Cleveland Clinic
Taussig Cancer Institute

A Cancer Center Designated by the
National Cancer Institute

CASE COMPREHENSIVE CANCER CENTER

Study Number: CASE 3413

ClinicalTrials.gov NCT #: NCT02073097

Study Title: A Phase I/II Study of Carfilzomib in Combination with R-CHOP (CR-CHOP) for Patients with Diffuse Large B -Cell Lymphoma.

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Sponsor:	Case Comprehensive Cancer Center
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Agents:	Carfilzomib, Rituximab, Doxorubicin,Vincristine, Cyclophosphamide, Prednisone
Supplied Agent:	Carfilzomib

SCHEMA

This is a multi-institution, open-label, phase I/II study designed to evaluate the safety and efficacy of carfilzomib in addition to R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) - CR-CHOP - for patients newly diagnosed diffuse large B-cell lymphoma.

ELIGIBILITY:
Patients with Newly Diagnosed Diffuse Large B-cell Lymphoma

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TREATMENT:

CR-CHOP cohorts beginning with dose level 1, escalated in standard 3 + 3 design to identify a recommended phase 2 dose (RP2D) which will be used for expanded cohort.

Dose Level	Carfilzomib dose	CHOP
-2	**11** mg/m^2 on day 1 and 2 every 21 days, cycles 1-6	Standard dose on day 3 every 21 days *Rituximab standard dose on Day 2
-1	**15** mg/m^2 on days 1 and 2 every 21 days, cycles 1-6	
1	**20** mg/m^2 days 1,2 every 21 days, cycles 1-6	
2	**20** mg/m^2 days 1,2 of cycle 1 followed by **27** mg/m^2 days 1,2 every 21 days for cycles 2-6.	
3	**20** mg/m^2 days 1,2 of cycle 1 followed by **36** mg/m^2 days 1,2 every 21 days for cycles 2-6.	
4	**20** mg/m^2 days 1,2 of cycle 1 followed by **45** mg/m^2 days 1,2 every 21 days for cycles 2-6	
5	**20** mg/m^2 days 1,2 of cycle 1 followed by **56** mg/m^2 days 1,2 every 21 days for cycles 2-6	

↓

DISEASE ASSESMENT
PET/CT scan : Baseline and after cycles 3 and 6

↓

DURATION OF TREATMENT AND FOLLOWUP
Continue until completion of planned 6 cycles of CR-CHOP and/or progression of disease; or unacceptable toxicities. Patients will then be monitored for disease status and survival for 24 months.

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APPENDIX D
Comprehensive List of Protocol Changes

1.0 INTRODUCTION

1.1 Diffuse Large B-Cell Lymphoma

Diffuse large B-cell lymphoma (DLBCL) is the most common type of lymphoma. Although combination of the anti-CD20 monoclonal antibody rituximab with cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP) usually results in complete remissions, many patients relapse or fail to respond to initial therapy. The 1–year progression free survival (PFS) is approximately 80% for all patients treated with R-CHOP [1]. However, the heterogeneity of clinical outcome depends on a number of host factors but cannot be reliably predicted based on conventional tumor histology.

At least two separate subgroups of DLBCL based on cell-of-origin have been identified by gene expression profiling: those derived from the germinal center (GC) and those derived from activated B-cells (ABC) [2]. Patients with DLBCL displaying the ABC phenotype have inferior survival than those with the GC subtype [1, 3, 4]. Specifically, the 1-year PFS for patients with the ABC phenotype of DLBCL is approximately 60%, compared to approximately 85% for those with the GC subtype [1].

Several diagnostic immunohistochemical (IHC) algorithms provide estimates of cell-of-origin. The most widely used approach is the Hans algorithm which has reasonable concordance with gene expression profiling [5, 6]. However, because of variability and lack of reproducibility for IHC algorithms to predict clinical outcome, a standardized test (MODAPLEX® System) to assign cell of origin from paraffin embedded tissue is in development at the Cleveland Clinic in collaboration with Primera Diagnostics [7].

The reasons for the difference in outcomes between subtypes of DLBCL are likely related to constitutive activation of NK-κB pathways in the ABC subgroup of DLBCL [8-10]. In addition, activated NK-κB may contribute to rituximab resistance and may represent a therapeutic target [11]. The proteasome inhibitors bortezomib and carfilzomib are an important new class of anticancer agents that have significant clinical activity in multiple myeloma as well as non-Hodgkin's lymphoma. Proteasome inhibitors likely act by many mechanisms including the inhibition of phosphorylated IκB degradation, resulting in inhibition of NK-κB.

Bortezomib is FDA-approved for previously treated mantle cell lymphoma and has been tested in combination with chemoimmunotherapy for DLBCL in both the upfront and relapsed setting. In a trial from the National Cancer Institute, bortezomib was combined with dose-adjusted infusional etoposide, vincristine, doxorubicin, cyclophosphamide and prednisone (dose-adjusted EPOCH) for patients with relapsed/refractory DLBCL [12]. In this study, a higher response and median overall survival was observed in the ABC compared to the GC subtype. The safety and efficacy of bortezomib in combination with R-CHOP in treatment-naïve lymphoma patients was evaluated in a phase I study that showed that this combination was effective and free of significant side effects. [13] In a separate study, patients with newly-diagnosed ABC DLBCL treated with

bortezomib in combination with R-CHOP had equivalent progression-free and overall survival relative to those with the GC subtype suggesting that additional anti-cancer activity provided by bortezomib overcame the higher risk features of the ABC subtype [14].

1.2 Carfilzomib

Carfilzomib is an irreversible proteasome inhibitor. Proteasome inhibition leads to the accumulation of polyubiquitinated protein substrates within cells and to the selective induction of apoptosis in malignant cells while sparing non-malignant cells.

The clinical development of carfilzomib has thus far focused as monotherapy primarily on patients with relapsed and refractory multiple myeloma (MM) who have few therapeutic options. In addition, carfilzomib is being evaluated as a component of combination therapy with lenalidomide treatment in earlier lines of therapy for patients with multiple myeloma.

There is very low incidence of clinically significant neuropathy in patients treated with carfilzomib, likely due to enhanced target selectivity *in vivo* [15]. A maximum tolerated dose (MTD) of carfilzomib was not formally identified in phase I testing, suggesting that enhanced anti-tumor effect without dose-limited toxicity account for the clinical activity in carfilzomib in bortezomib-refractory patients.

On 20 July 2012, Kyprolis™ (carfilzomib) for Injection was approved under the Food and Drug Administration (FDA) accelerated approval program for the treatment of patients with multiple myeloma who have received at least two prior therapies, including bortezomib and an immunomodulatory agent, and have demonstrated disease progression on or within 60 days of completion of the last therapy.

1.2.1 Pre-clinical Data

Carfilzomib (formerly PR-171) is a tetrapeptide epoxyketone-based irreversible inhibitor of the chymotrypsin-like (CT-L) activity of the 20S proteasome. Carfilzomib induces a dose-dependent suppression of proteasome CT-L activity in a wide range of tissues (with the exception of brain) in experimental animals. Inhibition of proteasome CT-L activity was comparable in whole blood and peripheral blood mononuclear cells (PBMCs).

In vitro experiments with continuous (72-hour) exposure to carfilzomib demonstrate potent pro-apoptotic activity across a broad panel of tumor-derived cell lines in culture including bortezomib-resistant tumor cell lines. Incubation of tumor cell lines with carfilzomib for as little as 1 hour (mimicking intermittent intravenous [IV] administration) leads to rapid inhibition of proteasome activity, followed by accumulation of polyubiquitinated proteins and induction of apoptotic cell death. Under these conditions, carfilzomib has little effect on normal (non-malignant) cells, which correlates with low incidence, both in animals and humans, of side effects such as myelosuppression and alopecia that are seen with many anticancer therapies.

Direct anti-tumor efficacy has been tested in immunocompromised mice implanted with a variety of tumor cell lines. In a human colorectal adenocarcinoma model, administration of carfilzomib on a twice-weekly Day 1/Day 2 schedule resulted in significant reduction in tumor size and was superior to a twice-weekly Day 1/Day 4 schedule, and a once-weekly dosing schedule.

Non-clinical repeat-dose toxicity studies were performed in rats and monkeys using 2 different dose schedules. Initially, Investigational New Drug (IND)-enabling 28-day toxicity studies were conducted using a 14-day cycle with carfilzomib administered as an IV bolus dosed daily for 5 days (once daily x 5) weekly followed by a 9-day rest period. Subsequently, International Conference on Harmonisation (ICH)-compliant, New Drug Application/ Marketing Authorisation Application (NDA/MAA)-enabling 6-and 9-month chronic toxicity studies in rats and monkeys, respectively, were conducted using a 28-day schedule in which carfilzomib was given daily dosing for 2 days (once daily x2) weekly for 3 weeks followed by a 12-day rest period; using this schedule, the dose-limiting toxicities
(DLTs) were cardiovascular and gastrointestinal. In the initial 28-day studies, as well as in the chronic 6-and 9-month studies, toxicity was observed in the gastrointestinal tract, bone marrow, and pulmonary and cardiovascular systems. At the maximum tolerated doses (MTDs) in all studies, a transient cyclical thrombocytopenia without a loss of megakaryocytes was the most prominent hematologic toxicity. Importantly, peripheral neuropathy (PN; behavioural and histopathologic) and myelosuppression (neutropenia and severe anemia) were not observed.

The effect of administration time (bolus vs. infusion) on the tolerability of carfilzomib was assessed in rats. When administered as an IV bolus (< 20 second push), a dose of 8 mg/kg resulted in mortality in 50% of the animals and was associated with dyspnea, lethargy, and increased blood urea nitrogen (BUN) and creatinine (consistent with pre-renal azotemia) in the surviving animals. A 30-minute IV infusion of the same dose was well tolerated without significant signs of toxicity or changes in BUN and creatinine. Proteasome inhibition was equivalent between bolus and infusion groups.

1.2.2 Clinical Data

The FDA approval of carfilzomib was based on the results of the Phase 2 PX-171-003-A1 study. Initial Phase 1 safety, pharmacokinetic (PK), pharmacodynamic (PD), and dose finding studies (total patients = 77) examined 2 different schedules of carfilzomib administration in patients with hematologic malignancies (MM [n=38], non-Hodgkin lymphoma [NHL], Waldenström macroglobulinemia [WM], and Hodgkin lymphoma). Study PX-171-001, a dose-escalation trial, assessed daily dosing once daily x5 of carfilzomib within Week 1 of a 2-week cycle at dose levels of 1.2 mg/m^2 to 20 mg/m^2 for at least 8 weeks in 29 patients. The MTD was 15 mg/m^2. Dose-Limiting Toxicities (DLTs) were observed in 2 of 5 patients enrolled in the 20 mg/m2 cohort: Grade 3 febrile neutropenia and Grade 4 thrombocytopenia.

Study PX-171-002 was presented in 2 separate study reports: Study PX-171-002 (Part 1) included 37 patients (21 with MM) who underwent sequential dose-

escalation of carfilzomib administered once daily x2 over a 28-day cycle. Although 3 patients, each at a different dose level experienced DLTs (renal failure, fatigue, and hypoxia) as defined in the protocol, no dose level (through 27 mg/m^2) met the criteria for the MTD of carfilzomib. However, based on the totality of the safety information available at that point in time, including reports of symptoms such as fever, chills, rigors, or dyspnea following dosing in some patients, further dose escalation was not pursued at that time.

Study PX-171-002 (Part 2) included 11 patients with refractory malignancies (7 with MM) who received either single-agent carfilzomib (20 mg/m^2 escalating to 27 mg/m^2 after Cycle 1 [20/27 mg/m^2]) or carfilzomib (20/27 mg/m^2) with dexamethasone (40 mg/wk). One of the 11 patients, in the carfilzomib/dexamethasone group experienced a DLT of Grade 3 liver function test abnormalities (aspartate aminotransferase [AST] and alanine aminotransferase [ALT]). However, the protocol-specified definition of the MTD (i.e., a dose in which = 17% of patients experienced a DLT) was not reached. Therefore, the regimen selected for further study was a "stepped-up" dosing schedule of 20 mg/m^2 in Cycle 1 followed by 27 mg/m^2 thereafter (referred to as the 20/27 mg/m^2 dose).

While Phase 1 studies were designed primarily to assess safety, efficacy was assessed as a secondary objective in both Phase 1 studies and durable tumor responses meeting International Myeloma Working Group (IMWG) and European Group for Blood and Marrow Transplantation (EBMT) criteria were observed during this early phase of testing. In Study PX-171-001, 2 of 9 patients with multiple myeloma achieved an objective response (1 partial response [PR], 1 minimal response [MR]) while receiving carfilzomib 11 mg/m^2 and 15 mg/m^2, respectively. In Study PX-171-002, presented in Study Report PX-171-002 (Part 1), responses of MR or better were observed in 5 of 21 patients with multiple myeloma, at doses of 15 mg/m^2 (n=1), 20 mg/m^2 (n=1), and 27 mg/m^2 (n=3). In Study PX-171-002, presented in Study Report PX-171-002 (Part 2), there were responses in 3 of 9 evaluable patients: 2 with PR in the single-agent carfilzomib group and 1 with an MR in the carfilzomib/dexamethasone group. Based upon the key safety, PK/PD, and efficacy findings, along with the observation of > 80% proteasome inhibition at higher dose levels of carfilzomib, the once daily x2 schedule at a dose of 20/27 mg/m^2 was selected for further testing in Phase 2.

Additional safety measures based on information from ongoing clinical carfilzomib studies were instituted in later studies, including tumor lysis syndrome (TLS) prophylaxis using hydration and administration of allopurinol. All patients were to receive dexamethasone (4 mg orally [PO]) prior to each dose of carfilzomib in Cycle 1, and as needed in subsequent cycles, to mitigate possible adverse events (AEs) temporally associated with dosing. These AEs may include events similar to cytokine release and are notable for fever, chills, dyspnea, and rigors occurring most commonly in the evening following the first or second infusion during the first cycle of therapy or the first escalation cycle of therapy. The regimen of carfilzomib of 20/27 mg/m^2 on a once daily x 2 dosing schedule, in concert with dexamethasone and TLS

prophylaxis, appeared to permit safe dosing during the first cycle, as well as dose-escalation in subsequent cycles for possible greater efficacy.

The key Phase 2 study of carfilzomib as monotherapy is Study PX-171-003, conducted in patients with relapsed and refractory multiple myeloma who had received prior bortezomib and an immunomodulatory drug (IMiD) agent. This study has been presented in 2 reports: Study report PX-171-003 – Part 1 (A0) presented the pilot study (n=46), which included IV carfilzomib administered at doses of 20 mg/m^2 throughout (although 3 patients continuing on study at the time of Amendment 1 were permitted to dose-escalate to 27 mg/m^2 in later cycles); and Study report PX-171-003 – Part 2 (A1) report presented the pivotal study designed to support initial US registration (n=266) which included carfilzomib administered in the stepped-up regimen (20/27 mg/m^2). The 2 reports of Study PX-171-003 included similar patient populations, enrolling patients with an unmet medical need by virtue of having been refractory to their last prior regimen and having previously received the available anti-myeloma therapies.

In addition, Phase 2 Study PX-171-004 provides additional supportive data that further characterize the safety and efficacy profile of carfilzomib in patients who are less heavily pre-treated and who may not be refractory. This study has been presented in 2 reports: .PX-171-004 – Part 1 report inclusive of patients with relapsed or refractory multiple myeloma who had received no more than 3 prior therapies, including bortezomib(n=35), and .PX-171-004 – Part 2 report inclusive of patients who were bortezomib-naïve (n=127). To further characterize the duration of clinical benefit, extension Study PX-171-010 was initiated to allow patients who had completed other carfilzomib studies to continue to receive carfilzomib treatment, thus providing additional information on duration of efficacy and on safety. To characterize the safety and dosing of carfilzomib in patients with renal impairment at baseline, Phase 2 Study PX-171-005 was conducted in 50 patients and 5 cohorts (3 cohorts of patients with decreased creatinine clearance, 1 cohort of patients with normal creatinine clearance, and 1 cohort of patients on hemodialysis). A carfilzomib dose of 15 mg/m^2 on the once daily x2 schedule was used for Cycle 1, with the option for dose-escalation to 20 mg/m^2 and 27 mg/m^2 in subsequent cycles, as tolerated.

Study PX-171-007 is an ongoing, actively enrolling study that was initially designed for patients with relapsed solid tumors. The study was amended to include the following changes: (1) addition of patients with relapsed and refractory multiple myeloma or lymphoma; (2) evaluation of a 30-minute IV infusion, rather than the 2 to 10-minute IV infusion, of carfilzomib (based on animal studies showing less toxicity with prolonged injection of higher doses); and (3) evaluation of carfilzomib in combination with dexamethasone. Amendment 2 included a stepwise increase in carfilzomib dose on Day 8 (i.e., an accelerated stepped-up regimen of 20 mg/m2 on Cycle 1, Days 1 and 2 only, followed by increased dose for the remainder of treatment), and this accelerated stepwise dose increase was maintained for subsequent amendments. Efficacy endpoints include overall response rate (ORR), duration of response (DOR), progression free survival (PFS), and time to progression (TTP).

The promising efficacy observed in the monotherapy program supported the parallel development of carfilzomib in combination with lenalidomide and low-dose dexamethasone, based on the hypothesis that this combination may result in the ability to deliver optimized proteasome inhibition leading to improved efficacy. Study PX-171-006, initiated in July 2008, was a Phase 1b trial to assess safety and preliminary efficacy of the combination of carfilzomib, lenalidomide, and low-dose dexamethasone (40 mg/week) (CRd), with both carfilzomib (15, 20, or 20/27 mg/m^2) and lenalidomide (10, 15, 20, 25 mg) escalated in sequential cohorts in patients with relapsed multiple myeloma. The primary endpoint was the MTD of both carfilzomib and lenalidomide given in combination with dexamethasone, and the secondary efficacy endpoints included ORR, DOR, PFS, and TTP. After an interim safety analysis of 40 patients (of a total of 84 patients enrolled), an MTD had not been reached. The Cohort 6 regimen (carfilzomib 20/27 mg/m^2 and lenalidomide 25 mg together with dexamethasone) was selected for the expansion phase of the study, and an additional 44 patients were enrolled and treated.

