our current standard practice.

The feasibility of administrating lenalidomide and ibrutinib in combination with rituximab with chemotherapy (DA-EPOCH) and the MTD have been previously determined in the PCYC-1124-CA clinical trial, conducted in patients with relapsed DLBCL. In this ongoing Phase 1b/2, open-label, non-randomized multicenter study, the safety and efficacy of ibrutinib and lenalidomide in combination with R-DA-EPOCH are being evaluated in subjects with relapsed/refractory Diffuse Large B-cell Lymphoma (DLBCL). A standard 3+3 design was employed in Part 1 to determine the maximum tolerated dose (MTD), which has been determined to be 560mg by mouth daily, and the MTD of lenalidomide was 25mg by mouth daily. The preliminary data from the trial was presented at the 2015 Annual Meeting of the American Society of Hematology (abstract 1527). In the dose escalation portion of the trial, no MTD was identified. Dose escalation was completed through the maximum dosing level. One DLT of diffuse alveolar damage was seen at the highest dose of lenalidomide tested. In this trial, the grade ≥3 adverse events (AEs) occurred in 14 (93%) patients. The most common grade ≥3 AEs (which occurred in >20% of patients) were anemia (60%), febrile neutropenia (47%), leukopenia (40%), neutropenia (40%), thrombocytopenia (40%), hypokalemia (40%), and hypotension (33%), which are considered generally in line with what would be expected from EPOCH chemotherapy alone. Serious AEs (SAEs) occurred in 14 patients (93%) including 2 cases (13%) of grade 2 atrial fibrillation.

Regarding the efficacy in this heavily pretreated population, in the 10 response evaluable patients (with at least one post-baseline radiological assessment), 2 patients had complete response (CR), 3 had partial response (PR), 2 patients had best response of stable disease, and 3 had progressive disease; 4 (67%) of 6 response evaluable non-GCB patients achieved objective response (CR/PR). Three patients continue treatment, 2 patients completed the protocol-specified treatment, and 10 patients discontinued treatment. Reasons for treatment

discontinuation included AEs (n=3), progressive disease (n=3), stem cell transplant after achieving CR/PR (n=2), disease worsening (n=1), and death (n=1)

As R-DA-EPOCH is more likely to result in toxicities than RCHOP, and because all of the drugs included in RCHOP are included in R-DA-EPOCH, we think it is appropriate to extrapolate the above data with R-DA-EPOCH to include R-CHOP. As mentioned in Section 2.11, the combination of RCHOP with ibrutinib and with lenalidomide has already been established as safe, and both drugs were increased to their single agent maximum dose without increased toxicity.

Based upon these results, we will utilize the previously determined MTD to evaluate efficacy of the rituximab, lenalidomide, and ibrutinib ("Smart Start") for up to two cycles prior to start of chemotherapy, followed by six cycles of rituximab, lenalidomide, ibrutinib, and chemotherapy (R-CHOP or DA-EPOCH) in patients with high risk non-GCB DLBCL.

3.2 Rationale of Study Design:

The phase II clinical trial is designed to determine the efficacy and safety of rituximab, lenalidomide, and ibrutinib alone and combined with chemotherapy.

Although the study design is novel for patients with untreated DLBCL, it has been utilized in previous clinical trials. As the "Smart Start" component of clinical trial will be given prior to standard cytotoxic chemotherapy, patients who have confirmed disease progression may start chemotherapy at any time during the first 2 cycles of "Smart Start" therapy, previously demonstrated to be tolerable in the PCYC-1124-CA trial.

This study design will allow for evaluation of the efficacy of both rituximab, lenalidomide, and ibrutinib without chemotherapy for up to two cycles and of rituximab, lenalidomide, ibrutinib combined with chemotherapy for six cycles.

4 PATIENT ELIGIBILITY

4.1 Inclusion criteria:

1. Histopathologically confirmed diagnosis of DLBCL of the non-GCB DLBCL subtype (appendix C).
2. No prior treatment except a prior limited-field radiotherapy, a short course of glucocorticoids ≤25mg daily of prednisone equivalent which must cease prior to day 1 of cycle 1, and/or cyclophosphamide for an urgent lymphoma related problem at diagnosis (e.g. epidural cord compression, superior vena cava syndrome).
3. Patient or durable power of attorney (DPA) for healthcare must be able to understand and voluntarily sign an IRB-approved informed consent form.
4. Age ≥ 18 years at the time of signing the informed consent.
5. Patients must have bi-dimensional measurable disease, as defined as radiographically apparent disease with the longest dimension of ≥1.5cm.
6. Patients with performance status of ≤3 (3 only allowed if decline in status is deemed related to lymphoma and felt potentially reversible by the treating physician) (Appendix D).
7. Serum bilirubin <1.5x ULN except in patients with Gilbert's syndrome as defined by > 80% unconjugated bilirubin; AST (SGOT) and ALT (SGPT) ≤ 3x ULN or < 5x ULN if hepatic metastases are present; ANC >1000/mm3 and platelets >100,000/mm3 unless deemed related to lymphoma involvement in the bone marrow and felt potentially reversible by the treating physician.
8. Renal function assessed by calculated creatinine clearance:
    a. Calculated creatinine clearance ≥ 30ml/min by Cockcroft-Gault formula. See section below, "Dosing Regimen", regarding lenalidomide dose adjustment for calculated creatinine clearance ≥ 30ml/min and < 60ml/min.
9. Patients must be willing to receive transfusions of blood products.
10. All study participants must be registered into the mandatory Revlimid REMS® program, and be willing and able to comply with the requirements of the REMS® program.
11. Women of childbearing potential must have a negative serum (β-human chorionic gonadotropin [β-hCG]) at screening and must adhere to the scheduled pregnancy testing as required in the Revlimid REMS® program.
12. Women of childbearing potential and men who are sexually active with a woman of childbearing potential must be practicing a highly effective method of birth control during and after the study (12 months for women

and 3 months for men), consistent with local regulations regarding the use of birth control methods for subjects participating in this clinical study. Men must agree to not donate sperm during and for up to 3 months after their conclusion of therapy on study. For females, these restrictions apply for 1 month after the last dose of study drug.

13. Able to take aspirin (81 mg) daily or alternative therapy as prophylactic anticoagulation

4.2 Exclusion Criteria:

1. Any serious medical condition including but not limited to uncontrolled hypertension, uncontrolled congestive heart failure within past 6 months prior to screening (Class 3 (moderate) or Class 4 (severe) cardiac disease as defined by the New York Heart Association Functional Classification), uncontrolled diabetes mellitus, active/symptomatic coronary artery disease, COPD, LVEF less than 40%, renal failure, active infection, history of invasive fungal infection, moderate to severe hepatic disease (Child Pugh Class B or C), active hemorrhage, laboratory abnormality, or psychiatric illness that, in the investigators opinion places the patient at unacceptable risk and would prevent the subject from signing the informed consent form. Patients with history of cardiac arrhythmias should have cardiac evaluation and clearance.
2. Pregnant or lactating females.
3. Known hypersensitivity to lenalidomide or thalidomide, ibrutinib, rituximab, etoposide, vincristine, doxorubicin, cyclophosphamide, or prednisone.
4. Known HIV infection. Patients with active hepatitis B infection (not including patients with prior hepatitis B vaccination; or positive serum Hepatitis B antibody). Known hepatitis C infection is allowed as long as there is no active disease and is cleared by GI consultation.
5. All patients with central nervous system involvement with lymphoma.
6. Diagnosis of prior malignancy within the past 2 years with the exception of successfully treated basal cell carcinoma, squamous cell carcinoma of the skin, carcinoma "in situ" of the cervix or breast. History of other malignancies are allowed if in remission (including prostate cancer patients in remission from radiation therapy, surgery or brachytherapy), not actively being treated, with a life expectancy > 3 years.
7. Significant neuropathy (Grades 2 or Grade 1 with pain) within 14 days prior to enrollment
8. Contraindication to any of the required concomitant drugs or supportive treatments or intolerance to hydration due to preexisting pulmonary or cardiac impairment including pleural effusion requiring thoracentesis or ascites requiring paracentesis not due to lymphoma.

9. Patients with active pulmonary embolism or deep vein thrombosis (diagnosed within 30 days of study enrollment).
10. Patients with severe bradycardia (heart rate <40 bpm, hypotension, light-headedness, syncope).
11. Major surgery within 4 weeks of study entry, or wound that is not healed from prior surgery or trauma.
12. History of stroke or intracranial hemorrhage within 6 months prior to study entry.
13. Requires anticoagulation with warfarin or equivalent vitamin K antagonists.
14. Requires chronic treatment with strong CYP3A inhibitors (see Appendix E).
15. Vaccinated with live, attenuated vaccines within 4 weeks of study entry.

5 Dosage and Administration Schedule:

5.1 Smart Start:

Patients will begin therapy on this clinical trial with the "Smart Start" portion of the trial. The Smart Start portion of the trial will be defined as shown in Table 4.

Table 4. Doses of "Smart Start" portion of the clinical trial

Drug Name	Dose	Route	Frequency per cycle	Day of therapy
Rituximab	375mg/m2	IV	Once	1
Ibrutinib	560mg	PO	Daily	1-21
Lenalidomide	25mg	PO	Daily	1-10

The dose of lenalidomide and ibrutinib in the Smart Start portion of the trial will be based on the recommended phase II dose (RP2D) determined in the PCYC-1124-CA clinical trial. Patients may decrease lenalidomide and ibrutinib (Table 9) if significant toxicities occur (as defined in Section 5.3.1).

Rituximab, lenalidomide, and ibrutinib will all start on Day 1 of a 21 day cycle in the Smart Start portion of the trial, and will be dosed for 1 day (Rituximab), 10 days (lenalidomide) and continuously (ibrutinib) for up to two cycles of therapy. The ibrutinib and lenalidomide capsules are to be taken around the same time each day with approximately 240 mL of water (ie, 8 ounces). The capsules should be swallowed whole and should not be opened, broken, or chewed. A cycle of therapy is defined as 21 days +/- 72 hours for holidays or other scheduling issues that will not allow the patient to be dosed exactly on schedule. After two cycles of Smart Start, or if disease progression is identified prior to the end of two cycle of Smart Start (as defined in Sections 6.3 and 7.1), all patients will start therapy with rituximab, lenalidomide, and ibrutinib combined with CHOP or DA-EPOCH chemotherapy as defined in Section 5.2.

As defined in Section 9, if the response rate in the Smart Start portion of the trial does not meet specified targets, the Smart Start portion of the trial may be closed prior to the completion of the trial. If so, all patients would start therapy with rituximab, lenalidomide, and ibrutinib combined with chemotherapy as defined in Section 5.2 as their initial cycle of therapy.

At the end of each cycle of the Smart Start portion of the trial, patients will bring their pill bottles to the clinic for evaluation by the research nurse to evaluate the number of remaining pills and assessment of compliance.

5.2 Chemotherapy:

5.2.1 Chemotherapy selection

The selection of R-DA-EPOCH or R-CHOP will be made by the treating physician based upon their preference. Factors that will be included in this decision are patient age, fitness to tolerate aggressive chemotherapy, and clinical trial adherence. The current standard practice at MD Anderson is to select either R-DA-EPOCH or R-CHOP based upon the above factors at the treating physician's discretion, which we will replicate in this protocol. The research team will document the rationale the treating physician provides for the selection for each patient. The selection of R-DA-EPOCH or R-CHOP will be specified prior to start of cycle 1 to avoid any possibility of bias favoring either chemotherapy regimen (e.g., selection of R-CHOP in patients who achieve a CR to RLI, or selection of R-DA-EPOCH in patients with stable disease after RLI).

As R-DA-EPOCH is considered to be equally effective as R-CHOP in treating newly diagnosed DLBCL based upon the phase III trial reported at the ASH 2016 meeting (NCT00118209), these chemotherapies will be considered equivilent for the current protocol.

After the Smart Start portion of the trial, patients will start therapy with rituximab, lenalidomide, and ibrutinib combined with chemotherapy (R-CHOP or DA-EPOCH) for six cycles. A cycle of therapy is defined as 21 days +/- 72 hours for holidays or other scheduling issues that will not allow the patient to be dosed exactly on schedule.

5.2.2 EPOCH

Dose-adjusted EPOCH will be administered in cycle 1 as shown in Table 5 at dose level 0.

