Phase II study of Dose-Reduced Consolidation Radiation Therapy in Patients with Diffuse Large B-cell Lymphoma

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A National Cancer Institute-designated Comprehensive Cancer Center

Sponsor:	PI – Duke Cancer Institute
Funding Source:	Department of Radiation Oncology
Protocol Source:	PI - Duke Cancer Institute
Duke IRB#:	Pro00100510

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1.0 BACKGROUND AND SIGNIFICANCE

Diffuse large B-cell lymphoma (DLBCL), the most common type of NHL (30% of all cases in North America and Western Europe)[1], comprises a heterogeneous group of neoplasms with multiple morphologic variants and subtypes described in the current WHO classification[2]. DLBCL is primarily a disease of older adults, with a median age of 64 years and a slight preponderance of men (55%). Just over half the patients (55%) have localized disease (stages I or II). As opposed to localized FL, where nodal presentations predominant, about half of patients with stage I-II DLBCL present with extranodal disease. Patients most often present with an enlarging peripheral nodal mass or with symptoms related to a primary extranodal site of involvement.

1.1 Chemotherapy and Radiation Therapy for Diffuse Large B-Cell Lymphoma

Chemotherapy followed by consolidation radiation therapy (RT) is a recognized treatment paradigm for stage I-II diffuse large B-cell lymphoma (DLBCL). This was initially established based on the results of two randomized trials conducted in the 1980s-1990s [3,4]. In these studies, chemotherapy consisted of CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone). The radiation dose was 30 Gy in the Eastern Cooperative Oncology Group (ECOG) study [3] after eight cycles of CHOP and 40-55 Gy in the Southwest Oncology Group (SWOG) study [4] after 3 cycles of CHOP. A British National Lymphoma Investigation (BLNI) randomized study subsequently showed no difference in freedom from local progression, progression-free survival, or overall survival between 30 Gy and 40-45 Gy[5] in DLBCL. Most, but not all, patients in the BLNI study were treated after chemotherapy. However, only a minority of patients received rituximab. Thus, 30 Gy became the standard dose for consolidation RT in early-stage DLBCL.

Since these initial studies were performed, the systemic therapy for DLBCL has been significantly improved with the addition of rituximab to the standard CHOP regimen. Several randomized studies have evaluated CHOP versus R-CHOP showing a significant improvement in both progression-free survival and overall survival with the addition of rituximab [6,7].

For patients with advanced (stage III-IV) DLBCL, chemoimmunotherapy is the cornerstone of treatment. Many strategies have been explored to improve upon CHOP and R-CHOP including more chemotherapy cycles[8], dose dense chemotherapy[9,10], more intensive chemotherapy regimens[11,12], maintenance rituximab[7], and high-dose chemotherapy and autologous stem cell transplant[13]. None have consistently improved survival compared with standard R-CHOP.

The role of consolidation RT is not as well defined in stage III-IV disease. In the rituximab era, series from M.D. Anderson[14], Duke[15], and Emory[16] have demonstrated improvements in local control[15,16] and survival[14,16] with consolidation RT, even when patients are in complete response by PET-CT. Data from prospective studies have suggested that RT may be advantageous in the presence of bulky disease. The RICOVER-60 trial was a four-arm randomized study comparing different chemotherapy regimens. Consolidation RT was delivered to sites of initial bulk (≥ 7.5 cm) or extranodal disease. At the conclusion of the trial, an additional cohort was accrued and treated with the most effective regimen from the randomized trial (R-CHOP-14 X 6 cycles) but without consolidation RT (referred to as the RICOVER-noRTh trial). When comparing the two arms receiving the same chemotherapy regimen, the addition of consolidation RT improved both PFS (75% versus 61%, $p<0.001$) and OS (90% versus 65%, $p=0.001$)[17]. Similarly, the German UNFOLDER trial (NCT00278408) prematurely closed the R-CHOP arms not receiving consolidation RT due to excess relapses in those with bulky disease (≥ 7.5 cm). Results from this trial have not yet been published.

1.2 PET-CT Assessment after Chemotherapy

Positron emission tomography-computed tomography (PET-CT) scans have become standard in lymphoma management both to assess disease extent at diagnosis as well as evaluate response to therapy. Patients treated with chemotherapy alone who have not achieved a complete response by PET-CT are at substantially higher risk of relapse compared with patients who achieve a negative post-chemotherapy PET-CT[18-20]. A positive PET-CT is also associated with an increased risk of local failure after chemotherapy and consolidation RT. In a study from Duke, patients with a positive post-chemotherapy PET-CT were at higher risk of in-field failure compared with patients with a negative post-chemotherapy PET after administration of consolidation RT[21]. Four-year in-field control was 97% with a negative PET versus 81% with a positive PET ($p<0.01$). The median RT dose was 30 Gy. Thus, PET scans help discriminate patients who have not had an optimal response to chemotherapy and are at increased incidence of disease relapse, including failure at original sites of disease, after a combined modality regimen. These patients may require a higher dose of consolidation radiation therapy and would not be candidates for this study.