Based on the results of these early-phase clinical trials, a series of Phase 3, registration enabling trials was initiated. Several Phase 3 studies in patients with multiple myeloma have been completing including PX-171-011,a Phase 3, randomized, open-label, multicenter study in patients with relapsed and refractory multiple myeloma, comparing carfilzomib 20/27 mg/m^2 with a "best supportive care" regimen (i.e., supportive measures plus 30 mg of prednisolone or 6 mg of dexamethasone given every other day plus optional cyclophosphamide), using similar eligibility criteria to that presented in StudyPX-171-003 – Part 2 (A1). Progression-free survival was similar between groups; overall response rate was higher with carfilzomib (19.1 vs 11.4%).

Based on findings from Study PX-171-006, a pivotal registration-enabling trial, Study PX-171-009, was initiated comparing CRd vs. lenalidomide plus dexamethasone (Rd) in 780 patients with relapsed multiple myeloma who have received 1–3 prior regimens, increased from 700 patients in Amendment 4. Study PX-171-009 received Special Protocol Assessment (SPA) review and agreement from the FDA in January 2010 and the study was initiated in July 2010 at centers in the United States (US), Canada, the European Union, Eastern Europe, Russia, and Israel. Progression-free survival was significantly improved with carfilzomib (median, 26.3 months, vs. 17.6 months in the control group; hazard ratio for progression or death, 0.69; 95% confidence interval [CI], 0.57 to 0.83; P=0.0001). The median overall survival was not reached in either group at the interim analysis. The Kaplan–Meier 24-month overall survival rates were 73.3% and 65.0% in the carfilzomib and control groups, respectively (hazard ratio for death, 0.79; 95% CI, 0.63 to 0.99; P=0.04). The rates of overall response (partial response or better) were 87.1% and 66.7% in the carfilzomib and control groups, respectively (P<0.001)[16]

Study 2011-003 was a Phase 3 multicenter, open-label, randomized trial comparing carfilzomib plus dexamethasone (Cd) or bortezomib (Velcade) plus dexamethasone (Vd) in patients with multiple myeloma whose disease has relapsed after at least 1, but not more than 3 prior therapeutic regimens. Between June 20,

2012, and June 30, 2014, 929 patients were randomly assigned (464 to the carfi lzomib group; 465 to the bortezomib group). Median progression-free survival was 18·7 months (95% CI 15·6–not estimable) in the carfi lzomib group versus 9·4 months (8·4–10·4) in the bortezomib group at a preplanned interim analysis (hazard ratio [HR] 0·53 [95% CI 0·44–0·65]; p<0·0001) [17].

Single-Patient INDs were first established in 2009 and were intended for patients who had never received carfilzomib and who did not qualify for any of the Amgen-sponsored clinical studies. In the latter part of 2009, after noting that a number of Single-Patient INDs were filed, the FDA recommended that, rather than continuing to file individual Single-Patient INDs, Amgen should consider providing a more formalized expanded access program. An Amgen-sponsored, Carfilzomib Multiple Myeloma Expanded Access Protocol (C-MAP) was therefore approved and initiated in the US in June 2011, in collaboration with the Multiple Myeloma Research Foundation (MMRF). This is a multi-center, expanded access, open-label (single-arm with no control group) study of carfilzomib for patients with relapsed and refractory multiple myeloma. The study is designed to provide access to patients with relapsed and refractory disease that have received at least 4 prior regimens and are not eligible for any other enrolling carfilzomib studies, prior to the potential commercial launch of carfilzomib in the US. This study is being conducted in up to 50 study sites in the US with a maximum enrolment of 500 patients under the current protocol design.

An Investigator-Sponsored Trial (IST) program was instituted in 2009 in order to allow investigators access to carfilzomib to conduct Non-Amgen-sponsored clinical trials to answer important questions of clinical relevance. The IST program includes studies in the US and European Union (EU) and affords testing of different combination therapies of carfilzomib with other agents, other doses of carfilzomib, different administrations, and different patient populations.

In November 2015, Amgen was acquired by Amgen, Inc. and the IST program was transitioned to the "Non-Amgen Sponsored Clinical Research Group (NASCR). Therefore, information regarding the drug supplier will now be referred to as Amgen, not Onyx as described previously.

1.2.3 Clinical Pharmacokinetics

In clinical studies, carfilzomib doses of 15 to 36 mg/m^2 lead to an average of 77% to 86% proteasome inhibition in whole blood and PBMCs at 1 hour after dosing. In PK studies, carfilzomib is cleared rapidly, with a mean terminal half-life ($t_{½}$) of 15, 7, and = 60 minutes in rats, monkeys, and humans, respectively. The predominant metabolites observed in rats, monkeys, and humans are peptide fragments and amino acids that are derived from carfilzomib and carfilzomib diol, indicating that peptidase cleavage and epoxide hydrolysis are the principal pathways of metabolism for carfilzomib; none of these metabolites inhibit the activity of the 20S proteasome. However, despite the rapid clearance of carfilzomib from the blood compartment, prolonged potent proteasome inhibition is observed. The pharmacodynamic (PDn)

half-life of carfilzomib is approximately 24 hours in rats and monkeys, and = 24 hours in humans.

At doses ≥ 15 mg/m^2, systemic clearance values on Day 1 of Cycle 1 ranged from 151 to 263 L/hr, exceeding liver blood flow, and terminal $t_{½}$ values were < 1 hour. On day 1 of cycle 1, average C_{max} values were 2,546 ng/mL and 3,060 ng/mL following administration of 15 and 20 mg/m^2, respectively. On Day 16 of Cycle 1, average C_{max} was 4,564 ng/mL following administration of 27 mg/m^2, indicating a dose proportional increase in C_{max} across the dose range of 15 to 27 mg/m2. In addition, a dose dependent increase in total exposure (AUC) was seen between 20 and 36 mg/m^2. Following repeated doses of carfilzomib at 15 and 20 mg/m^2, AUC and $t_{½}$ were similar on Days 1 and 15 or 16 of cycle 1, suggesting no systemic accumulation of carfilzomib. A trend towards decreased clearance, with a corresponding increase in AUC, was observed in females and patients greater than 65 years of age in the Phase 1 studies. In a population PK analysis (pooled data from 1,488 samples derived from 236 patients across 5 studies), neither gender nor age were included as covariates in the final PK model; there was no apparent effect of race on exposure to carfilzomib. PK data for the 15 mg/m^2 dose was generated in Study PX-171-005. PK data for the 20 mg/m^2, 27 mg/m^2, and 36 mg/m^2 doses were generated in Study PX-171-007.

1.3 R-CHOP

Cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) have been the mainstay of treatment for patients with advanced stage DLBCL since its development in 1970s. A milestone phase III trial found that complex regimens adding other chemotherapy agents to CHOP, (i.e. m-BACOD; ProMACE-CytaBOM, and MACOP-B) did not demonstrate any significant benefit in overall survival (OS), disease-free survival (DFS), or remission rate over CHOP [10-12]. The development of rituximab – a monoclonal antibody targeting to CD20 led to combining this agent with chemotherapy (R-CHOP).

1.3.1 Preclinical Data

Rituximab is a genetically engineered, chimeric murine/human monoclonal antibody directed against the CD20 antigen found on the surface of normal and malignant pre-B and mature B cells. The antibody is an IgG1 κ immunoglobulin containing murine light-and heavy-chain variable region sequences and human constant region sequences. Rituximab is composed of two heavy chains of 451 amino acids and two light chains of 213 amino acids (based on cDNA analysis) and has an approximate molecular mass of 145 kD. Rituximab has a binding affinity for the CD20 antigen of ~8.0 nM. There are a number of preclinical studies which suggest that rituximab exerts its therapeutic effect by some combination of antibody-dependent cell-mediated cytotoxicity (ADCC), complement and/or direct cell lysis. Determining the exam mechanisms of action of rituximab is an active area of investigation.

1.3.2 Clinical data

Several seminal studies demonstrated that the overall survival of patients with DLBCL is improved when rituximab is added to CHOP [16-18]. Standard dosing or R-CHOP is 375 mg/m^2 rituximab, 750 mg/m^2 cyclophosphamide, 50 mg/m^2 doxorubicin, and 2 mg vincristine all given intravenously on days 1 and 100 mg prednisone given orally on days 1–5 every 21 days for 6 cycles.

1.3.2 Clinical Pharmacokinetics

Rituximab likely acts synergistically with chemotherapy, in which case having therapeutic levels of rituximab throughout all cycles of therapy should be beneficial. Pharmacokinetic studies of rituximab used in R-CHOP-14 schedule showed that rituximab levels rise slowly and a plateau is attained only after 5 cycles [19]. Based on this observation, the German High Grade NHL Study Group (DSHNHL) evaluated the benefit of intensifying the rituximab dosing. This concept was combined with dose intensification of chemotherapy (R-CHOP-14). In the early phase of this DENSER-CHOP trial, increased infectious events occurred, but with increased supportive care in terms of prophylactic antimicrobials and PEG-filgrastim the regimen was felt to be safe and effective [20]. Nonetheless, this approach has not been generally adopted. This likely reflects the absence of data on its benefit, as well as the need for extensive antimicrobial prophylaxis and growth factor support, as well as observed and potential excess toxicity of the 14 day schedule.

1.4 Rationale

As described above, the addition of bortezomib appears to confer a higher response and median overall survival to DLBCL patients with the ABC compared to the GC subtype. However, a high incidence of neuropathy has limited the tolerability of bortezomib in combination with R-CHOP and can result in dose reductions [14]. To formally compare the benefit of bortezomib in combination with R-CHOP, there have been randomized phase III studies comparing R-CHOP ± bortezomib for DLBCL with the non-GC subtype (NCT00931918 in the U.S. and NCT01040871 in Europe).

Because the role of bortezomib in the upfront management of DLBCL is still unknown, there is considerable interest in exploring the benefit of carfilzomib in this setting, as this agent has no significant dose-limiting neuropathy. If the phase III studies of bortezomib show no advantage from the addition of this agent to the treatment of non-GC DLBCL, this may indicate lack of realization of the full potential therapeutic benefit of proteasome inhibition possibly due to neuropathy-related dose reductions. A positive result showing benefit from bortezomib would provide proof of principle for the use of proteasome inhibition in DLBCL and would suggest the potential for an even greater role for carfilzomib. Therefore, regardless of the outcome of current phase III studies of bortezomib in the upfront management for DLBCL, there is sound rational for exploring the effect of carfilzomib.

2.0 OBJECTIVES

2.1 Primary Objective (Phase I)

To determine the safety of carfilzomib in combination with R-CHOP (CR-CHOP) in patients with newly diagnosed DLBCL and identify a recommended phase II dose (RP2D).

2.2 Secondary Objectives (Phase II)

- To determine if CR-CHOP improves the rates of 1-year progression free survival (PFS) and overall survival (OS) in non-germinal center (non-GC) DLBCL patients relative to historical controls treated with R-CHOP
- To determine response rates (complete and partial remission) in non-GC DLBCL patients treated with CR-CHOP and compare to historical controls treated with R-CHOP.
- Because a proportion (~10%) of patients classified as non-GC by IHC algorithms may not have the ABC subtyped of DLBCL, an exploratory secondary objective will compare the PFS, OS and response rates of the ABC subgroup of patients with DLBCL as determined by the Gene Expression Profiling with those of the overall group of non-GC DLBCL.

3.0 STUDY DESIGN

3.1 Study Design Including Dose Escalation/Cohorts

Phase I

- The proposed study is a multi-institution, open-label, phase I/II study designed to evaluate the safety and efficacy of CR-CHOP for patients newly diagnosed DLBCL. Carfilzomib will be administered on days 1 and 2 of a 21 day cycle with standard dose R-CHOP for 6 cycles.

- Dose escalation proceeded using a standard 3 + 3 design as detailed in the Treatment Plan (Section 6.0). See schema on page 4 for details on dose escalation procedures used in Phase I.

Phase II

For the phase II portion of the study, 26 patients with newly diagnosed non-GC DLBCL will be treated with 6 cycles of CR-CHOP according to DL5 at **20** mg/m^2 days 1,2 of cycle 1 followed by **56** mg/m^2 days 1, 2 every 21 days for cycles 2-6 (per table above)

- Patients will be monitored for all adverse events.

- Response will be assessed by PET-CT after 6 cycles of therapy and on follow-up according to modified International Working Group criteria.

3.2 Number of Subjects

The phase I portion of other trial enrolled 24 patients in order to establish an RP2D. The phase II portion of the trial will enroll 26 non-GC DLBCL patients treated with CR-CHOP with carfilzomib at target doses of DL5, which has been found to be well tolerated without any DLT in phase I.

Assuming 24 of the 26 patients are evaluable, this number will be adequate to demonstrate an improvement in the 1-year PFS from 50% to 75% using a nonparametric (i.e., Kaplan-Meier) 2-sided time-to event (TTE) estimate with a significance of 5% and power of 80%. .

3.3 Replacement of Subjects

If a subject is withdrawn from the Phase I dose escalation cohort for any reason other than a DLT prior to completing the first 21 days of CR-CHOP treatment, a replacement subject will be enrolled and will be assigned to the same dose level.

If a subject is withdrawn from the Phase II study for reasons other than progressive disease prior to the cycle 2 assessments, a replacement subject may be enrolled as agreed upon by the sponsor and the investigators.

3.4 Expected Duration of Subject Participation

3.4.1 Duration of Therapy

- In the absence of treatment delays due to adverse events, treatment may continue for 6 cycles or until one of the following criteria applies:
  - Disease progression,
  - Intercurrent illness that prevents further administration of treatment,
  - The investigator considers it, for safety reasons, to be in the best interest of the patient,
  - Unacceptable treatment related toxicity, NCI CTC AE version 4.0 Grade 2, 3 or 4 that fails to recover to baseline or < Grade 3 in the absence of treatment within 4 weeks,
  - Any toxicity or other issue that causes a delay of study drug administration by more than 4 weeks,
  - General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator,
  - Patient decision to withdraw from treatment (partial consent) or from the study (full consent),
  - Pregnancy during the course of the study for a child-bearing participant
  - Death, or
  - Sponsor reserves the right to temporarily suspend or prematurely discontinue this study.

The date and reason for discontinuation must be documented. Every effort should be made to complete the appropriate assessments.

3.4.2 Duration of Follow Up

Patients will be followed for toxicity for 30 days after treatment has been discontinued or until death, whichever occurs first.

The clinical course of each event will be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause with a cut off of 24 months after completion of therapy.

Serious adverse events that are still ongoing at the end of the study period will necessitate follow-up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation will be recorded and reported immediately.

4.0 PATIENT SELECTION

Each of the criteria in the checklist that follows must be met in order for a patient to be considered eligible for this study. Use the checklist to confirm a patient's eligibility. The checklist must be completed for each patient and must be signed and dated by the treating physician.

Patient's Name:

_____

Medical Record #:

_____

Research Nurse /Study Coordinator Signature:

_____ **Date:** _____

Treating Physician [Print]:

_____

Treating Physician Signature: _____**Date** _____

4.1 Inclusion Criteria

_____ 4.1.1 Patients must have histologically confirmed diffuse large B-cell lymphoma (DLBCL). Patients with previously diagnosed indolent lymphoma (follicular lymphoma and marginal zone lymphoma but not small lymphocytic lymphoma) who have transformed to DLBCL are

eligible only if they have not previously been treated for indolent lymphoma.

4.1.2 Diagnosis of high grade B-cell lymphoma of non-germinal center subtype by Hans algorithm as outlined in Section 10.1.1.3.1.

_____ 4.1.3 Patients must have radiographically measurable disease.

_____ 4.1.4 Patients may have received brief (<15 days) treatment with glucocorticoids and/or 1 cycle of chemotherapy such as R-CHOP [or some component(s) thereof] for the diagnosis of B-cell lymphoma provided they had all necessary staging tests performed prior to R-CHOP including CT and/or PET/CT scans, echocardiogram and bone marrow biopsy. Treatment must occur within 60 days prior to enrollment.

Previous treatment ___YES _____ No
If Yes, Please List Treatment agents and dates:
_____

_____ 4.1.5 Age ≥18 years. Dosing or adverse event data are limited on the use of Carfilzomib in patients <18 years of age, therefore children are excluded from this study.

_____ 4.1.6 ECOG Performance status ≤ 2. Performance Status of 3 will be accepted if impairment is caused by DLBCL complications and improvement is expected once therapy is initiated. [See Appendix A].

_____ 4.1.7 Patient must have adequate hematologic, hepatic, and renal function as defined below:

_____ 4.1.7.1 Hemoglobin ≥ 7.0 g/dl
Hemoglobin: _____
Date of Test: _____

_____ 4.1.7.2 Absolute neutrophil count ≥1,500/mcL*
Absolute neutrophil count: _____
Date of Test: _____

_____ 4.1.7.3 Platelet count ≥ 100,000/mcL
Platelet count: _____
Date of Test: _____

_____ 4.1.7.4 Total bilirubin within normal institutional limits unless due to

Gilbert's disease
Total bilirubin: _____
Date of Test: _____

_____ 4.1.7.5 AST (SGOT) ≤ 2.5 X institutional upper limit of normal
AST (SGOT): _____
Date of Test: _____

_____ 4.1.7.6 ALT (SGPT) ≤ 2.5 X institutional upper limit of normal
ALT (SGPT): _____
Date of Test: _____

_____ 4.1.7.7 Creatinine clearance ≥45 mL/min calculated by Cockcroft-Gault or 24 hour collection
Creatinine clearance: _____
Date of Test: _____

_____ 4.1.8 Adequate cardiac function left ventricular ejection fraction (LVEF) > 50% as assessed by echocardiogram or MUGA (Multi Gated Acquisition Scan).

_____ 4.1.9 The effects of Carfilzomib on the developing human fetus are unknown. For this reason and because chemotherapeutic agents used in this study are known to be teratogenic, women of child-bearing potential and men must agree to use adequate contraception (double barrier method of birth control or abstinence) 2 weeks prior to initiation of treatment, for the duration of study participation and for 3 months after completing treatment. Should a woman become pregnant or suspect that she is pregnant while she or her partner is participating in this study, she should inform the treating physician immediately. Men must agree to refrain from sperm donation for at least 90 days after the last dose of carfilzomib.