Table 5. Doses of R-EPOCH at level 0

Drug Name	Dose	Route	Frequency per cycle	Day of Therapy
Rituximab	375mg/m2	IV	Once	1
Etoposide	50mg/m2/day	IV	Continuous IV infusion	1 – 4
Prednisone	100mg /day	PO	Daily	1 – 5
Vincristine	0.4mg/m2/day	IV	Continuous IV infusion	1 – 4
Cyclophosphamide	750mg/m2	IV	Once	5
Doxorubicin	10mg/m2/day	IV	Continuous IV infusion	1 – 4

5.2.2.1 EPOCH Dose Adjustments:

Cycles will be every 21 days, and each patient will start their subsequent cycle providing that the ANC is at least 1×10^9/L and the platelet count is at least 100×10^9/L. Pharmacodynamic dosing adjustment of doxorubicin, cyclophosphamide, and etoposide will occur based on twice weekly monitoring of complete blood counts to achieve limited absolute neutropenia count (ANC) below 500/μL. Dosing adjustments will proceed based upon relevant toxicities as shown in Table 6.

Table 6. Dose adjustment of doxorubicin, cyclophosphamide, and etoposide

Nadir Measurement	Dose Adjustment
ANC ≥ 0.5 $\times 10^9$/L	20% increase from previous cycle
ANC < 0.5 $\times 10^9$/L on 1 or 2 measurements	No change
ANC < 0.5 $\times 10^9$/L on > 2 measurements	20% decrease from previous cycle
Platelet < 25 $\times 10^9$/L	20% decrease from previous cycle

Rituximab, prednisone, vincristine, lenalidomide, and ibrutinib will not be dose adjusted based upon the schema in Table 6.

Dose adjustments for toxicity below starting dose level (level 0) apply to cyclophosphamide, etoposide, and doxorubicin. Increases of the doses of doxorubicin, cyclophosphamide, and etoposide will be capped at dose level +2 (Table 7).

If a patient is dose escalated to receive cyclophosphamide 1080mg/m2 (dose level 2), they will also receive mesna at a one to one ratio to the cyclophosphamide dose. The dose of mesna will be equivalent to the cyclophosphamide dose (mg/m2) and administered via continuous IV infusion beginning 1 hour prior to cyclophosphamide infusion and continuing for 12 hours by continuous infusion.

A cycle of therapy may be delayed up to 14 days for unresolved hematologic toxicity. In order to start the subsequent cycle, thrombocytopenia must be resolved to at least grade 1, and neutropenia must be resolved to at least grade 2, in keeping with standard of care management. There will be no hold for anemia, but transfusion is up to the treating physician and is strongly suggested

if the hemoglobin is <8g/dL.If hematologic toxicities are not resolved by day 15, the patient will need to be removed from the trial.

At the end of each cycle of the RLI-EPOCH portion of the trial, patients will bring their pill bottles to the clinic for evaluation by the research nurse to evaluate the number of remaining pills and assessment of compliance.

Table 7. Dose adjustment values					
Drugs	Drug Doses per Dose Levels (mg/mg/day)				
	-2	-1	0	1	2
Doxorubicin	8	10	10	12	14.4
Etoposide	40	40	50	60	72
Cyclophosphamide	480	600	750	900	1080

Dose reduction of chemotherapy agents for toxicity is further defined in Section 5.7.

5.2.3 R-CHOP

R-CHOP will be administered at standardized dosing in cycle 1 as shown in Table 8.

Table 8. Doses of R-CHOP				
Drug Name	Dose	Route	Frequency per cycle	Day of Therapy
Rituximab	375mg/m2	IV	Once	1
Cyclophosphamide	750mg/m2	IV	Once	1
Doxorubicin	50mg/m2	IV	Once	1
Vincristine	1.4mg/m2 (max dose 2mg)	IV	Once	1
Prednisone	100mg	PO	daily	1 – 5

Dose reduction of chemotherapy agents for toxicity is further defined in Section 5.7.

5.3 Lenalidomide and ibrutinib dosing:

The dose of lenalidomide and ibrutinib will be based on the recommended phase

II dose (RP2D) determined in the PCYC-1124-CA clinical trial. Patients may decrease lenalidomide (Tables9 and 10) if significant toxicity (as defined in Section 5.3.1) occur.

Table 9. Lenalidomide and Ibrutinib Dosing Modifications for toxicity during chemotherapy phase				
Level	Lenalidomide	Ibrutinib for <65 years of age	Ibrutinib for >/= 65 years of age	EPOCH or CHOP
1	25mg	560mg	420mg	Standard
-1	20mg	560mg	420mg	Standard
-2	10mg	560mg	420mg	Standard
-3	10mg	420mg	280mg	Standard

Table 10. Lenalidomide and Ibrutinib Dosing Modifications for toxicity during Smart Start		
Level	Lenalidomide	Ibrutinib
1	25mg	560mg
-1	20mg	560mg
-2	10mg	560mg
-3	10mg	420mg

Lenalidomide and Ibrutinib will both start on Day 1 of a 21 day cycle along with R-EPOCH or R-CHOP, and will be dosed for 10 days (lenalidomide) and continuously for the six cycles of therapy (ibrutinib), respectively. If it is identified that dose reductions are required in ≥ 4 of the first 10 patients, all subsequent patients would start at dose level -1. If dose reductions are required in ≥ 4 of the first 10 patients at dose level -1, all subsequent patients would start at dose level -2. If dose reductions are required in ≥ 4 of the first 10 patients at dose level -2, all subsequent patients would start at dose level -3.

Based upon information available as of July 2018 from the DBL3001 trial (PHOENIX), a Janssen-sponsored, randomized, double-blind, placebo-controlled phase 3 study of ibrutinib in combination with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) versus placebo in

combination with R-CHOP, in subjects with newly diagnosed non-germinal center b-cell subtype of diffuse large B-cell lymphoma (DLBCL), the protocol is being modified for patients ≥65 years of age. When a patient age ≥65 is enrolled on study, they will receive a maximum dose of 420mg of ibrutinib when administered in combination with chemotherapy.

For any patient enrolled on this study who is >=65 years of age and still on active therapy at the time of IRB approval of this amendment, they will receive ibrutinib 420mg for all subsequent cycles of therapy when combined with chemotherapy.

5.3.1 Dose Reduction plan for lenalidomide and ibrutinib:

Relevant toxicities for the adjustment of lenalidomide and ibrutinib will be defined as any toxicity during either the smart start period and the 6 cycles of treatment with R-CHOP or R-DA-EPOCH that meets one of the following criteria, where toxicity was defined as an adverse event at least possibly related to study treatment:

1. Any grade 3 or higher non-hematological toxicity possibly related to study medications and not controlled by appropriate medications per National Cancer Institute Common Terminology Criteria for Adverse Events v4.0 excluding grade 3 rash that resolves to < Grade 2 within 10 days with systemic corticosteroid treatment, fatigue, anorexia, nausea, fever without neutropenia, and tumor lysis syndrome.
2. Grade 3 rash that does not resolve to < Grade 2 within 10 days with corticosteroid treatment
3. Any grade Stevens-Johnson syndrome or toxic epidermal necrolysis
4. Grade 3-4 bullous dermatitis;
5. Any grade 2 or greater hemorrhagic event requiring medical intervention or any intracranial hemorrhage;
6. Any non-hematological toxicity requiring a delay of the next cycle of therapy for greater than 10 days;
7. Grade 4 neutropenia, thrombocytopenia, or anemia which does not respond to supportive care measures including transfusions or results in a delay of the next cycle of therapy for greater than 10 days.
8. If a patient requires a dose reduction of R-CHOP or R-EPOCH based upon hematologic toxicity as defined in Table 6, they would also have a mandatory dose reduction of ibrutinib and lenalidomide to the next lowest level as defined in Tables 9 and 10 for their next cycle of therapy. If the same patient is able to have a dose increase of R-CHOP or R-EPOCH on subsequent cycles, the dosing of ibrutinib and lenalidomide could be

increased to the previous level at the following cycle (e.g., from EPOCH level -1 on cycle 3 to R-CHOP or EPOCH level 0 on cycle 4, consider resume previous ibrutinib and lenalidomide on cycle 5 if cycle 4 R-CHOP or EPOCH increase was tolerable) after discussion of the principle investigator and the treating physician.

9. Based upon Bayesian toxicity monitoring rules established in section 9.2, if >3 patients in a cohort size of 10 require dose reduction of R-CHOP or R-EPOCH below level 0, future patients would require a mandatory dose reduction of ibrutinib and lenalidomide to the next lowest level as defined in Table 8.
10. If criteria 9 occurs (all future patients have a dose reduction of ibrutinib and lenalidomide based upon dose reductions in R-CHOP or R-EPOCH), a new safety criterion would be established. If ≥2 patients in the next 10 patients required a dose reduction of R-CHOP or R-EPOCH below level 0 despite the reduction in ibrutinib and lenalidomide, the trial would be placed on hold for new patient accrual and would be examined for the etiology of the unexpected hematologic toxicity. The trial may be re-opened only after the principal investigator modified the protocol to ensure safety of future patients in coordination with and with approval from the M.D. Anderson Cancer Center IND office and FDA monitors.

Renal Dysfunction dose adjustment for lenalidomide:

- CrCl > 60mL/minute: No dosage adjustment necessary
- CrCl 30 to 60 mL/minute: 10 mg once daily
- CrCl <30 mL/minute (non-dialysis dependent): 15 mg every 48 hours

Due to the known occurrence of hematologic toxicities with R-CHOP or DA-EPOCH, and the dose modification based upon occurrence of cytopenias, grade 4 hematologic toxicities will not be considered significant toxicities unless they meet the above time constraints. In addition, neutropenic fever incidence will be closely monitored, but will also not be considered a significant toxicity due to the known high rate of neutropenic fever with dose adjusted R-EPOCH and R-CHOP (20 – 30%).

If a significant toxicity is definitely attributed to ibrutinib or lenalidomide per the investigator's assessment, dosing with ibrutinib and or lenalidomide will be withheld. Ibrutinib and or lenalidomide treatment may resume as specified in Tables 9 and 10 after toxicity has resolved to grade 1 or completely. If the toxicity attributed the ibrutinib or lenalidomide as defined in Section 5.3.1 was considered life threatening such as Stevens-Johnson Syndrome or toxic

epidermal necrolysis, ibrutinib and lenalidomide will be discontinued permanently. If the toxicity attributed the ibrutinib or lenalidomide as defined in Section 5.3.1 does not resolve to at least grade 1 within 28 days (7 days beyond the expected 21 days cycles) of the start of a given therapeutic cycle, ibrutinib and lenalidomide will be discontinued for that cycle. Resumption of ibrutinib or lenalidomide would be only considered if the toxicity has resolved to baseline prior to the start of the next cycle, and the patient could be treated at a lower dose level (i.e., a patient treated at dose level -3 prior to this toxicity would not be eligible to resume ibrutinib or lenalidomide as they could not further dose reduce).

It should be noted that the dose reductions listed in Tables 9 and 10 will only be mandatory for future patients if the toxicity monitoring rule thresholds detailed in Section 9.2 are surpassed (i.e. dose reductions are required in ≥ 4 of the first 10 patients at the previous dose level). For an individual patient who experiences a toxicity detailed in Section 5.3.1 as significant, a mandatory dose reduction to the next lower level in tables 9 and 10 will occur for the following cycle. If the patient has no significant toxicities at the lower dose level during the following cycle, the principal investigator may allow re-escalation to the prior dosing level.

5.3.2 Drug Accountability:

The study drugs of ibrutinib and lenalidomide must be handled in strict accordance with the protocol and the container label, and must be stored at the study site in a limited-access area or in a locked cabinet under appropriate environmental conditions. Unused study drugs, and study drug returned by the subject, must be available for verification. The return of unused study drug (ibrutinib or lenalidomide), or used returned study drug for destruction, will be documented. Ibrutinib and lenalidomide should be dispensed under the supervision of the investigator or a qualified member of the study-site personnel, or by a hospital/clinic pharmacist. Study drugs will be supplied only to subjects participating in the study. Returned study drugs must not be dispensed again, even to the same subject. Study drugs may not be relabeled or reassigned for use by other subjects.

