# FRONTIER: Frontline Risk-adapted Optimization of Novel Targeted Immunotherapy Evaluation in High-Risk MCL

## Phase II Multicenter Trial of MB-CART2019.1 (Zamtocabtagene Autoleucel) Therapy as Frontline Consolidation for High-Risk Mantle Cell Lymphoma

## Version 1.0


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**Sponsored by Miltenyi and the National Institutes of Health**
**National Heart, Lung, and Blood Institute**
**National Cancer Institute**
**NCT# 07569965**
**IND# 19678**



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# PROTOCOL SYNOPSIS

## Phase II Multicenter Trial of MB-CART2019.1 (Zamtocabtagene Autoleucel) Therapy as Frontline Consolidation for High-Risk Mantle Cell Lymphoma

**Co-Principal Investigators:** Nirav Shah and Michael Jain

**Study Design:** This study is a prospective, multicenter Phase II study with participants receiving MB-CART2019.1 as frontline consolidation for high-risk mantle cell lymphoma (MCL).

**Primary Objective:** The primary objective is to estimate the one-year durable overall response rate DORR after frontline consolidation therapy with MB-CART2019.1.

**Secondary Objectives:** The secondary objectives include the assessment of overall and complete response rates (best and at day 90), response duration, non-relapse mortality (NRM), relapse/progression, overall survival, progression-free survival, event-free survival, and immune effector cell (IEC)-related toxicities in patients receiving MB-CART2019.1 therapy.

**Eligibility Criteria:** Eligible patients are ≥18 years of age with high-risk MCL, defined as meeting any one of the following criteria: high-risk by Mantle Cell Lymphoma International Prognostic Index Combined (MIPI-c), a simplified Mantle Cell Lymphoma International Prognostic Index (MIPI) score of ≥6.2, tumor protein 53 (TP53) mutation, ≥50% TP53 expression by immunohistochemistry, complex karyotype, Ki67 ≥50%, blastoid or pleomorphic histology with Ki67 ≥30%, leptomeningeal disease at diagnosis or the presence of a NOTCH1 mutation. Patients must have received 2 cycles of appropriate frontline systemic induction therapy and achieved a response of stable disease or better.

**Treatment Description:** Eligible patients will receive a single intravenous infusion of MB-CART2019.1 cells at a dose of 2.5x10^6 cells/kg following lymphodepleting chemotherapy.

**Accrual Objective:** The goal is 52 participants in total who receive MB-CART2019.1 therapy. Additional participants may be screened, consented, registered, and treated in order to reach accrual goals.

**Accrual Period:** The estimated accrual period is 2 years.

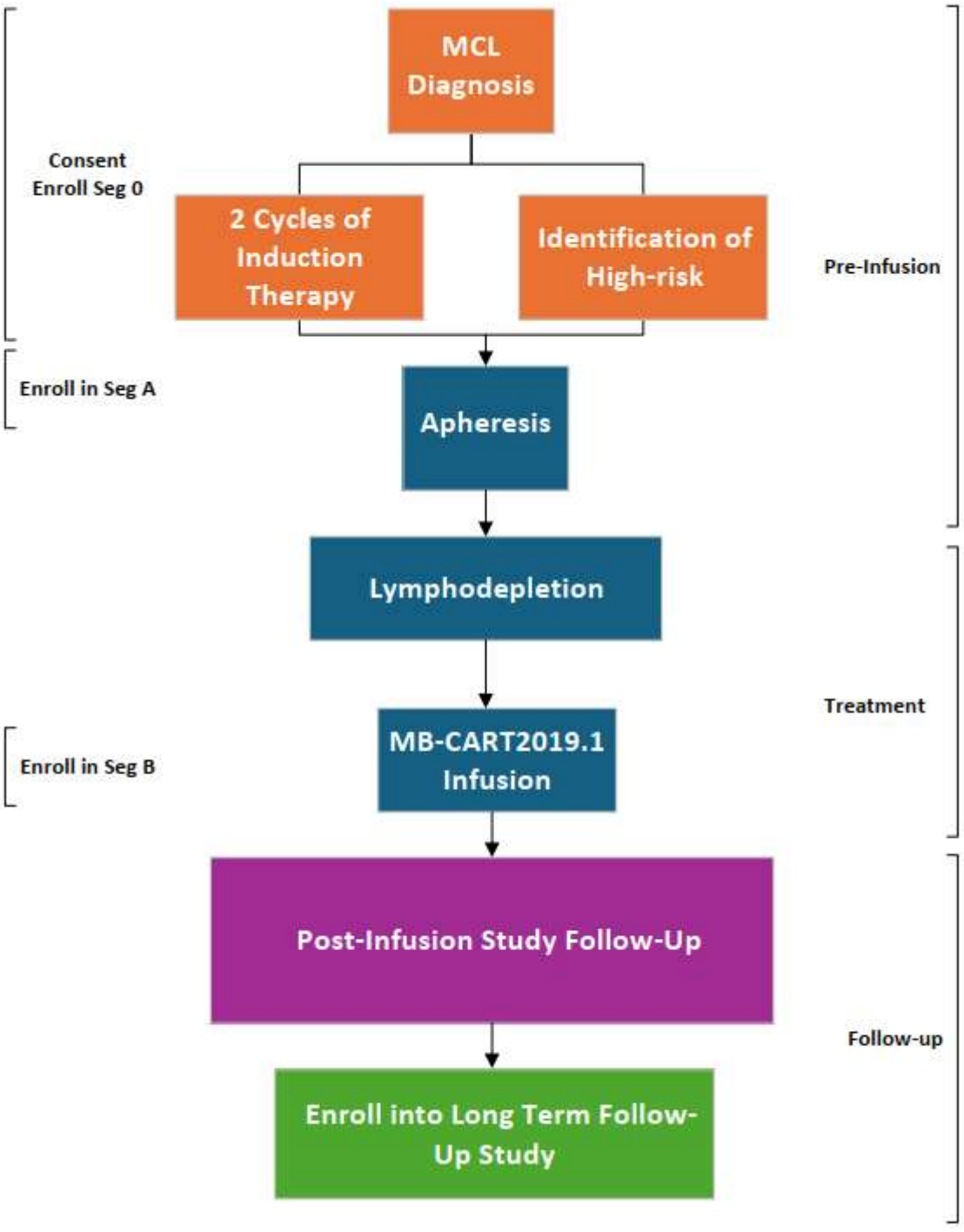
**Study Duration:** Participants will be followed for 1-year post-infusion.