Whether patients benefit from consolidation RT in the setting of a negative post-chemotherapy PET-CT has not been adequately examined. A large retrospective studies from MD Anderson[22] suggested that RT is still beneficial, even in the presence of a negative post-chemotherapy PET-CT. A randomized study from the LYSA/GOELAMS group compared 4-6 cycles of R-CHOP with and without RT (40 Gy) in stage I-II DLBCL who achieved a complete response by PET-CT[23]. Patients with bulky disease (> 7 cm) were excluded and 94% of patients had a very favorable modified International Prognostic Index (0-1). The study utilized a non-inferiority design with a delta of 10%. No per protocol analysis was provided. Using intention-to-treat analyses, event-free survival at 5 years was 89% with R-CHOP versus 92% with R-CHOP plus RT ($p=0.18$). There were no local failures in the arm receiving RT while 5/13 failures without RT involved an originally involved site.

1.3 Risk of In-field Failure after Combined Modality Therapy

In-field failure (disease recurrence within the radiation field) is rare after combined modality therapy. In three large randomized trials, crude in-field failure rates after CHOP and radiation therapy (30 to 40 Gy) ranged between 4% and 7% [3,24,25]. In these studies, rituximab was not administered and PET scans were not used to assess response to chemotherapy prior to consolidation RT. In patients treated at Duke University[26] and MD Anderson[27], with a median dose of 30 Gy in the setting of a negative post-chemotherapy PET-CT and utilization of rituximab, local control rates of >95% have been observed.

1.5 Rational for Radiation Therapy Dose Reduction

The British National Lymphoma Investigation randomized study showed no difference in freedom from local progression, progression-free survival, or overall survival between 30 Gy and 40-45 Gy[5]. Only 10% of the patients received rituximab and PET-CT imaging post-chemotherapy was not routinely performed.

A phase II prospective study from Duke University enrolled 62 patients with DLBCL NOS or primary mediastinal (thymic) B-cell lymphoma (PMBCL) between 2010 and 2016. Most (79%) had stage I-II disease with the remainder having advanced disease. Bulky disease (≥ 7.5 cm) was present in 40% of patients. All patients were treated to 19.5-20 Gy after achieving a complete response to 4-6 cycles of R-CHOP or R-EPOCH. With a median follow-up of 43 months, there was only 1 local recurrence (a patient with stage I PMBCL s/p 6 cycles of DA-EPOCH-R who developed a local recurrence 12 months later s/p excisional biopsy showing nodular sclerosis Hodgkin lymphoma. She received no further therapy and is disease-free 5 years later. She was scored as a local failure. An additional 6 patients developed distant recurrences, none of whom had evidence of local failure on imaging. The 5-year local control was 98% (95% CI 89% - 100%). Progression-free and overall survival at 5 years was 81% and 88%.

As long-term outcomes in localized DLBCL are favorable, decreasing the risk of late effects is critical. The risk of complications related to RT, including cardiac disease and secondary cancers, appear to be related to both dose [28] and volume [28,29]. If the dose and volume of RT can be reduced, while maintaining high rates of disease control, this would undoubtedly decrease the risk of side effects and long-term risks.

While a confirmatory phase III study would be ideal, the statistics of such a trial are prohibitive. A non-inferiority trial design with a 3% non-inferiority margin would require ~ 2800 patients. A 5% margin would require ~1130 patients. It is felt that a larger phase II study, if promising, would be sufficient to change standard of care. At a research conference of the International Lymphoma Radiation Oncology Group, it was determined that such a study should incorporate two major alterations from the original Duke study. First, only patients with DLBCL NOS would be studied, excluding patients with primary mediastinal (thymic) large B-cell lymphoma. Second, patients felt appropriate for 3 cycles of chemotherapy should be eligible.

2.0 PURPOSE

This phase II study will evaluate whether a reduction in the dose of consolidation RT in patients who achieve a negative post-chemotherapy PET-CT scan following 3 to 6 cycles of chemoimmunotherapy, will be associated with a low risk of in-field failure. The goal of this approach is to maintain excellent control rates while minimizing the risk of acute and late toxicity.