_____ 4.1.10 Subjects must have the ability to understand and the willingness to sign a written informed consent document.

_____ 4.1.11 International Prognostic Index must be documented:
ECOG performance status ≥2 _____ (1 point)
Age ≥60 _____ (1 point)
≥2 extranodal sites _____ (1 point)
LDH > upper limit of normal _____ (1 point)
Ann Arbor Stage III or IV _____ (1 point)
Is there evidence of transformation from indolent lymphoma? _yes_no

4.2 **Exclusion Criteria**

The presence of any of the following will exclude a patient from study enrollment.

_____ 4.2.1 Patients who have not recovered from adverse events due to agents administered more than 4 weeks earlier.

_____ 4.2.2 Patients who are receiving any other investigational agents.

_____ 4.2.3 Known CNS involvement by lymphoma. Patients at high risk for secondary CNS involvement but without neurologic symptoms suspected to be due to lymphoma are allowed to be enrolled and receive intrathecal chemotherapy including but not limited to methotrexate, cytarabine and glucocorticoids. Patients who are enrolled and subsequently identified to have pathologic confirmation of CNS involvement by lymphoma may be continued on study at the discretion of the principal investigator.

_____ 4.2.4 History of allergic reactions attributed to compounds of similar chemical or biologic composition to Carfilzomib or other agents (R-CHOP) used in this study.

_____ 4.2.5 Active congestive heart failure (New York Heart Association [NYHA] Class III to IV), symptomatic ischemia, or conduction abnormalities uncontrolled by conventional intervention or myocardial infarction within four months prior to enrollment.

_____ 4.2.6 Patients with uncontrolled intercurrent illness including, but not limited to ongoing or active infection, or psychiatric illness/social situations that would limit compliance with study requirements.

_____ 4.2.7 Pregnant or breastfeeding women are excluded from this study because Carfilzomib is a proteasome inhibitor with the potential for teratogenic or abortifacient effects. Because there is an unknown, but potential risk for adverse events in nursing infants secondary to treatment of the mother with Carfilzomib, breastfeeding should be discontinued if the mother is treated with Carfilzomib. These potential risks may also apply to other agents used in this study.

_____ 4.2.8 HIV-positive patients on combination antiretroviral therapy are ineligible because of the potential for pharmacokinetic interactions with Carfilzomib. In addition, these patients are at increased risk of lethal infections when treated with marrow suppressive therapy. Appropriate studies will be undertaken in patients receiving combination antiretroviral therapy when indicated.

_____ 4.2.9 Other malignancies within the past 3 years except for adequately treated carcinoma of the cervix or basal or squamous cell carcinomas of the skin, or low-risk prostate cancer after curative therapy, or low risk melanoma if treated with definitive therapy (such as excision) and expected to have a low likelihood of recurrence.

_____ 4.2.10 Patients who have had major surgical procedures or significant traumatic injury within 28 days prior to study treatment.
Date of Last Major Surgery: _____
Scheduled Day 1 of Protocol Treatment: _____

_____ 4.2.11 Patients who are reported to be of direct Asian-Pacific (China, Japan, Taiwan, Singapore, Republic of Korea, and Thailand) ancestry.

*with sponsor approval ANC criteria may be waived in the case of excessive disease infiltration of bone marrow

4.3 Inclusion of Women and Minorities

Both men and women are eligible for this trial. Minorities will not be excluded, however, patients of direct Asian -Pacific (China, Japan, Taiwan, Singapore, Republic of Korea, and Thailand) ancestry treated with Carfilzomib are at increased risk of cardiovascular events and should be excluded from the study to ensure patient safety. If there are questions about the any individual patient's candidacy, the case should be discussed with the Principal Investigator.

5.0 REGISTRATION

All subjects who have been consented are to be registered in the OnCore Database. For those subjects who are consented, but not enrolled, the reason for exclusion must be recorded.

All subjects will be registered through Cleveland Clinic and will be provided a study number by contacting Research Coordinator, Jackie Tomer (tomerj2@ccf.org), at 216-444-9814 by submitting the patient's completed eligibility packet.

6.0 TREATMENT PLAN

Table 2: Treatment Regimen

Agent	Premedications/hydration	Dose	Route	Schedule	Cycle Length
					21 days
Rituximab (Give First)	Acetaminophen (650 mg) PO and diphenhydramine (50 mg) PO or IV, 30 -60 minutes prior to each infusion[1].	375 mg/m^2	IV	Day 2	
Carfilzomib	Dexamethasone 10 mg IV and 250 mL of normal saline IV before each carfilzomib dose on day 1 and 2.[2]	According to dose level[3]	IV	Day 1,2	
Cyclophosphamide	1 Liter normal saline IV before infusion	750 mg/m^2	IV	Day 3	
Doxorubicin	Ondansetron 8 mg IV	50 mg/m^2	IV	Day 3	
Vincristine	-NA-	1.4 mg/m^2 (max 2 mg)	IV	Day 3	
Prednisone	-NA-	100 mg	PO	Any time of day during Day 3-7	
Pegfilgrastim[4,5]	-NA-	6 mg	SC	Day 4	
Acyclovir	-NA-	400 mg	PO	Twice/day from cycle 1, day 1 – 6 months after completion of cycle 6	

1. Hydroxyzine may be substituted in patients intolerant of diphenhydramine.
2. Repeat saline infusion before Carfilzomib administration in subsequent cycles if clinical evidence of tumor lysis in cycle 1. Patients should be monitored for signs of volume overload (shortness of breath, lower extremity edema) during IV fluid infusion.
3. See carfilzomib dosing, Table 1.
4. Filgrastim 300 or 480 mcg IV/SC daily x 10 days (beginning on day 4) may be substituted if pegfilgrastim is unavailable.
5. ONPRO™ (On Body Injection) is acceptable mode of administration of pegfilgrastim.

Abbreviations: IV (intravenous), PO (oral), SC (subcutaneous).

6.1 Agent Administration

- Treatment may be administered on an inpatient or outpatient basis.
- Acyclovir prophylaxis against varicella zoster virus (VZV) is mandated for all patients. Appropriate dose modifications for Carfilzomib and R-CHOP are described in Section 7.0

- Reported adverse events and potential risks of Carfilzomib and R-CHOP are described in Section 8.0.
- No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.
- No intra-patient dose escalation is allowed.

6.1.1 Carfilzomib

Patients will receive Carfilzomib at the dose specified by the dose level on Days 1 and 2 on a 21 day cycle. Carfilzomib will be administered IV over 30 (+/-10) minutes and will be given after Rituximab.

6.1.2 R-CHOP

Use actual weight when calculating surface area. The start of treatment doses for all drugs can be used for all cycles unless the BSA changes by > 5% in which case doses must be re-calculated. Acetaminophen (650 to 1000 mg) PO and diphenhydramine (25 to 50 mg) PO or IV are to be administered 30 to 60 minutes prior to starting each infusion of rituximab. Hydroxyzine may be substituted in patients intolerant of diphenhydramine. Since transient hypotension may occur during rituximab infusion, consideration should be given to withholding anti-hypertensive medications 12 hours prior to rituximab infusion. An IV bolus of 1 liter normal saline is given before and after R-CHOP as hydration to prevent cyclophosphamide-induced hemorrhagic cystitis.

a. Prednisone 100 mg orally day 3 through 7 of subsequent cycles.
b. Rituximab 375 mg/m^2 IV on day 2 of each cycle (every 21 days)
c. Cyclophosphamide 750 mg/m^2 IV Day 3 of each cycle (every 21 days)
d. Doxorubicin 50 mg/m^2 IV Day 3 of each cycle (every 21 days)
e. Vincristine 1.4 mg/m^2 IV (Maximum dose = 2.0 mg) Day 3 of each cycle (every 21 days)
f. Pegfilgrastim 6 mg SC day 4 (every 21 days). Filgrastim 300 or 480 mcg IV/SC daily days 1-10 may be substituted if pegfilgrastim is not available.ONPRO™ is also an acceptable method of administration.

6.1.3 Acyclovir

Patients will take prophylactic acyclovir 400 mg PO bid beginning on cycle 1, day 1 and continuing until 6 months after completion of cycle 6.

6.2 **Definition of Dose-Limiting Toxicity**

Management and dose modifications are outlined in Section 7.

Dose limiting toxicity will be defined as any of the following AEs that occur during cycle 1 for dose levels -2, -1 and 1 or during cycles 1 and 2 for dose levels

2-5 of study treatment (CR-CHOP) with severity graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0:

- Grade ≥ 3 AST/ALT elevation [exceptions may be made for transient (i.e., lasting < 7 Days) Grade 3 elevations of ALT/AST in the presence of known liver involvement by lymphoma and without evidence of other hepatic injury, if agreed by the Principal Investigator; and/or
- Grade 3 or 4 non-hematologic toxicity (excluding fatigue or anorexia lasting < 7 days, or Grade 3 nausea and/or vomiting that persists for < 2 days following appropriate supportive care).

A DLT is defined as any of the following treatment-related AE that occurs during the first cycle for dose levels -2, -1, ; or first and second cycle for dose levels 2-5 graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0:

- Grade 4 neutropenia lasting ≥ 7 days;
- Grade 3 or 4 neutropenia complicated by fever ≥ 38.0°C or infection;
- Grade 4 thrombocytopenia;
- Grade 3 thrombocytopenia complicated by hemorrhage;
- Grade 4 anemia.

6.3 Dose Escalation

Dose escalation is not applicable for Phase II.

6.4 Duration of Therapy (See Section 3.4.1)

6.5 Duration of Follow-Up (see Section 3.4.2)

7.0 DOSING DELAYS / DOSE MODIFICATIONS

All scheduled visits will have a ±3-day window due to unanticipated or unavoidable scheduling conflicts. For hematologic or other toxicity in the opinion of the treating physician attributable to Carfilzomib but not described elsewhere in the protocol, the dose of Carfilzomib may be reduced, after discussion with the study PI.

7.1 Hematologic Toxicity

On the day of starting each cycle, hematologic (absolute neutrophil count, hemoglobin and platelet) parameters must have resolved to baseline or grade 1. If these criteria are not met, therapy will be held by 1 week increments for a maximum of 4 weeks. If treatment cannot be given during that time frame the patient will be removed from study.

Table 4: Management of Hematologic Toxicity (DAY 1, Cycles 2-6)		
Grade of Event	**Management/Next Dose for Carfilzomib**	**Management/Next Dose for R-CHOP**
ANC ≥ 1200, and platelets ≥ 75,000 on day 1 of new cycle	No change in dose	No change in dose
ANC <1200 or platelets <75,000 on day 1 of new cycle	Hold carfilzomib until ANC > 1200 and platelets > 75,000. Check CBC weekly. Resume carfilzomib at one dose level below current.	Hold until resolves. Resume at same dose level. No change in dose.
*Patients requiring a delay of >2 weeks can be treated with off-protocol therapy. **Patients requiring two dose reductions can be treated with off-protocol therapy.		

7.2 Non-Hematologic Toxicity

Grade 2-4 non-hematologic toxicity (except fatigue or anorexia lasting < 7 days or Grade 3 nausea and/or vomiting that persists for < 2 days following appropriate supportive care or non-clinically significant grade 3 electrolyte abnormalities that have been corrected) that is treatment-related must return to a grade 1 or better prior to continuing treatment. If these criteria are not met, therapy will be held for a maximum of 2 weeks. If treatment cannot be given during that time frame the patient will be removed from study.

Following resolution of toxicity to grade ≤1, toxicities deemed related to carfilzomib will require dose reduction to next dose level lower as in Table 1.

For toxicities deemed to be related to R-CHOP, dose reductions will be given as indicated below. In the case of recurrence of the specific grade 3-4 non-hematologic toxicity, the patient will be removed from study. In the case of recurrence of grade 2 non-hematologic toxicity, continuation on the study will be at the discretion of the principal investigator.

7.2.1 Neuropathy

Given the well-documented and relatively high incidence of vincristine-induced peripheral neuropathy, dose modification of vincristine can be performed any time during treatment at the discretion of the investigator in accordance with institutional practices.

7.2.2 Hemorrhagic Cystitis

Patients should be adequately hydrated prior to and after cyclophosphamide as detailed in the treatment plan (Section 6.1, Table 2) and should be instructed to void frequently. Should gross hematuria develop, cyclophosphamide will be withheld until resolution of cystitis. Subsequent cycles will be given at 50% of the initial

dose of cyclophosphamide for one cycle and, if tolerated, increased to 75% of the full dose for remaining cycles.

7.2.3 Cardiac monitoring

Patients will be monitored closes for clinical signs and symptoms of hypervolemia, pulmonary edema or indications of congestive heart failure or suspected cardiac event. If clinical suspicion arises, further evaluation is at the discretion of the investigator but may include EKG, N-terminal pro-brain natriuretic peptide (NTp-BNP) measurement and possibly echocardiogram. If cardiac assessment reveals significant changes from baseline in cardiac function or significant elevations in NTp-BNP, further dosing with carfilzomib and doxorubicin can only proceed after with approval from the principal investigator and the sponsor.

7.2.4 If PRES is suspected, hold carfilzomib. Consider evaluation with neuroradiological imaging, specifically MRI, for onset of visual or neurological symptoms suggestive of PRES. If PRES is confirmed, permanently discontinue carfilzomib. If the diagnosis of PRES is excluded, carfilzomib administration may resume at same dose, if clinically appropriate. If condition recurs, permanently discontinue carfilzomib.

7.2.5 If thrombotic microangiopathy (TTP/HUS) is suspected, hold carfilzomib and manage per standard of care including plasma exchange as clinically appropriate. If TMA is confirmed and related to carfilzomib, permanently discontinue carfilzomib. If the diagnosis is excluded, carfilzomib can be restarted at the previous dose. If the condition recurs, permanently discontinue carfilzomib.

7.2.6 Hepatic Toxicity

If the bilirubin is between 1.5 and 3.0 mg/dl on day 1 of any cycle 2-6, doxorubicin dose will be reduced by 25% and vincristine dose must be reduced by 50%. If the hepatic function has returned to normal by day 1 of the subsequent cycle, full doses will be given. If bilirubin is > 3.0 mg/dl, doxorubicin and vincristine should delayed in 1 week increments for up to 2 weeks until < 3.0 mg/dl and then given with the above dose reductions. If bilirubin remains > 3.0 mg/dl, the Study Monitor must be contacted and the Study PI (or designee) will be notified and the patient will be discontinued from therapy.

7.2.7 Rituximab Hypersensitivity/Infusion Reactions

Because rituximab is known to cause hypersensitivity and infusion reactions, it will be infused with graduated incremental rates depending on whether it is being given as an initial dose (cycle 1) or subsequent dose (2-6), per institutional guidelines. As the severity of infusion reactions increase, the infusion of rituximab will be either slowed or held, as indicated in the accompanying table.

Table 7: Management of Rituximab Hypersensitivity/Infusion Reactions	
Grade of Event	**Management/Next Dose for Rituximab**
Grade 1*	Decrease infusion rate by one dose level
Grade 2*	Hold until ≤ Grade 1. The infusion can be resumed at one-half the previous rate when symptoms abate.
Grade 3*	Hold until ≤ Grade 1. The infusion can be resumed at one-half the previous rate when symptoms abate.
Grade 4**	Off protocol therapy.**
*Treatment of infusion-related symptoms with diphenhydramine and acetaminophen is recommended. Additional treatment with bronchodilators or IV saline may be indicated. **Epinephrine for subcutaneous injection, diphenhydramine hydrochloride for IV injection, corticosteroids as needed and resuscitation equipment for the emergency management of anaphylactic reactions will be available at the bedside prior to rituximab administration.	

Following the antibody infusion, the intravenous line should be maintained for medications as needed. If there are no complications after one hour of observation, the intravenous line may be discontinued.

In patients with detectable circulating lymphoma cells, it is strongly advised that the initial rituximab infusion rate be reduced to 25 mg/hr; these patients may experience more frequent and severe transient fever and rigors, shortness of breath, and hypotension. In patients with > 15,000 circulating lymphoma cells it is advisable to administer rituximab 100 mg total dose 1 day prior to the first scheduled rituximab (day -1), the remainder of the rituximab dose on day 0 and the full calculated dose beginning on day 1 of the study. IV dexamethasone premedication may be useful on days -1 and 0. For patients with > 50,000 circulating lymphoma cells contact the QA Specialist / Study Monitor, who will notify the Study Principal Investigator (PI) at registration prior to administration of rituximab for dose planning.. The PI (or designee) will develop with the treating physician a plan to incorporate additional pre-medications and fractionated rituximab dosing prior to day 1.

7.2.8 Non-Hematologic Toxicity attributable to doxorubicin and/or cyclophosphamide, excluding suspected carfilzomib toxicity, neuropathy, rituximab reactions, and hemorrhagic cystitis.

If non-hematologic toxicity is deemed to be due to the components of R-CHOP rather than carfilzomib and is not neuropathy, a rituximab reaction or hemorrhagic cystitis, the doses of doxorubicin and cyclophosphamide will be modified as indicated below.

If the investigator cannot determine whether non-hematologic toxicities are due to carfilzomib or R-CHOP, it will be assumed that they are due to carfilzomib and reduce the dose of this drug by one dose level as indicated in section 3.1, Table 1.

Table 8: Management of Non-Hematologic Toxicity attributable to R-CHOP, excluding suspected carfilzomib toxicity, neuropathy, rituximab reactions and hemorrhagic cystitis.			
Event Grade	**Management/Next Dose for Doxorubicin**	**Management/Next Dose for Cyclophosphamide**	**Management/Next Dose for Vincristine**
≤ Grade 1	No change in dose	No change in dose	No change in dose.
Grade 2	Hold until ≤ Grade 1 unless symptoms were not optimally medically managed. Resume at same dose level.	Hold until ≤ Grade 1. Resume at same dose level.	No change in dose.
Grade 3	Hold Doxorubicin until < Grade 2.* Resume at 75% of previous dose.**	Hold Cyclophosphamide until < Grade 2.* Resume at 75% previous dose.**	No change in dose
Grade 4	Discontinue Doxorubicin and treat patient with off protocol therapy.	Discontinue Cyclophosphamide and treat patient with off protocol therapy.	Discontinue vincristine and treat patient with off protocol therapy.
*Patients requiring a delay of >2 weeks should go off protocol therapy. **Patients requiring two dose reductions should go off protocol therapy.			