**Long Term Follow-Up:** Assessment of survival annually through 15 years after infusion will be completed using a separate long-term follow-up protocol.

**Pausing Guidelines:** NRM at Day 100 and treatment-limiting toxicity (TLT) at Day 28 will be monitored throughout the study. Safety pausing rules will monitor NRM through 100 days and TLT through 28 days post-MB-CART2019.1 infusion. The Day 100 NRM rate and Day 28 TLT rate are not expected to exceed 10%. If either rate exceeds this threshold, the NHLBI will be notified in order that the Data and Safety Monitoring Board (DSMB) can be advised.

**Correlative Studies:** Samples will be banked pre- and post-infusion for future submitted protocols for use of specimens.

# STUDY SCHEMA




Abbreviations: MCL = mantle cell lymphoma; Seg = segment

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# CHAPTER 1

## 1 BACKGROUND AND RATIONALE

### 1.1 Mantle Cell Lymphoma

Mantle cell lymphoma (MCL) is a rare B cell non-Hodgkin's lymphoma (NHL) with an annual incidence in the United States (US) of approximately 5,000, representing about 4-7% of all new cases of NHL. US cancer registry data suggest an increase in the incidence of MCL between 1992 and 2007, with an estimated prevalence of 20,000 patients [1]. It generally affects older adults with a median age at diagnosis of 68 years and is male predominant at a male to female ratio of 2:1. MCL is molecularly characterized by the presence of a t(11;14) translocation, resulting in cyclin D1 (a cell cycle protein and a type of tumor marker) overexpression, and typically presents with bright cluster of differentiation (CD)20 expression [2, 3].

Although a subset of patients present with indolent disease and can be simply observed, [4] the majority of patients will require treatment due to aggressive disease. Despite significant advances in diagnosis and risk stratification, the management of MCL has been historically challenging as frontline chemoimmunotherapy, although associated with a high response rate, is not curative, and relapses tend to be the rule rather than the exception [5]. The historical treatment strategy had been upfront induction chemotherapy followed by autologous hematopoietic cell transplantation (HCT) in "fit" patients with chemosensitive disease. Recent refinements to induction therapy that have improved outcomes include the addition of rituximab maintenance [6] and the incorporation or Bruton's tyrosine kinase (BTK) inhibitors (BTKis) as part of initial therapy and/or as maintenance [7]. In addition, the role of autologous HCT for all eligible patients in MCL is being redefined with recent clinical trials suggesting a lack of benefit compared to maintenance ibrutinib [8] and maintenance rituximab in patients with deep remission as defined by minimal residual disease negativity by ClonoSEQ assay [9].

While the advances in frontline therapy for MCL have improved outcomes for most MCL patients, there remains a pattern of ongoing relapses over time without a clear plateau in progression-free survival (PFS), highlighting the need for novel therapies. This is particularly true in the subset of patients with clinical or molecular features of high-risk disease, which represents 10-15% of newly diagnosed cases of MCL, and remain a clinically challenging group of patients to treat even in the contemporary era.

### 1.2 Background

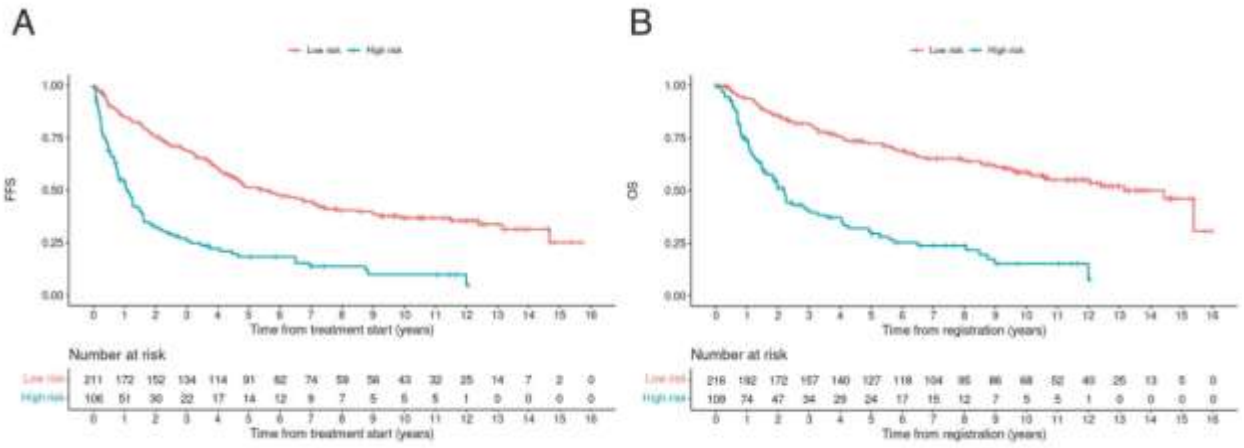
The definition of high-risk MCL has expanded over the years to include a variety of criteria reflecting its clinical and biological heterogeneity [10]. Historically the Mantle Cell Lymphoma International Prognostic Index (MIPI) had been used to risk stratify patients with MCL with a prognostic score assigned based on age, performance status, lactate dehydrogenase (LDH) and leukocyte count [11], with patients with high risk MIPI (≥ 6.2) enrolled in several European clinical trials having a median overall survival (OS) of 29 months. The Ki-67% expression has also evolved as an important prognostic score for MCL with a high Ki-67 (≥ 50%) showing a median OS of 20 months compared to a median OS of 118 months in patients with low Ki-67 [12]. Subsequently, the Ki-67 index was added to the MIPI score to create the Mantle Cell Lymphoma International Prognostic Index Combined (MIPI-c), an improved risk stratification tool [13] with patients on European MCL clinical trials with a high risk MIPI-c defined as high MIPI score and Ki-67 ≥ 30% demonstrating a 5-year OS of 17%. Blastoid and pleomorphic histology is another high-risk feature of MCL, characterized by blastic morphology of lymphoma cells and a high