2.1 Hypothesis

Hypothesis- After more effective systemic therapy (employing rituximab), and confirmation of optimal response to chemotherapy (negative post-chemotherapy PET-CT), the RT dose can be safely reduced from 30 Gy to 20 Gy while maintaining high rates of local control.

3.0 OBJECTIVES

3.1 Primary Objective

To determine if high rates of local control can be maintained after a reduction in the RT dose (from 30 Gy to 20 Gy) after 3 to 6 cycles of chemo-immunotherapy

3.2 Secondary Objectives

3.2.1 To determine disease-free survival and overall survival after chemotherapy and low-dose (20 Gy) consolidation radiation therapy.

3.2.2 To identify patterns of failure after combined modality therapy using lower doses of consolidation RT

3.3 Design and Procedure

This study will initially open at Duke University as a single site. Christopher Kelsey, MD will serve as the study Principal Investigator at Duke. It is anticipated that ~40 subjects will be accrued to the study at Duke over 4 years.

The protocol will open at up to 10 additional sites nationally and internationally. All sites will follow the same protocol. The accrual goal for the combined sites is approximately 240 subjects. Each site will operate independently and obtain IRB approval to open the study at their institution and each site will run the study as a single institutional study. Data from all sites will be merged for the interim and final analyses. Chemotherapy treatment, laboratory results, PET-CT imaging, treatment planning, radiation treatment delivery, adverse events, disease-free survival and overall survival data will be merged for analysis of treatment planning and dose parameters for managing subjects with DLBCL.

The participating centers, in addition to Duke University include the Mayo Clinics, SingHealth (Singapore), Yonsei University (Korea), Juntendo University (Japan), Brigham and Women's Hospital/Dana-Farber Cancer Institute, University of Rochester Wilmot Cancer Center, MD Anderson Cancer Center, University Hospital Motol (Czech Republic) and the University of Torino (Italy), though other centers are expected to also participate. Limited data sets will be shared when fully executed Collaborative Research Agreements are in place between Duke and each participating site.

We plan to evaluate the clinical course of subjects treated on protocol and record the presence or absence of progression and long-term side effects at the time of each follow-up appointment. With this information, we will be able to determine if high (≥95%) rates of local control can be maintained with a reduced course of RT (20 Gy) after 3-6 cycles of chemo-immunotherapy. Subjects will be followed for up to 10 years via the electronic medical record, post completion of radiation therapy.

Given the increased sample size needed within the statistical framework of the study, we require a multi-institutional collaboration such as this to perform this phase II study.

4.0 PATIENT RECRUITMENT

This is a prospective, phase II, single arm study. Ascertainment of eligibility will be determined by review of the medical records of patients with DLBCL seen in the medical oncology or radiation oncology clinics by members of the study team. The subject population (with no gender or minority restrictions) will include adult patients meeting the eligibility criteria. Inclusion of women and

minorities is encouraged. All patients must sign an IRB-approved informed consent prior to enrollment. Consent will be obtained after completing chemo-immunotherapy.

5.0 PATIENT SELECTION

5.1 Eligibility

1. ≥ 18 years of age.
2. Histologic documentation of stage I-IV diffuse large B-cell lymphoma, not otherwise specified (DLBCL NOS), as defined by the 2016 WHO classification[30]. This would include all entities within this category including germinal center B-cell and non-germinal center B-cell subtypes and those with a double expressor phenotype. Also eligible are stage I-IV high-grade B-cell lymphoma with *MYC* and *BCL2* and/or *BCL6* rearrangements and high-grade B-cell lymphoma, NOS. Patients presenting with a concurrent indolent lymphoma at the time of original diagnosis are eligible[31].
3. Completion of at least 3 cycles of a rituximab-containing, anthracycline-based combination chemotherapy regimen (R-CHOP preferred but not mandated).
4. Negative interim PET-CT scan performed within 2 weeks of the final cycle of chemoimmunotherapy or negative post-chemotherapy PET-CT performed within 10 weeks after the final cycle of chemoimmunotherapy. This is defined as a score of 1-3 on the PET Five Point (Deauville) Scale using the Modified Lugano Response Criteria for Non-Hodgkin's Lymphoma (Appendix 1)
5. ANC ≥ 1000 and platelet count ≥ 40,000
6. Negative serum pregnancy test in women of child-bearing potential within 24 hours of initiating RT for DUHS patients; external sites will follow their institutional guidelines on the type and timing of test used to confirm negative pregnancy
7. Signed study-specific informed consent.

5.2 Ineligibility

1. Primary central nervous system lymphoma, primary cutaneous DLBCL, leg type, T-cell/histiocyte-rich large B-cell lymphoma, primary mediastinal (thymic) large B-cell lymphoma, or other distinct non-Hodgkin lymphomas arising from large B-cells included in the WHO classification
2. Consolidation or prophylactic RT to the testicle
3. Prior low-grade lymphoma (e.g., transformed follicular lymphoma)
4. Any absolute contraindications to irradiation.

