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**TITLE:** 5-5-5 Adaptive Bridging Radiation Therapy (ABRT) for Relapsed/Refractory B-cell Lymphoma Prior to CAR T-cell Therapy

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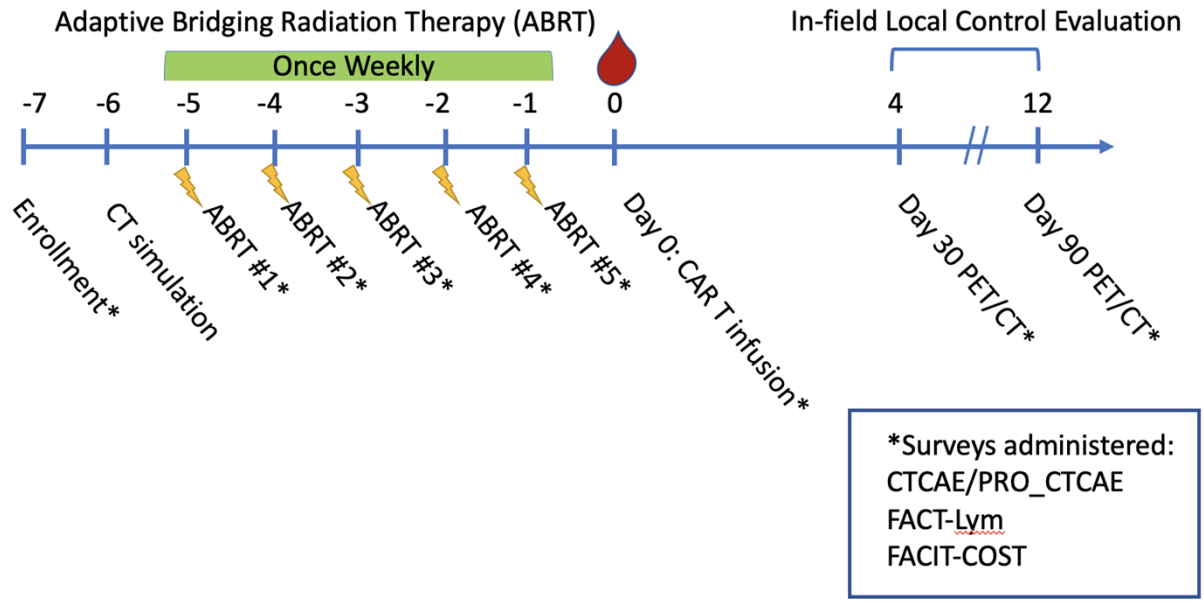
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**SCHEMA**


Adaptive Bridging Radiation Therapy (ABRT)
Once Weekly
In-field Local Control Evaluation
-7
-6
-5
-4
-3
-2
-1
0
4
12
Enrollment*
CT simulation
ABRT #1*
ABRT #2*
ABRT #3*
ABRT #4*
ABRT #5*
Day 0: CAR T infusion*
Day 30 PET/CT*
Day 90 PET/CT*
*Surveys administered:
CTCAE/PRO_CTCAE
FACT-Lym
FACIT-COST

# 1. INTRODUCTION

## 1.1 Study Disease

Non-Hodgkin lymphoma (NHL) is a heterogeneous group of cancers originating in B lymphocytes, T lymphocytes or natural killer cells. In the United States, B cell lymphomas represent 80-85% of cases reported. In 2023, approximately 80,000 new cases of NHL and over 20,000 deaths related to the disease were estimated to occur[1]. Non-Hodgkin lymphoma is the most prevalent hematologic malignancy and is the seventh leading site of new cancers among men and women and account for 4% of all new cancer cases and 3% of deaths related to cancer[1]. Large B-cell lymphomas represent the most common sub-group of NHL, of which further details are provided below on the more common entities[2].

### 1.1.1 Diffuse Large B-cell Lymphoma

Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of large B-cell lymphoma, accounting for approximately 30% of NHL cases. There are approximately 22,000 new diagnoses of DLBCL in the United States each year. In the past two decades, progress has been made in understanding the biological heterogeneity of DLBCL and in improving survival with combinations of CHOP and immunotherapy. The addition of rituximab into combination therapies for DLBCL have greatly improved patient outcomes. However, patients with chemotherapy-refractory DLBCL following treatment still have a particularly dire prognosis, with historically no curative treatment options[3].

The population with the highest unmet need continues to consist of patients who do not respond to first line combination chemotherapy (typically R-CHOP) or who do not respond to their last course of combination chemotherapy, as the disease is mostly insensitive to subsequent combination chemotherapy (typically R-ICE, R-ESHAP) (Table 1). In a review of 64 patients with DLBCL with disease progression during first line chemotherapy or only transient response (≤90 days) after end of induction treatment, the response rate to second line therapy was 15% and the median overall survival (OS) was 6 months, and no patient survived more than 26 months after first diagnosis[4]. An analysis of outcome in 1126 patients with DLBCL after first line R-CHOP included 33 patients with primary refractory DLBCL who received second line therapy with curative intent. Only 3 (9%) patients were able to receive autologous stem cell transplantation (ASCT), and only 1 (3%) patient achieved long term survival[5]. Seshadri et al analyzed 120 patients who did not respond to second line platinum-based chemotherapy regimens (e.g., R-ICE) and showed that only 14% responded to their third line therapy[6]. Ardeshna et al. followed 19 patients with large B-cell lymphoma, and 9 patients with TFL who did not respond to second line chemotherapy[7]. Only 5 of the 28 total patients (18%) responded to third line chemotherapy.



**Table 1. Historical Responses in Refractory NHL (SD or PD to Last Line of Therapy)**

| Setting | Outcome to Subsequent Therapy |
|---|---|
| **Refractory to 1st line** | |
| [8](n=28) | ORR 21% |
| [4](n=64) | ORR 15%, median OS 6 mos |
| [7](n=5) | ORR 0% |
| [5](n=33) | Proceeded to ASCT 9%, 3% survived > 1 year |
| [9](n = 111) | ORR 23%, median OS 10 mos |
| [10](n=10) | ORR 10% |
| **Refractory to 2nd line** | |
| [11](n=55) | Median OS 5 mos |
| [7](n=28) | ORR 18%, median OS (large B-cell lympohoma) <6 mos |
| [6](n=73) | ORR 14% |
| **Relapsed post ASCT** | |
| [12](n=45) | Median OS 8 mos |

These consistently discouraging results demonstrate that new treatment options are urgently needed for patients whose tumors have demonstrated a lack of response to chemotherapy.