5.4 Prophylactic medications:

5.4.1 Prophylaxis for Tumor Lysis Syndrome (TLS)

All patients with bulky lymphadenopathy must receive prophylaxis for TLS prior to the initiation of study treatment. This includes appropriate hydration consisting of a fluid intake of approximately 2 L/day starting 1 day prior to the first dose of

rituximab, lenalidomide, and ibrutinib and administration of allopurinol (300 mg/day orally) or a suitable alternative treatment starting prior to Cycle 1, Day 1 for the first cycle of therapy. Allopurinol can be continued longer than the first cycle if the treating physician wishes, however this will not be mandated. All patients should then be carefully monitored during the initial weeks of treatment.

5.4.2 Venous Thrombosis:

Based upon prior trial data, it will be required for all patients to receive either aspirin (81 – 325 mg PO daily) or another prophylaxis agent while on lenalidomide. Exceptions will be made if a patient has a previous history of significant bleeding or other condition which makes anticoagulation unsafe in the determination of the principal investigator, as ibrutinib may increase the risk of hemorrhage in patients receiving antiplatelet or anticoagulant therapies. For further instructions for invasive procedures, see Section 5.7.6.

The choice of VTE prophylaxis agent relies upon the investigator's discretion and should be tailored to the subject's individual risk/benefit profile by taking into account the individual thrombotic risk, bleeding risk, and the quality of compliance with the VTE prophylaxis.

VTE prophylaxis may need to be held during therapy due the potential of thrombocytopenia associated with either DA-EPOCH, CHOP, lenalidomide, or ibrutinib. For guidelines regarding VTE management related to thrombocytopenia, refer to Table 11.

Table 11

NCI CTCAE Toxicity Grade v 4.0	Action Required
Thrombocytopenia* ≥Grade 3 (platelet count <50,000/mm³	□ Withhold anticoagulation □ Monitor CBC at least every seven days □ If thrombocytopenia resolves to < Grade 3 (>50,000/mm^3), restart anticoagulation unless other contraindication

5.4.3 Administration of Granulocyte Colony-Stimulating Factor

Neutropenia prophylaxis with granulocyte-colony stimulating factor (G-CSF) is required during all cycles which include R-DA-EPOCH and R-CHOP. However, the selection of a particular drug, for example filgrastim, pegfilgrastim, or other is per treating physician discretion..

5.4.4 Infections Prophylaxis

Pneumocystis jirovecii pneumonia prophylaxis is required. However, the drug, dose and schedule selection are per treating physician discretion.

Additional antibiotic, antiviral, and antifungal prophylaxis is not required. However, treating physicians will be allowed to administer antibiotic, antiviral, and antifungal prophylactic medications if they desire. The use of live viral vaccines is contraindicated.

5.4.5 CNS Lymphoma Prophylaxis

Subjects at risk for CNS involvement may receive CNS lymphoma prophylaxis treatment. At risk for CNS involvement is defined as high LDH with ≥2 extranodal disease sites, testicular, vertebral body, bone marrow, paranasal sinus, renal, or adrenal involvement, or at the discretion of the treating physician. The following may be considered by the investigator: 4 – 8 doses of intrathecal methotrexate and/or cytarabine administered during the systemic treatment. CNS prophylaxis with IV drugs is not permitted. For further instructions for invasive procedures, see Section 5.7.6.

5.4.6 Hepatitis B Prophylaxis

To prevent Hepatitis B reactivation, patients who are hepatitis B Core Ab+ but hepatitis B sAg - negative may have low levels of hepatitis B viremia and should undergo a blood PCR test for hepatitis B viral load. All patients at risk of reactivation will have a PCR analysis of blood for viral loads performed pretreatment and during treatment. If the PCR test can detect a quantifiable hepatitis B viral load, patients should have this value repeated every therapeutic cycle. Additionally, these patients will receive appropriate treatment for hepatitis B reactivation prophylaxis. If the PCR analysis is unable to detect a quantifiable hepatitis B viral load, no further hepatitis B testing will be required.

5.4.7 Bowel Prophylaxis

In addition, it is suggested that all patients be treated with a bowel regimen to avoid constipation. The goal of this regimen to ensure at least one soft bowel motion every 24 hours while on study. The treating physician should consider sodium docusate 100mg capsule; take one to two capsules once a day Days 1-7 of each cycle. If needed can double the frequency to two capsules every 12 hours. If needed add oral lactulose 15-30 ml prn/ every 6 hours.

5.5 Radiation Therapy:

The treating physician may prospectively, prior to start of initial therapy, choose to give local radiotherapy after study chemotherapy has completed for the treatment of a particular site of bulky disease or a large mass. In the case of consolidation treatment, bulky disease is defined as ≥ 7.0 cm. However, the decision to treat and the location to be treated must be determined during the Screening Period. In this case, the consolidation radiotherapy will not count as a treatment event for the progression endpoints, unless there is evidence of active disease at the site and radiation is indicated for treating active disease.

If the investigator should decide at anytime after Cycle 1 Day 1 to give consolidation treatment, or to switch treatment to a different lesion, receipt of consolidation treatment will count as a progression endpoint and data will be censored.

5.6 Treatment for Subjects who Develop CNS Disease While on Study:

Patients with known CNS lymphoma are excluded from this study. For those subjects who develop CNS disease after they are enrolled in this study, CNS disease will be treated according to standard institutional guidelines and will be removed from the study.

5.7 Dose modifications of chemotherapy drugs for adverse events:

5.7.1 Ileus and constipation:

Symptomatic ileus/constipation may occur as a result of neurotoxicity from vincristine, however it is usually unnecessary to stop the vincristine altogether. Every effort should be made to not unnecessarily reduce doses. Ileus/constipation is usually worse during the first cycle, and thus prophylactic bowel care is important. If vincristine dose is reduced for this toxicity, it can often be returned to full dose on subsequent cycles without recurrence of severe ileus/constipation. If ileus or constipation requires hospitalization, reduce vincristine 25% on the subsequent cycle. If symptoms resolve after vincristine reduction, increase dose to previous level on subsequent cycles.

Suggested Bowel Regimen – goal of at least one soft bowel motion every 24 hours while on study

Adults: Sodium Docusate 100mg capsule; take one to two capsules once a day Days 1-7 of each cycle. If needed can double the frequency to two capsules every 12 hours. If needed add oral lactulose 15-30 ml prn/ every 6 hours.

5.7.2 Sensory neuropathy

Table 12 Sensory Neuropathy Dosing Adjustments	
Grade	% Dose of Vincristine
1	100%
2	100%
3	50%
4	0%

5.7.3 Motor neuropathy

Table 13 Motor Neuropathy Dosing Adjustments	
Grade	% Dose of Vincristine
1	100%
2	75%
3	25%
4	0%

If neuropathy resolves to a lower grade, doses for that lower grade may be reinstituted at investigator discretion. If the grade of neuropathy increases after being re-escalated, doses must be reduced for the appropriate toxicity grade and may not be re-escalated, even if neuropathy resolves again to a lower grade.

5.7.4 Hepatic and Renal Dysfunction

No dose modifications of chemotherapy are required for hepatic dysfunction thought related to DLBCL manifestations.

Etoposide should be reduced 25% on cycle one for creatinine clearance < 50 cc/min. If the creatinine clearance remains low on subsequent cycles, etoposide should remain at the reduced level as in the previous cycle. Etoposide should be returned to full dose (or escalated if indicated) once creatinine clearance > 50 cc/min. No other dose modifications for abnormal renal indices will be made for enrolled patients.

Monitor patients with liver dysfunction for signs of ibrutinib toxicity and follow dose modification guidance as needed. It is not recommended to administer ibrutinib to patients with moderate or severe hepatic impairment (Child-Pugh classes B and C).

5.7.5 Dose Modification for Obese Patients:

All dosing is based on the patient's BSA as calculated from actual weight. There is no documented adverse impact of treatment of obese patients when dosing is performed according to actual body weight.

5.7.6 Dose Modification for patients who require invasive procedures:

For any planned surgery or invasive procedure requiring sutures or staples for closure, ibrutinib should be held at least 7 days prior to the intervention and should be held at least 7 days after the procedure, and restarted at the discretion of the investigator when the surgical site is reasonably healed without serosanguineous drainage or the need for drainage tubes.

For planned minor procedures (such as a central line placement, lumbar puncture, needle biopsy, thoracentesis, or paracentesis) ibrutinib should be held for at least 3 days prior to the procedure and should not be restarted for at least 3 days after the procedure. For bone marrow biopsies that are performed while the subject is on ibrutinib, it is not necessary to hold ibrutinib for these procedures.

For emergency procedures, ibrutinib should be held after the procedure until the surgical site is reasonably healed, for at least 7 days after the urgent surgical procedure, or at the discretion of the investigator.

5.7.7 Dose modifications for use with CYP3A inhibitors:

As stated in the exclusion criteria, patients who require use of a strong CYP3A inhibitor will not be eligible for enrollment on this clinical trial. If a patient requires a moderate CYP3A inhibitor (Appendix E: e.g., fluconazole, darunavir, erythromycin, diltiazem, atazanavir, aprepitant, amprenavir, fosamprevir, crizotinib, imatinib, verapamil, and ciprofloxacin), the dose of ibrutinib should be reduced to 140mg daily. If a patient requires use of a strong CYP3A inducer (e.g., carbamazepine, rifampin, phenytoin, or St. John's Wort), ibrutinib should be held temporarily while the patient is on the strong CYP3A inducer. Ideally, the treating physician could avoid usage of moderate CYP3A inhibitors or CYP3A inducers and keep ibrutinib at full dosing.

5.8 Management of rash:

For Grade ≥3 rash, hold ibrutinib and lenalidomide until rash improves to Grade ≤1, then resume at original dose if duration of grade 2 or greater rash was <10 days with corticosteroids (for the first episode), or lower dose as clinically

indicated as detailed in Tables 9 and 10. Treatment with topical hydrocortisone is preferred as initial therapy along with antihistamines PO daily is recommended. If worsening or not improving, 40 mg prednisone PO or equivalent daily for 10 days (with or without taper) may be utilized. Allopurinol should be discontinued if rash is thought to be at least possibly related to allopurinol. If the rash fails to resolve to < grade 2 within 10 days of corticosteroid therapy, then resume at the next lower dosing level in Tables 9 and 10.

6 STUDY EVALUATIONS

6.1 Screening Evaluations

- A history and physical examination, including determination of height, weight and performance status should be performed within 28 days prior to enrollment
- The following laboratory studies should be performed within 28 days prior to enrollment:
    - CBC with differential, Serum chemistries – sodium (Na), potassium (K), chloride (Cl), glucose, bicarbonate (CO_2), blood urea nitrogen (BUN), creatinine (Cr), calcium (Ca), magnesium (Mg), phosphorus, total protein, albumin, alkaline phosphatase, aspartate transaminase (AST), alanine transaminase (ALT), total bilirubin, fractionated bilirubin, uric acid, lactate dehydrogenase (LDH), β-2 microglobulin, and urinalysis.
- Females of reproductive potential will undergo serum pregnancy testing with β-HCG within 28 days prior to enrollment.
- Quantitative immunoglobulins (IgG, IgA, and IgM) within 28 days prior to enrollment.
- Baseline blood test for occult fungal infection (+/- 3 days). The test, either Galactomannan or Fungitell, will be determined case by case based upon availability.
- HIV, Hepatitis C viral antibody, Hepatitis B surface antigen, Hepatitis B core antibody within 28 days prior to enrollment. Hepatitis B DNA PCR will be obtained as needed, detailed in Section 5.4.6.
- The following staging studies should be performed within 28 days prior to enrollment:
    - CT scans of neck, chest, abdomen, and pelvis;
    - PET/CT Scan
    - Chest X-ray – PA and lateral;
    - Magnetic Resonance Imaging of head will be required for the next 15 patients enrolled as of 7/13/16, and at the investigator's discretion beyond. Imaging of the spine may be obtained if clinically indicated
    - Unilateral Bone marrow biopsy and aspirate
    - An electrocardiogram
    - A transthoracic echocardiogram or nuclear medicine heart scan to determine the ejection fraction
    - Lumbar Puncture for flow cytometry, glucose, protein, cell count and cytology **only if clinically indicated** at the discretion of the treating physician.