8.0 ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

The following is a list of AEs (Section 8.1) and the reporting requirements associated with observed AEs (Sections 8.3 and 8.4).

The clinical course of each event will be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause.

Serious adverse events (SAEs) that are still ongoing at the end of the study period will necessitate follow-up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation will be recorded and reported immediately.

8.1 Adverse Events and Potential Risks

8.1.1 Carfilzomib

Toxicities include cardiac arrest, new onset or worsening of pre-existing congestive heart failure, pulmonary arterial hypertension, infusion reactions (characterized by a spectrum of systemic symptoms including fever, chills, arthralgia, myalgia, facial flushing, facial edema, vomiting, weakness, shortness of breath, hypotension, syncope, chest tightness, or angina), tumor lysis syndrome, hemorrhage, thrombocytopenia, hepatic toxicity and hepatic failure, increase in blood creatinine, renal failure, peripheral neuropathy, thorombotic microangiopathy (including hemolytic uremic syndrome and thrombotic thrombocytopenic purpura), posterior reversible encephalopathy syndrome, venous thromboembolism and herpes zoster reactivation

8.1.2 Cyclophosphamide

Toxicities include 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.

8.1.3 Doxorubicin

Toxicities include 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.

8.1.4 Pegfilgrastim

Toxicities include rare anaphylactic reactions with the first dose; bone pain at sites of active marrow with continued administration. Local reactions at injection sites. Constitutional symptoms, increased alkaline phosphatase, LDH, uric acid; worsening of pre-existing inflammatory conditions. Please refer to the package insert for a complete listing of all toxicities.

8.1.5 Prednisone

Toxicities include insomnia, agitation, 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.

8.1.6 Rituximab

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. Other reactions include tumor lysis syndrome, cytopenias including prolonged pancytopenia, marrow hypoplasia, and late onset neutropenia. There is an increased rate of infectious events, hepatitis B reactivation. Please refer to the package insert for a complete listing of all toxicities.

8.1.7 Vincristine

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

8.1.8 Acyclovir

Toxicities include neurologic toxicity including agitation, tremors, delirium, hallucinations, and myoclonus, with higher risk in patient with renal insufficiency. Please refer to package insert for a complete listing of all toxicities.

8.1.9 Use of contraception – Females

Females of childbearing potential should be advised to avoid becoming pregnant while being treated with carfilzomib. Given that carfilzomib was clastogenic in the in vitro chromosomal aberration test in peripheral blood lymphocytes, as a precaution, females of childbearing potential and/or their male partners should use effective contraception methods or abstain from sexual activity during and for 30 days after treatment with carfilzomib. If pregnancy occurs during this time, patients should be apprised of the potential hazard to the fetus.

Based on its mechanism of action and findings in animals, carfilzomib can cause fetal harm when administered to a pregnant woman. Carfilzomib caused embryo-fetal toxicity in pregnant rabbits at doses that were lower than in subjects receiving the recommended dose. Carfilzomib administered to pregnant rats and rabbits during the period of organogenesis was not teratogenic at doses up to 2 mg/kg/day in rats or up to 0.8 mg/kg/day in rabbits. If carfilzomib is used during pregnancy, or if the subject becomes pregnant while taking this drug, she should inform the investigator or study staff immediately. The investigator should notify Amgen of the pregnancy and discuss follow-up with the subject. It is not known if carfilzomib will reduce the efficacy of oral contraceptives. Due to an increased risk of venous thrombosis associated with carfilzomib, subjects currently using oral contraceptives or a hormonal method of contraception associated with a risk of thrombosis should consider an alternative method of effective contraception.

8.1.10 Use of contraception – Males

Males of reproductive potential should be advised to avoid fathering a child while being treated with carfilzomib. The potential for carfilzomib to be transferred via semen and its effect on sperm are unknown. Male subjects treated with carfilzomib and/or their female partners (if of childbearing potential) should use effective contraceptive methods or abstain from sexual activity while treated with carfilzomib and for 90 days after treatment. If pregnancy occurs during this time, patients should be apprised of the potential hazard to the fetus.

Male subjects should be advised to inform the investigator or study staff immediately in the event that their female partner becomes pregnant during the study. Upon receipt of this information, the investigator should notify Amgen of the pregnancy and discuss follow-up regarding the pregnancy outcome with the subject.

8.2 Definitions

8.2.1 Adverse Events (AEs)

An adverse event (AE) is any unfavorable or unintended event, physical or psychological, associated with a research study, which causes harm or injury to a research participant as a result of the participant's involvement in a research study. The event can include abnormal laboratory findings, symptoms, or disease associated with the research study. The event does not necessarily have to have a causal relationship

with the research, any risk associated with the research, the research intervention, or the research assessments.

Adverse events may be the result of the interventions and interactions used in the research; the collection of identifiable private information in the research; an underlying disease, disorder, or condition of the subject; and/or other circumstances unrelated to the research or any underlying disease, disorder, or condition of the subject. In general, adverse events that are at least partially the result of (a) or (b) would be considered related to the research, whereas adverse events solely related to (c) or (d) would be considered unrelated to the research.

8.2.2 Significance of AEs

External adverse events are adverse events experienced by subjects enrolled in multicenter clinical trials at sites other than the site(s) over which the Institutional Review Board has jurisdiction. **Internal adverse events** are adverse events experienced by subjects enrolled at the site(s) under the IRB's jurisdiction for either multicenter or single-center research projects. The significance of AEs is used to describe the patient/event outcome or action criteria associated with events that pose a threat to a patient's life or functioning (i.e., moderate, severe or life threatening). Based on the National Cancer Institute Guidelines for the Cancer Therapy Evaluation Program, severity can be defined by the following grades of events:

- **Grades 1** are mild adverse events. (e.g., minor event requiring no specific medical intervention; asymptomatic laboratory findings only; marginal clinical relevance)

- **Grades 2** are moderate adverse events (e.g., minimal intervention; local intervention; non-invasive intervention; transfusion; elective interventional radiological procedure; therapeutic endoscopy or operation).

- **Grades 3** are severe and undesirable adverse events (e.g., significant symptoms requiring hospitalization or invasive intervention; transfusion; elective interventional radiological procedure; therapeutic endoscopy or operation).

- **Grades 4** are life threatening or disabling adverse events (e.g., complicated by acute, life-threatening metabolic or cardiovascular complications such as circulatory failure, hemorrhage, sepsis; life–threatening physiologic consequences; need for intensive care or emergent invasive procedure; emergent interventional radiological procedure, therapeutic endoscopy or operation).

- **Grades 5** are fatal adverse event resulting in death.

8.2.3 Serious Adverse Events (SAEs)

- A serious adverse event (SAE) is any adverse experience occurring at any dose that results in any of the following outcomes:
    - Results in death.
    - Is a life-threatening adverse experience. The term life-threatening in the definition of serious refers to an adverse event in which the subject was at risk of death at the time of the event. It does not refer to an adverse event which hypothetically might have caused death if it were more severe.
    - Requires inpatient hospitalization or prolongation of existing hospitalization. Any adverse event leading to hospitalization or prolongation of hospitalization will be considered as serious, UNLESS at least one of the following expectations is met:
        - The admission results in a hospital stay of less than 12 hours OR
        - The admission is pre-planned (i.e., elective or scheduled surgery arranged prior to the start of the study) OR
        - The admission is not associated with an adverse event (e.g., social hospitalization for purposes of respite care.
        - However it should be noted that invasive treatment during any hospitalization may fulfill the criteria of "medically important" and as such may be reportable as a serious adverse event dependent on clinical judgment. In addition where local regulatory authorities specifically require a more stringent definition, the local regulation takes precedent. Results in persistent or significant disability/incapacity. The definition of disability is a substantial disruption of a person's ability to conduct normal life's functions.
    - Is a congenital anomaly/birth defect
    - Is an important medical event. Important medical events that may not result death, be life-threatening, or require hospitalization may be considered a serious adverse 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 disease or disorders, or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

8.2.4 Expectedness

An expected adverse event is an event previously known or anticipated to result from participation in the research study or any underlying disease, disorder, or condition of the subject. The event is usually listed in the Investigator Brochure, consent form or research protocol.

An unexpected adverse event is an adverse event not previously known or anticipated to result from the research study or any underlying disease, disorder, or condition of the subject.

8.2.5 Attribution

Attribution is the relationship between an adverse event or serious adverse event and the study drug. Attribution will be assigned as follows:

- Definite – The AE is clearly related to the study drug.
- Probable – The AE is likely related to the study drug.
- Possible – The AE may be related to the study drug.
- Unlikely – The AE is doubtfully related to the study drug.
- Unrelated – The AE is clearly NOT related to the study drug.

8.3 Reporting Procedures for All Adverse Events

All participating investigators will assess the occurrence of AEs throughout the subject's participation in the study. Subjects will be followed for toxicity for 30 days after treatment has been discontinued or until death, whichever occurs first. The clinical course of each event will be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause.

The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject which occur after the subject has signed the informed consent are fully recorded in the subject's case report form, subject's medical records, and/or any other institutional requirement. Source documentation must be available to support all adverse events.

A laboratory test abnormality considered clinically relevant (e.g., causing the subject to withdraw from the study), requiring treatment or causing apparent clinical manifestations, or judged relevant by the investigator, should be reported as an adverse event.

The investigator will provide the following for all adverse events:

- Description of the event
- Date of onset and resolution
- Grade of toxicity
- Attribution of relatedness to the investigational agent
- Action taken as a result of the event
- Outcome of event

In this study, descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 available at http://ctep.cancer.gov will be utilized for AE reporting.

Investigative sites will report adverse events to their respective IRB according to the local IRB's policies and procedures in reporting adverse events.

SERIOUS ADVERSE EVENT REPORTING AND DOCUMENTATION REQUIREMENTS

The Investigator-sponsor must be notified of the occurrence of any SAE within 24 hours of the investigator, designee, or site personnel's knowledge of the event. The Investigator-sponsor is responsible for notifying the appropriate health authorities (HAs), ethics committees (ECs), and investigators, of any expedited, annual, or other periodic safety reports in accordance with applicable regulations. Any safety report submission will cross reference the Amgen investigational new drug (IND) or clinical trial approval (CTA) number.

The Investigator is also responsible for notifying the local ECs in accordance with local regulations. Additionally, the Investigator-sponsor is responsible for reporting SAEs to Amgen as described in SAE Reporting by Investigator-sponsor toAmgen.

8.4 Serious Adverse Event Reporting Procedures

Serious adverse events that occur beginning with the signing of the informed consent form, during treatment, or within 30 days of the last dose of treatment must be reported to the Cleveland Clinic Principal Investigator.

Investigative sites will report serious adverse events to their respective IRB according to the local IRB's policies and procedures in reporting serious adverse events.

8.4.1 SAE Reporting by Investigator-Sponsor to Amgen

The Investigator-sponsor must inform Amgen in writing by e-mail or fax at the contact information listed below for all SUSARs that are judged as reasonably related to the Amgen study drug. Site will transmit the final CIOMS of that event to Amgen within twenty-four (24) hours of submitting the report to the applicable regulatory authority.

For regulatory reporting purposes, an event of "Death, Cause Unknown" from the study shall be processed as a SUSAR. All forms must be completed and provided to Amgen in English.

The Individual Case Safety Report (ICSR) may be referred to as an individual safety report or SAE Report, including Pregnancy Exposure Reports and Follow up Reports. The ICSR must be as complete as possible, at a minimum including event reference number, protocol name and number, investigator contact information, specific patient identifiers (e.g., initials, patient number, date of birth or age, or gender), the name of the suspect Study Drug, the date and dosage(s) of exposure, event, the date(s) of event, country of event, "Serious" Criteria, Relationship/causality of Study Drug, Hospitalization history for the event, Event status/outcome, Relevant history (including diagnostics, laboratory values, radiographs, concomitant medications, and event treatment, and narrative summary.

Sponsor shall be responsible for collecting all SAEs and Pregnancy and Lactation Exposure Reports and will exercise commercially reasonable due diligence to obtain follow-up information on incomplete SAE or Pregnancy and Lactation Exposure Reports. In the event that the Company requires clarification or further information on individual SAE or Pregnancy and Lactation Exposure Reports, Company will not contact non-party investigators directly, but will route all such inquiries through Sponsor for forwarding to such investigator(s). Sponsor will be responsible to ensure such inquiries are completed and timely provided to Company.

Information not available at the time of the initial report (e.g., an end date for the SAE, discharge summaries, lot numbers, relevant laboratory values, scan data and autopsy reports) which are received after the initial report must be documented on a follow-up form, and submitted to Amgen in the same timelines as outlined above. Sponsor shall be responsible for obtaining follow-up information for the SAEs and demonstrate diligence in attempting to obtain such information by, among other things, maintaining written records of such attempts.

Other aggregate analysis including reports containing safety data generated during the course of the study is to be submitted to Amgen at the time the sponsor ISS submits to anybody governing research conduct i.e. RA, IRB etc. Final study report including unblinding data when applicable and reports of unauthorized use of a marketed product to be submitted to Amgen at the time the sponsor ISS submits to anybody governing research conduct i.e. RA, IRB etc. but not later than one calendar year of study completion.

Sponsor will provide an annual IND report to Amgen. Reports containing safety data generated during the course of the study is to be submitted to Amgen at the time the sponsor submits to anybody governing research conduct, i.e. regulatory authorities and IRBs. Sponsor will support reconciliation of all ICSRs at the end of the study at a minimum.

Pregnancy Reporting by Investigator-sponsor to Amgen

Report Pregnancy and potential infant exposure including Lactation, within ten (10) calendar days of Sponsor awareness. Provide to Amgen the SAE reports associated with pregnancy. SUSARs are to be reported within twenty-four (24) hours of submitting the report to the applicable regulatory authority.

Carfilzomib should not be characterized as an abortifacient.

To report an SAE or other safety related information to Amgen please use:

Drug Safety Reporting Phone Number:
888-814-8653 (U.S. Toll-Free);
805-480-9205 (Toll);
Email: svg-ags-in-us@amgen.com.

The SAE transmittal form is included as an appendix at the end of the protocol The lead study coordinator (Jackie Tomer) will be responsible for reporting all SAE's to Amgen.

8.4.3 Multi-Center Trials with Cleveland Clinic Investigator as Principal Investigator

For multi-site trials where a Cleveland Clinic investigator is serving as the Principal Investigator, each participating investigator is required to abide by the reporting requirements set by the protocol.

Participating investigators must report all serious adverse events that occur after the subject has signed the informed consent form to the Cleveland Clinic Principal Investigator within 24 hours of discovery or notification of the event. Initial serious adverse event information and all amendments or additions must be recorded on **FDA Form 3500A for mandatory reporting (Medwatch).** Relevant medical records should be faxed as soon as they become available. The Cleveland Clinic Principal Investigator will review and assess the SAE and follow the reporting requirements in Section 8.4.1 and 8.4.2 and communicate results to all investigational sites. The participating investigator must provide follow-up information on the SAE. Report Serious Adverse Events by email to cancersaeinbox@ccf.org and CC the Sponsor-Investigator hillb2@ccf.org and lead study coordinator.

Serious adverse events occurring after conclusion of the study AND thought to be possibly related to the investigational agent will be collected and reported within 24 hours of discovery or notification of the event.

Each investigative site will be responsible to report SAEs that occur at that institution to their respective IRB. It is the responsibility of each participating investigator to report serious adverse events to the study sponsor and/or others as described above

8.5 Data Safety Toxicity Committee

It is the Case Comprehensive Cancer Center's Principal Investigator's responsibility to ensure that ALL serious adverse events are reported to the Case Comprehensive Cancer Center's Data Safety Toxicity Committee. This submission is simultaneous with their submission to the Sponsor or other Regulatory body.

9.0 PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational or commercial agents administered in this study can be found in Section 8.

9.1 Carfilzomib

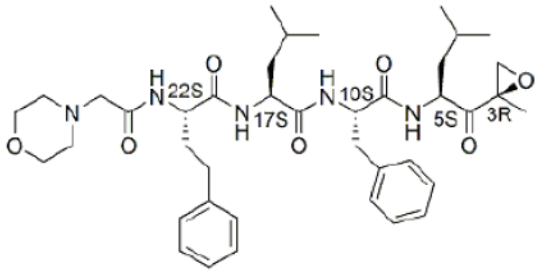
Chemical Name: (2S)-N-((S)-1-((S)-4-methyl-1-((R)-2-methyloxiran-2-yl)-1-oxopentan-2ylcarbamoyl)-2-phenylethyl)-2-((S)-2-(2-morpholinoacetamido)-4-phenylbutanamido)-4methylpentanamide.

Other Names: Formerly referred to as PR-171

Classification: Proteasome Inhibitor, Anti-neoplastic Agent.

Molecular Formula: $C_{40}H_{57}N_5O_7$

Chemical Structure:



Mode of Action: Inhibitor of the chymotrypsin-like activity of the 20s proteasome

Metabolism:

Carfilzomib is rapidly and extensively metabolized following IV administration to rats, monkeys, and humans. The predominant metabolites are peptide fragments and the diol of carfilzomib, with no unique metabolites identified in humans, suggesting that peptidase cleavage and epoxide hydrolysis are the principal pathways of metabolism in all these species. The metabolites do not inhibit proteasome activity. Cytochrome P450-mediated pathways are not significant in the overall metabolism of carfilzomib.

Carfilzomib is also rapidly metabolized by peptidases and expoxide hydrolases in vitro upon incubation with rat blood and tissue homogenates derived from the lung, kidney, and liver, further corroborating the extrahepatic mechanisms of metabolism *in vivo*.

The volume of distribution at steady state (Vss) was 0.3–2 L/kg and 0.3–1.1 L/kg for rats and monkeys, respectively. Due to metabolism in a variety of tissues and the irreversible covalent binding of carfilzomib to the 20S proteasome, the Vss values may underestimate the extent of tissue distribution of carfilzomib. Potent proteasome

inhibitory effects in a variety of tissues following IV administration to rats at different dose levels, and detection of radioactivity in a variety of tissues with an IV administration of [^{3}H-Phe]-carfilzomib to rats at 2 mg/kg (12 mg/m^2), indicated rapid and wide distribution of carfilzomib to tissues, except brain.