### 1.1.2 Primary Mediastinal B-cell Lymphoma and Follicular Lymphoma

Primary mediastinal B-cell lymphoma (PMBCL) has distinct clinical, pathological, and molecular characteristics compared to DLBCL. PMBCL is thought to arise from thymic (medullary) B cells and represents approximately 3% of patients diagnosed with large B-cell lymphoma. PMBCL is typically identified in the younger adult population in the fourth decade of life with a slight female predominance[13,14]. Gene expression profiling suggests deregulated pathways in PMBCL overlap with Hodgkin lymphoma. Initial therapy of PMBCL generally includes anthracycline-containing regimens with rituximab with or without involved field radiotherapy. A Phase 2, prospective study of infusional dose-adjusted etoposide, doxorubicin, and cyclophosphamide with vincristine, prednisone, and rituximab (DA-EPOCH-R) demonstrated radiotherapy may not be required[15].

Follicular lymphoma (FL), a B cell lymphoma, is the most common indolent (slow-growing) form of NHL, accounting for approximately 20% to 30% of all NHLs. Some patients with FL will transform (TFL) histologically to DLBCL which is more aggressive and associated with a poor outcome. Histological transformation to DLBCL occurs at an annual rate of approximately 3% for 15 years with the risk of transformation continuing to drop in subsequent years. The biologic mechanism of histologic transformation is unknown. Initial treatment of TFL is influenced by prior therapies for follicular lymphoma but generally includes anthracycline-containing regimens with rituximab to eliminate the aggressive component of the disease[16].

Treatment options for relapsed/refractory PMBCL and TFL are similar to those in DLBCL. Given the low prevalence of these diseases, no large prospective randomized studies in these patient populations have been conducted. Patients with chemotherapy refractory disease have a similar or worse prognosis[17] to those with refractory DLBCL.

In addition, the international, multicohort retrospective non-Hodgkin lymphoma research (SCHOLAR-1) study retrospectively evaluated outcomes in patients with chemorefractory DLBCL, PMBCL, and TFL. SCHOLAR-1 integrated data from two Phase 3 studies (LYSARC-CORAL and Canadian Cancer Trials Group LY.12) and 2 observational cohorts (MD Anderson Cancer Center and Mayo Clinic/University of Iowa Specialized Program of Research Excellence). Among 861 patients, 635 were included based on chemorefractory search criteria. Outcomes were consistently poor, regardless of refractory subgroup and across cohorts. The results of SCHOLAR-1 indicated that patients with chemorefractory, aggressive DLBCL represent a homogenous patient population with a response rate of 26% (complete response [CR] rate of 7%) and median overall survival of 6.3 months[18].



### 1.1.3 High Grade B-cell Lymphoma with MYC and BCL2 Rearrangement

In 2016, the World Health Organization (WHO) introduced a new category of large B-cell lymphomas called high grade B-cell lymphoma (HGBCL). This designation includes large B-cell lymphomas with MYC and BCL2 and/or BCL6 rearrangements that are phenotypically intermediate to DLBCL or B-cell lymphoma, unclassifiable (this latter category has since been eliminated). Concomitant MYC and BCL2 rearrangements in large B-cell lymphomas are associated with a poor prognosis - this category is now separately defined by the WHO in 2022[19].

### 1.1.4 Mantle Cell Lymphoma

Mantle cell lymphoma is an aggressive B cell lymphoma that most commonly presents with advanced stage disease, with the IGH::CCND1 fusion associated with t(11;14)(q13;q32) found in >95% of patients[19]. Many patients have an indolent presentation, without a need for therapy for months to years, whereas other patients have rapidly progressive therapy, requiring immediate therapy. Heretofore, the disease was incurable, with relapses common following systemic therapy and autologous stem cell transplantation, with historically a median survival of 3-5 years[20]. Rituximab therapy has improved survival outcomes in recent years, and the advent of BTK inhibitors and other targeted therapies is improving outcomes for patients with relapsed/refractory disease[20], albeit many patients will have progressive disease after becoming refractory to these therapies.

### 1.1.5 CAR T-cell Therapy for B Cell Lymphomas

MGH and BWH/DFCI are on the forefront of academic institutions employing chimeric antigen receptor (CAR) T-cell therapy, with hundreds of patients already treated here since the first FDA approval of axi-cel (axicabtagene ciloleucel; Yescarta)[21] and tis-acel (tisagenlecleucel; Kimrayah)[22] in 2017. Additional products, including liso-cel (lisocabtagene maraleucel)[23] and brexu-cel (brexucabtagene autoleucel)[24], have been approved, with the latter being the first CAR T-cell therapy for mantle cell lymphoma. For large B cell lymphoma, both axi-cel[25] and liso-cel[26] have recently been shown to have improved outcomes in the second line setting relative to high-dose chemotherapy/autologous stem cell transplantation, further increasing the number of patients eligible for CAR T-cell therapy. In addition, dozens of new protocols of investigational CAR T-cell therapy are underway at MGH, making it amongst the most active cellular therapy research programs across the world.

CAR T-cell therapy is an exciting example of genetically modifying a patient's T cells to target tumor cells for death for patients with the above relapsed/refractory hematologic malignancies who otherwise have very limited, if any, remaining options to achieve cure. A patient first undergoes apheresis to collect peripheral blood mononuclear cells (PBMCs)[21]. The T cells are isolated in a manufacturing laboratory and are genetically engineered most commonly via a viral vector to target an antigen displayed by the patient's tumor cells, which thus far has been CD19. These cells are then expanded and cryopreserved, for shipment back to the hospital. The patient is admitted for infusion of the CAR T-cells, basically a re-introduction of modified T cells into the patient's body. The time from eligibility determination for CAR T cells to the infusion of the CAR T cells can take as long as 2-3 months[21].
While response rates range from 50 - 80%, durable responses are seen in 30-40% of DLBCL patients at long term time points, demonstrating that 60% of patients will eventually relapse following CAR T cell therapy[22,27,28].