6.2 Pretreatment Evaluation

- A lymphoma-specific history and physical examination should be performed within 3 working/business days prior to the start of therapy
- weight and performance status
- The following laboratory studies should be performed within 3 working/business days prior to the start of therapy:
    - CBC with differential, Serum chemistries – sodium (Na), potassium (K), chloride (Cl), glucose, bicarbonate (CO_2), blood urea nitrogen (BUN), creatinine (Cr), calcium (Ca), magnesium (Mg), phosphorus, total protein, albumin, alkaline phosphatase, aspartate transaminase (AST), alanine transaminase (ALT), total bilirubin, fractionated bilirubin, uric acid, lactate dehydrogenase (LDH), and urine analysis. Serum β-HCG in women of child-bearing potential.
- For correlative studies, 70 ml of blood sample [one purple top tube (10 ml) and 6 heparin containing green top tubes (60 ml)] will be collected within 3 working/business days prior to the first dose of “Smart Start” therapy. These samples will be transported within 6 hours of collection to Dr. Neelapu’s laboratory for processing at the South Campus Research Building I, Room 2.2206, at M. D. Anderson Cancer Center (MDACC). Blood from purple top and green top tubes will be processed for isolation of plasma and peripheral blood mononuclear cells (PBMC), respectively using standard laboratory protocols.
- In consenting patients, (optional) core needle biopsies and fine needle aspirates (FNA) will be obtained by Interventional Radiology (IR) from accessible lymph node under ultrasound or CT-scan guidance within 28 days prior to the first dose of “Smart Start” therapy, and will be processed and stored under our IRB-approved Lymphoma Tissue Bank protocol 2005-0656. All patients who enroll on this trial will be consented for 2005-0656, and will have their samples protected under our standard procedures outlined in 2005-0656. Whenever feasible, up to 3 cores will be obtained using 18 (preferred) or 20 gauge needles as deemed appropriate by an Interventional Radiologist. The three cores will be processed as follows: i) the first core biopsy specimen will be preserved in RNAlater for microarray studies; ii) second core will be formalin-fixed and paraffin-embedded for IHC; and iii) third core will be viably frozen for DNA, RNA, or protein isolation and possible flow cytometry if FNA is not usable. FNA sample will be analyzed by flow cytometry. These samples will be transported in RNAlater (core # i)/formalin (core # ii)/normal saline (cores # iii and FNA) within 6 hours of collection on ice to Dr. Davis’/Neelapu’s laboratory for processing at the South Campus Research Building I, Room

4.3206, at MDACC. If fresh biopsies are not feasible at baseline, archival tissue from prior tumor biopsy may be used for biomarker studies. If there is no lymph node safely accessible for FNA, as deemed by the FNA clinic or IR, this biopsy will not be obtained and the patient will proceed with therapy regardless of this biopsy.

6.3 Evaluation during therapy

- A lymphoma-specific history and physical examination should be performed within 3 working/business days prior to the start of each therapeutic cycle
- weight and performance status assessment within 3 working/business days prior to the start of each therapeutic cycle
- The following laboratory studies should be performed within 3 working/business days prior to the start of each therapeutic cycle:
    - CBC with differential, Serum chemistries – sodium (Na), potassium (K), chloride (Cl), glucose, bicarbonate (CO_2), blood urea nitrogen (BUN), creatinine (Cr), calcium (Ca), magnesium (Mg), phosphorus, total protein, albumin, alkaline phosphatase, aspartate transaminase (AST), alanine transaminase (ALT), total bilirubin, fractionated bilirubin, uric acid, lactate dehydrogenase (LDH). Serum β-HCG in women of child-bearing potential.
- Blood test for occult fungal infection (+/- 3 days). The test that was obtained in 6.1 for a given patient, either Galactomannan or Fungitell, will be obtained prior to start of cycle 2 and cycle 3, which may proceed will the test results are pending.
- The following staging studies should be performed at the conclusion of cycle 2 (or earlier if the treating physician has a strong clinical suspicion of disease progression prior to the end of “Smart Start” therapy):
    - PET/CT scan
- The following staging studies should be performed at the conclusion of cycle 4 (assuming 2 cycles of “Smart Start”, 2 cycles of rituximab, lenalidomide, ibrutinib, with chemotherapy) if PET/CT scan after cycle 2 had less than CR:
    - PET/CT Scan
- If the scan at the end of “Smart Start” occurred prior to the end of cycle 2, and as a result of progressive disease the patient received less than 2 cycles of “Smart Start” therapy, the scan detailed above to occur after cycle 4 would occur after conclusion of 2 cycles of rituximab, lenalidomide, ibrutinib, with chemotherapy.
- The following laboratory studies should be performed twice weekly after the completion of therapy during each therapeutic cycle:

- CBC with differential. Additional laboratory studies can be obtained at the discretion of the treating physician.

- For correlative studies, 70 ml of blood sample [one purple top tube (10 ml) and 6 heparin containing green top tubes (60 ml)] will be collected on day 8 (+/- 72 hours) of the first cycle of "Smart Start" therapy, and pre-therapy on day 1 of the second cycle of "Smart Start" therapy. The same samples will collected pre-therapy on day 1 of the third cycle of chemotherapy (cycle 5 of therapy total if receiving 2 cycles of "Smart Start". A single purple top tube (10ml) will be collected pre-therapy on day 1 of each therapeutic cycle. These samples will be transported within 6 hours of collection to Dr. Neelapu's laboratory for processing at the South Campus Research Building I, Room 2.2206, at M. D. Anderson Cancer Center (MDACC). Blood from purple top and green top tubes will be processed for isolation of plasma and peripheral blood mononuclear cells (PBMC), respectively using standard laboratory protocols.
- In consenting patients, (optional) core needle biopsies and fine needle aspirates (FNA) will be obtained by IR from an accessible lymph node which is deemed to be low-risk for complication by MD Anderson IR staff, using ultrasound or CT-scan guidance 10 days (+/- 96 hours) after the first dose of "Smart Start" therapy, following the guidelines for holding ibrutinib detailed in Section 5.7.6. Whenever feasible, up to 3 cores will be obtained using 18 (preferred) or 20 gauge needles as deemed appropriate by an Interventional Radiologist. The three cores will be processed as follows: i) the first core biopsy specimen will be preserved in RNAlater for microarray studies; ii) second core will be formalin-fixed and paraffin-embedded for IHC; and iii) third core will be snap frozen for DNA, RNA, or protein isolation. FNA sample will be analyzed by flow cytometry. These samples will be transported in RNAlater (core # i)/formalin (core # ii)/normal saline (cores # iii and FNA) within 6 hours of collection on ice to Dr. Davis'/Neelapu's laboratory for processing at the South Campus Research Building I, Room 4.3206, at MDACC.

6.4 Evaluation after conclusion of therapy

- A history and physical examination should be performed within 3-4 weeks after the start of the final therapeutic cycle
- The following laboratory studies should be performed within 3-4 weeks after the start of the final therapeutic cycle:
  - CBC with differential, Serum chemistries – sodium (Na), potassium (K), chloride (Cl), glucose, bicarbonate (CO_2), blood urea nitrogen (BUN), creatinine (Cr), calcium (Ca), magnesium (Mg), phosphorus,

total protein, albumin, alkaline phosphatase, aspartate transaminase (AST), alanine transaminase (ALT), total bilirubin, fractionated bilirubin, uric acid, lactate dehydrogenase (LDH).

- The following staging studies should be performed 3 weeks (+/- 1 week) after the start of the final therapeutic cycle (scan at end of therapy, EOT) :
  - PET/CT scan
  - Unilateral Bone marrow biopsy and aspirate (only if positive at the pre-treatment bone marrow obtain in 6.1.6 was positive for lymphoma)
  - Core needle biopsy or fine needle aspiration of lymph nodes with suspicion of residual lymphoma.
  - For correlative studies, 70 ml of blood sample [one purple top tube (10 ml) and 6 heparin containing green top tubes (60 ml)] will be collected. The same samples will collected pre-therapy on day 1 of the third cycle of chemotherapy (cycle 5 of therapy total if receiving 2 cycles of “Smart Start”. These samples will be transported within 6 hours of collection to Dr. Neelapu’s laboratory for processing at the South Campus Research Building I, Room 2.2206, at M. D. Anderson Cancer Center (MDACC). Blood from purple top and green top tubes will be processed for isolation of plasma and peripheral blood mononuclear cells (PBMC), respectively using standard laboratory protocols.

6.5 Post-Treatment Follow Up

- A history and physical examination should be performed every 3 months (+/- 4 weeks) during the first year after the EOT scan
- The following laboratory studies should be performed every 3 months (+/- 4 weeks) during the first year after the EOT scan:
  - CBC with differential, Serum chemistries – sodium (Na), potassium (K), chloride (Cl), glucose, bicarbonate (CO_2), blood urea nitrogen (BUN), creatinine (Cr), calcium (Ca), magnesium (Mg), phosphorus, total protein, albumin, alkaline phosphatase, aspartate transaminase (AST), alanine transaminase (ALT), total bilirubin, uric acid, lactate dehydrogenase (LDH).
  - For correlative studies, 10 ml of blood sample [one purple top tube}. This sample will be transported within 6 hours of collection to Dr. Neelapu’s laboratory for processing at the South Campus Research Building I, Room 2.2206, at M. D. Anderson Cancer Center (MDACC). Blood from purple top tube will be processed for isolation of plasma and peripheral blood mononuclear cells (PBMC), respectively using standard laboratory protocols.

- The following staging studies should be performed every 3 months (+/- 4 weeks) during the first year after the EOT scan:
    - PET/CT Scan or CT Scan with IV/oral contrast (CT is preferred if EOT PET/CT showed no FDG avid or suspicious lesions)
- A history and physical examination should be performed every 4 months (+/- 8 weeks) during the second year after the EOT scan
- The following laboratory studies should be performed every 4 months (+/- 8 weeks) during the second year after the EOT scan:
    - CBC with differential, Serum chemistries – sodium (Na), potassium (K), chloride (Cl), glucose, bicarbonate (CO_2), blood urea nitrogen (BUN), creatinine (Cr), calcium (Ca), magnesium (Mg), phosphorus, total protein, albumin, alkaline phosphatase, aspartate transaminase (AST), alanine transaminase (ALT), total bilirubin, uric acid, lactate dehydrogenase (LDH).
    - For correlative studies, 10 ml of blood sample [one purple top tube] will be collected. This sample will be transported within 6 hours of collection to Dr. Neelapu's laboratory for processing at the South Campus Research Building I, Room 2.2206, at M. D. Anderson Cancer Center (MDACC). Blood from purple top tube will be processed for isolation of plasma and peripheral blood mononuclear cells (PBMC), respectively using standard laboratory protocols.

- The following staging studies should be performed every 4 months (+/- 8 weeks) during the second year after the EOT scan:
    - PET/CT Scan or CT Scan with IV/oral contrast (CT is preferred if EOT PET/CT showed no FDG avid or suspicious lesions)
- For active surveillance on this clinical protocol, patients will be followed for two years from completion of therapy. Beyond the second year after EOT scan, restaging imaging, laboratory studies, and history and physical examination schedule will not be controlled by the protocol and will be determined by the treating physician. When available, information from the medical record related to clinical outcomes beyond two years may be recorded by the research team, but will not be utilized for initial outcomes analysis.

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7 CRITERIA FOR RESPONSE

7.1 Response Criteria:

This trial will use the Lugano criteria(71) when evaluating primary end points. Responses must last for at least 4 weeks off treatment.

For detailed explanations, please refer to J Clin Oncol, 2014. http://jco.ascopubs.org/content/early/2014/08/11/JCO.2013.54.8800.abstract.

Table 14 Lugano Staging Criteria

Response	PET-CT Based Response	CT-Based Responses
CR	Complete metabolic response Score 1, 2, or 3 with or without a residual mass on 5 point scale It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (eg, with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake	Complete Radiographic Response Target Nodes/nodal masses must regress to <= 1.5cm in longest dimension No extralymphatic sites of disease
PR	Partial Metabolic Response Score 4 or 5 with reduced uptake compared with baseline and residual masses of any size At interim, these findings suggest responding disease As end of treatment, these findings indicate residual disease	Partial Remission (all of the following): >=50% decrease in sum of the product of diameters of up to 6 target measureable nodes and extranodal sites When a lesion is too small to measure on CT, assign 5 mm x 5mm as default value When no longer visible on CT, assign 0 x 0 mm For a node 5 mm x 5mm, but smaller than normal, use actual measurement
SD	No metabolic response Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	Stable disease < 50% decrease in sum of the product of diameters of up to 6 target measureable nodes and extranodal sites, no criteria for disease progression are met
PD	Progressive metabolic disease Score 4 or 5 with an increase in intensity of uptake from baseline and/or New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	Progressive disease requires at least one of the following: An individual node/lesion must be abnormal with: LDi _ 1.5 cm and Increase by _ 50% from PPD nadir and An increase in LDi or SDi from nadir 0.5 cm for lesions _ 2 cm 1.0 cm for lesions _ 2 cm In the setting of splenomegaly, the splenic length must increase by _ 50% of the extent of its prior increase beyond baseline (eg, a 15-cm spleen must increase to _ 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline

8 SUBJECT COMPLETION/WITHDRAWAL

8.1 Completion

A subject will be considered to have completed the study if he or she has died before the end of the study, has not been lost to follow up, or has not withdrawn consent before the end of study.