proliferation index [10], with this subgroup historically performing worse than classical MCL with a 5-year OS of 38% (compared to 75% for classical MCL) with standard chemoimmunotherapy. Outcomes from previous clinical trials and real-world studies in high-risk MCL patients are summarized in Table 1. Figure 1 shows a comparison of OS and failure-free survival (FFS) in high-risk versus low-risk MCL patients and Figure 2 shows the impact of tumor protein 53 (TP53) mutations on OS and progression-free survival (PFS) in patients from the Nordic MCL2 and MCL3 clinical trials.

**Table 1: Clinical Trials Outcomes and Real-World Analyses for High-Risk Mantle Cell Lymphoma Patients**

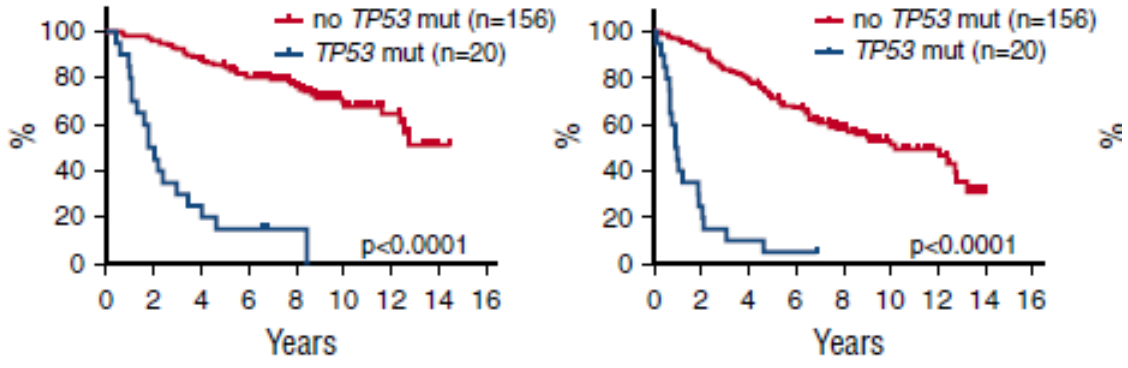
| Study Design | High risk Population | Median PFS | Source |
|---|---|---|---|
| **Post-Hoc Subgroup Analysis from Prospective Studies** | | | |
| **Phase II trial Ri-BVD chemotherapy** | 12 patients tp53 mutations | 7 months | [14] |
| **Sub-analysis from NORDIC II and III clinical trials** | 20 patients with tp53 mutations | 10.8 months | [15] |
| **Lenalidomide-Venetoclax-Rituximab untreated MCL** | 5 patients tp53 mutations | 9 months | [16] |
| **Shine Study, BR-Ibrutinib P53 patients/Blastoid** | 25 patients tp53 mutated<br>19 patients blastoid | 28.8 months p53/<br>24.6 months for blastoid | [17] |
| **BOVEN Regimen, Prospective Trial** | 25 patients TP53 mutated<br>1/3 low Ki67 | 2-year PFS 72% | [18] |
| **Real World/Retrospective Analyses of High-Risk populations** | | | |
| **Untreated, Blastoid MCL, retrospective review** | 20 patients blastoid | 20 months | [19] |
| **Untreated Blastoid MCL, retrospective** | 17 patients blastoid | 10.3 months | [20] |
| **Retrospective review of NORDIC MCL2 and MCL3 studies** | 20 patients with tp53 mutations<br>29 patients with Tp53 deletions | 0.9 months tp53 mutated<br>3.1 years tp53 deleted | [15] |
| **High risk defined as high-risk MIPI C, p53>50% expression (sub-analysis MCL Younger, Elder, EU trials)** | 109 patients with high-risk disease | 1.1 years failure free survival | [10] |
| **Tp53 mutated MCL, multicenter retrospective review** | 234 patients tp53 | 11.4 months | [21] |

**Figure 1: Median FFS and OS for High Risk (High MIPI-c and p53 Expression >50%) vs Low Risk Patients with MCL Treated on MCL Younger and Elderly Trials [10]**




Abbreviations: FFS = failure-free survival; MCL = mantle cell lymphoma; MIPI-c = Mantle Cell Lymphoma International Prognostic Index Combined; OS = overall survival; PFS = progression-free survival

**Figure 2: Prognostic Impact of TP53 Mutations on OS (left) and PFS (right) from Nordic MCL2 and MCL3 Trials [15]**




Abbreviations: MCL = mantle cell lymphoma; mut = mutation; OS = overall survival; PFS = progression-free survival; TP53 = tumor protein 53

The above table and figures demonstrate the unmet need in patients with high risk MCL with poor outcomes with frontline therapy.