### 1.1.6 Radiation Therapy as Bridging Therapy Prior to CAR T-Cell Therapy

Patients who are eligible for CAR T-cell therapy may have localized masses in a limited number of sites which are symptomatic or may become symptomatic in the 2-3 month timeframe between eligibility determination and CAR T-cell therapy infusion. As such, bridging therapy is defined as treatment, whether it is systemic therapy, radiation therapy, or both, given between apheresis (which generally takes place within 2-4 weeks after eligibility determination) and CAR T-cell infusion to control symptomatic disease and/or maintain performance status by preventing progression of disease which may become symptomatic, to allow patients to safely wait until CAR T-cells are ready to be infused[29]. In bone marrow transplant patients, radiotherapy is administered for localized refractory/relapsed sites, including bulky masses, in the peritransplant setting[30] . Similarly, radiation therapy has been utilized as bridging therapy prior to CAR T-cell therapy, and in multiple case series, has shown to be effective for local control, without increasing the toxicities of subsequent CAR T-infusion[29]. There is no standard dose/fractionation for bridging radiation therapy that is established to be most efficacious - reports generally range



from 1 to 4 weeks of daily radiation therapy, with dose/fractionation decided based on the site and size of disease, adjacent normal tissues at risk of toxicities, timeline to CAR T infusion, and clinician judgement[29]. Based on historical data, daily radiation therapy for 30-45 Gy over 10-25 fractions has routinely been utilized, but it is unclear if daily radiation is truly necessary before a curative therapy (CAR T-cell therapy) when the primary goal is to palliate symptoms from disease, with minimal side effects from bridging therapy so patients have optimal performance status when undergoing CAR T[29]. Hypofractionated radiation therapy (given at > 2 Gy per fraction) appears to be as effective as conventionally fractionated radiation therapy, and lower doses may be sufficient for local control. Wright et al. showed that 8 Gy in 2 fractions can lead to 50% overall local response rate in DLBCL, which was not statistically different from palliative doses that were 3 times greater[31]. While there was a trend towards worse local control relative to higher doses, at 0-6 months after radiation, the local progressive-free survival was indistinguishable compared to higher dose regimens[31]. Thus, there is a need to explore lower, hypofractionated doses of radiation therapy in the bridging therapy setting, in which there is limited time to administer radiation therapy. Likely, there are many more patients who could benefit from radiation therapy who are not referred for it due to concerns of the number of treatments, side effects of radiation, and a fixed timeline to CAR T infusion.

### 1.1.7 Adaptive Radiation Therapy

The typical radiation therapy workflow consists of a CT simulation for radiation planning followed by 1-2 weeks of plan development prior to commencing radiation therapy. After the plan is developed, the radiation therapy is not modified in any way with regard to dose, fractionation, or field size. Only substantial changes in tumor size, patient weight, and misalignments as a result would lead to a replanning process that starts with a repeat CT simulation, due to the significant excess efforts and interruption of treatment required to personalize the radiation therapy. Adaptive radiation therapy, based on CT-linac or MRI-linac technology[32,33], allows the possibility to modify the radiation plan at each fraction based on real-time imaging as there is change in tumor anatomy, to maximize tumor control and reduce normal tissue toxicity with real-time personalization of radiation therapy, using artificial intelligence (AI) under physician and physicist supervision. To our knowledge, while studies exist in solid tumors[34], there are no published or active clinical trials to investigate adaptive radiation therapy in lymphoma.

## 1.2 Rationale

Taken together, the high response rates of various dose/fractionation schemes of bridging radiation therapy and of hypofractionated lower dose radiation in DLBCL, the limited time between apheresis and CAR T-cell therapy infusion, and the availability of adaptive radiation therapy technology (Varian Ethos), allow the investigation of a unique dose/fractionation pattern and radiation delivery platform to optimize bridging radiation therapy dose in terms of logistics, time, cost, and toxicities of radiation therapy. There is no established consensus for radiation dose/fractionation for the purposes of bridging radiation therapy in lymphoma prior to CAR T-cell therapy. This setting represents an opportunity to tailor the radiation dose/fractionation for the individual patient using adaptive radiation therapy given the logistical constraints within which radiation therapy needs to be delivered.

# 2. OBJECTIVES

The Varian Ethos offers an opportunity to investigate a novel dose/fractionation scheme in patients with relapsed/refractory B-cell lymphoma who are being planned to undergo CAR T-cell therapy. We propose using once weekly, adaptive radiation therapy at a dose of 5 Gy per fraction for up to 5 fractions over 5 weeks (‘5-5-5’) in patients who require bridging radiation therapy. The goals of weekly, adaptive therapy are to 1) limit toxicities from radiation; 2) limit patient time spent receiving radiation therapy; 3) allow for further radiation therapy after CAR T cell therapy in cases of partial response to CAR T cell therapy; 4) allow more patients to benefit from radiation therapy in the bridging setting by alleviating toxicity and resource concerns from the patient and referring physician perspective.

In patients with relapsed/refractory B-cell lymphoma referred for bridging therapy prior to CAR T-cell therapy, we hypothesize that once-weekly, CBCT-guided adaptive radiation therapy is feasible, safe, and provides adequate local control. Our specific aims are as follows:



1. To assess the feasibility of once weekly, CBCT-guided adaptive radiation therapy
2. To determine the safety and toxicity profile of once weekly adaptive radiation therapy
3. To evaluate the in-field local control at 30 and 90 days post-CAR T-cell therapy

The patient-centric focus of this study is important to emphasize. Using the Varian Ethos, once weekly adapted radiation therapy can be performed in under 45 minutes, from set-up to replanning to radiation delivery. This is in stark contrast to conventionally fractionated daily radiation therapy delivered for several weeks, prior to the 2-4 week inpatient hospitalization for CAR T-cell therapy. On board cone beam CT scanning would enable computation of tumor size changes from one fraction to the next, spaced 1 week apart, with AI replanning under physician guidance at each fraction, to optimize the dose to the lymphoma and limit dose to critical normal structures that would ordinarily be overdosed in cases of tumor shrinkage. Reduction of normal structure dose is anticipated to reduce the toxicities of radiation therapy, and may help patients have a better quality of life and performance as they are admitted for CAR T-cell therapy.