8.2 Discontinuation of Study Treatment

Subjects who discontinue any component of therapy without disease progression will continue study drugs (lenalidomide and/or ibrutinib) until therapy is completed, disease progression, or unacceptable toxicity, whichever occurs first. If study drugs are discontinued for persistent toxicities as defined in Section 5.3.1, any remaining study treatment (i.e., rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone [or equivalent]) may continue.
Investigators are encouraged to keep subject experiencing clinical benefit (ie, PR, CR, or stable disease) in the study unless significant toxicity puts the subject at risk or routine noncompliance puts the study outcomes at risk. If a subject's study treatment must be discontinued, this will result in automatic withdrawal of the subject from the study.

A subject's study treatment should be discontinued if:
-The subject experiences overt disease progression or relapse
-Unacceptable toxicity
-The subject becomes pregnant
-The subject refuses further treatment
-A serious protocol violation has occurred, as determined by the principal investigator
-The investigator believes that for safety reasons (eg, adverse event) it is in the best interest of the subject to discontinue study treatment

If a subject discontinues study treatment before the onset of disease progression, End-of-Treatment and post-treatment assessments should be obtained and follow up of scheduled assessments should be continued. Refer to Section 6.4 for instructions regarding post-treatment efficacy assessments. The reason(s) a subject discontinues treatment will be recorded.

8.3 Withdrawal From the Study

A subject will be withdrawn from the study for any of the following reasons:
-Withdrawal of consent

-The principal investigator discontinues the study

-Lost to follow up

If a subject is lost to follow up, every reasonable effort must be made by the study site personnel to contact the subject and determine the reason for discontinuation/withdrawal. The measures taken to follow up must be documented. When a subject withdraws before completing the study, the reason for withdrawal is to be documented. Subjects who withdraw may be replaced at the discretion of the principal investigator.

9 Statistical Considerations

9.1 Study Design

This will be a single-center, Phase II clinical trial in patients with newly diagnosed diffuse large B-cell lymphoma. The tolerability and efficacy of administrating rituximab with lenalidomide and ibrutinib alone ("Smart Start") and with chemotherapy (RLI-EPOCH or RLI-CHOP) will be evaluated. The attribution of the backbone chemotherapy R-CHOP of DA-EPOCH will not be randomized. The treating physician will have discretion to choose either R-CHOP of R-DA-EPOCH as backbone chemotherapy. DA-EPOCH dosing will be adjusted based upon published criteria in DA-EPOCH containing cycles 2 – 6, and will be capped at dose level +2).

9.2 Phase 2 clinical trial dosing and sample size

Based upon data from the PCYC-1124-CA, dosing has been selected for testing in up to 60 patients with newly diagnosed ABC DLBCL. It is anticipated that we will accrue approximately a 1:1 ratio of R-CHOP and R-DA-EPOCH treated patients, but the trial will not restrict the allocation. Patients will start with RLI alone **prior to the use of chemotherapy** ("Smart Start") for ≤2 cycles, followed by 6 cycles of RLI with R-CHOP or dose adjusted (DA) EPOCH. The primary objective is to determine the overall response rate (ORR) defined as either complete response (CR) or partial response (PR) of RLI alone up to 2 cycles, and CR rate observed at the end of 6 cycles of RLI with chemotherapy. Secondary objectives include determination of the ORR at the end of the treatment, survival outcomes (progression free and overall survival at 1 year), and safety of RLI with R-CHOP or DA-EPOCH.

In this trial, we are going to both monitor the standard futility and toxicity and evaluate the feasibility of introducing the smart start portion within the trial. Two independent monitoring rules will be proposed for each of them. Note that the overall trial will not be stopped due to lack of efficacy in the smart start portion.

A Bayesian method by Thall et al (1995) will be used for futility and toxicity monitoring. The relevant toxicities for dose adjusting ibrutinib and lenalidomide as defined in section 5.3.1 will be referred to as "Tox". The trial will be stopped early if:

$$\Pr(\text{CR rate} < 0.70 \mid \text{data}) > 0.90$$

or

$$\Pr(\text{Tox rate} > 0.30 \mid \text{data}) > 0.90$$

That is, the trial will be stopped early if there is more than a 90% probability that

the CR rate at the end of all therapy including 6 cycles of RLI-chemotherapy is lower than 70% or if there is more than a 90% probability that the Tox rate is higher than 30%. We assume that CR and Tox follow a prior distribution of beta (0.7, 0.3) and beta (0.3, 0.7), respectively.

The above futility and toxicity monitoring rules will be implemented by a cohort size of 10, starting from the 10th patient enrolled. The corresponding stopping boundaries are listed in the following Table 15.1 and Table 15.2. For example, if there are less than 5 patients to achieve CR in the first 10 patients who complete RLI-chemotherapy, stop the trial early due to futility. The trial also needs to be stopped early due to the agent is too toxic if there are 6 or more patients to experience Tox, as defined in Section 5.3.1, among the first 10 patients. If a toxicity threshold (Table 13.1) is achieved prior to completing a 10 patient-sized cohort, the trial would be stopped prior to completing the 10 patient-sized cohort. In addition, an additional safety rule will be implemented that if >3 patients per 10 patient cohort require a dose reduction of R-CHOP or R-EPOCH, all future patients would be treated starting at the next lowest level of ibrutinib and lenalidomide as defined in Table 8.

If >3 patients require a dose reduction below level 0 of chemotherapy, a new safety criterion would be established. If ≥2 patients in the next 10 patients required a dose reduction of chemotherapy below level 0 despite the reduction in ibrutinib and lenalidomide, the trial would be placed on hold for new patient accrual and would be examined for the etiology of the unexpected hematologic toxicity. The trial may be re-opened only after the principal investigator modified the protocol to ensure safety of future patients in coordination with and with approval from the M.D. Anderson Cancer Center IND office and FDA monitors.

Table 15.1: The stopping boundaries of Phase II trial

Number of patients evaluated	Recommend stopping if ≤ Complete Responses observed	Recommend stopping if ≥ Toxicities observed
10	0-4	6-10
20	0-11	9-20
30	0-17	13-30
40	0-24	16-40
50	0-30	20-50
60	Always stop with this many patients	

Table 15.2: The operating characteristics are summarized in the following table (based on simulations from 10,000 trials).

True CR Rate	True Toxicity Rate	Prob (stop the trial early)	Average number of patients treated
0.55	0.10	0.874	27.1
	0.30	0.900	25.2
	0.50	0.996	16.1
0.70	0.10	0.205	52.7
	0.30	0.367	46.7
	0.50	0.972	19.9
0.85	0.10	0.003	59.9
	0.30	0.207	52.6
	0.50	0.965	20.9

In addition, we use an independent Bayesian futility monitoring for the innovative smart start feature in our design. The smart start portion will be ceased early if

$$\Pr(\text{OR rate of RLI alone} < 0.50 \mid \text{data}) > 0.90$$

i.e., there is more than a 90% posterior probability that the ORR of up to 2 cycles of RLI alone is lower than 50%, and thus treat all remaining patients with RLI plus chemotherapy in cycle 1. The corresponding stopping boundaries are listed in the following Table 15.3 and Table 15.4. The monitoring rule will be implemented by a cohort size of 10, with a prior distribution of beta (0.5, 0.5) for OR.

Table 15.3: The stopping boundaries of Smart Start.

Number of patients evaluated	Recommend stopping if ≤ Overall Responses observed in Smart Start
10	0-2
20	0-7
30	0-11
40	0-15
50	0-20
60	Always stop with this many patients

Table 15.4: The operating characteristics are summarized in the following table (based on simulations from 10,000 trials).

True OR Rate of Smart Start	Prob(stop the trial early)	Average number of patients treated
0.30	0.969	20.5
0.50	0.219	52.0
0.70	0.003	59.9

The above stopping boundaries and operating characteristics are calculated using Multc Lean (v.2.1.0) design software downloaded from http://biostatistics.mdanderson.org/SoftwareDownload.

A total accrual of 60 patients without early termination will provide 95% confidence interval of the CR rate with a maximum width of 0.26.
A 1:1 repartition of the backbone chemotherapy R-CHOP of DA-EPOCH will be targeted, with the goal of having approximately 30 patients treated in both arms. As the chemotherapy regimens of R-CHOP and R-DA-EPOCH are considered equally effective, we will analyze the groups of R-CHOP and R-EPOCH together for the Primary Objective of CR after RLI-chemotherapy, and separately for secondary end points, however the trial will not be powered to directly compare the groups.

9.3 Analysis Plan

Data analysis will be performed using SAS or R, as appropriate. The OR rate of smart start, CR rate of RLI+chemotherapy, DLT rate, and OS/PFS rate at the landmark time point of 1 year will be summarized by frequency and 95% confidence interval. Patients who received at least one dose of the treatment drug will be evaluable for toxicity outcomes. Toxicities will be summarized by dose levels, by grade and by their relationship to the treatment. The intent-to-treat patients will be used for the primary efficacy analysis, patients who lost-to-follow up in the first 3 cycles will be treated as failures. The distribution of time-to-event endpoints including OS and PFS will be estimated by Kaplan -Meier Estimate. Comparison of time-to-event endpoints by important subgroups will be made using the log-rank test. Cox proportional hazard regression will be employed for multivariate analysis on time-to-event outcomes.

9.4 Correlative Study endpoints

The following correlative studies will be performed in Dr. Neelapu, Dr. Davis, or an MD Anderson Core laboratory using the blood, serum, and biopsy samples.

9.4.1 To determine whether rituximab, lenalidomide, and ibrutinib enhances the frequency and function of tumor-specific T-cells in the peripheral blood, the phenotype and function of T cells will be assessed as follows:

Phenotypic studies for T cells. PBMC (1 x 10^5 per tube) will be analyzed by

multiparametric flow cytometry on 6-color, 8 parameter FACS Canto (BD Pharmingen) after staining with a panel of antibodies in 2 separate tubes. Tube 1: PBMC will be stained with CD3, CD4, CD8, CD45RO, CD69, and PD-1 to determine the percentage of total T cells, CD4+ T cells, CD8+ T cells, effector/memory (CD45RO+) T cells within each subset, activation status (CD69+) of T cells within each subset, and PD-1 expression within each subset. Tube 2: PBMC will be stained with CD3, CD4, CD8, CD45RO, CD62L, CD27, CD127 and CCR7 to determine the percentage of effector memory T cells (CD45RO+CD27-CCR7-, CD62L-CD127+) and central memory T cells (CD45RO+CD27+CCR7+, CD62L+CD127+) within CD4+ and CD8+ T-cell subsets. The absolute number of each of these T-cell subsets in the peripheral blood of the patients will be calculated using the following formula: (absolute number of lymphocytes per μl of blood on the CBC analysis) x (% of T-cell subset in lymphocyte gate).

9.4.2 To determine whether rituximab, lenalidomide, and ibrutinib enhances the $CD4^+$ and/or $CD8^+$ T-cell infiltration in the tumor, the following studies will be performed on the core biopsy samples:

Immunofluorescence studies. To determine whether administration of rituximab, lenalidomide, and ibrutinib enhances the $CD4^+$ and/or $CD8^+$ T cell numbers at the tumor site, we will perform flow cytometry as described in 9.5.1 on FNA samples from baseline and day 14 after rituximab, lenalidomide, and ibrutinib.