TP53 mutations, which occur in ~10% or more of newly diagnosed MCL, have been associated with poor prognosis, with a median OS of 1.8 years in patients with TP53 mutated disease treated with intensive chemoimmunotherapy compared to an OS of 12.7 years in TP53 wildtype MCL [15]. Although not all TP53 mutations can be detected by immunohistochemistry (IHC), high TP53 expression, defined as ≥50%, is also associated with inferior outcomes. In an analysis of patients treated on European MCL trials, high risk MIPI-c or p53 expression >50% identified a high risk patient population who had a median failure-free survival of 1.1 years and OS of 2.2 years (compared to 5.6 years and 13.2 years, respectively for patients who did not have these features) [10]. Although more rarely tested, there are other non-TP53 mutations which are also associated with worse outcomes in MCL including NOTCH1 mutation [22].

A complex karyotype (CK) defined as 3 or more chromosomal abnormalities (not including t(11;14)) is also associated with inferior survival with a retrospective analysis demonstrating that patients with CK had a median OS of 4.5 years compared to 11.6 years for patients without a CK [23]. Finally, although rare, central nervous system (CNS) involvement with MCL, although seen in <1% of patients at diagnosis, is associated with dismal outcomes with a median OS from time of CNS diagnosis of 3.7 months [24].

For patients with high-risk MCL, the clinical course is often complicated by early relapse, poor response to chemotherapy, or progression into the central nervous system [22]. These patients require second- or third-line therapies largely consisting of BTKis or CD19-based chimeric antigen receptor (CAR) T-cell (CAR-T) therapy. For patients with relapsed MCL and *TP53* mutation, the median overall survival (OS) with ibrutinib, a BTKi, was only 10.6 months. Similarly, for relapsed MCL with a Ki67% greater than 50% and treated with acalabrutinib, the median progression-free survival (PFS) was only 6.4 months. These data demonstrate that BTKis are insufficient to treat high-risk MCL, particularly in the relapsed setting.

In the BOVen clinical trial, 25 patients with TP53-mutated MCL were treated with zanubrutinib, obinuzumab, and venetoclax with a 2-year PFS and OS of 72% and 76%, respectively, supporting the feasibility of a frontline clinical trial in high-risk patients [18]. Although further follow up and a larger study are needed to confirm these results, this approach is moving to the frontline setting for many high-risk patients. However, this is a 24-cycle treatment and it is currently unknown if patients will start to relapse once they come off therapy.

### 1.3 CAR-T cell Therapy for Relapsed/Refractory MCL

The advent of CD19-directed CAR-T therapy has transformed the salvage landscape in relapsed/refractory (R/R) MCL. The pivotal ZUMA-2 study with brexucabtagene autoleucel (brexu-cel) and subsequent real-world experiences have demonstrated remarkable efficacy with one large meta-analysis reporting complete response (CR) rates of 74%, and 12-month PFS of 53% [25]. ZUMA-2 cohort 3, evaluating BTKi-naïve patients, reported a similarly encouraging CR rate of 73%, and a 12-month PFS of 75% [26].

A limiting factor with brexu-cel remains the increased prevalence of CAR-T associated toxicities, including Grade ≥3 cytokine release syndrome (CRS), which occurred in 15%, and Grade ≥3 immune effector cell associated neurotoxicity syndrome (ICANS), which occurred in 31% of patients treated in the Zuma-2 clinical trial [27]. Additionally, a recent real-world study of the US Lymphoma CAR-T Consortium, consisting of 16 centers, reported a 20% intensive care unit admission rate [28]. In addition, subgroup analyses of high-risk disease from these consortiums have identified inferior efficacy and durability in PFS (HR 3.82 for high-risk MIPI; HR 1.98 for TP53 aberrant). A recent analysis from the Center for International Blood and Marrow Transplant Research (CIBMTR) demonstrated a 9% one-year non-relapse mortality (NRM) and similar rates of Grade 3+ CRS and ICANS as reported in the ZUMA-2 trial [29]. Finally, a recent update of the pivotal ZUMA-2 trial demonstrated that relapse remains a barrier to CD19-based CAR T-cell therapy with a median PFS of approximately 24 months for the entire patient population [30].

More recently, liso-cel, another CD19 CAR-T cell therapy has been approved for the treatment of relapsed/refractory MCL after 2 or more lines of prior therapy. In the Transcend NHL 001 clinical trial, 88 patients with MCL were treated with liso-cel with a CR rate of 72.3% and median PFS of 15.3 months [31]. This treatment has a lower toxicity than brexu-cel with only 1% of patients having Grade 3 or higher CRS and 9% of patients with Grade 3 or higher ICANS. However, the median PFS of this treatment was even shorter than reported with Brexu-cel at 15.3 months, highlighting the need for additional therapies, particularly for patients with high risk MCL.

### 1.3.1 Dual Targeted anti-CD20/anti-CD19 CAR T cells

While brexu-cel and liso-cel have represented an important therapeutic advance in the R/R space, relapses still occur in a significant proportion of patients, and antigen escape with loss of CD19 expression has been described as one major mechanism of resistance. This ubiquitous observation in multiple disease settings has provided the rationale for developing dual-targeted CAR constructs designed to mitigate antigen loss-related progression. In addition, CD20 is a particularly important target in MCL given its significantly higher CD20 expression compared to normal B cells [32] as well as the overall survival benefit confirmed with the CD20 targeting of rituximab as maintenance therapy after autologous HCT [6].