6.0 PRETREATMENT EVALUATION

1. A complete history and physical examination
2. Complete blood count (CBC) at least 3 weeks after the last cycle of chemo-immunotherapy.
3. Re-staging PET-CT obtained after completing chemo-immunotherapy or interim PET-CT performed within 2 weeks of the final cycle of chemo-immunotherapy.
4. Negative serum pregnancy test for women of child-bearing potential

7.0 REGISTRATION PROCEDURE

The patients will be recruited from the clinics of medical oncology by their treating physician or by the radiation oncologist from his/her practice. Only radiation oncologists listed as Key Personnel for this study may enroll patients on this study. The patient's primary medical oncologist will be appraised of

the patient's intent to participate in the study. Following verification of eligibility the patient will be assigned a sequential study ID number.

8.0 TREATMENT

8.1.1 Radiation Therapy

Radiation therapy is to be initiated ideally within 4 weeks of completing chemo-immunotherapy, but no later than 10 weeks after day 1 of the final cycle of chemo-immunotherapy.

Technique and Equipment

All patients will be treated using three-dimensional RT, intensity-modulated RT, or volumetric modulated arc RT with either photons or protons as appropriate based on clinical circumstances.

Treatment Planning

Patients will be treated using involved-site radiation therapy (ISRT) as delineated for nodal [32] and extranodal[33] non-Hodgkin lymphomas. Briefly, the gross tumor volume (GTV) will include the original extent of disease. A clinical target volume (CTV) will include the original extent of disease adjusted to exclude normal tissues that were clearly uninvolved though previously displaced by the GTV, imaging uncertainties between diagnostic and treatment planning scans, as well as possible microscopic disease in the immediate vicinity of the GTV. In some cases, an internal target volume (ITV) can be defined that will take into account target motion from respiration. The CTV will be enlarged to account for uncertainties in daily patient positioning to create a planning target volume (PTV). CTV and PTV expansions will be left to the discretion of the treating physicians based on their clinical judgment.

Stage I disease- The CTV will include all sites of original involvement.

Stage II disease- The CTV will normally include all sites of original involvement. In rare circumstances, if the treating radiation oncologist feels inclusion of all original sites is not clinically advantageous, consolidation of only certain sites (such as bulky disease) is acceptable.

Stage III-IV disease- The CTV will be individualized based on the clinical presentation. When appropriate, consolidation of all sites originally involved is encouraged. However, consolidation of only certain sites (such as sites of bulky disease or limited skeletal involvement) is acceptable.

Treatment

RT will be administered daily, 5 days/week. Patients will be treated with 1.5-2 Gy fractions to a total dose of 19.5-20 Gy. Daily image guidance recommended but not mandated.

Treatment Interruptions during RT

Treatment breaks due to RT-induced toxicity are expected to be very rare but permitted at the discretion of the treating radiation oncologist and/or medical oncologist. When clinically indicated, treatment breaks of ≤ 3 treatment days will not be considered a protocol deviation.

9.0 EVALUATIONS DURING AND AFTER TREATMENT

9.1 During Radiation Therapy

All patients will be evaluated by the attending radiation oncologist weekly during RT or more frequently if indicated.

9.2 Withdrawal Criteria

1. Non-compliance with protocol requirements.
2. Patient request or withdrawal of consent.

9.3 Follow-up

Follow-up schedule will be at the discretion of the treating physician. Optimally, patients will return every 6 months for the first two years to Radiation Oncology and annually thereafter for follow-up. Their medical oncologist will also evaluate the patient routinely per standard evaluation practices. All follow-up examinations, including laboratory work and imaging studies will be performed at the discretion of the treating physicians. However, if a patient relapses, PET-CT imaging at the time of imaging is highly recommended to ascertain sites of disease recurrence in relation to the radiation treatment fields.

10.0 CONFIDENTIALITY and PROTECTION of RESEARCH SUBJECTS

All study-related materials will be stored electronically on password-protected DUHS maintained servers. All personnel involved in the conduct and analysis of data from the study will have ethics training in the protection of research subjects.

11.0 PROTOCOL MANAGEMENT and DATA COLLECTION

This study will be conducted in accordance with applicable Federal regulations, radiation therapy standards and Duke University School of Medicine policies. Data will be entered on the study specific e-forms within a timely manner. Subjects will be followed up to 10 years via the electronic medical record, post completion of radiation therapy.