An *in vitro* protein-binding study using equilibrium dialysis demonstrated that approximately 97% of carfilzomib is bound to human plasma proteins, which is similar to rats and monkeys. Cytochrome P450-mediated pathways are not significant in the overall metabolism of carfilzomib.

Elimination

Excretion of [^{3}H-Phe]-carfilzomib was determined by quantitative whole-body autoradiography in rats receiving a single IV bolus administration of 2 mg/kg (12 mg/m^2). Urine and feces accounted for 14.1% and 18% of the dosed radioactivity, respectively, at 168 hours post-dose. Approximately 44% of the administered radioactivity remained in tissues, indicating slow elimination of drug-derived radioactivity, likely due to incorporation of ^{3}H-phenylalanine into cellular proteins. Excretion was also determined in bile duct-cannulated rats following a single IV bolus administration of 2 mg/kg. Carfilzomib was excreted mainly in the form of metabolites with less than 1% of the dose excreted intact. About 57% of the dose was recovered within 24 hours of dosing in both bile and urine samples. The limited recovery was likely due to target binding in cells unable to synthesize new proteasomes (e.g., red blood cells [RBCs]) and peptidic metabolites that cannot be differentiated from endogenous components.

Product description:

Carfilzomib for Injection will be provided as a sterile frozen liquid or lyophilized powder containing carfilzomib for administration as a slow IV push. Both the frozen and reconstituted lyophilized presentations are equivalent in quantitative composition, which consists of 2 mg/mL solution of carfilzomib Free Base in 10 mM sodium citrate buffer (pH 3.5) containing 10% (w/v) sulfobutylether-β-cyclodextrin (SBE-β-CD, Captisol®). Individually cartoned single-use vial contain a dose of 60 mg of carfilzomib as a white to off-white lyophilized cake or powder. Carfilzomib vials contain no antimicrobial preservatives and are intended only for single use.

Stability:

Unopened vials of carfilzomib are stable until the date indicated on the package when stored in the original package at 2°C to 8°C (36°F to 46°F). Retain carfilzomib in the original package to protect from light. The reconstituted solution contains carfilzomib at a concentration of 2 mg/mL. When refrigerated (2° - 8° C; 36° - 46°F), the reconstituted drug is stable for 24 hours in a vial, syringe or IV bag with 5% dextrose in water (D5W). At room temperature ((15° - 30° C, 59° - 86° C), thee reconstituted drug is stable for 4 hours in a vial, syringe or IV bag in D5W.

Route of administration*:*

Carfilzomib for Injection is administered as a slow IV push for a period of up to 30 minutes. Subjects should have a dedicated line for drug administration whenever possible. The line must be flushed with 20 cc of normal saline immediately before and after drug administration. If a dedicated line is not possible, the existing infusion line must be flushed with a minimum of 20 cc of normal saline before and after drug administration.

Each dose will consist of Carfilzomib for Injection administered on a mg/m2 basis, and should be based on the subject's actual calculated body surface area (BSA) at baseline. Subjects with a BSA > 2.2 m^2 will receive a dose based upon a 2.2 m^2 BSA. Subjects should be well hydrated prior to dosing with carfilzomib.

Drug Procurement:

Carfilzomib will be supplied for this study by Amgen, Inc.

Drug Accountability: The investigator or designated study personnel are responsible for maintaining accurate dispensing records of the study drug. All study drugs must be accounted for, including study drug accidentally or deliberately destroyed. Under no circumstances will the investigator allow the investigational drug to be used other than as directed by the protocol. If appropriate, drug storage, drug dispensing, and drug accountability may be delegated to the pharmacy section of the investigative site.

Drug Destruction: At the completion of the study, there will be a final reconciliation of drug shipped, drug consumed, and drug remaining. This reconciliation will be logged on the drug reconciliation form, signed and dated. Any discrepancies noted will be investigated, resolved, and documented prior to return or destruction of unused study drug. Drug destroyed on site will be documented in the study files.

9.2 Cyclophosphamide

Chemical Name:	2-[bis(2-chloroethyl)amino]tetrahydro-2H-1,3,2-oxazaphosphorine 2-oxide monohydrate.
Other Names:	Cytoxan™
Classification:	Nitrogen Mustard, Antineoplastic Agent
Molecular Formula:	molecular formula $C_7H_{15}Cl_7N_2O_2P \cdot H_2O$
Mode of Action:	An activated form of cyclophosphamide, phosphoramide mustard, alkylates or binds with many intracellular molecular structures, including nucleic acids. Its cytotoxic action is primarily due to cross-linking of

strands of DNA and RNA, as well as to inhibition of protein synthesis.

Metabolism:

Absorption: Systemic: Bioavailability: > 75%
Metabolism: Systemic: Hepatic
Excretion Systemic: Renal, 5 to 25% unchanged. In dialysis: cyclophosphamide is dialyzable. Systemic: Renal: 5 to 25% unchanged
Elimination Half Life

Systemic: Unchanged drug—3 to 12 hours.
Systemic: 3 to 12 h

Product description: white crystalline powder

Solution preparation: reconstitute with NS to inject directly , (infusion) dissolve in Sterile Water for Injection, USP (25 mL for 500 mg, 50 mL for 1 g, 100 mL for 2 g); then dilute in D5W, 5% dextrose in 0.9% normal saline (D5NS) or lactated ringers (D5LR or LR**).**

Storage requirements*:* Storage at or below 77°F (25°C) is recommended; this product will withstand brief exposure to temperatures up to 86°F (30°C) but should be protected from temperatures above 86°F (30°C).

Stability: Reconstituted lyophilized cyclophosphamide is chemically and physically stable for 24 hours at room temperature or for six days when refrigerated.

Route of administration*:* Short intravenous infusion over 30-60 minutes.

Drug Procurement: Cyclophosphamide must be obtained from commercial sources.

9.3 **Doxorubicin**

Chemical Name: 14-Hydroxydaunomycin

Other Names: Doxorubicin Hydrochloride

Classification: Anthracycline, Antineoplastic Agent

Molecular Formula: $C_{27}H_{29}NO_{11}$

Mode of Action: DNA intercalation

Metabolism:

A) Distribution Sites
   1) Protein Binding: 74% to 76%
   2) Other Distribution Sites
   Placenta: Placenta concentrations of doxorubicin were 1.2nmol/g of tissue when a single patient received doxorubicin about 48 hours before delivery. Umbilical cord concentrations were 0.08 nmol/g in the same patient.

B) Distribution Kinetics
   1) Distribution Half-Life: 5 minutes
   2) Volume of Distribution: 20 to 30 liters/kilogram

C) Metabolism Sites and Kinetics
   Liver, extensive Changes in liver function caused by hepatocellular carcinoma result in elevated plasma concentrations of doxorubicinol rather than doxorubicin [21].

D) Metabolites
   1) Doxorubicinol, active.
   2) Adriamycine aglycones.

E) Kidney
   1) Renal Excretion: 5% to 12%
   2) Only 1% appears in the urine over 5 days; less than 1% appears in the urine as aglycones [22].

F) Other
   (1) Bile, 40% and (2) Feces, 50% [23].

G) Parent Compound
   1) Elimination Half-life: 20 to 48 hours.

H) Metabolites: Doxorubicinol, 20 to 48 hours.

Product description:

Doxorubicin Hydrochloride Injection is a sterile parenteral, isotonic solution in either single dose of multi-dose vials.

Solution preparation:

After reconstitution, solution is stable at room temperature for 7 days and in the refrigerator between 2 and 8 degrees C for 15 days. Protect from sunlight.

Storage requirements*:*

Store powder at controlled room temperature between 15 and 30 degrees C (59 and 86 degrees F). Store in original carton to protect from light. Discard any unused portion

Stability:

Doxorubicin 8 mg/500 mL in glucose 5% was stable for 7 days when stored in PVC (polyvinyl chloride) bags at 4 degrees C with light protection. There was also no loss of doxorubicin when infused via PVC infusion bags with PVC administration.

Doxorubicin 2 mg/mL was stable for up to 14 days at 3 or 23 degrees C and for an additional 28 days at 30 degrees C in portable pump reservoirs.

Doxorubicin was stable (less than 10% loss of potency) for 24 days in 0.9% sodium chloride stored at 25 degrees C in PVC (polyvinyl chloride) mini bags and syringes at a pH of 6.47. Also, doxorubicin was stable for at least 43 days in 0.9% sodium chloride (pH, 6.47) and 5% dextrose (pH, 4.36) at 4 and -20 degrees C.

Although doxorubicin does react with aluminum, the reaction is slow and does not result in a substantial loss of potency [263]. Doxorubicin reconstituted with 0.9% sodium chloride injection or sterile water for injection to a concentration of 2 mg/mL and combined with steel, plastic, or aluminum was examined for color, pH, and potency. In the first 24 hours, pH changed from 4.8 to 4.9 in solutions containing plastic or steel. In the aluminum-containing solution, the pH changed from 4.8 to 5.2 and the solution changed to a darker ruby red. There was no change in potency in any of the solutions containing steel and aluminum, respectively. No precipitation was noted; therefore, doxorubicin may be safely injected through an aluminum-hubbed needle. However, reconstituted doxorubicin should not be stored in syringes capped with aluminum-hubbed needles.

Route of administration*:*

(1). For IV use only; do not administer IM or subcutaneously (SC)

(2). Administer slowly into freely running IV of Sodium Chloride Injection, USP or D5W over not less than 3 to 5 minutes, depending on the size of the vein and the dosage; avoid veins over joints or those with poor drainage; Butterfly(R) needle inserted into a large vein is preferable.

(3). Care should be taken to avoid extravasation as severe local tissue necrosis will occur; extravasation may occur with or without burning or stinging, and even if there is blood return on aspiration of the needle(4). If extravasation is suspected, immediately stop administration and restart in another vein; intermittently apply ice to the site for 15 minutes, 4 times daily for 3 days.

Drug Procurement: Doxorubicin must be obtained from commercial sources.

9.4 **Pegfilgrastim**

Chemical Name:	N-(3-hydroxypropyl)methionylcolony-stimulating factor (human), 1-ether with α-methyl-ω-hydroxypoly(oxyethylene)
Other Names:	Neulasta™, recombinant methionyl human granulocyte colony-stimulating factor (G-CSF)
Classification:	Hematopoietic Growth Factor
Molecular Formula:	$C_{849}H_{1348}N_{223}O_{244}S_9•(C_2H_4O)_n$
Mode of Action:	Biosynthetic hematopoietic agent that affects the proliferation and differentiation of neutrophils within bone marrow.
Metabolism:	Renal. Neutrophil receptor binding is an important factor in pegfilgrastim clearance. Serum clearance is related to the number of circulating neutrophils; serum concentrations of the drug decline rapidly with resolution of neutropenia.

Product description:

Pegfilgrastim is provided in a dispensing pack containing one syringe.

Solution preparation:

Pegfilgrastim is supplied as a preservative- free solution containing 6 mg (0.6 mL) at a concentration of 10 mg/mL in a single-dose syringe with a 27 gauge, 1/2 inch needle with an UltraSafeÒ Needle Guard.

Storage requirements*:*

Pegfilgrastim should be stored refrigerated at 2° to 8°C (36° to 46°F); syringes should be kept in their carton to protect from light until time of use. Shaking should be avoided. Before injection, pegfilgrastim may be allowed to reach room temperature for a maximum of 48 hours but should be protected from light..

Stability:

Pegfilgrastim left at room temperature for more than 48 hours should be discarded. Freezing should be avoided; however, if accidentally frozen, pegfilgrastim should be allowed to thaw in the refrigerator before administration. If frozen a second time, pegfilgrastim should be discarded.

Route of administration: Subcutaneous injection

Drug Procurement:
Pegfilgrastim will be obtained from commercial sources.

9.5 Prednisone

Chemical Name: 17, 21-dihydroxypregna-1, 4-diene-3,11,20-trione

Other Names: N/A

Classification: Adrenal Glucocorticoid, Immune Suppressant

Molecular Formula: $C_{21}H_{26}O_5$

Mode of Action: Prednisone is an adrenocortical steroid with salt-retaining properties. It is a synthetic glucocorticoid analog, which is mainly used for anti-inflammatory effects in different disorders of many organ systems. It causes profound and varied metabolic effects, modifies the immune response of the body to diverse stimuli and is also used as replacement therapy for adrenocortical deficient patients .

Metabolism:

Absorption

A) Bioavailability
1) Oral, regular release: 92%

Distribution

A) Distribution Sites
1) Protein Binding 70%, The active metabolite, prednisolone, is nonlinearly bound to transcortin and albumin .

B) Distribution Kinetics
1)) Volume of Distribution 0.4 to 1 L/kg

Metabolism Sites and Kinetics

Liver, extensive.

a) The liver reduces the 11-oxo group of prednisone to form the biologically active steroid, prednisolone.

b) Historically, prednisolone has been recognized as the primary metabolite of prednisone; however, some work has established that prednisone and prednisolone undergo complex reversible metabolism. After oral doses of prednisone or prednisolone, the plasma concentration-time profiles for both agents are superimposable.

Product description:
Available as 1 mg, 2.5 mg, 5 mg, 10 mg, 20 mg, and 50 mg tablets and as oral solution (5 mg/5 ml)

Solution preparation:
Available as commercially-available oral tablets or pre-prepared oral solution.

Storage requirements:
Store at controlled room temperature at 25 degrees C (77 degrees F), with excursion permitted between 15 and 30 degrees C (59 and 86 degrees F). Protect tablets from moisture.

Stability: Tablets are stable at room temperature until the date noted on the packaging.

Route of administration: Oral

Drug Procurement: Prednisone must be obtained from commercial sources.

9.6 Rituximab

Chemical Name: IDEC-C2B8, Chimeric anti-CD20 monoclonal antibody,

Other Names: Rituxan™, Mabthera™

Classification: Monoclonal antibody, antineoplastic agent

Molecular Formula: $C_{6416}H_{9874}N_{1688}O_{1987}S_{44}$

Mode of Action: Rituximab binds with high affinity to CD20-positive cells, performs human effector functions *in vitro*, and depletes B cells *in vivo*. The FAb domain of rituximab binds to the CD20 antigen on B-lymphocytes and the Fc domain recruits immune effector functions to mediate B cell lysis *in vitro*. The biological effect is manifested by

B-cell depletion in peripheral blood, lymph nodes, and bone marrow.

Metabolism: Not fully understood. Generally believed to be degraded nonspecifically in the liver.

Product description: Rituximab is a sterile, clear, colorless, preservative-free liquid concentrate for intravenous (IV) administration.

Solution preparation:

Using appropriate aseptic technique, withdraw the necessary amount of rituximab and dilute to a final concentration of 1 to 4 mg/mL into an infusion bag containing either 0.9% Sodium Chloride or 5% Dextrose in Water. Gently invert the bag to mix the solution. Discard any unused portion left in the vial. Caution should be taken during the preparation of the drug, as shaking can cause aggregation and precipitation of the antibody.

Storage requirements:

Rituximab is a sterile, clear, colorless, preservative-free liquid concentrate for intravenous (IV) administration. The product is formulated for intravenous administration in 9.0 mg/mL sodium chloride, 7.35 mg/mL sodium citrate dihydrate, 0.7 mg/mL polysorbate 80, and Sterile Water for Injection. The pH is adjusted to 6.5.

Stability:

Rituximab is biologically and chemically stable at 2°C to 8°C (36°F to 46°F) and has a proposed shelf life stability of 30 months. Once reconstituted into IV bags, rituximab is chemically stable for up to 24 hours at 2°C to 8°C (36°F to 46°F), followed by up to 24 hours at room temperature (23°C). However, since rituximab solutions do not contain preservative, diluted solutions should be stored refrigerated (2°C to 8°C). No incompatibilities between rituximab and polyvinylchloride or polyethylene bags have been observed. Rituximab vials should be protected from direct sunlight. Rituximab vials are intended for single use only. Do not use beyond the expiration date stamped on the carton.

Route of administration*:*

DO NOT ADMINISTER AS AN INTRAVENOUS PUSH OR BOLUS. Do not infuse rituximab Concurrently with another IV solution or other IV medications. Premedication, consisting of acetaminophen 650 mg to 1000 mg PO and diphenhydramine 25 to 50 mg IV or PO, will be administered before each infusion of rituximab. Premedication may attenuate infusion-related events. Since transient hypotension may occur during rituximab infusion, anti-hypertensive medications will be withheld 12 hours prior to rituximab infusion.

Rituximab is administered intravenously. An in-line filter is not required. Administer per institutional guidelines.

Rituximab infusion must be interrupted for severe reactions. If the patient experiences fever and rigors, the antibody infusion is discontinued. The severity of the side effects will be evaluated. In most cases, the infusion can be resumed at a 50% reduction in rate (e.g., from 100mg/hr to 50mg/hr) when symptoms have completely resolved. Most patients who have experienced non-life-threatening infusion-related reactions have been able to complete the full course of rituximab therapy.

Following the antibody infusion, the intravenous line should be maintained for medications as needed. If there are no complications after one hour of observation, the intravenous line may be discontinued.. The patient should be treated according to the best available local practices and procedures. In patients with detectable circulating lymphoma cells, the initial infusion rate must be reduced to 25 mg/hr; these patients may experience more frequent and severe transient fever and rigors, shortness of breath, and hypotension.

NOTE: In addition, alternative rituximab infusion rates (i.e., "rapid rituximab infusion") can be used per institutional guidelines as long as the total number of milligrams of rituximab is the same and that "rapid infusion" is not administered with the patient's first rituximab cycle. Further, a rituximab infusion time should not be less than 90 minutes in duration.

Drug Procurement: Rituximab must be obtained from commercial sources.