MB-CART2019.1 (LV20.19; zamtocabtagene autoleucel or zamto-cel) is a tandem CAR-T construct designed to overcome antigen loss and broaden therapeutic reach by simultaneously binding both CD19 and CD20, In addition to its unique construct design, zamto-cel is manufactured using the CliniMACS Prodigy automated closed system platform.

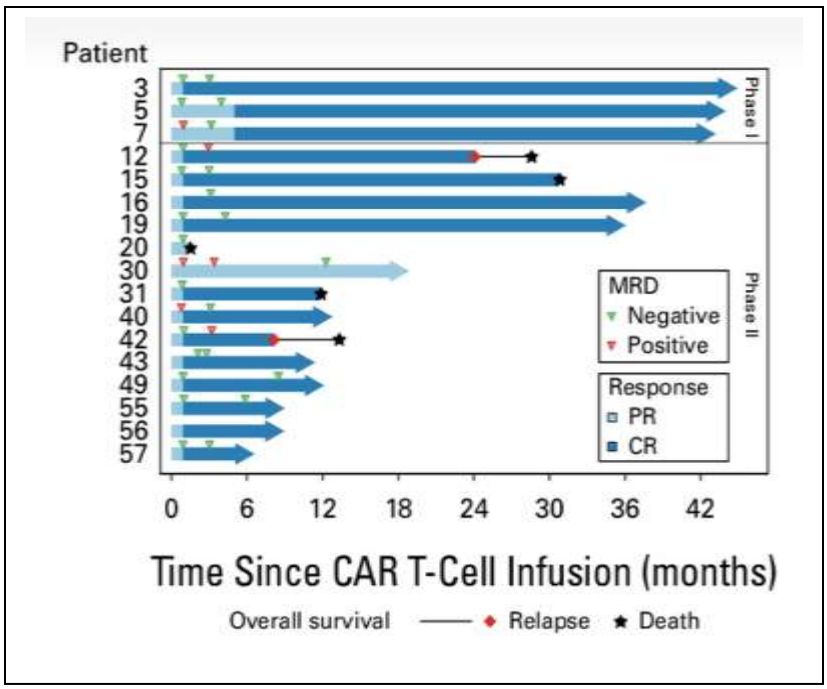
In the initial phase 1 dose escalation and expansion study of LV20.19 CAR T-cells with an identical construct as Zamto-cel but slightly different manufacturing process (NCT030190550) for B-cell malignancies, a safe dose of 2.5 x $10^6$ cells/kg was identified, with an overall response rate of 82% and low rates of Grade 3-4 CRS (5%, n=1) [33]. However, among patients treated at dose levels less than the identified goal dose, the only patient with a durable response was a multiply relapsed MCL patient who received 2.5 x $10^5$ cells/kg. Despite the lower dose, there was significant *in vivo* expansion and clinical efficacy. This supported further investigation of this product in MCL, particularly given the rationale that MCL, with its particularly bright CD20 expression, may be more sensitive to CD20 targeting.

Several modifications were made to improve the persistence and quality of the CAR20.19 product due to the observations of late relapse after loss of persistence of CAR20.19 T cells in a subset of patients with early CR. These included modification of manufacturing parameters to use a combination of interleukin (IL)-7 and IL-15 instead of IL-2 for cell expansion and optimizing manufacturing by an adaptive process with a goal of 8-days to limit culture time (with the flexibility to extend to 12 days if needed to reach the target dose). This was based on the hypothesis that an earlier harvested product would result in a less differentiated CAR T cell product with increased numbers of stem-cell memory (SCM) and central memory (CM) CAR T cells. This was tested in a prospective multi-arm trial of IL-7/IL-15 expanded LV20.19 CAR T cells (NCT04186520) [2]. Again, this trial utilized the identical lentiviral construct as the drug product proposed in this clinical trial (Zamto-cel). This phase I/II trial included a dedicated cohort for relapsed, refractory MCL patients and accrued 17 patients (phase I, N=3; phase II, N=14) as planned. All patients achieved the protocol-specified target cell dose. Thirteen patients received an 8-day product, and the remaining four patients received a 12-day product. Fourteen of 17 patients received a fresh (non-cryopreserved) infusion. The 8-day products were enriched for T-SCM/CM phenotype cells with significantly lower number of terminally differentiated effector memory (EMRA) T-cells in the CD4 compartment ($p<0.05$) than 12-day products. The median age of the MCL cohort was 63 (50-74 years) and 15 (88%) were male. The MCL cohort was enriched for high-risk disease with nearly 50% of patients harboring either a TP53 aberration, complex cytogenetics, or a high-risk MIPI score. Despite a median of 4 (range 3-8) prior lines of therapy, manufacturing was successful in all patients.

The Day 28 overall response rate (ORR) was 100%, CR rate was 76%, and partial response (PR) was 24% when considering all 17 patients. A ClonoSEQ minimal residual disease (MRD) assay was performed in 13 patients who achieved CR within 90 days after CAR20.19 T cell therapy; 10 of 13 (77%) patients were MRD negative. At a median follow-up of 15.8 months, the CR rate

was 88% and MRD negative rate was 80%, with a 1-year duration of response (DOR) of 93% and PFS of 80%. Figure 3 is a Swimmers Plot of clinical outcomes of patients treated on this trial.