9.4.3 *Statistical considerations for 9.4.1 and 9.4.2.* The percentage of various T-cell subsets will be collected at each of the planned time points. Spaghetti plots will be used to show the biomarker measurements change overtime. Longitudinal analysis including mixed effects model for time dependent outcomes will be performed. The percentage change for the biomarkers from 14 days after the first infusion to a follow-up time point will be calculated. The correlations among the percentage changes for different biomarkers will be assessed by scatter plots and Spearman's correlation coefficient. The association between the percentage change and patient's clinical outcome such as overall response will be evaluated. Wilcoxon rank sum test will be used to test the difference in percentage change of biomarker between the response group and the non-response group. The percentage change will also be dichotomized into two categories (high vs. low) based on a cutoff point which will be determined after examination of the data. Fisher's exact test will be used to assess the associations between the dichotomized variables for percentage change and clinical response.

9.4.4 To evaluate changes in T-cell subsets by phenotypic studies before and after rituximab, lenalidomide, and ibrutinib treatment at the different time points, we will perform a two-sided paired t-test (significance level of 0.05) for the experiments proposed under 9.5.1 and 9.5.2.

9.4.5 To evaluate the mutational and gene expression data from RNA-Seq of tumor biopsy material, the following analyses will be performed. We will effectively have 3 clinically defined patient clinical groups, represented by Groups A-C. Group A: Responsive to RLI; Group B: non-responsive to RLI but responsive to RLI with chemotherapy; and Group C: Non-responsive to RLI or RLI with chemotherapy. The baseline biopsy from all groups will be evaluated with RNA sequencing (RNA-Seq)(72), in comparison with germline DNA, to determine gene expression, translocations, and mutations including those known to correlate with ibrutinib resistance (e.g., *BTK, PLCγ2, MYD88*, *CARD11, CD79A/B*).(5, 66-68, 73) To attempt correlation of GEP data with clinical responses to RLI and RLI-chemotherapy separately by comparing baseline aggregate expression data between response groups A-C, a regression analysis will be performed. We will also perform RNA-Seq on the paired FNA biopsies from day 14 to compare the baseline and on-therapy data to evaluate for therapy-induced GEP changes. It is assumed that the majority of patients will be in Group A, but we will attempt to compare aggregate expression data from baseline and on therapy across Groups A-C. Data from RNA-Seq will be processed using published methods, including standard quality assessments and R software packages.(72, 74, 75) Gene expression will be compared against the continuous variable of tumor regression percentage and/or changes in LymphoSIGHT values, and analyzed using Gene Set Enrichment Analysis (GSEA)(76) to evaluate for processes in the tumor cells and microenvironment which are associated with response to R-CHOP, but have an unknown relevance to RLI.(5) RNA-Seq will also allow detection and quantification of mutated genes in each sample, either present in baseline samples or arising de novo in day 14 samples: these will be analyzed for correlation with response, to identify those which may help to understand or predict resistance to RLI. Comparison of intra-patient paired samples will help to overcome inter-patient differences in GEP and mutation analyses, as shown in the analysis of our pidilizumab trial.(77) We will also perform RNA-Seq on biopsies of residual disease, and potentially perform focused deep sequencing of DNA from residual tumor, PBMC (germline), and initial biopsy. The RNA-Seq will be carried out at Center for Lymphoid Cancer-BC Cancer Agency at Vacouver, BC, Canada.

9.4.6 Analysis of LymphoSIGHT data

We will utilize a stratified Cox regression model to evaluate the association between LymphoSIGHT values and imaging response data.

10 REPORT OF ADVERSE EVENTS

10.1 REPORTING REQUIREMENTS

All adverse clinical experiences must be recorded and reported, regardless of attribution, according to the table "Recommended Adverse Events Recording Guidelines", after they were documented in the treating physician's clinic note, utilizing the NCI CTC v4.0 to determine terminology and grade. Serious adverse events will be captured from the time of the first protocol-specific intervention, until 30 days after the last dose of drug, unless the participant withdraws consent. For discontinued patients, follow up on serious adverse events will be conducted up to 30 days from last treatment by study drug.

Attribution	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Unrelated	Phase I	Phase I	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III
Unlikely	Phase I	Phase I	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III
Possible	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III
Probable	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III
Definitive	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III

10.2 Adverse event classifications

Adverse Event (AE) – Any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research in which a subject is administered a medicinal (investigational or non-investigational) product. An adverse event does not necessarily have a causal relationship with the treatment.

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

Expected AE - Any AE with specificity or severity that is consistent with the

current Investigator Brochure (IB) or consistent with the risk information described in the Informed Consent Document (ICD) or general investigational plan.

Individual Case Safety Report (ICSR)

A valid ICSR must contain the four minimum criteria required to meet regulatory reporting requirements.

- an identifiable subject (but not disclosing personal information such as the subject's name, initials or address)
- an identifiable reporter (investigational site)
- a Janssen medicinal product
- an adverse event, outcome, or certain special situations

The minimum information required is:

- suspected Janssen medicinal product (doses, indication)
- date of therapy (start and end date, if available)
- batch or lot number, if available
- subject details (subject ID and country)
- gender
- age at AE onset
- reporter ID
- adverse event detail (AE verbatim in English), onset date, relatedness, causality, action taken, outcome, (if available)
- Janssen protocol ID

Product Quality Complaint (PQC)

A product quality compliant is defined as any suspicion of a product defect related to a potential quality issue during manufacturing, packaging, release testing, stability monitoring, dose preparation, storage or distribution of the product, or delivery system. Not all PQCs involve a subject. Lot and batch numbers are of high significance and need to be collected whenever available.

Examples of PQC include but not limited to:

- Functional Problem: e.g., altered delivery rate in a controlled release product
- Physical Defect: e.g. abnormal odor, broken or crushed tablets/capsules
- Potential Dosing Device Malfunction: e.g., autoinjector button not working, needle detaching from syringe
- Suspected Contamination

- Suspected Counterfeit

Serious Adverse Event (SAE) – Any AE associated with the subject's participation in research that:

- results in death;
- is life-threatening, (places the subject at immediate risk of death from the event as it occurred). An adverse event or suspected adverse reaction is considered ''life-threatening'' if, in the view of Principal Investigator, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death;
- results in inpatient hospitalization or prolongation of existing hospitalization;
- results in persistent or significant disability/incapacity;
- is a suspected transmission of any infectious agent via a medicinal product
- results in a congenital anomaly/birth defect; or
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).
    - Important medical events as defined above may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the IND Sponsor, the IND Office.

NOTE: DEATH FOR ANY REASON SHOULD BE REPORTED AS A SERIOUS ADVERSE EVENT.

Hospitalization

For reports of hospitalization, it is the sign, symptom or diagnosis which led to the hospitalization that is the serious event for which details must be provided.

Any event requiring hospitalization or prolongation of hospitalization that occurs during the study must be reported as a serious adverse event, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness or adverse event (e.g., social reasons such as pending placement in long-term care facility)
- Surgery or procedure planned before entry into the study. [Note: Hospitalizations that were planned before the start of data collection and where the underlying condition for which the hospitalization was planned has not worsened will not be considered serious adverse events. Any adverse event that results in a prolongation of the originally planned hospitalization is to be reported as a new serious adverse event.]

Life-Threatening Conditions

Disease progression should not be recorded as an adverse event or serious adverse event term; instead, signs and symptoms of clinical sequelae resulting from disease progression/lack of efficacy will be reported if they fulfill the serious adverse event definition.

Unexpected (Unanticipated) AE - Any AE, with specificity or severity that is not consistent with the current IB, or the applicable product reference safety information, or not consistent with the risk information described in the informed consent document or general investigational plan.

http://www.imbruvica.com/hcp/?utm_source=google&utm_medium=cpc&utm_campaign=Imbruvica&utm_term=imbruvica&utm_content=ibrutinib-+Exact|mkwid|ssjPpM0Gh_dc|pcrid|39412243694

10.3 Adverse event relationship to study drug

The following classification will be used to determine whether an AE is related to the study drug, CT-011:

- Definite - It is clearly related
- Probable - It is likely related
- Possible - It may be related
- Unlikely - It is doubtfully related
- Unrelated - It is clearly NOT related

Definitely related – Events directly or indirectly attributed to study drug, and/or study participation. Events occurring with sufficient frequency to suggest that

they are not random. The event follows a temporal sequence from the time of drug administration and follows a known response pattern to the study drug. It occurs immediately following the study drug administration, improves on stopping the drug, or reappears on repeat exposure.

Probably related – The event follows a reasonable temporal sequence from the time of drug administration, and follows a known response pattern to the study drug and cannot be reasonably explained by other factors. There is a reasonable response to withdrawal of the drug. Rechallenge information is not available or advisable.

Possibly related – The event has a reasonable temporal relationship to the study drug administration and follows a known response pattern to the study drug. However, a potential alternate etiology may be responsible for the event. The effect of drug withdrawal is unclear. Rechallenge information is unclear or lacking.

Unlikely – The adverse event is doubtfully related to the investigational agent.

Unrelated – Events that would occur regardless of study participation, including events that are clearly random occurrences. If the frequency of the event suggests a possible connection to the study intervention, then it should be considered related. If the event is clearly related to other factors, such as a patient's clinical state, therapeutic interventions, or concomitant medications, the event would be considered unrelated to therapy.

10.4 Adverse Events of Special Interest

Events that Janssen Scientific Affairs is actively monitoring as a result of a previously identified signal (even if non-serious), and are listed below:

- Major Hemorrhage

Major hemorrhage is defined as any hemorrhagic event that is Grade 3 or greater in severity or that results in 1 of the following: intraocular bleeding causing loss of vision, the need for a transfusion of 2 or more units of red cells or an equivalent amount of whole blood, hospitalization, or prolongation of hospitalization.

- Intracranial Hemorrhage

Any intracranial hemorrhage adverse event, including subdural hematoma/hemorrhage, epidural hematoma/hemorrhage and intracerebral hemorrhage, of any grade severity, will be captured as an event of special interest.

- Other Malignancies

In addition to all routine AE reporting, all new malignant tumors, including solid tumors, skin malignancies and hematologic malignancies, are to be reported for the duration of study treatment and during any protocol-specified follow-up periods including post-progression follow-up for overall survival.

10.5 Pregnancy

All initial reports of pregnancy must be reported to Janssen Scientific Affairs by the study-site personnel within 24 hours of their knowledge of the event. Abnormal pregnancy outcomes (eg, spontaneous abortion, stillbirth, and congenital anomaly) are considered serious adverse events and must be reported as a Serious Adverse Event.

Any subject who becomes pregnant during the study must discontinue further study treatment.

Because the effect of the study drug on sperm is unknown, pregnancies in partners of male subjects included in the study will be reported by the study-site personnel within 24 hours of their knowledge of the event. Please reference Appendix F and G for additional information.

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

10.6 Special Reporting Situations

When a report contains a Janssen product, an identifiable patient, and identifiable reporter, the following events represent Special Reporting Situations:

- Drug exposure during pregnancy (maternal and paternal)
- overdose of a Janssen medicinal product
- pregnancy exposure (maternal and paternal)
- exposure to a Janssen medicinal product from breastfeeding
- suspected abuse/misuse of a medicinal Janssen product
- inadvertent or accidental exposure to a medicinal Janssen medicinal product
- any failure of expected pharmacological action (i.e., lack of effect) of a Janssen medicinal product
- unexpected therapeutic or clinical benefit from use of a Janssen medicinal product
- medication error involving a Janssen product (with or without patient exposure to the medicinal Johnson & Johnson product, e.g., name confusion)
- suspected transmission of any infectious agent via a medicinal product.

These safety events may not meet the definition of an adverse event; however, from Janssen Scientific Affairs, LLC perspective, they are treated in the same manner as adverse events. Special situations should be recorded on the Adverse Event page of the CRF.

Any special situation that meets the criteria of a serious adverse event should be recorded on a Serious Adverse Event Report Form and be reported to Janssen Scientific Affairs, LLC **within 24 hours of becoming aware of the event.**

10.7 Adverse event reporting

General guidelines – Toxicity will be scored using CTC AE Version 4.0 for toxicity and adverse event reporting. A copy of the CTCAE Version 4.0 can be downloaded from the CTEP homepage (http://ctep.info.nih.gov). All appropriate treatment areas should have access to a copy of the CTC AE Version 4.0. All adverse clinical experiences must be recorded according to the table "Recommended Adverse Events Recording Guidelines", after they were documented in the treating physician's clinic note, utilizing the NCI CTC v 4.0 to determine terminology and grade. Serious adverse events will be captured from the time of the first protocol-specific intervention, until 30 days after the last dose of drug, unless the participant withdraws consent. For discontinued patients, follow up on serious adverse events will be conducted up to 30 days from last treatment of study drug.