9.7 Vincristine

Chemical Name:	(3aR,3a1R,4R,5S,5aR,10bR)-methyl 4-acetoxy-3a-ethyl-9-((5S,7S,9S)-5-ethyl-5-hydroxy-9-(methoxycarbonyl)-2,4,5,6,7,8,9,10-octahydro-1H-3,7-methano[1] azacycloundecino[5,4-b]indol-9-yl)-6-formyl-5-hydroxy-8-methoxy-3a,3a1,4,5,5a,6,11,12-octahydro-1H-indolizino[8,1-cd]carbazole-5-carboxylate
Other Names:	Oncovin™
Classification:	Vinca alkaloid, mitotic inhibitor, antineoplastic agent
Molecular Formula:	$C_{46}H_{56}N_4O_{10}$
Mode of Action:	Vincristine sulfate, an oncolytic vinca alkaloid, has an unknown mechanism of action, although it is thought to be related to the arrest of replicating cells at the metaphase stage through prevention of microtubule formation in the mitotic spindle.
Metabolism:	

Absorption Protein binding: yes
Metabolism Hepatic; P450 CYP3A subfamily
Excretion Fecal: about 80% Renal: 10% to 20%
Dialyzable: no (hemodialysis)
Elimination Half Life 85 h (19 h to 155 h)

Product description:

Vincristine sulfate is a white to off-white powder. Each mL contains vincristine sulfate, 1 mg (1.08 µmol); mannitol, 100 mg; and water for injection, qs. Acetic acid and sodium acetate have been added for pH control. The pH of Vincristine Sulfate Injection, USP ranges from 3.5 to 5.5.

Solution preparation:.

Dilute only in NS or D5W; do not dilute in solutions that raise or lower the pH outside the range of 3.5-5.5. Dispense with provided sticker or overwrap that states "FATAL IF GIVEN INTRATHECALLY. FOR INTRAVENOUS USE ONLY".

Storage requirements*:*

The ready-to-use solution should be refrigerated during storage, however, no specific temperature recommendations are provided by the manufacturer. Protection from light has been recommended. If stored at room temperature (15 to 30 degrees C) or in a cool place (8 to 15 degrees C), vincristine sulfate is stable for 1 month. If then refrigerated, the stability of vincristine sulfate is as originally labeled by the manufacturer (Lilly).

Stability:

Vincristine sulfate in 5% dextrose injection is stable for 24 hours in both glass and PVC containers

Route of administration*:*

Syringes should not be used for vincristine administration. Administering via a mini bag infusion is recommended to protect against accidental intrathecal administration. Administer via free-flowing intravenous (IV) needle or catheter; inject directly into vein or into tubing of a running IV infusion within 1 minute. Vincristine is considered a vesicant. Care should be taken to avoid extravasation.

Drug Procurement: Vincristine must be obtained from commercial sources.

9.8 Acyclovir

Chemical Name: 2-amino-1,9-dihydro-9-[(2-hydroxyethoxy)methyl]-6H-purin-6-one

Other Names: Zovirax™

Classification: nucleoside analogue, antiviral agent

Molecular Formula: $C_8H_{11}N_5O_3$

Mode of Action: Acyclovir is converted into acyclo-guanosine monophosphate by viral thymidine kinase and further phosphorylated into the active triphosphate form by cellular kinases. Acyclo-GTP is then incorporated into viral DNA during synthesis, causing premature chain termination

Metabolism:

Absorption Absorption from GI tract is variable and incomplete; 10–30% of an oral dose may be absorbed. 9 – 33% is protein bound.
Metabolism Metabolized partially to 9-carboxymethoxymethylguanine;[a] also converted intracellularly in cells infected with herpes viruses to acyclovir triphosphate
Excretion Excreted principally in urine as unchanged drug
Elimination Half Life 2.1 – 3.5 hours

Product description:

Acyclovir is a white, crystalline powder. Each 400-mg tablet of Zovirax contains 400 mg of acyclovir and the inactive ingredients magnesium stearate, microcrystalline cellulose, povidone, and sodium starch glycolate. Each teaspoonful (5 mL) of ZOVIRAX Suspension contains 200 mg of acyclovir and the inactive ingredients methylparaben 0.1% and propylparaben 0.02% (added as preservatives), carboxymethylcellulose sodium, flavor, glycerin, microcrystalline cellulose, and sorbitol.

Solution preparation:.

The maximum solubility in water at 37°C is 2.5 mg/mL. It is available in capsules, tablets or as a suspension (200 mg/5 ml).

Storage requirements*:*

Capsules and tablets should be stored in tight, light-resistant containers between 15–25°C. The suspension should be maintained between 15–25°C.

Stability:
Capsules and tablets should be taken within the expiration date per manufacturer's guidelines.

Route of administration:
Orally twice/day

Drug Procurement: Acyclovir must be obtained from commercial sources.

10.0 CORRELATIVE / SPECIAL STUDIES

10.1 Correlative Studies to Determine Cell-of-Origin (COO) by the Gene Expression Profiling

The purpose of this correlative study is to assign COO by both immunohistochemistry and the gene expression profiling to each DLBCL patient treated with CR-CHOP in order to provide insight into the differential effect of carfilzomib on the clinical outcomes including progression-free survival (PFS) and overall survival (OS).

10.1.1 Background

10.1.1.1 COO in DLBCL as defined by Gene Expression Profiling

Lymphoma classification was originally based exclusively on histologic assessment of biopsy specimens. Immunohistochemical (IHC) methods were added as part of the Revised European-American Lymphoma (REAL) and, more recently, the World Health Organization (WHO) Classification schemas. In recent years, it has been increasingly recognized that B-cell malignancies can be categorized based on the cell of origin (COO) based on the stage of differentiation of the lymphocyte that undergoes transformation. These include lymphoma arising from B-cells that reside within the lymph node germinal center (GC) and are actively involved in immunoglobulin gene somatic hypermutation and those that are derived from post-germinal center activated B-cells (ABC) [24, 25]. Gene expression profiling (GEP) was the first technique that could accurately stratify DLBCL into sub-types with different outcomes [2, 3].

There are well-described differences in the molecular pathogenesis of each of the two major subtypes of DLBCL. For instance, the GC subtype harbors the t(14;18) translocation in approximately 35% of cases, resulting in constitutive over-expression of the anti-apoptotic protein Bcl-2. In contrast, the transcription factor Nuclear Factor Kappa-B (NF-κB) is constitutively active in the ABC subtype [26, 27] often due to mutations in CARD11 or MYD88, chronic B-cell receptor activation and inactivation of A20 [8-10, 28].

10.1.1.2 Correlation of COO with clinical outcomes of DLBCL

In retrospective analysis, DLBCL-GC patients identified by GEP have superior overall survival relative to DLBCL-ABC when treated with CHOP (76% vs. 16% 5-year OS, P<0.001) [2]. These findings have been validated in subsequent larger series including patients treated with chemotherapy in combination with rituximab [1, 3]. Lenz et al. reported a series of 233 R-CHOP treatment patients whose tumors were characterized using GEP in which the 5 year OS was 60% for the DLBCL-GC group compared to a rate of 39% in patients with non-GC subtype (P < 0.001) [1]. Of note, a third subtype of mediastinal large B-cell lymphoma was found to have a molecular signature similar to Hodgkin's lymphoma and had a prognosis more similar to the DLBCL-GC group.

10.1.1.3 Methods to predict COO

10.1.1.3.1 Hans algorithm

Several techniques have been developed to apply IHC staining of paraffin embedded tissue to assign DLBCL to a particular subtype. The Lymphoma/Leukemia Molecular Profiling Project (LLMPP) used sequential detection of CD10 (if positive in ≥30% of cells suggests GC subtype) followed by BCL6 (if < 30% of cells stain positive suggests non-GC subtype) and, in cases of positive Bcl-6 staining (≥30% of cells), MUM1 to differentiate between GC) (<30% cells) and non-GC subtypes (≥30% of cells) [5]. This is shown schematically in the accompanying figure. This algorithm of Hans, *et al.* showed the DLBCL-GC sub-group to have superior overall survival relative to the non-GCB group.

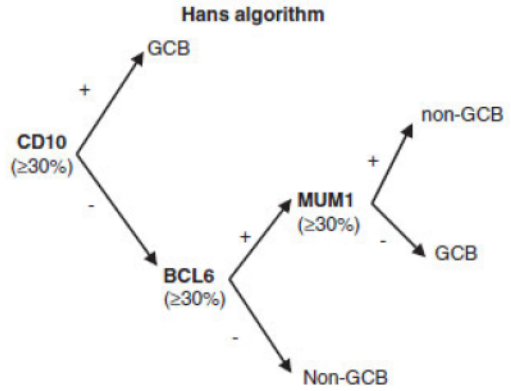


Figure: Application of Hans Algorithm as Assign Cell of Origin (COO) Using Immunohistochemical (IHC) Staining

10.1.1.3.2 Choi Algorithm and Tally Method

Other algorithms, including the methods of Choi, *et al* and Meyer, *et al.*, incorporate stains for additional proteins (GCET1, FoxP1 and LMO2) [29, 30].

The latter is the so-called "Tally" method which tallies the presence or absence of proteins found in GC (CD10, GCBET1) or ABC (Mum1, FoxP1) subtypes of DLBCL and invokes the presence LMO2 as "tiebreaker" to assign cases of equivocal scoring to the GC group [30]. A non-GCB subtype as identified by the Tally method was associated with worse event-free survival (EFS) as well as overall survival (OS). Because of technical difficulties and lack of reproducibility in the staining for GCET1 and FoxP1, the Choi and Tally method have inherent limitations that have limited their widespread adoption.

10.1.1.3.3 Reproducibility of IHC Algorithms

Although the Hans algorithm is the most widely used IHC-based technique for determining COO, it is not standardized and displays significant variability, even at highly experienced centers. Neither the Spanish Grup per l'Estudi dels Limfomes de Catalunya i Balears (GELCAB) nor the Nordic HOVON group were able to validate the use of IHC to predict outcomes of patients with DLBCL [31, 32].

The lack of reproducibility of IHC algorithms was further highlighted by the experience reported from 8 highly experienced laboratories that comprised the Lunenburg Lymphoma Biomarker Consortium [33, 34]. Although there was high agreement between centers for staining with CD20 and CD10, other stains such as Bcl-6, Mum-1 and Ki-67 were highly unreliable. No single center was identified as consistently more reliable than the others.

10.1.1.3.4 Alternative System

Given the poor reproducibility of IHC-based approaches to assign COO and the cumbersome/expensive nature of GEP technique alternative methods for determining COO from formalin-fixed paraffin-embedded (FFPE) tissue are in development. Full details will be amended to the Correlative Methods, Section 10.1.1.3.5 in the future.10.1.2

10.1.1.3.5 Newer approaches

New multiomics approaches have been developed to simultaneously study the impact of tumor specific gene mutations on gene expression and clinical outcomes. Such analysis will be performed in collaboration with Dr. Sandeep Dave at Duke University.

Rationale for Analysis

See Section 14.0

10.1.3 Collection of Specimens

Original tissue biopsies (representative paraffin tissue block) that were used to establish the diagnosis of DLBCL will be sent to central biorepository for the cutting, waxing and storing unstained slides. Because these tissues are formalin

fixed and paraffin embedded, transportation of these samples at ambient temperature is satisfactory. If the tissue block is unavailable, for an excisional biopsy or large incisional biopsy (>2 cm^2 area of tissue): 8 unstained sections on charged slides (cut at 2-4 micron) AND 2 ten micron sections are requested. For a needle core or small biopsy (< 2 cm^2): 8 unstained sections on charged slides (cut at 2-4 micron) AND 8 ten micron sections are requested. Tissue blocks will returned to the originating site within 30 business days of receipt by the biorepository.

10.1.4 Handling of Specimens

The clinical investigator or his/her designee in charge of the research subject will be responsible for having the original diagnostic specimen (paraffin-embedded tissue block and all relevant reports including diagnostic report, immunohistochemical data, flow cytometry data, and molecular pathology studies associated with the specimen) sent to the central biorepository for collection, handling and storage. At the end the study, the unstained slides will be batched by the biorepository, and sent to Dr. Eric D. Hsi, MD at Wake Forest University for the cell of origin (COO) analysis utilizing DuoSeq:

Wake Forest Baptist Medical Center
Attn: Jordan Bouldin
Wake Receiving- Commons Dock
1 Medical Center Blvd.
Winston Salem, NC 27157

Confirmation of the diagnosis of DLBCL by the CCF department of hematopathology is not a requirement for inclusion in the trial and will not be required for initiation of therapyPlease send all correlative samples to the below address. Contact the lead
study coordinator upon shipment.

Attn: Durkin/Chilton/Ondrejka
Cleveland Clinic Central Biorepository
Pathology and Laboratory Medicine Institute
Cleveland Clinic
2119 East 93rd. Street
Desk L15
Cleveland, OH 44106

11.0 STUDY PARAMETERS AND CALENDAR

11.1 Study Parameters

11.1.1 Screening Evaluation

Screening studies and evaluations will be used to determine the eligibility of each subject for study inclusion. All evaluations must be completed ≤ 28 days prior to administration of protocol therapy, except where otherwise indicated or - in the case of patients who received 1 cycle of R-CHOP [or some component(s) thereof] prior to study enrollment, a CT and/or PET/CT, echocardiogram and bone marrow biopsy must have been obtained prior to treatment. The window for the additional screening procedures may be extended for an additional 14 days prior to initial SOC therapy. If only a CT or PET/CT was completed prior to SOC therapy, as long as there is evidence of measureable disease and tumor measurements are available for response assessment, the other scan may be omitted. Scans should be completed within 56 days of pre-study therapy.

- Informed Consent
- Demographics
- Medical History
- Complete Physical Examination
- Height
- Weight
- Vital signs including: blood pressure, pulse, respiratory rate and temperature.
- Concurrent Medications Assessment including prescription medications, over-the-counter (OTC) medications and natural/herbal supplements.
- ECOG Performance Status
- Baseline Symptoms Assessment
- Laboratory Studies:
    - Complete Blood Count (CBC) with differential and platelets
    - Serum Chemistries: albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, SGOT [AST], SGPT [ALT], sodium, lactate dehydrogenase (LDH) level, uric acid, phosphorous.
    - Calculated creatinine clearance will be determined using Cockcroft-Gault formula if creatinine and/or BUN are abnormal.
    - Serum ß-HCG for women of childbearing potential
    - Urinalysis
    - Remote Hepatitis Panel (Hepatitis B Surface Antigen, Hepatitis B Surface Antibody, Hepatitis B Core Antibody, Hepatitis C antibody)
    - HIV testing
- EKG
- MUGA or echocardiogram (must be completed ≤ 6 months prior to administration of protocol therapy) unless there is clinical evidence for new cardiac symptoms within period of time since the cardiac assessment.

- CT scan of neck, chest, abdomen and pelvis with oral and IV contrast (neck may be omitted at discretion of treating physician)
- PET/CT scan as baseline tumor imaging assessmentBone Marrow Aspirate and Biopsy with cytogenetics (within 90 days of treatment)
    - May be omitted at sponsor discretion if bone marrow assessment and FISH are available from another biopsy to obtain full baseline staging
- Diagnostic biopsy material sent to Cleveland Clinic for COO determination.

11.1.2 Treatment Period

In the case of patients who received 1 treatment of R-CHOP [or some component(s) thereof] prior to study enrollment, will begin the study with Cycle 1 study treatment (R-CHOP dose 2). Patients should receive at least 6 full doses of R-CHOP (between SOC and study treatment combined) unless otherwise specified, but upon investigator discretion may complete the 6th Cycle of on-study CR-CHOP (7 total doses).

Patients first cycle that includes Carfilzomib should always start at 20mg/m^2 regardless if they received prior treatment, then resume with 56 mg/m^2.

Windows

- Treatment cycles are 21 days long.
- A visit window of ± 3 days is allowed for labs
- A visit window of ± 3 day is allowed for treatment.
- A visit window of ± 14 days is allowed for 6-month follow-up visits.

Cycle 1, Day 1

- Physical Examination
- Weight
- Vital signs including: blood pressure, pulse, respiratory rate and temperature.
- Concurrent Medications Assessment including prescription medications, over-the-counter (OTC) medications and natural/herbal supplements.
- ECOG Performance Status
- Baseline Symptoms Assessment
- Adverse Event Evaluation
- Laboratory Studies:
    - Complete Blood Count (CBC) with differential and platelets.
    - Serum Chemistries: albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, SGOT [AST], SGPT [ALT], sodium, lactate dehydrogenase (LDH) level, uric acid, phosphorous.
- Calculated creatinine clearance will be determined using Cockcroft-Gault formula if creatinine and/or BUN are abnormal.

- Carfilzomib Administration
- Initiate acyclovir.

Cycle 1, Day 2

- Vital signs including: blood pressure, pulse, respiratory rate and temperature.
- Carfilzomib administration
- Rituximab administration
- Adverse Event Evaluation

Cycle 1, Day 3

- Vital signs including: blood pressure, pulse, respiratory rate and temperature.
- CHOP administration

Cycle 1, Day 4

- Pegfilgrastim administration or ONPRO™ wearable device

Cycle 1, Day 8 - optional

- The following laboratory studies may be performed on day 8 per MD discretion:
  - Complete Blood Count (CBC) with differential and platelets
  - Serum Chemistries: albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, SGOT [AST], SGPT [ALT], sodium, lactate dehydrogenase (LDH) level, uric acid, phosphorous.
  - Calculated creatinine clearance will be determined using Cockcroft-Gault formula if creatinine and/or BUN are abnormal.

Cycles 2-6, Day 1

- Physical Examination
- Weight
- Vital signs including: blood pressure, pulse, respiratory rate and temperature
- Concurrent Medications Assessment including prescription medications, over-the-counter (OTC) medications and natural/herbal supplements.
- ECOG Performance Status
- Adverse event evaluation
- Laboratory Studies:
  - Complete Blood Count (CBC) with differential and platelets
  - Serum Chemistries: albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium,

total protein, SGOT [AST], SGPT [ALT], sodium, lactate dehydrogenase (LDH) level, uric acid, phosphorous.
    - Calculated creatinine clearance will be determined using Cockcroft-Gault formula if creatinine and/or BUN are abnormal.
- Carfilzomib Administration

Cycles 2-6, Day 2

- Vital signs including: blood pressure, pulse, respiratory rate and temperature.
- Carfilzomib administration
- Rituximab administration

Cycles 2-6, Day 3

- Vital signs including: blood pressure, pulse, respiratory rate and temperature.
- CHOP administration

Cycles 2-6, Day 4

- Pegfilgrastim administration or ONPRO™ wearable device

Cycles 2-6, Day 8 - Optional

- Laboratory Studies without clinical visit may be performed on day 8 at MD discretion
    - Complete Blood Count (CBC) with differential and platelets

Cycle 3, Day 15-21

In the case of patients who received 1 cycle of R-CHOP [or some component(s) thereof] prior to study enrollment, interim scans will be conducted after 3 cycles of CR-CHOP have been administered (C3 D15-21 of protocol therapy) , this should be after 4 total rounds of treatment for these patients.