The following data points will be collected:

1. Institution-specific identification number
2. Treating institution
3. Date of initial diagnosis
4. Age at diagnosis
5. Gender
6. Ann Arbor Stage
7. LDH (normal or elevated)
8. Number of extranodal sites involved
9. ECOG Performance Status
10. Largest tumor size
11. Cell of origin (Germinal center or non-germinal center) if available
12. Double hit phenotype (*MYC* gene rearrangement with translocation of *BCL2* or *BCL6* by FISH) if available
13. Double expressor phenotype (MYC and BCL2 overexpression by IHC) if available
14. Chemotherapy regimen
15. Number of cycles administered
16. Date of last chemotherapy cycle
17. Post-chemotherapy PET-CT Deauville Score

18. Date of trial enrollment
19. Radiation method (3D/IMRT/VMAT/Protons)
20. Date of first and last RT fractions
21. RT daily dose
22. Total Dose
23. Sites Treated (Comprehensive or Selective)
24. Disease Relapse and Patterns of Failure
25. Late effects of RT (2nd malignancies, cardiac complications, miscellaneous)
26. Date of last follow-up
27. Date and cause of death

12.0 RISKS/BENEFIT ASSESSMENT

Radiation therapy is a recognized treatment modality for patients with DLBCL. The risks of treatment are expected to be less since a lower dose of RT will be employed. It is possible that 20 Gy is insufficient which may increase the risk of disease recurrence which may necessitate further treatment. With smaller RT doses, it is expected that both acute and long-term toxicity will be less.

The side effects of RT are related to the site treated.

Likely acute side effects

- Fatigue
- Radiation dermatitis, usually mild
- Xerostomia, mucositis, and/or dysguesia if the head and neck is in the radiation field.
- Esophagitis if the chest is in the radiation field
- Nausea and/or diarrhea if the abdomen is in the radiation field

Less likely acute side effects

- Decrease in blood counts, which may result in bleeding or infection

Likely late side effects

- Skin in the treated area may appear tanned and may stay this way for a number of years after radiation

Less likely late side effects

- Xerostomia if the head is in the radiation field
- Hypothyroidism if the neck is in the radiation field\
- Heart disease which may result in a faster onset of atherosclerotic and/or valvular disease if the chest is in the radiation field
- Pneumonitis (inflammation of the lungs) causing cough or shortness of breath if the chest is in the radiation field

Rare

- Developing a radiation-induced malignancy.

12.1 Acute Toxicities from RT

Severe acute toxicity from 20 Gy of radiation therapy is expected to be rare. In the phase II study from Duke University, only 18% of patients developed grade 2 non-hematologic toxicity, most commonly mucositis or esophagitis. Only 3% of patients developed grade 3 non-hematologic toxicity, all self-limiting. As a lower dose of radiation therapy is being administered compared with standard of care, acute toxicities will not be recorded.

12.2 Late Toxicities from RT

The PI is responsible for the identification and documentation of possible late adverse events (>90 days from initiation of treatment) from treatment, including cases of second malignancies, cardiac disease, hypothyroidism, etc.

Attribution of adverse events (AEs) will be indicated as follows:

Definite: The AE is clearly related to the study therapy
Probably: The AE is likely related to the study therapy
Possible: The AE may be related to the study therapy
Unlikely: The AE is doubtfully related to the study therapy
Unrelated: The AE is clearly NOT related to the study therapy

AEs will be assessed according to the CTCAE (Common Terminology Criteria for Adverse Events) version 5.

12.2.1 Reporting of Adverse Events

No specific reporting requirements for AEs.

12.3 Serious Adverse Events (acute or late)

An AE is considered "serious" if in the opinion of the investigator it is one of the following outcomes:

- Fatal
- Life-threatening
- Constitutes a congenital anomaly or birth defect
- A medically significant condition (defined as an event that compromises subject safety or may require medical or surgical intervention to prevent one of the three outcomes above).
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant incapacity or substantial disruption to conduct normal life functions.

12.3.1 Reporting of SAEs

SAEs will be reported to the IRB as per institutional policy.

12.4 Other Reportable Information

The study team will adhere to the institutional policy on subjects and pregnancy stringently.