**Specific Aim 1:** To assess the feasibility of once weekly, CBCT-guided adaptive radiation therapy

Patients who meet the below eligibility criteria will undergo CT simulation for radiation planning with an IMRT plan, with a planned dose of up to 25 Gy in 5 fractions. Patients will be scheduled once weekly for treatment on the Ethos for adaptive radiation (see Schema). The total time from initial CBCT acquisition through end of treatment will be recorded, as well as time for recontouring of structures, plan development, and treatment delivery.

Guided by Ethos CBCT, we aim to personalize the number of fractions, the total dose of radiation, and the volume of irradiated field at each fraction. During each adaptive treatment, the target volume will be re-contoured, and evaluated by the attending radiation oncologist and a new treatment plan optimized for the current day's anatomy. As even relapsed/refractory lymphoma is expected to shrink significantly with single fraction radiation based on prior clinical experience, if at any timepoint following 1 or more fractions of radiation therapy there is ≥10% shrinkage in any dimension on Ethos CBCT compared to the previous fraction or ≥30% shrinkage compared to first fraction, treatment can be withheld for the planned session and patient can be reassessed the following week for additional radiation therapy (as long as the patient is not to be admitted for CAR T cell therapy at that timepoint). The total number of delivered fractions may be less than 5, if sufficient target shrinkage is seen on the Ethos CBCT at an earlier fraction, or timeline to CAR T is shorter than 5 weeks. The target volume and 3 sets of dimensions (axial, sagittal, coronal) will be recorded at each fraction based on CBCT. Using these quantitative data, we will also work with a statistician to develop a model to predict lymphoma shrinkage with once weekly adaptive radiation therapy.

As patient safety is of paramount importance, based on clinical judgement, treatment can also be withheld or dose-reduced if there is significant concern for organs-at-risk dose-tolerance or for worsening patient toxicities. While we do not expect growth of lymphoma during radiation therapy, for targets measuring ≥5 cm, if there is ≥20% growth in any dimension on Ethos CBCT between fractions, the patient will be transitioned to a conventional daily radiation plan to deliver up to 30 Gy in 10 fractions. This threshold of 20% was selected as a smaller increase in size could represent edema due to radiation-related inflammation. For smaller masses <5 cm, evaluation of tumor-related edema relative to size may be challenging and such non-bulky disease is less likely to be of clinical consequence if the size remains <5 cm. The patient can also be transitioned to conventional daily radiation therapy based on clinical judgement if there is concern for harm due to progressive lymphoma within the radiation field at any timepoint.

**Specific Aim 2:** To determine the safety and toxicity profile of once weekly adaptive radiation therapy

For adverse event (AE) assessment, the Investigator must determine both the severity of the AE and the relationship of the AE to radiation treatment (Common Terminology Criteria for Adverse (CTCAE) version 5.0). In addition, the recruited patients will be invited to complete 3 surveys via REDCap. Patients will self-report adverse event outcomes pertaining to the region of interest as per their radiation treatment field at enrollment and at every fraction, using Patient Reported Outcomes – CTCAE (PRO-CTCAE) version 1.0. The second survey will be used to assess aspects of health-related quality of life, which will be measured using the 42- item Functional Assessment of Cancer Therapy – Lymphoma (FACT-Lym) questionnaire. The third survey will evaluate financial distress experienced by the enrolled lymphoma patients (FACIT-COST). All of these will be administered prior to beginning radiation, at



every fraction, at CAR T infusion, and days 30/90 following CAR T-cell therapy. A member of the team will call the patient to review RedCap surveys with any technical difficulties and may be filled out by study staff via a phone conversation with the patient.

- **CTCAE term (AE description) and grade**: All non-CRS/ICANS toxicities will be graded per CTCAE by the Investigator. The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site:
  http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

- **PRO-CTCAE**: Patients will also have the opportunity to self-report adverse event outcomes. The descriptions and grading scales found in the NCI Patient Reported Outcomes Common Terminology Criteria for Adverse Events (PRO-CTCAE) version 1.0 will be utilized. A copy of the possible items for PRO-CTCAE can be downloaded from the NCI website. Patient will be asked to fill out the applicable section of the survey depending on their radiation treatment site, including items for pain and mood for all patients:
  https://healthcaredelivery.cancer.gov/pro-ctcae/instrument.html

- **FACT-Lym**: 42- item Functional Assessment of Cancer Therapy – Lymphoma is a measure of quality of life for lymphoma patients. The list of questions is available here:
  https://www.facit.org/measures/FACT-Lym

- **FACIT-COST**: 12-item assessment of financial toxicity experienced by cancer patients. The list of questions is available here:
  https://www.facit.org/measures/FACIT-COST

**Specific Aim 3:** To evaluate the in-field local control at 30 and 90 days post-CAR T cell therapy

We aim to assess the efficacy of '5-5-5' adaptive bridging radiation therapy in terms of local control. As per aim 1, the changes in target size will be detailed at each fraction. As standard of care following CAR T-cell therapy, patients have a PET/CT for response assessment at day 30 and day 90 following CAR T-cell infusion. Based on these PET/CTs, local control will be assessed as per the following definitions:

**Complete response (CR):** compatible with Deauville score of 1-3 on PET/CT
**Partial response (PR):** compatible with Deauville score of 4-5 on PET/CT, with shrinkage as compared to CT simulation scan
**Stable disease (SD):** compatible with Deauville score of 4-5 on PET/CT, with size stable compared to CT simulation scan
**Progression of disease (POD):** compatible with Deauville score of 4-5 on PET/CT, with increase in size compared to CT simulation scan

The Deauville score is a 5-point scoring system for lymphoma based on uptake relative to the mediastinal blood pool and liver (also known as PET 5PS[35]) – this is defined as per the following: 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[35].