- CT scan of neck, chest, abdomen and pelvis with oral and IV contrast (neck may be omitted at discretion of treating physician).
- PET scan is optional.

Off Treatment visit (to be conducted 4-8 weeks of Day 1 of last treatment or after completion of consolidation radiation therapy)

- Physical Examination
- Weight
- Vital signs including: blood pressure, pulse, respiratory rate and temperature.
- Concurrent Medications Assessment including prescription medications, over-the-counter (OTC) medications and natural/herbal supplements.
- ECOG Performance Status
- Adverse event evaluation
- Laboratory Studies:
    - Complete Blood Count (CBC) with differential and platelets

    - Serum Chemistries: albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, SGOT [AST], SGPT [ALT], sodium, lactate dehydrogenase (LDH) level, uric acid, phosphorous.
    - Calculated creatinine clearance will be determined using Cockcroft-Gault formula if creatinine and/or BUN are abnormal.
- EKG
- Echocardiogram
- Bone marrow biopsy (may be omitted if screening bone marrow biopsy was negative for involvement for lymphoma).
- CT scan of neck, chest, abdomen and pelvis with oral and IV contrast (neck may be omitted at discretion of treating physician) to be obtained 4-8 weeks after Day 1 of last treatment cycle.
- PET scan to be obtained between 4-8 weeks after day 1 of last treatment cycle. For patients receiving adjuvant or post-chemotherapy radiation treatment, PET and/or CT can be deferred until after completion of radiation.
- Response assessment (See Section 12.0)

Follow-Up (held at a minimum of 6, 12 and 24 months after D1 of last treatment cycle – one month = 30 days or after completion of consolidation radiation therapy)

- Physical Examination
- Weight
- Vital signs including: blood pressure, pulse, respiratory rate and temperature.
- Concurrent Medications Assessment including prescription medications, over-the-counter (OTC) medications and natural/herbal supplements.
- ECOG Performance Status
- Adverse event evaluation
- Laboratory Studies:
    - Complete Blood Count (CBC) with differential and platelets
    - Serum Chemistries: albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, SGOT [AST], SGPT [ALT], sodium, lactate dehydrogenase (LDH) level, uric acid, phosphorous.
    - Calculated creatinine clearance will be determined using Cockcroft-Gault formula if creatinine and/or BUN are abnormal.
- CT neck/chest/abdomen/pelvis (may omit neck if not deemed clinically indicated by investigator)
- Response Assessment
- Discontinue acyclovir (Month 6 only)
- ECHO at 6 month follow up visit

If a patient progresses during treatment or off study, they only will only be followed for survival at the above time points.

11.2 Study Calendar

		Cycle 1					Cycle 2					Cycle 3						Cycles 4-6						
	Screening[b]	Day 1	Day 2	Day 3	Day 4	Day 8[n],	Day 1	Day 2	Day 3	Day 4	Day 8[n],	Day 1	Day 2	Day 3	Day 4	Day 8,	Day 15-21	Day 1	Day 2	Day 3	Day 4	Day 8,	Off Treatment	Follow-Up[j]
Informed Consent[a]	X																							
Medical History	X																							
Physical Exam	X	X					X					X						X					X	X
Concurrent Meds	X	X					X					X						X					X	X
Vital Signs (T, P, R, BP)	X	X	X	X			X	X	X			X	X	X				X	X	X			X	X
Height	X																							
Weight	X	X					X					X						X					X	X
ECOG Performance Status	X	X					X					X						X					X	X
CBC w/ Differential	X	X				X[d]	X				X[d]	X				X[d]		X				X[d]	X	X
Serum Chemistry[c]	X	X				X[c]	X					X						X					X	X
Urinalysis	X																							
Baseline Symptoms or AE evaluation	X	X	X				X					X						X					X	X
EKG	X																						X	
ECHO/MUGA[e]	X																						X	X
Bone marrow biopsy/aspirate [M]	X																						X[L]	
CT neck/chest/abd/pelvis[f]	X[g]																X[g]						X	X[j]
FDG-PET scan[g]	X																optional						X[g]	
Response Assessment																							X	X
ß-hCG[h]	X																							
Remote Hepatitis Panel	X																							
HIV testing	X																							
MGene expression and mutation ®	X																							
Carfilzomib		X	X				X	X				X	X					X	X					
Rituximab			X					X					X						X					
CHOP				X					X					X						X				
Pegfilgrastim (or ONPRO™)					X					X					X						X			

a: Informed consent must be signed ≤ 28 days of start of study treatment. If signature is outside that window the patients must either initial and date their original consent or sign a new consent.

b: Pre-study H&P and all labs must be ≤ 28 days from start of treatment unless otherwise specified. Tumor measurements and radiologic evaluations must be ≤42 days from start of treatment unless otherwise specified.

c: C1D1 labs do not have to be repeated if baseline labs were drawn ≤ 21 days prior to day 1. All labs during treatment must be completed within 48 hours before the treatment day. Chemistry includes: albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, uric acid, potassium, total protein, SGOT [AST], SGPT [ALT], sodium. Cycle 1 Labs do not need to be performed prior to day 4 of treatment.

d. For Dose Levels 1-5 on Day 8; Phase 2 – this is only necessary per investigator discretion

e. May obtain ECHO and/or MUGA as baseline confirmation of LVEF. May be obtained up to 6 months prior to screening. During follow-up ECHO to be obtained at 6 month follow-up visit.

f. Neck CT may be omitted at the discretion of the investigator if felt to not be clinically useful.

g: All pre-study and end of treatment radiological evaluations must be performed by CT Scan and FDG-PET Scan. Interim CT (FDG/PET is optional) must be obtained between days 15 and 21 of cycle 3 but formal assessment of response will not be done at this time point. . Off-treatment CT scan and FDG-PET scan to be completed 4-8 weeks after day 1 of last treatment unless patient is undergoing consolidation radiation therapy in which case response assessment studies can be deferred until after radiation..

h. Serum pregnancy test (WOCBP) must be completed < 72 hours before beginning treatment.

i: Follow up for PD, resolution of treatment related toxicities, survival must be conducted at a follow-up appointment 4-8 weeks after D1 of last treatment. Long term follow-up should be conducted at 6, 12, and 24 months for 2 years, and subsequently based on discretion of individual investigator and results should be recorded on the applicable long term follow up case report forms. If a patient progresses on long term follow up, only survival data is needed.

j: CT to be obtained at 6, 12, and 24 months after day 1 of last treatment.

k End of treatment bone marrow biopsy may be omitted if screening bone marrow biopsy was negative for involvement by lymphoma.

l. Not required at screening but should be performed if the gene expression and mutation analysis at the conclusion of the study

m. Bone marrow biopsies done within 90 days of screening visit are acceptable

n. Day 8 assessments are optional per MD discretion

12.0 RESPONSE ASSESSMENT

Although response is not the primary endpoint of this trial, patients with measurable disease will be assessed by standard criteria based upon the Revised Response Criteria for Malignant Lymphoma (Appendix C) [36]. All patients will be required to have pre-treatmen FDG-PET/CTt, interim (cycle 3 Day **15-21**) CT scans and end of treatment response assessment via FDG-PET/CT.

All pre-study and end of treatment radiological evaluations must be performed by CT Scan and FDG-PET/CT Scan to be centrally reviewed at Cleveland Clinic for formal response assessment. Interim CT (interim FDG-PET/CT is optional) must be obtained between days 15 and 21 of cycle 3, but formal response assessment is not required at this time point. Off Treatment FDG-PET/CT scan to be completed 4-8 weeks after Cycle 6, day 1.

For the purpose of disease measurement during follow-up, i.e., assessing disease progression after achieving response, patients will also get a baseline and end of treatment CT scan. Follow up will be as per institutional or physician practice but CT scans must be obtained at months 6, 12 and 24 after cycle 6, day 1.

12.1 Antitumor Effect – Hematologic Tumors

The 2007 International Working Group Revised Response Criteria for Malignant Lymphoma will be used the following categories of response: Complete Response (CR), Partial Response (PR), Stable Disease (SD), Relapse and Progression (PD). In the case of stable disease, follow-up assessments must have met the SD criteria at least once after study entry at a minimum interval of six weeks[36].

The following guidelines are to be used for establishing tumor measurements at baseline and for subsequent comparison:

- The six largest dominant nodes or extranodal masses must be identified at baseline.
- If there are 6 or fewer nodes and extranodal masses, all must be listed as dominant.
  If there are more than 6 involved nodes or extranodal masses, the 6 largest dominant nodes or extranodal masses should be selected according to the following features:
  - nodes should be clearly measurable in at least two perpendicular measurements
  - nodes should be from as disparate regions of the body as possible
  - nodes should include mediastinal and retroperitoneal areas of disease whenever these sites are involved.

- Measurements for all dominant nodes and extranodal masses will be reported at baseline. Measurements on non-dominant nodes are not required. The lymph nodes or extranodal masses selected for measurement should be measured in two perpendicular diameters, one of which is the

longest perpendicular diameter. The lymph nodes should be measured in centimeters to the nearest one tenth of a centimeter (e.g. 2.0 cm, 2.1cm, 2.2 cm, etc.)

- The two measured diameters of each lymph node site or extranodal mass should be multiplied giving a product for each nodal site or extranodal mass. The product of each nodal site should be added, yielding the sum of products of the diameters (SPD). The SPD will be used in determining the definition of response for those who have less than a complete response.

12.1.1 Complete Response (CR)

Complete Response (CR) Complete disappearance of all detectable clinical evidence of disease, and disease-related symptoms if present prior to therapy.

- For lymphomas for which the FDG-PET/CT scan was positive prior to therapy: a post-treatment residual mass of any size is permitted as long as it is FDG-PET/CT-negative by investigator assessment.
- For lymphomas for which the FDG-PET/CT scan was positive prior to therapy: a post-treatment residual mass of any size is permitted as long as it is FDG-PET/CT-negative.
- If the pretreatment FDG-PET/CT scan was negative: all lymph nodes and extranodal masses must have regressed on CT to normal size (< 1.5 cm in their greatest transverse diameter for nodes > 1.5 cm prior to therapy). Previously involved nodes that were 1.1-1.5 cm in their long axis and > 1.0 cm in their short axis prior to treatment must have decreased to < 1 cm in their short axis after treatment.
- The spleen and/or liver, if considered enlarged prior to therapy on the basis of a physical examination or CT scan, should not be palpable on physical examination, and nodules related to lymphoma should disappear. However, no normal size can be specified because of the difficulties in accurately evaluating splenic and hepatic size and involvement. For instance, a spleen considered normal size may contain lymphoma, whereas an enlarged spleen may not necessarily reflect the presence of lymphoma, but variations in anatomy, blood volume, the use of hematopoietic growth factors, or other causes.
- If the bone marrow was involved by lymphoma prior to treatment, the infiltrate must have cleared on repeat bone marrow biopsy. The biopsy sample on which this determination is made must be adequate (with a goal of > 20 mm unilateral core). If the sample is indeterminate by morphology, it should be negative by immunohistochemistry. A sample that is negative by immunohistochemistry but demonstrating a small population of clonal lymphocytes by flow cytometry will be considered a CR until data become available demonstrating a clear difference in patient outcome.
- NOTE: Complete Remission/unconfirmed (CRu): Using the above definition for CR and that below for PR, eliminates the category of CRu.

12.1.2 Partial Response (PR)

The designation of PR requires all of the following

- A > 50% decrease in sum of the product of the diameters (SPD) of up to 6 of the largest dominant nodes or extranodal masses. These nodes or masses should be selected according to the following: (a) they should be clearly measurable in at least 2 perpendicular dimensions; if possible, they should be from disparate regions of the body; (b) they should include mediastinal and retroperitoneal areas of disease whenever these sites are involved.
- No increase in the size of other nodes, liver or spleen.
- Bone marrow assessment is irrelevant for determination of a PR if the sample was positive prior to treatment. However, if positive, the cell type should be specified, e.g. large-cell lymphoma or small cleaved cell lymphoma.
- No new sites of disease.

12.1.3 Stable Disease (SD)

- Failing to attain the criteria needed for a PR or CR, but not fulfilling those for progressive disease (see below).
- For FDG-avid lymphomas: FDG-PET/CT should be positive at prior sites of disease with no new areas of involvement on the post-treatment CT or FDG-PET/CT.
- For variably FDG-avid lymphomas/FDG-avidity unknown: For patients without a pretreatment FDG-PET/CT scan or if the pre-treatment FDG-PET/CT was negative, there must be no change in the size of the previous lesions on the post-treatment CT scan.

12.1.4 Progressive Disease (PD)

For determination of relapsed and progressive disease, lymph nodes should be considered abnormal if the long axis is more than 1.5 cm, regardless of the short axis. If a lymph node has a long axis of 1.1 to 1.5 cm, it should only be considered abnormal if the short axis is more than 1 cm. Lymph nodes < 1 x < 1 cm will not be considered as abnormal for relapse or progressive disease. Treatment decisions in patients with presumed refractory, relapsed or progressive disease should not be made solely on the basis of a single FDG-PET/CT scan without histologic confirmation.

- Appearance of any new lesion more than 1.5 cm in any axis during or at the end of therapy, even if other lesions are decreasing in size. Increased FDG uptake in a previously unaffected site should only be considered relapsed or progressive disease after confirmation with other modalities, including biopsy. In patients with no prior history of pulmonary lymphoma, new lung nodules identified by CT are mostly benign. Thus, a therapeutic decision should not be made solely on the basis of the FDG-PET/CT without histologic confirmation.

- At least a 50% increase from nadir in the SPD of any previously involved nodes or extranodal masses, or in a single involved node or extranodal mass, or the size of other lesions (e.g. splenic or hepatic nodules). To be considered progressive disease, a lymph node or extranodal mass with a diameter of the short axis of less than 1.0 cm must increase by > 50% and to a size of 1.5 cm x 1.5 cm or more than 1.5 cm in the long axis.

- At least a 50% increase in the longest diameter of any single previously identified node or extranodal mass more than 1 cm in its short axis.

- Lesions should be FDG-PET/CT positive if the lesion was FDG-PET/CT positive before therapy unless the lesion is too small to be detected with current FDG-PET/CT systems (< 1.5 cm in its long axis by CT).

- Measurable extranodal disease should be assessed in a manner similar to that for nodal disease. For these response criteria, the spleen is considered nodal disease. Disease that is only assessable (e.g., pleural effusions, bone lesions) will be recorded as present or absent only, unless, while an abnormality is still noted by imaging studies or physical examination, it is found to be histologically negative.

12.2 **Definitions of Time Periods**

12.2.1 Duration of response

This is measured, only in responders, from the documented beginning of response (CR or PR) to the time of relapse.

12.2.2 Disease-free survival

Survival is defined as the date of study entry to the date of death. Disease-free survival is measured from the time of occurrence of disease-free state (e.g. the adjuvant setting following surgery or radiation therapy) or attainment of a complete remission) to disease recurrence or death from lymphoma or acute toxicity of treatment. This definition may be complicated by deaths that occur during the follow-up period that are unrelated to the lymphoma and there is controversy as to whether such deaths should be considered as events or censored at the time of occurrence. Whereas it is often possible to identify those deaths related to the lymphoma, there is the potential for bias in the attribution of deaths.

12.2.3 Disease-specific survival

Disease-specific survival (e.g., lymphoma-specific survival, cause-specific survival) is potentially subject to bias because the exact cause of death is not always easy to ascertain. To minimize the risk of bias, the event should be recorded as death from lymphoma, or from toxicity from the drug. Death from unknown causes

should be attributed to the drug. For certain trials, time to next lymphoma treatment may be of interest, defined as time from the end of primary treatment until the initiation of the next therapy.

12.2.4 Progression-free survival

Progression-free Survival (PFS) is defined as the time from entry onto study until lymphoma progression or death from any cause. PFS reflects tumor growth and, therefore, occurs prior to the endpoint of overall survival. In addition, PFS is not confounded by the administration of subsequent therapy. Whether a prolongation of PFS represents direct clinical benefit or a surrogate for clinical benefit depends on the magnitude of the effect and the risk-benefit ratio of the therapy under investigation. Unlike survival, the precise date of progression is generally unknown. It may be defined as the first date of documentation of a new lesion or enlargement of a previous lesion, or the date of the scheduled clinic visit immediately after radiologic assessment has been completed. Where there is missing information, censoring of the data may be defined as the last date at which progression status was adequately assessed or the first date of unscheduled new anti-lymphoma treatment.

12.2.5 Time to progression

Time to progression (TTP) is defined as the time from study entry until lymphoma progression or death due to lymphoma. In TTP, deaths from other causes are censored either at the time of death or at an earlier time of assessment, representing a random pattern of loss from the study. TTP is not as useful as PFS unless the majority of deaths on a study are unrelated to the lymphoma due to the efficacy of the treatment and/or prolonged follow up

12.2.6 Time to treatment failure

Time to treatment failure (event-free survival) is measured from the time from study entry to any treatment failure including discontinuation of treatment for any reason, such as disease progression, toxicity, patient preference, initiation of new treatment without documented progression, or death. This composite endpoint is generally not encouraged by regulatory agencies because it combines efficacy, toxicity and patient withdrawal.

12.3 **Response Review**

Responses will be reviewed by the investigator (PI or co-investigator) who is treating the patient at each participating site. Patients who have been treated with 3 or more cycles of R-CHOP containing any doses of carfilzomib will be available for response assessment.

13.0 RECORDS TO BE KEPT / REGULATORY CONSIDERATIONS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 8.0 (Adverse Events: List and Reporting Requirements).