12.5 Safety Oversight Committee (SOC)

The Duke Cancer Institute SOC is responsible for annual data and safety monitoring of DUHS sponsor-investigator phase I and II, therapeutic interventional studies that do not have an independent Data Safety Monitoring Board (DSMB). The primary focus of the SOC is review of safety data, toxicities and new information that may affect subject safety or efficacy. Annual safety reviews includes but may not be limited to review of safety data, enrollment status, stopping rules if applicable, accrual, toxicities, reference literature, and interim analyses as provided by the sponsor-investigator. The SOC in concert with the DCI Monitoring Team oversees the conduct of DUHS cancer-related, sponsor-investigator greater-than-minimal-risk intervention studies that do not have an external monitoring plan, ensuring subject safety and that the protocol is conducted, recorded and reported in accordance with the protocol, standing operating procedures (SOPs), Good Clinical Practice (GCP), and applicable regulatory requirements. The DCI Safety Oversight Committee (SOC) will perform annual reviews on findings from the DCI Monitoring Team visit and additional safety and toxicity data submitted by the Principal Investigator.

12.6 External Data and Safety Monitoring Board (DSMB)

Not applicable.

13. QUALITY CONTROL AND QUALITY ASSURANCE

13.1 Monitoring

This clinical research study will be monitored both internally by the PI and institutionally by the Duke Cancer Institute (DCI). In terms of internal review, the PI will continuously monitor and tabulate possible late adverse events occurring ≥ 90 days after completing radiation therapy. Appropriate reporting to the Duke University Medical Center IRB will be made for serious adverse events, whether acute or late. The PI of this study will also continuously monitor the conduct, data, and safety of this study to ensure that:

The Interim analysis occurs as scheduled;
Stopping rules are enforced if applicable;
Risk/benefit ratio is not altered to the detriment of the subjects;
Appropriate internal monitoring of late AEs and acute or late SAEs and outcomes is done;
Over-accrual does not occur;
Under-accrual is addressed with appropriate amendments or actions;
Data are being appropriately collected in a reasonably timely manner.
DCI review and monitoring of this protocol occurs in accordance with the NCI-approved Data and Safety Monitoring Plan. Briefly, protocol review begins with an initial review by the Cancer Protocol Committee (CPC), which assesses the ethics and safety of the protocol. Documentation of these assessments will be maintained. Formal, independent monitoring will be conducted by the DCI Monitoring Team after the first 3 subjects are enrolled, followed by annual monitoring of 1-3 subjects

until the study is closed to enrollment and subjects are no longer receiving study interventions that are more than minimal risk. DCI Monitoring Team reports and additional data/safety/toxicity reports submitted by the PI will be reviewed by the Safety Oversight Committee (SOC) on an annual basis. Additional monitoring may be prompted by findings from monitoring visits, unexpected frequency of serious and/or unexpected toxicities, or other concerns. Monitoring visits may also be initiated upon request by DUHS and DCI Leadership, CPC, SOC, a sponsor, an investigator, or the IRB.

External study sites will be self-monitored (see Appendix 2). The Duke study team will collect monitoring reports if available from external sites which have subjects enrolled. External site self-monitoring reports and quarterly study conference call minutes will be submitted to the Duke IRB during study continuing renewal.

13.2 Audits

The Duke School of Medicine Office of Audit, Risk and Compliance (OARC) office may conduct confidential audits to evaluate compliance with the protocol and the principles of GCP. The PI agrees to allow the OARC auditor(s) direct access to all relevant documents and to allocate his/her time and the time of the study team to the OARC auditor(s) in order to discuss findings and any relevant issues.

OARC audits are designed to protect the rights and well-being of human research subjects. OARC audits may be routine or directed (for cause). Routine audits are selected based upon risk metrics generally geared towards high subject enrollment, studies with limited oversight or monitoring, Investigator initiated Investigational Drugs or Devices, federally-funded studies, high degree of risk (based upon adverse events, type of study, or vulnerable populations), Phase I studies, or studies that involve Medicare populations. Directed audits occur at the directive of the IRB or an authorized Institutional Official.

OARC audits examine research studies/clinical trials methodology, processes and systems to assess whether the research is conducted according to the protocol approved by the DUHS IRB. The primary purpose of the audit/review is to verify that the standards for safety of human subjects in clinical trials and the quality of data produced by the clinical trial research are met. The audit/review will serve as a quality assurance measure, internal to the institution. Additional goals of such audits are to detect both random and systemic errors occurring during the conduct of clinical research and to emphasize "best practices" in the research/clinical trials environment.

13.3 Data Management and Processing

13.3.1 Study Documentation

Study documentation includes, but is not limited to, source documents, case report forms, monitoring logs, appointment schedules, study team correspondence with sponsors or regulatory bodies/committees, and regulatory documents that can be found in the DCI-mandated "Regulatory Binder", which includes but is not limited to signed protocol and amendments, approved and signed informed consent forms, FDA Form 1572, CAP and CLIA laboratory certifications, and clinical supplies receipts and distribution records.

Source documents are original records that contain source data, which is all information in original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source documents include but are not limited to hospital

records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial. When possible, the original record should be retained as the source document. However, a photocopy is acceptable provided that it is a clear, legible, and an exact duplication of the original document.