**Figure 3: Swimmers Plot of MCL Patients Treated with LV20.19 CAR T Cell Therapy (Same Construct as Proposed MB-CART2019.1)**




Sixteen of 17 (94%) patients experienced CRS, but all were Grades 1-2. Three of 17 (18%) patients experienced ICANS within 28 days of infusion (n=2 Grade 3 and n=1 Grade <3). Two patients developed Grade 1 ICANS beyond day-28. Both these patients had immense expansion of lymphocytes in the CSF (total nucleated cell count of 386/μL and 1005/μL) with CAR+ T cells present, demonstrating the ability to potentially clear leptomeningeal disease with this construct. Both received only a single dose of intrathecal hydrocortisone (no systemic steroids), with resolution of neurotoxicity within 24 hours of administration [2]. Three patients died from infection (1 from meningoencephalitis, 1 from gram negative rod sepsis, and 1 from Covid-19).

These data and others have led to the clinical development of zamto-cel through several large multi-center clinical trials. The feasibility of manufacturing and treating patients in a multi-institution trial with zamto-cel has been demonstrated with the DALY II USA trial for large B cell lymphoma [34, 35]. In this trial, 69 patients received zamto-cel and 91.3% of these patients were able to be treated with a fresh, in specification product with a toxicity profile similar to what was reported in the phase 1 trial. Thirty-two patients (46.4%) experienced CRS (all Grade 1-2) and 12 patients (17.4%) experienced ICANS (Grade 3). One patient experienced immune effector cell-associated hemophagocytic lymphohistiocytosis-like syndrome (IEC-HS) which resolved after 2 days. This trial established the safety and feasibility of administering zamto-cel in a multicenter study with a fresh-to-fresh infusion.

Taken together, the results of these early-phase studies indicate dual targeting of CD20 and CD19 can result in high rates of deep and durable remission with a favorable toxicity profile in a R/R MCL population. The combination of efficacy, favorable toxicity profile, and feasibility of adaptive manufacturing suggests that the product zamto-cel may represent a meaningful advance beyond current standard of care (SoC) therapeutics, and if so, would warrant evaluation in a larger, multicenter cooperative group trial.

### 1.4 Rationale for Study

Historical clinical outcomes in high-risk MCL patients have been notably poor. Recent data demonstrates that patients with high-risk MIPI-c or p53 expression >50% experienced significantly shorter survival metrics, with a median failure-free survival of only 1.1 years and OS of 2.2 years, compared to 5.6 years and 13.2 years respectively for low-risk disease patients [5]; Table 1 While earlier studies reported median OS of only 2.5 to 3.6 years (30 to 43 months), recent advances in intensive induction chemotherapy, new agents, and increased use of hematopoietic stem-cell transplantation (although this is rapidly evolving) have improved median OS to 5 to 7 years. However, outcomes remain suboptimal for high-risk patients [11, 36].

In this clinical trial, a prospective, single arm, open-label, multi-center Phase II study design will be employed to evaluate autologous T cells engineered against both CD19 and CD20 antigens. The selection of this design is justified by the historically poor clinical outcomes in high-risk MCL patients and the rarity of the patient population. The multicenter approach will involve approximately 25 clinical sites, predominantly located in the US.

MB-CART2019.1 is an autologous T cell product engineered to target both CD19 and CD20 antigens that are present on B cells. The manufacturing will take place at Miltenyi Biotec San Jose, CA, utilizing the CliniMACS Prodigy closed system for manufacture [37]. The dose selection (see Section 2.4.2.5 for dose details) is based on comprehensive clinical evidence from previous trials. This construct and dose proposed for this clinical trial was validated in a Phase I/II single center study of LV20.19 (same construct as zamto-cel) in relapsed, refractory MCL which demonstrated an ORR of 100% in 17 MCL patients with a favorable safety signal with no cases of Grade 3+ CRS. (Shah NN JCO 2025).

In this study, MB-CART2019.1 will be implemented as frontline consolidation therapy. A Phase I study at Medical College of Wisconsin (NCT03019055), using the identical construct as MB-CART2019.1, demonstrated remarkable efficacy when administered as second or third-line therapy, with an ORR of 91% at the highest dose level [37]. In addition, the feasibility of successfully manufacturing and treating patients with zamto-cel has been demonstrated in a phase 2 multicenter trial for diffuse large B-cell lymphoma (DLBCL) with a >90% success rate in administering a fresh product with a short vein to vein time of 14 days in a heavily pre-treated population with lymphodepletion initiated during manufacturing [38].

The primary hypothesis is that the 1-year durable overall response rate for patients who receive frontline consolidation of high risk MCL patients with MB-CART2019.1 (zamtocabtagene autoleucel) is higher than 55%. For a one-sided 2.5% significance level, a sample size of 52 participants was determined to provide at least 80% power to detect a 1-year durable overall response rate is 75%, an improvement of 20% over the null durable overall response rate of 55%. The null hypothesis of 55% is supported by evidence from previous studies in the field of lymphoma, where researchers estimated 2-year PFS rates ranging from 20-50% in MCL patients with adverse-risk features (Table 1) [36].

Mechanistically, since CD20 is a key target in MCL and CD19 is an established target for CAR T-cell therapy, we hypothesize that dual targeting of both targets could lower relapse and lead to higher durable overall response rate and overall survival for high-risk MCL. We propose a single arm clinical trial since feasibility, efficacy, and safety of this approach as frontline consolidation in a multicenter setting has not yet been demonstrated. We hypothesize that CAR20.19 T cells will improve the one-year durable overall response rate in patients with high-risk MCL when given as a consolidation therapy early in their clinical course. Given the biological high CD20 expression in MCL and prior phase I/II data with CAR20.19 (identical construct to MB CART2019.1), we are optimistic that this proposal provides a unique opportunity to improve outcomes in patients with high-risk MCL.