When an adverse event occurs, the following information and assessments should be recorded:

i) The signs, symptoms, or diagnosis of the event.
ii) The adverse event severity, using the criteria outlined above.
iii) The relationship of the event to the study drug as outlined above.
iv) The description of any action taken regarding study drug disposition.
v) Any required therapy, medication, treatment, or diagnostic procedure.

The Principal Investigator (PI) or physician designee is responsible for the appropriate medical management of all adverse events. The PI or physician designee must evaluate each adverse experience for its seriousness and determine attribution to study drug.

The investigator must appraise all abnormal laboratory results for their clinical significance. If any abnormal laboratory result is considered clinically significant, the investigator must provide details about the action taken with respect to the test drug and about the patient's outcome.

10.7.1 *Serious adverse events reporting* – All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in "The University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy for Investigators on Reporting Unanticipated Adverse Events for Drugs and Devices". Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to the IND Office, regardless of attribution (within 5 working days of knowledge of the event).

All life-threatening or fatal events, that are unexpected, and related to the study drug, must have a written report submitted within **24 hours** (next working day) of knowledge of the event to the Safety Project Manager in the IND Office.

- Unless otherwise noted, the electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and MDACC IRB.
- Serious adverse events will be captured from the time of the first protocol-specific intervention, until 30 days after the last dose of drug, unless the participant withdraws consent. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.
- Additionally, any serious adverse events that occur after the 30 day time period that are related to the study treatment must be reported to the IND Office. This may include the development of a secondary malignancy.

Reporting to FDA:
Serious adverse events will be forwarded to FDA by the IND Sponsor (Safety Project Manager IND Office) according to 21 CFR 312.32.

It is the responsibility of the PI and the research team to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor's guidelines, and Institutional Review Board policy.

10.8 Maintenance of Safety Information

Safety information will be maintained in a clinical database/repository in a retrievable format. At a minimum, at the end of the treatment phase (="last patient off treatment") as well as the end of the follow-up phase (="last patient out") of the Study, the Institution/Principal Investigator shall provide all adverse events, both serious and non-serious, in report format. However, in certain circumstances more frequent review of the safety data may be necessary, e/g/ to

fulfill a regulatory request, and as such the data shall be made available within a reasonable timeframe at Janssen Scientific Affairs' request.
RedCAP will be used for data entry. REDCap will be the AE database. **Concomitant medications will be captured in the medical record.**

10.9 Reconciliation of SAEs

At a minimum, on a quarterly basis and at the end of the Study, Janssen Scientific Affairs will provide to the Principal Investigator, a listing of all SAEs reported to Janssen Scientific Affairs. Principal Investigator will review this listing and provide any discrepancies to the Janssen Scientific Affairs.

Upon request, Principal Investigator shall provide Janssen Scientific Affairs with a summary list of all SAEs, and AEs of Special Interest and Special Reporting Situation reports to date, for reconciliation purposes.

1. Procedures for Reporting Safety Data and Product Quality Complaints (PQCs) for Janssen Medicinal Products to the COMPANY
   All adverse events and special situations, whether serious or non-serious, related or not related, following exposure to a Janssen medicinal product are to be documented by the investigator and recorded in the CRF and in the subject's source records. Investigators must record in the CRF their opinion concerning the relationship of the adverse event to a Janssen medicinal product.

   All (serious and non-serious) adverse events reported for a Janssen medicinal product should be followed-up in accordance with clinical practice.

   1.1. SAEs and Special Reporting Situations
   All serious adverse events that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject's participation in the study, must be followed until any of the following occurs:
   - The event resolves
   - The event stabilizes
   - The event returns to baseline, if a baseline value/status is available
   - The event can be attributed to agents other than the study drug or to factors unrelated to study conduct
   - It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

The INVESTIGATOR will transmit all SAEs and special situations following exposure to a Janssen product under study in a form provided by Janssen Scientific Affairs, LLC in accordance with the section entitled Transmission Methods, in English within 24-hours of becoming aware of the event(s).

In the event the study is blinded, the INVESTIGATOR will submit an unblinded SAE or pregnancy exposure report to Janssen Scientific Affairs, LLC.

All follow-up information for serious adverse events that are not resolved at the end of the study or by the time of patient withdrawal must be reported directly by the INVESTIGATOR, within 24 hours becoming aware, to Janssen Scientific Affairs, LLC using the Janssen Scientific Affairs, LLC Serious Adverse Event Report

All available clinical information relevant to the evaluation of a related SAE, or special situation is required.

- The INVESTIGATOR is responsible for ensuring that these cases are complete and if not are promptly followed-up. A safety report is not considered complete until all clinical details needed to interpret the case are received. Reporting of follow-up information should follow the same timeline as initial reports.

- Copies of any and all relevant correspondences with regulatory authorities and ethics committees regarding any and all serious adverse events, irrespective of association with the Janssen Product under study, are to be provided to Janssen Scientific Affairs, LLC using a transmission method in Section 10 within 24 hours of such report or correspondence being sent to applicable health authorities.

1.2. Non-Serious AEs

All non-serious adverse events should be reported to Janssen Scientific Affairs, LLC according to the timeframe outlined in the Research Funding Agreement section entitled Reporting of Data.

1.3. PQC Reporting

A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of patients, investigators, and Janssen Scientific Affairs, LLC, and are mandated by regulatory agencies worldwide. Janssen Scientific Affairs, LLC has established procedures in

conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information. Lot and/or Batch #s shall be collected or any reports failure of expected pharmacological action (i.e., lack of effect). The product should be quarantined immediately and if possible, take a picture.

All initial PQCs involving a Janssen medicinal product under study must be reported to Janssen Scientific Affairs, LLC by the INVESTIGATOR within 24 hours after being made aware of the event. The Janssen contact will provide additional information/form to be completed.

If the defect for a Janssen medicinal product under study is combined with either a serious adverse event or non-serious adverse event, the INVESTIGATOR must report the PQC to Janssen Scientific Affairs, LLC according to the serious adverse event reporting timelines. A sample of the suspected product should be maintained for further investigation if requested by Janssen Scientific Affairs, LLC.

2. Reporting Procedures for Reporting Safety Data and Product Quality Complaints (PQCs) for Non-Janssen Medicinal Products
   For SAEs, special reporting situations and PQCs following exposure to a non-Janssen medicinal product under study, the INVESTIGATOR should notify the appropriate regulatory/competent authority or the manufacturer of that medicinal product (in the absence of appropriate local legislation) as soon as possible.
3. Transmission Methods

   The following methods are acceptable for transmission of safety information to Janssen Scientific Affairs, LLC:
   - Electronically via Janssen SECURE Email service (preferred)
   - For business continuity purposes, if SECURE Email is non-functional:
     - Facsimile (fax), receipt of which is evidenced in a successful fax transmission report
   - Telephone (if fax is non-functional).

11 Study Calendar

	Screening	Obtain ≤ 28d of cycle 1	Obtain ≤3 d pre-cycle 1 – 2 of Smart Start	Obtain d 8 cycle 1 of Smart Start	Obtain d10 cycle 1 of Smart Start	Obtain at end of Smart Start (cycle 2 or sooner if progression)	Obtain <3 d pre-cycle 3-8 (RLI-chemotherapy cycles)	Obtain at end of cycle 4 (after 2 cycles of RLI-chemotherapy)	Obtain twice weekly during cycle 3-8 (RLI-chemotherapy cycles)	Obtain within 3 to 4 weeks after start of cycle 8 (End of Therapy)	Obtain every 3 months during year 1 and every 4 months during year 2 after End of Therapy testing
Informed Consent		X									
Lymphoma-relevant History and Physical		X	X				X			X	X
Performance status Assessment		X	X				X				
MRI		X									
Blood test for occult infection		X[8,9]			X[8,9]						
Vital Signs			X				X				
Routine Clinical Laboratory Assessment[1]		X	X				X			X	X
Urinalysis		x	x								
CBC									X		
Pregnancy testing[7]		X	x				x				
Quantitative Immunoglobulins		X									
HIV, HCV, HBV testing		X									
DLBCL Confirmation Biopsy	X[2]	X[2]									
FDG PET/CT	X[2]	X[2]				X		X		X	X[5]
CT with IV contrast of neck – pelvis[3]	X[2]	X[2]									X[5]
Chest X-ray	X[2]	X[2]									
ECG	X[2]	X[2]									
Echo or MUGA	X[2]	X[2]									
Correlative Blood Draw		X	X[6]	X			X			X	X[4]
Correlative Tumor Biopsy		X			X						

Bone Marrow Biopsy		X								X[4]	
Lumbar Puncture		X[4]									

1: Routine clinical laboratory assessment will include: CBC with differential, Serum chemistries – sodium (Na), potassium (K), chloride (Cl), glucose, bicarbonate (CO2), blood urea nitrogen (BUN), creatinine (Cr), calcium (Ca), magnesium (Mg), phosphorus, total protein, albumin, alkaline phosphatase, aspartate transaminase (AST), alanine transaminase (ALT), total bilirubin, uric acid, and lactate dehydrogenase (LDH), fractionated bilirubin, Beta 2 Mircoglobulin (only at 28D prior to treatment), and other testing at the discretion of the treating physician.
2: These tests are standard of care tests required of all patients treated by the M.D. Anderson Department of Lymphoma for newly diagnosed DLBCL. As these tests are not protocol specific, they may be obtained at the discretion of the treating physician during the screening period (i.e., they will be allowed for protocol analysis if they are obtain as routine standard of care testing prior to the patient undergoing screening for the protocol) as long as completed within 28 days of start of therapy.
3: CT with IV contrast may be obtained simultaneously with FDG PET/CT scans as per MD Anderson Diagnostic Imaging protocols.
4: This test is not required by the protocol and will be obtained at the discretion of the treating physician if deemed necessary for initial disease workup or follow up of initial results to evaluate for response.
5. At follow up time points, either FDG PET/CT or CT with IV and oral contrast are acceptable
6. Per Section 6.3 and 6.4 an additional purple top tube (10ml) will be obtained prior to the start of each additional cycle of therapy and in follow up
7. Within 24 hours prior to starting lenalidomide, then weekly for the first 28 days.
8.Baseline blood test for occult fungal infection (+/- 3 days). The test, either Galactomannan or Fungitell, will be determined case by case based upon availability.
9.Blood test for occult fungal infection (+/- 3 days). The test that was obtained in 6.1 for a given patient, either Galactomannan or Fungitell, will be obtained prior to start of cycle 2 and cycle 3, which may proceed will the test results are pending.
N.B.: All time points mentioned in the Study Flowchart are detailed in Section 7, and are included in this table format for easy visualization. The time points in section 6 include +/- time windows to account for scheduling issues/delays. Any discrepancies between Section 6 and the Study Flowchart will be resolved in favor of Section 6.

12 Appendix A: Chemotherapy Information

12.1 Rituximab

Rituximab (Rituxan®) is a humanized monoclonal antibody against CD20 a receptor in the surface of malignant B-cell lymphocytes. The drug has activity against aggressive and non-aggressive NHL of B-cell origin, and has been used in combination with chemotherapy.

12.1.1 Supply

Rituximab is commercially available.

Rituximab is provided in pharmaceutical grade glass vials containing 10 mL (100 mg) or 50 mL (500 mg) at a concentration of 10 mg of protein per milliliter. Please refer to the FDA-approved
package insert for rituximab for product information, extensive preparation instructions, and a comprehensive list of adverse events.

12.1.2 Storage

Rituximab for clinical use should be stored in a secure refrigerator at 2º to 8°C.

12.1.3 Preparation

Rituximab will be diluted to a final volume of 0.9% Sodium Chloride or 5% Dextrose Injection to prepare a standard product with concentration of 2 mg/ml. Caution should be taken during the
preparation of the drug, as shaking can cause aggregation and precipi

tation of the antibody

12.1.4 Stability

After dilution, rituximab is stable at 2-8 degrees C (36-46 degrees F) for 24 hours and at room temperature for an additional 24 hours.