13.3.2 Case Report Forms (CRFs)

REDCAP database will be the primary data collection document for the study. The CRFs will be updated in a timely manner following acquisition of new source data. Only the PI and persons listed as key personnel are permitted to make entries, changes, or corrections in the CRF.

An audit trail will be maintained automatically by the electronic CRF management system, REDCAP. All users of this system will complete user training, as required or appropriate per regulations.

13.3.3 Data Management Procedures and Data Verification

Clinical research coordinators will have access to REDCAP based on their specific roles in the protocol. The designated data manager will be managing the REDCAP database.

Completeness of entered data will be checked automatically by the eCRF system, and users will be alerted to the presence of data inconsistencies. Additionally, the data manager, and clinical research coordinators will cross-reference the data to verify accuracy. Missing or implausible data will be highlighted for the PI requiring appropriate responses (i.e. confirmation of data, correction of data, completion or confirmation that data is not available, etc.).

The database will be reviewed and discussed prior to database closure, and will be closed only after resolution of all remaining queries. An audit trail will be kept of all subsequent changes to the data.

13.3.4 Coding

All medical terms will be coded with MedDRA (Medical Dictionary for Regulatory Activities).

13.3.5 Study Closure

Following completion of the studies, the PI will be responsible for ensuring the following activities:

- Data clarification and/or resolution
- Review of site study records for completeness

13.0 COSTS

Radiation therapy is a standard of care for DLBCL. All costs of the treatment as well as follow-up examinations will be billed to the patient or their insurance carrier.

14.0 STATISTICAL CONSIDERATIONS

Statistical Analysis of Primary Objective

This trial will accrue 240 patients (total from all sites) over a time period of approximately 4 years (~5 patients per month). All patients will be followed for up to 10 years after study entry. The primary

objective is to confirm that a 5-year local control rate of 95% can be maintained with dose-reduced consolidation radiation therapy. Local control is defined as absence of disease recurrence within the radiation therapy field treated on study. Time-to-local-failure is defined as date of enrollment to date of local failure. At the time of disease recurrence, those with evidence of progression at site(s) treated with radiation therapy will be scored as a local failure while those patients without evidence of local failure will be censored. However, censored patients will be followed for evidence of subsequent local failure during their clinical follow-up for descriptive purposes.

We will test the null hypothesis that the 5-year local control rate is ≤ 0.90 versus the alternative hypothesis that the 5-year local control rate is ≥ 0.95. The final analysis will be conducted at the end of year 6 post study activation of the trial at Duke (2 years after the last patient is enrolled on study).With 240 patients enrolled over 4 years and followed for 2 years after the last patient is entered this hypothesis can be tested with approximately 81% power (1-sided α=0.1). At the final analysis the expected numbers of events under the null and alternative hypotheses are 19.0 and 9.0, respectively. A long-term analysis will be conducted after all patients have been followed for 5 years, approximately 9 years from activation of the trial at Duke. At the time of the long-term analysis approximately 24 and 12 events, respectively, are expected under the null and alternative hypotheses.

One interim analysis for futility will be conducted after 185 person-years (PY) of follow-up is reached (approximately 2.5 years from study activation). The minimum cumulative incidence needed to accept the null hypothesis and stop the trial is 0.021 (4/185). Based on simulations (N=5,000) the probability of early stopping under this stopping rule is 0.44 under the null hypothesis and 0.07 under the alternative... If the observed local recurrence rate at the interim analysis is < 4/185 the trial will continue to completion. If accrual is less than 3-4 patients per month the futility stopping rule will be revised to reflect the actual accrual rate.

All statistical analyses will include all patients enrolled at all participating centers.

Statistical Analysis of Secondary Objective 1
Disease-free survival (DFS) will be defined as the time from on-study to first disease progression (local or distal) or death due to any cause, whichever comes first. Overall survival will be defined as the time from on-study to death due to any case. Both distributions will be estimated with the Kaplan-Meier method. The 5-year DFS rate and the 5-year overall survival rate will be estimated with their 80% confidence intervals.

Statistical Analysis of Secondary Objective 2
To examine the patterns of failure, we will tabulate the various ways that patients failed up until the time of the analysis. For example, these ways will include local only, local + distant, and distant only.