13.1 Data Reporting

The OnCore Database will be utilized, as required by the Case Comprehensive Cancer Center, to provide data collection for both accrual entry and trial data management. OnCore is a Clinical Trials Management System housed on secure servers maintained at Case Western Reserve University. OnCore properly used is compliant with Title 21 CFR Part 11. Access to data through OnCore is restricted by user accounts and assigned roles. Once logged into the OnCore system with a user ID and password, OnCore defines roles for each user which limits access to appropriate data. User information and password can be obtained by contacting the OnCore Administrator at oncore-registration@case.edu.

OnCore is designed with the capability for study setup, activation, tracking, reporting, data monitoring and review, and eligibility verification. This study will utilize electronic Case Report Form completion in the OnCore database. A calendar of events and required forms are available in OnCore.

13.2 Regulatory Considerations

The study will be conducted in compliance with ICH guidelines and with all applicable federal (including 21 CFR parts 56 & 50), state or local laws.

13.2.1 Written Informed Consent

13.2.2 Provision of written informed consent must be obtained prior to any study-related procedures. The Principal Investigator will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risks and benefits of the study as well as the subject's financial responsibility. Subjects must also be notified that they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided. The original, signed written Informed Consent Form must be kept with the Research Chart in conformance with the institution's standard operating procedures. A copy of the signed written Informed Consent Form must be given to the subject.

13.2.3 Subject Data Protection

In accordance with the Health Information Portability and Accountability Act (HIPAA), a subject must sign an authorization to release medical information to the sponsor and/or allow the sponsor, a regulatory authority, or Institutional Review Board access to subject's medical information that includes all hospital records relevant to the study, including subjects' medical history.

This study will access electronic medical records systems to obtain medical information for the subjects enrolled to this study.

In order to insure patient safety, investigators and study personnel must have up-to-the-minute health information for subjects enrolled to this study. Therefore, electronic medical records must be utilized to obtain medical information in a timely manner.

Accessing Electronic Medical Records for University Hospitals (UH)

The following electronic systems will be used: IDX program to access scheduling information; UH Physician Portal to access lab results and physician notes; PCOSS LITE as necessary to locate archived medical records; COPATH to locate archived pathology records; PACS to access radiology imaging results; and MySecureCare (Sunrise Clinical Manager) to access some or all of the above information when this application is fully functional.

Access to these systems is required for the life of this research study. Information obtained from electronic systems will be copied into the Seidman Cancer Center Clinical Trials Unit research chart and/or printed (lab results, physician notes, etc.) and stored in the research chart. Research charts are kept secure and destroyed according to UH policy.

Study data will be obtained by the PI, co-investigators, study coordinator, and/or data manager for this study via password-protected login. Donna Kane is a Case Western Reserve University employee with a University Hospitals email address and IT&S log on ID and Password. Donna Kane will be assessing EMR to obtain data required by the study. All study personnel involved in this research will adhere to the UH policies regarding confidentiality and Protected Health Information (PHI).

Accessing Electronic Medical Records for Cleveland Clinic Foundation (CCF).

For Cleveland Clinic, the electronic systems utilized will be EPIC, COPATH to locate archived pathology records; and AGFA and/or EasyViz to access radiology imaging results

Access to these systems is required for the life of this research study. Information obtained from electronic systems will be copied into the Taussig Cancer Institute research chart and/or printed (lab results, physician notes, etc.) and stored in the research chart. Research charts are kept secure and destroyed according to CCF policy.

Study data will be obtained by the PI, co-investigators, study coordinator, and/or data manager for this study via password-protected login. Jackie Tomer is a Cleveland Clinic employee with a CCF email address and IT&S log on ID and Password. Jackie Tomer will be assessing EMR to obtain data required by the study. All study personnel involved in this research will adhere to the CCF policies regarding confidentiality and PHI.

13.2.4 Retention of Records

The Principal Investigator of The Case Comprehensive Cancer Center supervises the retention of all documentation of adverse events, records of study drug receipt and dispensation, and all IRB correspondence for as long as needed to comply with national and international regulations. No records will be destroyed until the Principal Investigator confirms destruction is permitted.

13.2.5 Audits and Inspections

Authorized representatives of the sponsor, a regulatory authority, an Independent Ethics Committee (IEC) or an Institutional Review Board (IRB) may visit the Center to perform audits or inspections, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the protocol, Good Clinical Practice (GCP), guidelines of the International Conference on Harmonization (ICH), and any applicable regulatory requirements.

13.2.6 Data Safety and Monitoring Plan

This protocol will adhere to the policies of the Case Comprehensive Cancer Center Data and Safety Monitoring Plan in accordance with NCI regulations.

14.0 STATISTICAL CONSIDERATIONS

The goal of the phase I portion of the trial is to define a RP2D by using a standard 3 + 3dose escalation scheme, as outlined in section 3. The phase I study will require between 18-24 patients.

The phase II portion of the trial will require 26 patients with non-GC DLBCL treated with CR-CHOP with carfilzomib at the MTD to achieve 24 evaluable patients. This will allow for the potential to demonstrate an improvement in the 1-year PFS from 50% to 75% using a nonparametric (i.e., Kaplan-Meier) time-to event (TTE) estimate with a significance of 5% and power of 80%.

We estimate that we will accrue 1-2 patients/month during the phase I portion of the study and 2-4 patients/month during the phase II portion. Estimated time for accrual of the phase II portion of the study is less than 24 months.

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APPENDIX A

PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale	
Grade	**Descriptions**
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed < 50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed > 50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

APPENDIX B

IWC RESPONSE CRITERIA (adapted from [37])

IWC+PET-Based Response Designations	Description
CR	CR by IWC with a completely negative PET
	CRu, PR, or SD by IWC with a completely negative PET and a negative BMB if positive prior to therapy
	PD by IWC with a completely negative PET and CT abnormalities (new lesion, increasing size of previous lesion) ≥1.5 cm (≥ 1.0 cm in the lungs) and negative BMB if positive prior to therapy
CRu	CRu by IWC with a completely negative PET but with an indeterminate BMB
PR	CR, CRu, or PR by IWC with a positive PET at the site of a previously involved node/nodal mass
	CR, CRu, PR, or SD by IWC with a positive PET outside the site of a previously involved node/nodal mass
	SD by IWC with a positive PET at the site of a previously involved node/nodal mass that regressed to < 1.5 cm if previously > 1.5 cm, or < 1 cm if previously 1.1-1.5 cm
SD	SD by IWC with a positive PET at the site of a previously involved node/nodal mass (i.e., residual mass)
PD	PD by IWC with a positive PET finding corresponding to the CT abnormality (new lesion, increasing size of previous lesion)
	PD by IWC with a negative PET and a CT abnormality (new lesion, increasing size of previous lesion) of < 1.5 cm (< 1.0 cm in the lungs)

Abbreviations: IWC+PET, International Workshop Criteria plus positron emission tomography; CR, complete response; BMB, bone marrow biopsy; CT, computed tomography; CRu, unconfirmed complete response; PR, partial response; SD, stable disease; PD, progressive disease.

APPENDIX C

Data Reconciliation Listing
Investigator Sponsored Study
Amgen ISS Category 2
Transmittal Form
Carfilzomib

20159838 / IST-CAR-547

To: Amgen NASCR, Phone No: 7(805) 447-5390 Fax No: (805) 449-4522	**AMGEN ISS PROTOCOL #:**_____ Sponsor: Taussig Cancer Center- CASE COMPREHENSIVE CANCER CENTER Sponsor Contact Name: _____ Fax No:_____ Phone No:_____ Date: _____

Use this form as a cover page ONLY for Data Reconciliation line listings.

Fax transmission contents:

To be sent in regular intervals per contractual agreement:

☐ Data Reconciliation Line Listing # of Reports Submitted: _____

Period from _____ to _____
DD/MMM/YYYY DD/MMM/YYYY

For multi-country studies please indicate countries of transmitted report origin:

Total # of pages in this transmission, including cover page: _____

APPENDIX D

Comprehensive List of Protocol Changes

Version 1 : 9/6/2013

- Updated treatment calendar
- Updated dose levels
- Updated DLT criteria
- Updated management of study drug toxicities
- Added acyclovir to study treatment as antiviral prophylaxis

Version 2 : 5/27/2014

- Added more information regarding Cardiac Monitoring under the dose reduction/dose delay sections (Section 7)

Version 3 : 7/14/2014

- Clarification that Filgrastim may be substituted if pegfilgrastim is not available.
- Specification indicating that DLT data will be recorder during study cycle 1 of treatment (
- Additional lab tests were removed from cycle 2-6, day 8 The included tracked version of the protocol provides a more comprehensive view of the revisions made.

Version 4 : 1/5/2015

- Specify what procedures would occur on day 8 and 9 of each cycle for dose levels 2-4.
- The screening period was extended from 12 days to 28 days.
- The IB was updated to include additional risk information. Information previously in section 6.4.8 "Myelodysplastic Syndrome and Acute Myeloid Leukemia (heading title and text) was replaced with "Posterior Reversible Encephalopathy Syndrome.
- Updated table and associated text for adverse drug reactions was also added.

Version 5 : 2/24/2015

- Replaced ICEPLEX terminology to MODAPLEX terminology throughout document - Added inclusion criteria 4.1.2 - Patients must have radiographically measureable disease –
- Deleted inclusion criteria 4.1.5 - Life expectancy >6 months in the opinion of and documented by investigator –
- Updated Research Coordinator contact in Section 5.0 - Registration –

    - Added DLT wording and clarified information for patients in dose levels >= 2 in Section 7.1 - Hematologic Toxicity and in Table 5 –
- Updated Section 10.1.1.3.4 - The MODAPLEX System - to add Qiagen information - Updated Section 10.1.3 - Collection of Specimens - changing number of sections on slides requested, adding additional slide information, and added contact information. - Updated Section 10.1.4 - Handling of Specimens –
- Added information about return of slides and added Section 10.1.4.1 - Site Shipping Instructions –
- Replaced Calendar and Calendar Key in Section 11.2 to make it more readable and added superscripts to further clarify which procedures are required for Dose Levels 2-6 - Corrected typographical and formatting errors throughout the document

Version 6 : 8/28/2015

- Removal of Dr. Brian Bolwell as list of co-investigators
- Addition of Christopher D'Andrea as co-investigator
- Increase from 3-month to 6-month for follow-up visit window.
- Vital signs including: blood pressure, pulse, respiratory rate and temperature. (dose levels 2-6 only)
- Protocol amended to indicate that grade 2,3 and 4 (not just grade 3-4) non-hematologic toxicity (except fatigue or anorexia lasting < 7 days or Grade 3 nausea and/or vomiting that persists for < 2 days following appropriate supportive care or non-clinically significant grade 3 electrolyte abnormalities that have been corrected) that is treatment-related must return to a grade 1 or better prior to continuing treatment. In the case of recurrence of grade 2 non-hematologic toxicity, continuation on the study will be at the discretion of the principal investigator.
- Window of time for MUGA or echocardiogram extended to be within 6 months prior to administration of protocol therapy unless there is clinical evidence for new cardiac symptoms within period of time since the cardiac assessment.
- Duration of therapy modified to indicate that: "In the absence of treatment delays due to adverse events, treatment may continue for 6 cycles or until one of the following criteria applies:
- Unacceptable treatment related toxicity, NCI CTC AE version 4.0 Grade 2, 3 or 4 that fails to recover to baseline or < Grade 3 in the absence of treatment within 4 weeks].
- Steroid premedication clarified to include repeat dexamethasone in with all subsequent treatments if infusion reactions occur in cycle 1, day 1 unless being given as part of rituximab pre-medication

- Exit PET and CT scan to be obtained between 4-8 weeks after cycle 6, day 1. (not 42-50 days)

- Exclusion criteria clarified to indicate : Known CNS involvement by lymphoma. Patients at high risk for secondary CNS involvement but without neurologic symptoms suspected to be due to lymphoma are allowed to be enrolled and receive intrathecal chemotherapy including but not limited to methotrexate, cytarabine and glucocorticoids. Patients who are enrolled and subsequently identified to have pathologic confirmation of CNS involvement by lymphoma may be continued on study at the discretion of the principal investigator.
- Any DLT as defined in Section 6.2 will result in a dose reduction. In the event of day 8±1 laboratory testing reveals an ANC <100/mm^3, hemoglobin <6.5g/dL, or platelets nadir <25,000/mm^3 for patients in dose level 4, carfilzomib dosing will be held on days 8 and 9 of the current cycle ~~and reduced to one dose level lower on day 1 of the subsequent cycle, provided that the day 1 parameters are met (ANC ≥ 1200/mm^3 and platelets ≥ 75,000/mm^3)~~. ~~Should the patient develop a recurrent DLT as defined in Section 6.2, a 2nd dose reduction of carfilzomib will be required.~~ Treatment can resume after allowing recovery to the day 1 criteria assuming treatment has not been delayed for more than 2 weeks. Otherwise, the study drugs must be discontinued (see Criteria for Discontinuation of Study Drug, section 3.4.1.)
- Off treatment visit: CT and PET scan to be obtained between 4-8 weeks after cycle 6, day 1. For patients receiving adjuvant or post-chemotherapy radiation treatment, PET and/or CT can be deferred until after completion of radiation.
- Calendar updated
- Reporting to sponsor (Amgen) updated

Version7 : 11/5/2015

- Added specific section in Inclusion Criteria 4.1.1 to indicate where the Hans Algorithm is located in the protocol.
- Removed specific steroid information in Inclusion Criteria 4.1.3.
- Clarified when Carfilzomib will be administered in Section 6.1.1 (after Rituximab).
- Updated the Study Parameters and Calendar in Section 11 to ensure procedures are consistently listed in each location.
- Updated personnel who will access EMR for CCF in Section 13.2.2.
- Corrected typos and formatting errors throughout document.

Version 8 : 4/13/2016

- Updated hemoglobin from 9.0 g/dl to 7.0 g/dl in section 4
- Updated acyclovir dosing in table 2
- Updated nurse contact for SAE reporting
- Increased window to 14 days for follow up visits

Version 9 : 5/10/2016

- Updated Prednisone dosing to days 3-7
- Added CMC to D8 for dose level 4
- Updated study calendar to include con meds and baseline symptoms

Version 10 : 9/9/2016

- Updated Creatinine Clearance from 60 to 45
- Clarified that Modaplex testing is not a requirement for screening

Version 11 : 2/1/2017

- Added NCT# to cover page, removed Dr. Smith as Co-I
- Updated dose level 4 (carfilzomib)
- Added dose level 5
- Updated study calendar (only safety labs needed for D8 on dose levels 4 and 5)
- Visit on D9 is no longer required
- Update RN contact for SAE reporting
- Updated DLT section to include dose level 5
- Clarified that OnPro is acceptable for pegfilgrastim administration
- Removed modaplex testing

Version 12: 2/27/2017

- This is an administrative updated for clerical error noted in protocol amendment 11. Updating table on pages 5 and 20 to correct error on dose level 4. Carfilzomib will be administered at 20 mg/m2 in Cycle 1 followed by 45 mg/m2 for cycles 2-6.

Version 13: 2/1/2018

- Updating RP2D throughout protocol
- Removing dose modification guidelines for Vincristine, allowing for physician discretion given frequency of peripheral neuropathy (section 7.2.1 and Table 6-Management of Neuropathy).
- Changing contact for SAE's from RN to Regulator Coordinator
- Clarifying collection and handling of specimens (sections 101.3 and 10.1.4)
- Updating screening window to 28 days, this was previously listed in change history but was not executed in the protocol

- Adding 90 day window for screening bone marrow biopsy
- Making interim PET scan optional because this is not used for disease assessment
- Adding Florida as a participating site
- Updating Onyx to Amgen throughout protocol for consistency, Onyx was acquired by Amgen in 2015.
- Updating SAE reporting contact information and providing coversheet in Appendix D

Version 14: 4/10/2018

- Adding physician and sponsor-investigator discretion on dose reducing Carfilzomib in the event of any toxicity.

Excluding patients of direct Asian-Pacific (China, Japan, Taiwan, Singapore, Republic of Korea, and Thailand) ancestry due to a safety notice that was released by Amgen

Version 15: 8/1/2018

- Removed previous standard of care procedures for Rituxan administration
- Added an ECHO at the 6 month follow up visit
- Updated section on contraception use for males and females

Version 16: 11/14/2018

- Made Day 8 labs optional
- Added Roswell Park as a sub-site
- Clarified inclusion criteria
- Updated eligibility criteria to include 1 cycle of prior treatment for DLBCL within 60 days of enrollment
- Added HIV testing during screening
- Added address for correlative samples
- Updated Sub-text on the calendar to match protocol

Version 17: 2/18/2020

- Exclusion: now allows low risk, fully treated melanoma
- Now allows for sponsor approval for ANC abnormalities due to BM infiltration
- Clarified acyclovir inconsistancies: Acyclovir to start C1D1
- Removed specific language on rituximab administration, updated to "per institutional guidelines"
- Updates screening window for patients with SOC R-CHOP to also include anything 14 days prior to their SOC R-CHOP (does not include the scans, those don't have a specified window)

- Allows for either a CT or PET to be omitted in patients with SOC R-CHOP as long as there is evidence of measureable disease and available TM for response assessment
- BMB can be waived by sponsor if BM staging and FISH are available from another type of biopsy
- SOC R-Chop should be considered a cycle. Patients should receive 1 cycle R-CHOP, then 5 cycles of CR-CHOP. A 6th Cycle of CR-CHOP is allowed per investigator discretion (7 total cycles)
- Interim scans should be done after 3 cycles of CR-CHOP no matter if they received SOC R-CHOP. So for some patients scans may be done 4 total treatments.
- Extending scan window from 28 to 42 days for those who begin with CR-CHOP
- Extending scan window to 56 days prior to SOC therapy for those who begin with R-CHOP
- Removed appendix B – no longer applicable
- Clarified EOT visit is 4-8 weeks from D1 of last cycle of treatment
- Clarification that patients who progress should only be followed for survival

Version 17: 2/11/2022

- Removed Lisa Rybicki
- Removed Dr. Eric Hsi
- Added Dr. Sarah Ondrejka
- Added gene mutation and copy number analysis at laboratory of Dr. Sandeep Dave at Duke University.