Additionally, overall response to CAR T-cell therapy will be documented with respect to CR, PR, SD, or POD.

## 2.1 Study Design

Ten patients who fulfill the eligibility criteria will be enrolled in a pilot study to investigate the hypothesis that once-weekly, CBCT-guided adaptive radiation therapy is feasible, safe, and provides adequate local control. The treatment paradigm is entitled '5-5-5 Adaptive Bridging Radiation Therapy (ABRT)' for 5 Gy of adaptive radiation



delivered every 5 business days (1 week apart) for 5 weeks prior to CAR T-cell therapy infusion. After consent, patients undergo CT simulation. Enrollment must occur prior to the first fraction ABRT. Once weekly thereafter for 4 additional weeks, patients again have appointments for ABRT – during these sessions, the radiation therapy is replanned in real-time as needed, with inclusion of rules to hold radiation therapy for significant shrinkage of tumor (≥10% shrinkage in any dimension on Ethos CBCT compared to the previous fraction or ≥30% shrinkage compared to first fraction). If radiation therapy is held based on these rules at a scheduled ABRT session, as long as this is not the 5th scheduled ABRT session, the patient will be re-evaluated for further radiation therapy at the next scheduled ABRT session the following week. The patient will not receive further radiation therapy if this is the fifth scheduled ABRT session as there are no other ABRT sessions scheduled after the fifth session. As patient safety is of paramount importance, based on clinical judgement, treatment can also be withheld or dose-reduced if there is significant concern for organs-at-risk dose-tolerance or for worsening patient toxicities. While we do not expect growth of lymphoma during radiation therapy, for targets measuring ≥5 cm, if there is ≥20% growth in any dimension on Ethos CBCT between fractions, the patient will be transitioned to a conventional daily radiation plan to deliver up to 30 Gy in 10 fractions.

Enrollment will be held while AE data is being reviewed once first 5 patients complete ABRT. Any patients already enrolled after the 5th patient has completed the final ABRT fraction will continue on the ABRT protocol and would transition to conventional radiation therapy as per protocol only given the built-in safety mechanism.

All of the surveys detailed above ( CTCAE version 5.0 filled by investigator; 3 surveys filled by patients: FACT-Lym, FACIT-COST, and PRO-CTCAE version 1.0) will be administered prior to beginning radiation, at every fraction, and at CAR T infusion, and days 30/90 following CAR T-cell therapy. In-field local control will be evaluated on standard-of-care day 30 and day 90 PET/CTs following CAR T-cell therapy infusion.

### 2.2 Primary Objectives

The primary objective is to assess the feasibility of once weekly, CBCT-guided adaptive radiation therapy using the 5-5-5 ABRT paradigm, based on the proportion of enrolled patients who are able to undergo radiation under this protocol, without needing to transition to daily radiation therapy for disease progression prior to CAR T-cell therapy infusion.

### 2.3 Secondary Objectives

Secondary objectives include determination of proportion of patients developing grade 3 or higher radiation-related toxicity based on CTCAE at any timepoint, and in-field local control at 30 and 90 days post-CAR T cell therapy.

Exploratory endpoints include evaluation of patient-reported AEs, lymphoma quality of life, and financial toxicity.

## 3. PARTICIPANT SELECTION

All subjects must sign and date the IRB/IEC approved consent form before initiating any study specific procedures or activities that are not part of a subject's routine care.

Each subject who enters the screening period will receive a unique subject identification (ID) number before any study specific procedures or activities are initiated. This number will be used to identify the subject throughout the study and must be used on all study documentation related to the subject. Furthermore, the subject identification number must remain constant throughout the entire clinical study, it must not be changed after enrollment or if the subject is rescreened or retreated.

### 3.1 Eligibility Criteria

Patients meeting the following eligibility criteria will be enrolled. For inclusion, patients must have:



1) Diagnosis of relapsed or refractory B-cell lymphoma (including, but not limited to diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma, DLBCL arising from follicular lymphoma, follicular, and mantle cell lymphoma). Diagnosis can be made by clinical indication and does not need to be confirmed by surgical pathology results.
2) Being planned to undergo CAR T-cell therapy (patients can be enrolled prior to apheresis)
3) At least 1 measurable lesion according to the Lugano criteria[35]. Lesions that have been previously irradiated will be considered measurable only if progression has been documented following completion of radiation therapy. Re-irradiation is allowed for these patients. More than 1 lesion can be targeted as per radiation oncologist discretion. If disease is palpable, physical examination alone may be sufficient measurement for disease if a recent PET/CT or CT is not available as a radiologic measurement of the disease can be obtained during CT simulation.
4) Age ≥18 years
5) Eastern Cooperative Oncology Group (ECOG) performance status of less than or equal to 3.
6) Ability to understand and the willingness to sign a written informed consent document

### 3.2 Exclusion Criteria

Exclusion criteria include:

1) Any medical condition likely to interfere with assessment of safety or efficacy of RT.
2) CNS-only disease as the site for bridging radiation therapy (which cannot be reliably evaluated on CT). Patients with CNS disease with extra-axial involvement that can be evaluated on CT remain eligible.
3) Patient likely unable to lay supine for 45 minutes
4) Women of child-bearing potential who are pregnant because of the potentially dangerous effects of the preparative chemotherapy on the fetus or infant. Females who have undergone surgical sterilization or who have been postmenopausal for at least 2 years are not considered to be of childbearing potential
5) In the investigator's judgment, the subject is unlikely to complete all protocol-required study visits or procedures, including follow-up visits, or comply with the study requirements for participation.

### 3.3 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this trial.

## 4. PRETREATMENT EVALUATIONS/MANAGEMENT

Medical history and ECOG performance status will be determined. No other evaluations are needed at screening.

## 5. REGISTRATION PROCEDURES

### 5.1 General Guidelines for DF/HCC Institutions

Institutions will register eligible participants in the Clinical Trials Management System (CTMS) OnCore. Registrations must occur prior to the initiation of protocol therapy. Any participant not registered to the protocol before protocol therapy begins will be considered ineligible and registration will be denied.