Appendix 1

Modified Lugano Response Criteria for Non-Hodgkin's Lymphoma

PET Five Point Scale

1 No uptake above background
2 Uptake ≤ mediastinum
3 Uptake > mediastinum but ≤ liver
4 Uptake moderately > liver
5 Uptake markedly higher than liver and/or new lesions
X New areas of uptake unlikely to be related to lymphoma

Appendix 2

Multi-site plan for Phase II study of Dose-Reduced Consolidation Radiation Therapy in Patients with Diffuse Large B-cell Lymphoma

Individual site responsibilities

1) All participating sites to this study will operate as single institution sites.
2) Each site is responsible to obtain their institutional IRB approval to open the study to subject enrollment
3) Each site is responsible for compliance with all regulatory documents; regulatory compliance is defined as according to their institutional, state and national regulations/policies according to geographic location.
4) Each site PI or designee is responsible for site study start up meetings and assurance that research education training of key personnel is adhered to in accordance with Good Clinical Practice (GCP) and required institutional research education requirements.
5) Each site will facilitate and adhere to their institutional internal/routine monitoring policies.
6) Each site will provide IRB approval notices and self-monitoring reports, if available to the Duke study team when requested.

Duke Cancer Center Radiation Oncology Responsibilities:

1) A fully executed Collaborative Research Agreement must be in place between Duke and each participating site. Agreements will be processed through the Duke Office of Research Contracts (ORC). Duke Radiation Oncology Clinical Trials staff will be responsible to initiate all agreements through ORC.
2) The study coordinator will request a copy of the site specific IRB initial study approval notice and retain these on file.
3) The study coordinator is responsible to ensure that amendments concerning study procedures and/or treatment to the study protocol will be communicated clearly and efficiently to all participating sites.
4) When the Duke IRB issues a Notice of Approval (NOA), the study coordinator will inform all participating sites via email. Tracked copies of the amended study documents will be sent to each site with the Duke NOA with the expectation that sites will complete an amendment submission within one month to their institutional IRB.
5) Key personnel changes will be communicated ONLY when a KP change involves a site PI.
6) The Duke study coordinator will request enrollment statuses from each site monthly. A record of the total enrollment numbers will be retained at Duke.
7) Radiation Oncology will arrange quarterly conference calls with all sites to discuss study progress/clarifications/ review adverse events. All participating sites are expected to attend the call.
8) The Duke PI and his designees will be available via phone and email to answer study related questions throughout the life of the study.
9) **The Duke Cancer Center will serve as a central statistical center by ensuring:**
(i) the privacy of subjects and the confidentiality of data are adequately maintained with a study specific password protected REDCap database

(ii) designated key personnel at each collaborating institution will have a REDCap account and will have completed the Secure Usage Agreement (SUA) before access can be assigned https://redcap.dtmi.duke.edu/redcap/.
Site-specific Data Access Groups will assign each user to a specific group. This will isolate records to specific groups. Data Access Groups restrict viewing of data within a database; users at each site should only be able to view data from their site but not any other sites.
(iv) the Duke PI and biostatisticians named to key personnel will have access to all site data entered in the database. The Duke PI is responsible for overseeing data entry is completed in accordance with the protocol requirements.

10) Data Safety monitoring:

(i) Section 12.1 of the protocol states severe acute toxicity from 20 Gy of radiation therapy is expected to be rare. A lower dose of radiation therapy is being administered compared with standard of care. Further, this is a single arm study without a comparator arm. For these two reasons, acute toxicities will not be recorded. The primary objective is to confirm that a 5-year local control rate of 95% can be maintained with dose-reduced consolidation radiation therapy. Time-to-local-failure is defined as date of enrollment to date of local failure.

(ii) The PI is responsible to monitor and tabulate possible late adverse events occurring ≥ 90 days (to include local failure) after completing radiation therapy. Appropriate reporting to the IRB for serious adverse events, whether acute or late will be adhered to.
Late toxicities that are of particular interest in long-term follow up are cardiac disease, hypothyroidism, pneumonitis and the incidence of secondary cancers. Secondary cancers will be categorized whether they developed within or outside the RT field.

(iii) During the quarterly conference calls with active sites study progress and review of adverse events, including cases of lymphoma disease progression will be completed. These calls will include administrative reports by site that describe subjects screened, enrolled, completed, and discontinued of the study population.

(iv) Prior to the conference calls the Duke study team will prepare safety reports documenting late toxicities and summarizing safety data/ adverse events.

(v) During the conference calls late adverse events, acute and late serious adverse events, primary and secondary endpoint data (local and distant disease failures), as well as any other information requested by the PI will be discussed in detail. In terms of internal review, the PI will continuously monitor and tabulate the incidence and the type of late adverse events occurring. Documentation of conference calls will be maintained by the Duke study team.

(vi) Interim analysis will occur as described in the protocol. Interim analyses reports will be prepared by statisticians named to key personnel. Stopping rules will be enforced if applicable

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