# CHAPTER 2

## 2 STUDY DESIGN

### 2.1 Study Overview

This is a prospective, single arm, open label, multi-center, Phase II study of MB-CART2019.1 (Zamtocabtagene Autoleucel) therapy as frontline consolidation for high-risk Mantle Cell Lymphoma participants. Participants will be enrolled on the study after diagnosis and before the end of their second cycle of induction therapy.

Participants will undergo single day leukapheresis according to institutional standards with the goal of obtaining a minimum of 1 x $10^9$ mononuclear cells (MNC) for manufacture of MB-CART2019.1 cells. All participants will receive conditioning lymphodepletion regimen beginning on Day -5 consisting of cyclophosphamide and fludarabine in order to induce lymphocyte depletion and create an optimal environment for expansion of MB-CART2019.1 cells *in vivo*. The chemotherapy will be planned so that it completes at least 2 days BEFORE the infusion of the MB-CART2019.1 cells. On Day 0, fresh MB-CART2019.1 cells will be administered intravenously (IV) once certificate of analysis testing is satisfactorily completed, infusing over approximately 5-15 minutes (or as a free flowing IV can administer). MB-CART2019.1 cells will be administered at a dose of 2.5 x $10^6$ ±20% cells/kilogram. Should the participant not be able to receive fresh MB-CART2019.1 cells within the shelf-life, the procedure described in Section 2.4.2.5.4 should be followed. Should the participant not be able to receive fresh MB-CART2019.1 cells within the shelf-life due to participant safety reasons, MBCART2019.1 cells may be cryopreserved at the sponsor's central manufacture-site.

All participants will be monitored closely after treatment for toxicity, anti-tumor effects, patient-reported outcomes (PROs), and for persistence of CAR in blood samples and functionality of transduced T cells.

### 2.2 Hypotheses and Objectives

Primary Hypothesis

This study is designed to determine the efficacy of MB-CART2019.1 cells administered as part of frontline treatment following initiation of induction therapy and a conditioning lymphodepletion regimen in participants with high risk MCL. The hypothesis is that MB-CART2019.1 administered as a non-cryopreserved (fresh) infusion at a dose of 2.5x10^6 cells/kg will improve the one-year durable overall response rate in patients with high-risk MCL when given as consolidation therapy early in their clinical course for patients receiving in specification product.

#### 2.2.1 Study Objectives

##### 2.2.1.1 Primary Objective

To describe the one-year durable overall response rate of patients receiving MB-CART2019.1 therapy as frontline consolidation for high-risk mantle cell lymphoma**.**

##### 2.2.1.2 Secondary Objectives

The secondary objectives include the assessment of overall and CR rates (best and at day 90), response duration, NRM, relapse/progression, OS, progression-free survival (PFS), event-free

survival (EFS), and immune effector cell (IEC)-related toxicities in patients receiving MB-CART2019.1 therapy.

#### 2.2.1.3 Exploratory Objectives

The exploratory objectives of the protocol include assessments of toxicities, adverse events (AEs), patient reported outcomes, MRD, clinical outcomes, correlative laboratory assays, and evaluation of treatment efficacy in those patients with an "Out-of-Specification MB-CART2019.1 Product".

## 2.3 Patient Eligibility

### 2.3.1 Inclusion Criteria

1. Age ≥18 years
2. Stage II-IV mantle cell lymphoma
    a. Patients with gastrointestinal MCL involvement alone will be excluded
3. Diagnosis of MCL requires histologic confirmation by either overexpression of cyclin D1 OR presence of t(11;14) (q13; q32) translocation
    a. Subject should have a tumor biopsy sample (at least 5 unstained slides of tissue or tissue block) available prior to MB-CART2019.1 infusion, preferably collected pre-induction.
    b. If archival tissue is not available, the patient may be enrolled after discussion with the protocol chair and/or protocol officer
4. High Risk Disease at diagnosis, defined as having at least ONE of the criteria below:
    a. High risk MIPI-c (as calculated by https://www.european-mcl.net/home/scores-mipi-mipi-c-19.html)
    b. Simplified MIPI high-risk ≥6.2
    c. TP53 mutation OR ≥50% TP53 expression by IHC
    d. Complex Karyotype [e.g. 3 or more cytogenetic abnormalities, excluding the presence or absence of t(11:14)]
    e. Ki67≥ 50%
    f. Blastoid or pleomorphic histology with Ki-67 ≥30%
    g. Leptomeningeal Disease at diagnosis
    h. NOTCH1 mutation
5. Received 2 cycles of appropriate systemic induction therapy (among below selected regimens), which includes a CD20 antibody +/- cytotoxic therapy +/- oral targeted therapy (e.g., BTKi, immunomodulatory imid drugs), with the following considerations:
    a. CD20 antibody alone does not count towards a cycle of treatment
    b. For BTKis and/or lenalidomide a cycle is defined as up to 28 days and will be based on institutional treatment regimens.
    c. Intrathecal chemotherapy will not count towards a cycle of treatment

d. Radiation therapy will not count towards a cycle of treatment

e. Selected regimens include Bendamustine + CD20 antibody with or without a BTK inhibitor, R-CHOP or R-CHOP like regimens with or without BTK inhibitor (TRIANGLE-like regimen), R-DHAP/R-DHAX, CD20 antibody + BTK inhibitor, Lenalidomide + Rituximab, CD20 antibody + BTK inhibitor + BCL-2 inhibitor (BOVEN-like regimens), Bendamustine-cytarabine-rituximab combination, or any high-dose ARA-C containing regimen

6. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 at screening. ECOG performance status of 2 at screening is allowed if the decrease in performance status is attributed to lymphoma