An investigator will confirm eligibility criteria and a member of the study team will complete the protocol-specific eligibility checklist.

Following registration, participants may begin protocol therapy. Issues that would cause treatment delays should be discussed with the Principal Investigator (PI) of the registering site. If a participant does not receive protocol therapy following registration, the subject must be taken off study in the CTMS (OnCore) with an appropriate date and reason entered.



### 5.2 Registration Process for DF/HCC Institutions

Applicable DF/HCC Policy REGIST-101 must be followed.

### 5.3 General Guidelines for Other Investigative Sites

N/A

### 5.4 Registration Process for Other Investigative Sites

N/A

## 6. RADIATION THERAPY

5-5-5 Adaptive Bridging Radiation Therapy (ABRT) consists of 5 Gy of adaptive radiation delivered every 5 business days (1 week apart) for up to 5 weeks prior to CAR T-cell therapy infusion – of note, an allowance is made for 3-7 business days between fractions, due to holidays, patient schedule, and machine availability. Systemic therapies will be allowed to be concurrently administered at the discretion of the referring medical oncologist.

Protocol treatment must begin within 6 weeks after enrollment (preferably within 2 weeks, but up to 6 weeks after enrollment is allowable, primarily for insurance-related radiation approval delays).

### 6.1 Dose Specifications: IMRT (delivered via ABRT)

6.1.1 Dose will be normalized such that at least 95% of the PTV receives at least 95% of the prescription dose. The maximum recommended dose within the PTV is 115% of the prescribed dose. Radiation oncologist discretion will be allowed for under coverage given that the goal of radiation therapy is bridging to CAR T cell therapy rather than a radiation therapy as a cure.

6.1.2 Participants treated entirely via EBRT shall receive prescription doses to the PTV (with the above constraints).

### 6.2 Technical Factors

6.2.1 RT will be delivered with megavoltage equipment at energies ≥6 MV.

6.2.2 ABRT will be administered via Varian Ethos.

### 6.3 EBRT Localization, Simulation, and Immobilization

Simulation will be CT-based in all cases. The use of contrast at the time of simulation is optional. Participants will be positioned on a flat tabletop with a customized immobilization for stabilization and setup reproducibility. CT images should be acquired at a slice thickness of ≤3 mm. Target volumes (Section 6.4.1) and normal critical structures (Section 6.4.1.5) will be defined in the slices in which they are visualized.

### 6.4 Treatment Planning/Target Volumes



6.4.1 The definition of volumes will be in accordance with the ICRU Report #50: Prescribing, Recording, and Reporting Photon Beam Therapy.

6.4.1.1 The Gross Tumor Volume (GTV) is defined by the physician as all known disease as defined by the planning CT.

6.4.1.2 The Clinical Target Volume (CTV) is the GTV plus areas considered to contain microscopic disease, delineated by the treating physician. This is an optional target as microscopic disease may or may not be a concern.

6.4.1.3 The Planning Target Volume (PTV) will provide a margin around the CTV and/or GTV to compensate for the variability of treatment set up and internal organ motion. A range of 3-10 mm around the CTV is required to define each respective PTV. Superior and inferior margins (capping) should be 3-10 mm depending on the thickness and spacing of the planning CT scan. Careful consideration should be made when defining the 3-10 mm margin in 3 dimensions.

6.4.1.4 The ICRU Reference Points are to be located in the central part of the PTV and, secondly, on or near the central axis of the beams. Typically these points should be located on the beam axes or at the intersection of the beam axes.

6.4.1.5 Normal Critical Structures will be defined when adjacent to the PTV – a list is not provided as lymphoma may be in any site of the body. The radiation oncologist will define normal critical structures such as lungs, kidneys, spinal cord, esophagus, and salivary glands when they are adjacent to the PTV.

6.4.1.6 The PTV forms the entire target as described. Intensity modulated radiotherapy (IMRT) using inverse planning is permitted with constraints placed to adhere to critical structure dose limitations as defined above.

## 6.5 Critical Structures

Critical structure dose constraints shall remain consistent with 5 fraction constraints as described by Timmerman et al. utilized for stereotactic body radiation therapy[36]– given the lower total dose (25 Gy) on this lymphoma trial compared to stereotactic radiation used for solid tumors, many of the constraints will easily be achieved. While every effort should be made to deliver prescription doses to the PTV as specified while adhering to these constraints, it is recognized that certain anatomical factors may prevent this. It is also recognized that the benefits of ensuring adequate PTV coverage by radiation may be prioritized relative to sparing of normal structures at the discretion of the radiation oncologist.

## 6.6 Treatment Verification

6.6.1 For IMRT, the intensity profiles of each beam must be independently verified and compared to the planned field intensity.

6.6.2 Per fraction on-line target localization (CBCT) to account for interfraction tumor change, organ motion, and setup variability are required for Ethos treatments.

6.6.3 Management of Radiation Dose to the Patient from Daily Localization

According to the literature, the estimates of patient dose per imaging study for various imaging systems vary considerably. The doses from helical MV CT scans on a Tomotherapy unit are estimated to be in range from 1 to 3 cGy, similar to doses reported for kV cone beam CT on Elekta Synergy machine. The



doses for MV cone beam CT vary from 1 cGy to 10 cGy depending on the field size. Thus, the doses for 3D imaging systems used one time each day are in the range of 0.1 to 10 cGy and can contribute from 0.06 to 6% to a daily dose of 1.8 Gy. As a technique of controlling participant dose, it is recommended that a QA procedure be established at each institution to verify the accuracy of the image registration software on a daily basis. This QA check should be performed by the therapists operating a particular treatment device and is aimed at reducing the use of repeat imaging to check that the registration software has functioned properly when a shift of participant position is carried out. Additionally, it is not recommended that an institution use a daily imaging technique that delivery greater than 3 cGy/day to the patient. This limit dictates that repeat imaging on a particular day is held to a minimum when systems that deliver up to 3 cGy per study are used.

## 6.7 Quality Assurance

### 6.7.1 Documentation Requirements

The institution will archive treatment prescription and verification images for later review by the study chair if requested. At least one CBCT from each fraction shall be acquired and kept for evaluation if requested except where geometrically impractical.