12.1.5 Administration

A peripheral or central intravenous line will be established. During rituximab infusion, a patient's vital signs (blood pressure, pulse, respiration, temperature) should be monitored according to the standard of care. Medications readily available for the emergency management of anaphylactoid reactions should include: epinephrine (1:1000, 1 mg/mL) for subcutaneous injection diphenhydramine hydrochloride for intravenous injection, and resuscitation equipment.

Prophylaxis against hypersensitivity and infusion-related reactions associated with rituximab will include acetaminophen 650 mg and diphenhydramine hydrochloride 50-100 mg administered 30 to 60 minutes prior to starting rituximab. Patients will also receive their first dose of prednisone 60 mg/m2 (or a glucocorticoid equivalent dose of an alternative steroid) at least 60 minutes before rituximab treatment commences.

Rituximab will be administered as an intravenous infusion at 375 mg/m2 on day 1 of each cycle of DA-EPOCH, immediately prior to starting etoposide + doxorubicin + vincristine administration.

The initial dose rate at the time of the first rituximab infusion should be 50mg/hour (25 mL/hr) for the first 30 minutes. If no toxicity is seen, the dose rate may be escalated gradually in 50 mg/hour (25 mL/h) increments at 30 minute intervals) to a maximum of 400 mg/hour (maximum rate = 200 mL/h).

Second and Subsequent Doses (select the appropriate administration timing based upon the following parameters):

90-minute Administration

If the first dose of rituximab was well tolerated, subsequent doses may be administered over 90 minutes with ~20% of the total dose given in the first 30 minutes, and remaining ~80% of the total dose administered over the subsequent 60 minutes. The 90-minute infusion scheme is not recommended for patients with clinically significant cardiovascular disease, previous significant rituximab infusional reactions, or high circulating lymphocyte counts (≥5000/mcL).

Standard Administration for Second & Subsequent Infusions

Patients who tolerate initial treatment without experiencing infusion-related adverse effects but for whom the 90-minute infusion scheme during subsequent treatments is considered inappropriate, may receive subsequent rituximab doses at the Standard Rate for Subsequent Infusions, which is as follows:

Begin at an initial rate of 100 mg/hour (50 mL/h) for 30 minutes. If administration is well tolerated, the administration rate may be escalated gradually in 100-mg/hour (50-mL/h) at 30-minute intervals to a maximum rate of 400 mg/hour (maximum rate = 200 mL/h).

12.1.6 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 with fatal outcome, has been reported and is characterized in patients with a high number of circulating malignant cells (≥25,000 ul) 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 inpatients with high numbers of circulating malignant cells (≥25,000/mm2) 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: rituximab induced B-cell depletion in 70% to 80% of patients with NHL and 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 rituximab 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 rituximab 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. The reported cases had multiple risk factors for PML, including the underlying disease and long-term immunosuppressive therapy or chemotherapy. 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 gastro-intestinal 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.

See the rituximab Investigator Brochure for additional details regarding

safety experience with rituximab.

12.2 Cyclophosphamide:

Cyclophosphamide is an alkylating agent. The usual dosing in lymphoma patients is 750mg/m2 IV once or 300mg/m2 IV q12 hours over 3 days. The main adverse effects include cytopenias, nausea, vomiting, hemorrhagic cystitis, and alopecia.

Refer to the FDA approved package insert for complete product information.

12.2.1 Supply:

Commercially available in white crystalline formulation for intravenous injection, in vials containing 100 mg, 200 mg, 500 mg, 1gm, and 2 gm.

12.2.2 Storage and preparation:

Intact vials stable at room temperature (not to exceed 30oC). Reconstitute with appropriate amounts of 0.9% NaCl to produce a final concentration of 20 mg/ml. Discard solution after 24 hours at room temperature. Stable up to 6 days if refrigerated (2-8C).

12.2.3 Administration:

Cyclophosphamide will be diluted in 100 mL of D5W or 0.9% NaCl and infused over 30 minutes or according to institutional standard. Patients will be instructed to drink an adequate amount of fluids and empty their bladders frequently during cyclophosphamide administration.

12.2.4 Toxicities:

Myelosuppression, nausea and vomiting, hemorrhagic cystitis, and alopecia. Cystitis can be largely prevented by maintaining a good state of hydration and good urine flow during and after drug administration using the following. Please refer to the package insert for a complete listing of all toxicities.

12.2.5 Hydration Guidelines:

All patients should receive 0.9% NS at 500 mL/h during cyclophosphamide infusion.

12.3 Vincristine:

Vincristine is a vinca alkaloids commonly utilized in lymphomas, leukemias, and other tumors. The main adverse effects include constipation, and peripheral neuropathy. The usual dosing in lymphoma is 1.4 mg/m² to a maximum of 2 mg, or 0.4mg/m2/day over 4 days in the DA-EPOCH or CHOP regimen.

Refer to the FDA approved package insert for complete product information.

12.3.1 Supply:

Commercially available in 1 mg, 2 mg, and 5 mg vial sizes. Each ml contains 1 mg of vincristine, 100 mg mannitol, 1.3 mg methylparaben, and 0.2 mg propylparaben. Drug should be stored at 2-8C and should be protected from light.

12.3.2 Toxicities:

Peripheral neuropathy, autonomic neuropathy, and alopecia. Local necrosis if injected subcutaneously. Please refer to the package insert for a complete listing of all toxicities.

12.4 Doxorubicin

Doxorubicin is an anthracycline, which is commonly used in the treatment of lymphomas and sarcomas. The usual dosing is 50mg/m2 either as a bolus, or 25mg/m2 IV continuous infusion over 48 hours, although the DA-EPOCH regimen doses doxorubicin at 10mg/m2 continuous infusion daily over 4 days.

Refer to the FDA approved package insert for complete product information.

12.4.1 Supply:

Commercially available in 10, 20, 50, 100 and 150 mg vials with 50, 100, 250, 500 and 750mg of lactose, respectively.

12.4.2 Toxicities:

Myelosuppression, stomatitis, alopecia, nausea and vomiting, and acute and chronic cardiac toxicity, manifested as arrhythmias or a congestive

cardiomyopathy, the latter uncommon at total cumulative doses less than 500 mg/m2. The drug causes local necrosis if infiltrated into subcutaneous tissue. Please refer to the package insert for a complete listing of all toxicities.

The rate of anthracycline-induced cardiomyopathy is generally described as <5%, though the risk increases with increased drug exposure.

12.4.3 Administration: The maximum concentration is 5 mg/mL, which can be given as in a standard IVPB fluid volume of 50 mL at a maximal IVPB rate of 15 minutes.

12.5 Etoposide

Refer to the FDA approved package insert for complete product information.

12.5.1 Supply:

Commercially available as a concentrate for parenteral use in 100 mg vials; each ml contains 20 mg etoposide, 2 mg citric acid, 30 mg benzyl alcohol, 80 mg polysorbate 80, 650 mg of polyethylene glycol 300, and 30.5% alcohol.

12.5.2 Toxicities:

Myelosuppression, nausea, vomiting, anaphylactoid reactions, alopecia, and hypotension if infusion is too rapid. Please refer to the package insert for a complete listing of all toxicities.

12.6 Prednisone

Prednisone is a steroid with multiple clinical applications, generally including anti-inflammation, although prednisone is known to have activity against lymphoproliferative disorders, including lymphoma and leukemia. The usual dosage is 10 to 100 mg orally daily.

Refer to the FDA approved package insert for complete product information.

12.6.1 Supply:

Commercially available in a large number of oral dosage strengths

including pills and liquid formulations. Tablets should be stored in well-closed containers at temperatures between 15-30C.

12.6.2 Doses:

Prednisone utilization will be simplified by using only 20- and 50-mg tablets to produce a fixed dose

12.6.3 Toxicities:

Proximal muscle weakness, glucose intolerance, thinning of skin, redistribution of body fat, Cushingoid facies, immunosuppression, and propensity to gastrointestinal ulceration. Please refer to the package insert for a complete listing of all toxicities.

13 Appendix B. Revised IPI

Revised International Prognostic Index

The risk factors used in calculating the Revised International Prognostic Index are shown below.

Give 1 point for each criterion met:

a) Age >60 years

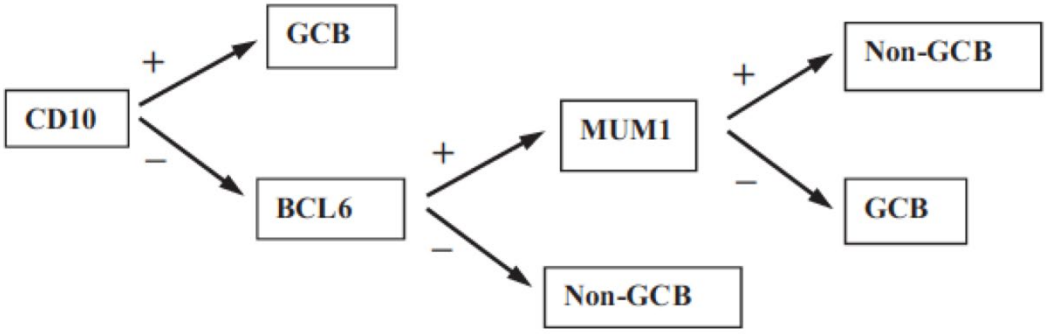
b) Stage III or IV disease

c) Serum LDH greater than upper limit of local normal range

d) Eastern Cooperative Oncology Group performance status >=2

e) More than 1 extranodal site of disease

14 Appendix C. Decision Tree for Immunohistochemistry Classification of DLBCL



Source: Hans CP, Weisenburger DD, Greiner TC, et al. Confirmation of the molecular classification of diffuse large
B-cell lymphoma by immunohistochemistry using a tissue microarray. Blood. 2004;103(1):275-282

15 Appendix D Eastern Cooperative Oncology Group Performance Status Scale

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

Source: Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5(6):649-655.

16 Appendix E. Inhibitors and Inducers of CYP3A

Examples of inhibitors and inducers of CYP3A can be found at the following website:

http://medicine.iupui.edu/clinpharm/ddis/table.aspx

and

http://www.pharmacologyweekly.com/content/pages/online-drug-therapy-tables

The list below reflects information obtained from the Indiana University, Division of Clinical Pharmacology, Indianapolis, IN website

Inhibitors of CYP3A

Strong inhibitors:	**All other inhibitors:**
INDINAVIR	amiodarone
NELFINAVIR	NOT azithromycin[a]
RITONAVIR	chloramphenicol
CLARITHROMYCIN	boceprevir
ITRACONAZOLE	ciprofloxacin
KETOCONAZOLE	delaviridine
NEFAZODONE	diethyl-dithiocarbamate
SAQUINAVIR	fluoxetine-metabolite norfluoxetine
TELITHROMYCIN	fluvoxamine
Moderate inhibitors:	gestodene
aprepitant	imatinib
erythromycin	mibefradil
diltiazem	mifepristone
fluconazole	norfloxacin
grapefruit juice	norfluoxetine
Seville orange juice	star fruit
verapamil	telaprevir
Weak inhibitors:	troleandomycin
cimetidine	voriconazole

[a] Azithromycin is unique in that it does not inhibit CYP3A.

Inducers of CYP3A

efavirenz	phenobarbital
nevirapine	phenytoin
barbiturates	pioglitazone
carbamazepine	rifabutin
glucocorticoids	rifampin
modafinil	St. John's wort
oxcarbazepine	troglitazone

17 Appendix F. United States Product Insert for Ibrutinib

N.B. The USPI is included for information purposes, but in the case of discrepant information between the protocol and USPI regarding information for this protocol, the language in the protocol will be utilized unless otherwise stated. For adverse events in prior clinical trials with ibrutinib, the data in the USPI is more detailed than the protocol and should be used as a reference if any questions arise about issues with hemorrhage, infections, cytopenias, atrial fibrillation, secondary primary malignancies, tumor lysis syndrome, and embryo-fetal toxicities.

18 Appendix G. United States Produce Insert for Lenalidomide

N.B. The USPI is included for information purposes, but in the case of discrepant information between the protocol and USPI regarding information for this protocol, the language in the protocol will be utilized unless otherwise stated. For adverse events in prior clinical trials with lenalidomide, the data in the USPI is more detailed than the protocol and should be used as a reference if any questions arise about issues with embryo-fetal toxicity, hematologic toxicities, venous and arterial thromboembolism, increased mortality, secondary primary malignancies, hepatotoxicity, allergic reaction, tumor lysis syndrome, tumor flare reactions, and impaired stem cell mobilization.

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