### 6.7.2 Compliance Criteria

**Cases which meet criteria as stated in Section 6.1.1 will be scored as per protocol.** Cases in which PTV coverage criteria are not met, but that at least 90% of the PTV receives at least 90% of the prescription will be scored as a minor deviation unless the radiation oncologist specifies that it was done for concerns of safety. Undercoverage below this will be scored as a deviation unacceptable unless the radiation oncologist specifies that it was done for concerns of safety.

#### 6.7.2.1 Acceptable dose heterogeneity will be as follows

The maximum point dose to normal critical structures outside the PTV including the unspecified tissue should not exceed 110% of the prescription dose. The treating physician must carefully consider the tolerance dose/volume to each critical normal structure and unspecified tissue.

## 6.8 Dose Specifications/Technical Considerations: SBRT/Brachytherapy

N/A

## 6.9 Radiation Quality Assurance Reviews

The study PI in this trial will oversee quality assurance reviews for patients treated in those respective fashions. RT quality assurance reviews will be ongoing and performed remotely. RT quality assurance reviews will be facilitated by study PI.

## 6.10 Radiation Adverse Events

6.10.1 All participants will be seen at each fraction by their treating radiation oncologist (or covering radiation oncologist) while undergoing therapy, also as required by Ethos. Any observations (symptoms/side effects) with respect to the site(s) to which radiation is being delivered will be recorded.

6.10.2 Clinical discretion may be used in managing radiotherapy-related side effects.



### 6.11 Radiation Adverse Event Reporting

See Section 6.10.1 for additional Adverse Events information and Appendix E for Adverse Event Reporting Requirements.

## 7. DRUG THERAPY

N/A

## 8. SURGERY

N/A

## 9. OTHER THERAPIES

Lymphoma-directed systemic therapies may be administered concurrently with radiation at the discretion of the patient's medical oncologist.

## 10. TISSUE/SPECIMEN SUBMISSION

N/A

## 11. PARTICIPANT ASSESSMENTS

**Table 2: Schedule of Assessments (SOA)**

| Procedures | Screening | Enrollment & RT Planning | ABRT | Post-CAR T period | | EDC Timepoints |
|---|---|---|---|---|---|---|
| Day | Any time after patient is eligible for CAR T cell therapy | Within 4 weeks prior to first fraction | At each fraction (up to 5 fractions) | Day 30 Post-CAR T (± 30 days) | Day 90 Post-Treatment (± 30 days) | |
| Medical history | X | | | | | Baseline |
| ECOG Performance Status | X | | | | | Baseline |
| CTCAE | | X | X | X | X | Baseline, during treatment at each fraction, 30 and 90 day follow up. |
| Patient surveys: PRO-CTCAE, FACT-Lym FACIT-COST[A] | | X | X | X | X | Baseline, during treatment at each fraction, 30 and 90 day follow up. |
| PET-CT or CT-based disease assessment | | | | X | X | 30 and 90 day follow up |
| RT Planning | | X | | | | Baseline |
| ABRT | | | X | | | During treatment at each fraction |

A. Surveys can be administered after consent, prior to enrollment.

As standard of care following CAR T-cell therapy, patients have a PET/CT for response assessment at approximately day 30 and day 90 following CAR T-cell infusion. Based on these PET/CTs, local control will be assessed as per the following definitions:

**Complete response (CR):** compatible with Deauville score of 1-3 on PET/CT
**Partial response (PR):** compatible with Deauville score of 4-5 on PET/CT, with shrinkage as compared to CT simulation scan
**Stable disease (SD):** compatible with Deauville score of 4-5 on PET/CT, with size stable compared to CT simulation scan
**Progression of disease (POD):** compatible with Deauville score of 4-5 on PET/CT, with increase in size compared to CT simulation scan

Additionally, overall response to CAR T-cell therapy will be documented with respect to CR, PR, SD, or POD.

## 12. DATA COLLECTION

**Table 3: Data Items**

| Data Item | Forms Due Complete |
|---|---|
| Eligibility checklist | Enrollment |
| Informed consent | Enrollment |
| Radiation plan | Prior to first fraction |
| ABRT plan | At each fraction |
| Tumor measurement records | Completed at baseline and at each fraction |
| CTCAE | Completed at baseline, at each fraction, and day 30/day 90 post-CAR T |
| Patient surveys: PRO-CTCAE, FACT-Lym FACIT-COST | Completed at baseline, at each fraction, and day 30/day 90 post-CAR T |
| Local and overall response assessment based on PET/CT and/or CT | Day 30/day 90 post-CAR T |

Only grade 3 and higher toxicities, related and unrelated to therapy, will be collected in InForm.

## 13. STATISTICAL CONSIDERATIONS

### 13.1 Study Design/Endpoints

For this pilot study, our primary outcome of interest is feasibility, with a priori considering 80% of eligible patients undergoing adaptive RT (rather than needing to transition to standard RT due to local growth of lymphoma during radiation) as a criterion for success. We plan to enroll 10 patients. It is possible that the number enrolled is larger than this if there are enrolled patients who do not start ABRT such that there are still 10 patients who undergo ABRT. Using best clinical judgement and resources available, 10 patients are deemed to be sufficient to gauge feasibility as per review by the radiation oncologists designing this protocol and Varian (the funder of this protocol).

### 13.2 Sample Size, Accrual Rate and Study Duration

We expect to enroll 10 patients over 10 months – with the trial open at MGH and DFCI/BWH, with over 300 patients receiving CAR T-cell therapy per year, even if only 10% of patients undergo bridging radiation therapy, accrual can possibly be done much sooner. Once patients have completed CAR T-cell therapy, they will be followed



for 3 months. Below is our estimated project duration:

i. Prior to study open: 2 month
ii. Enrollment period: 10 months
iii. Follow-up period: 2 months
iv. Report and publication phase: 6 months
v. **Total (sum of above): 20 months**

## 13.3 Stratification Factors

N/A

## 13.4 Interim Monitoring Plan

The physician PI and co-PIs will comprise the Safety Review Committee (SRC). The SRT will review safety data when 5 subjects have undergone ABRT. The study will be stopped if any patients develop grade 4 or higher toxicity attributed to RT rather than to lymphoma progression or other cause as per SRT. The study will also be stopped if > 50% of patients need to be switched to conventional radiation due to ≥20% growth of lymphoma (when measuring ≥ 5 cm) in any dimension during ABRT (within the radiation field). Enrollment will be held while AE data is being reviewed once first 5 patients complete ABRT. Any patients already enrolled after the 5$^{th}$ patient has completed the final ABRT fraction will continue on the ABRT protocol and would transition to conventional radiation therapy as per protocol only given the built-in safety mechanism – this means that every patient enrolled after the 5$^{th}$ patient will remain enrolled on ABRT protocol and only transition to conventional RT if stipulated by the protocol (based on size/percentage of growth).

## 13.5 Analysis of Primary Endpoints

**Feasibility rate**

The feasibility rate of successfully undergoing ABRT without a need to transition to conventional radiation therapy and exact 2-sided 95% confidence intervals will be generated.

## 13.6 Analysis of Secondary Endpoints

**Objective Response Rate**

The incidence of objective response and exact 2-sided 95% confidence intervals will be generated.

**Descriptive analyses may occur at any time.** Univariate descriptive statistics with t-tests will be used to analyze pre- and post-RT QOL and toxicity data – please see section 2 for instrument details.

## 13.7 Reporting and Exclusions

### 13.7.1 Evaluation of Toxicity

All participants will be evaluable for toxicity from the time of their first treatment. Participants will be excluded if they do not start ABRT.

### 13.7.2 Evaluation of the Primary Efficacy Endpoint

All eligible participants included in the study will be assessed for response/outcome to therapy, even if there are protocol therapy deviations. Participants will be excluded if they do not start ABRT.

## 14. REGULATORY CONSIDERATIONS

### 14.1 Data Safety Monitoring

The DF/HCC Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity and accrual data from this study. The committee is composed of clinical specialists with experience in oncology and who have no direct relationship with the study. Information that raises any questions about participant safety will be addressed with the Sponsor-Investigator and study team.

The DSMC generally reviews each protocol up to four times a year or more often if required to review toxicity and accrual data. Information to be provided to the committee may include: up-to-date participant accrual; current dose level information; DLT information; all grade 2 or higher unexpected adverse events that have been reported across all sites; summary of all deaths occurring with 30 days of intervention for Phase I or II protocols; for gene therapy protocols, summary of all deaths while being treated and during active follow-up; any response information; audit results, and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

## 15. PUBLICATION PLAN

The results will be made public within 12 months of reaching the end of the study. The end of the study is the time point at which the last data items are to be reported, or after the outcome data are sufficiently mature for analysis, as defined in the section on Sample Size, Accrual Rate and Study Duration. If a report is planned to be published in a peer-reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors. A full report of the outcomes should be made public no later than three (3) years after the end of the study.



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## APPENDIX A PERFORMANCE STATUS CRITERIA

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



## APPENDIX B STUDY PARAMETERS

**Table 2: Schedule of Assessments (SOA)**

| **Procedures** | **Screening** | **Enrollment & RT Planning** | **ABRT** | **Post-CAR T period** | |
|---|---|---|---|---|---|
| Day | Any time after patient is eligible for CAR T cell therapy | Within 4 weeks prior to first fraction | At each fraction (up to 5 fractions) | Day 30 Post-CAR T (± 30 days) | Day 90 Post-Treatment (± 30 days) |
| Medical history | X | | | | |
| ECOG Performance Status | X | | | | |
| CTCAE | | X | X | X | X |
| Patient surveys: PRO-CTCAE, FACT-Lym FACIT-COST | | X | X | X | X |
| PET-CT or CT-based disease assessment | | | | X | X |
| RT Planning | | X | | | |
| ABRT | | | X | | |

ABRT – Adaptive Bridging Radiation Therapy

## APPENDIX E ADVERSE EVENT REPORTING REQUIREMENTS

### Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site

- **For expedited reporting purposes only:**
  - AEs for the radiation above should be reported only if the adverse event varies in nature, intensity or frequency from the anticipated toxicity as determined by the radiation oncologist

- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.
  - Unlikely – The AE *is doubtfully related* to the study treatment.
  - Unrelated – The AE *is clearly NOT related* to the study treatment.

### Adverse Event Reporting

In the event of an unanticipated problem or life-threatening complications treating investigators must immediately notify the PI.

Investigators **must** report to the PI any adverse event (AE) that occurs after the initial dose of study treatment, during treatment, or within 30 days of the last dose of treatment on the local institutional SAE form.

Adverse Event Reporting Guidelines

All participating sites will report AEs to the Sponsor-Investigator per DF/HCC requirements, and the IRB of record for each site as applicable per IRB policies. The table below indicates which events must be reported to the DF/HCC Sponsor-Investigator.

| Attribution | DF/HCC Reportable Adverse Events(AEs) | | | | |
|---|---|---|---|---|---|
| | **Gr. 2 & 3 AE Expected** | **Gr. 2 & 3 AE Unexpected** | **Gr. 4 AE Expected** | **Gr. 4 AE Unexpected** | **Gr. 5 AE Expected or Unexpected** |
| Unrelated Unlikely | Not required | Not required | 5 calendar days[#] | 5 calendar days | 24 hours* |
| Possible Probable Definite | Not required | 5 calendar days | 5 calendar days[#] | 5 calendar days | 24 hours* |
| # If listed in protocol as expected and not requiring expedited reporting, event does not need to be reported. | | | | | |
| * For participants enrolled and actively participating in the study ***or*** for AEs occurring within 30 days of the last intervention, events must be reported within 1 business day of learning of the event. | | | | | |

**Reporting to Hospital Risk Management**

Participating investigators will report to their local Risk Management office any participant safety reports, sentinel events or unanticipated problems that require reporting per institutional policy.

**Routine Adverse Event Reporting**

All Adverse Events **must** be reported in routine study data submissions to the PI including CTCAE forms.