7. Disease response assessment of either complete response, partial response, or stable disease by Lugano 2014 criteria assessed by 18F-fluorodeoxyglucose (FDG)-positron emission tomography (PET)/computed tomography (CT) (preferred) or contrast enhanced CT scans including neck/chest/abdomen/pelvis [39] after 2 cycles of induction therapy. If the participant has history of CNS disease, then he/she must have no history of or active parenchymal disease on magnetic resonance imaging (MRI)

   a. Leptomeningeal alone disease is allowable if it is not clinically progressive or worsening from baseline assessment

8. Subjects of childbearing or child fathering potential must be willing to practice birth control from the time of enrollment on this study until 1 year post-infusion

### 2.3.2 Exclusion Criteria

1. Unable to give informed consent
2. Any disease progression that occurs during the first 2 induction cycles
3. A creatinine clearance (as estimated by direct urine collection, Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI], or Cockcroft-Gault Equation or institutional standard) < 45 mL/min
4. Cardiac ejection fraction (EF) < 45% as determined by an echocardiogram (ECHO) or Multigated Radionuclide Acquisition scan (MUGA) (if range is provided, the upper value of the range may be used for assessing eligibility)
5. Resting $O_2$ saturation < 92% on room air
6. Serum alanine aminotransferase (ALT) / aspartate aminotransferase (AST) ≥ 5 times the Upper Limit of Normal (ULN) for age
7. Total bilirubin >1.5 mg/dL, except in individuals with Gilbert's syndrome
8. Absolute neutrophil count (ANC) < 1000/μL unless related to bone marrow infiltration by mantle cell lymphoma. No short-acting granulocyte colony-stimulating factor (G-CSF) use within 7 days of ANC evaluation
9. Platelet count < 50,000/μL unless related to bone marrow infiltration or hypersplenism by mantle cell lymphoma. No transfusions within 7 days of assessment.
10. Absolute CD3 count < 50/μL at screening
11. Known history of infection with human immunodeficiency virus (HIV)

12. Known active infection with hepatitis B (hepatitis B surface antigen [HBsAg] positive). If there is a history of treated hepatitis B, the viral load must be polymerase chain reaction (PCR) negative; antiviral prophylaxis is required if HBsAg negative and anti-hepatitis B core (HBc) positive
13. Known active infection with hepatitis C virus (anti-HCV antibody positive). If patient has a positive hepatitis C antibody, the viral load must be undetectable per quantitative PCR and/or nucleic acid testing
14. No seizure history within 6 months prior to enrollment
15. Known history of cerebral vascular accident (CVA) within prior 12 months
16. Known history or presence of autoimmune CNS disease, such as multiple sclerosis, optic neuritis or other immunologic /or inflammatory diseases
17. Presence of active CNS disorder that, in the judgment of the investigator, may impair the ability to evaluate neurotoxicity
18. Uncontrolled bacterial, viral, or fungal infection at the time of enrollment.
    a. Uncontrolled is defined as currently taking medication and with progression or no clinical improvement on adequate medical treatment
19. Pregnant or breast-feeding woman
20. Previous or concurrent malignancy with the following exceptions:
    a. Adequately treated basal cell or squamous cell carcinoma (adequate wound healing is required prior to study entry)
    b. In situ carcinoma of the cervix or breast, treated curatively and without evidence of recurrence for at least 2 years prior to the study
    c. Adequately treated breast or prostate carcinoma on hormonal therapies such as Lupron or tamoxifen and in clinical remission of ≥ 2 years -or- low-grade untreated prostate cancer under observation
    d. A primary malignancy which has been completely resected / treated with curative intent and in complete remission of ≥ 2 years
    e. Subjects with prior or concurrent malignancy whose natural history or treatment does not have the potential to interfere with safety and efficacy assessment are eligible for this trial after discussion with protocol chair or protocol officer
21. Severely immunocompromised participants e.g. due to current systemic treatment of non-neurologic autoimmune disease (e.g. Crohn's disease, rheumatoid arthritis, systemic lupus erythematosus)
22. Medical condition requiring prolonged use of systemic corticosteroids equivalent to prednisone >10 mg/day.
23. History of myocardial infarction, cardiac angioplasty or stenting, unstable angina, or other clinically significant cardiac disease within 6 months of enrollment
24. For systemic therapy or radiation therapy, at least 2 weeks or 5 half-lives, whichever is shorter, must have elapsed at the time of scheduled leukapheresis
    a. BTKis can be continued through apheresis until one day prior to start of lymphodepletion
25. Baseline neurologic deficits that would interfere with therapy or monitoring, determined using Immune Effector Cell-Associated Encephalopathy (ICE) Assessment at baseline

26. History of severe immediate hypersensitivity reaction to any of the agents in this study
27. Refusal or inability to participate in additional lentiviral gene therapy long-term follow-up (LTFU) protocol
28. Prior CAR-T therapy for any indication or systemic gene-modifying therapy for B cell lymphoma
29. Prior allogeneic stem cell transplant for any indication.
30. Prior bispecific T cell engaging (BITE) antibodies for cancer therapy
31. Prior T cell receptor-engineered T cell therapy

## 2.4 Treatment Plan

The investigational agent on this study is the MB-CART2019.1 cells administered after a 3-day conditioning chemotherapy lymphodepletion regimen consisting of fludarabine and cyclophosphamide. The treatment plan is shown in Table 2.

**Table 2: Treatment Plan**

| | Type of medicinal product | Source |
|---|---|---|
| **Experimental treatment** | | |
| MB-CART2019.1 | Investigational medicinal product (IMP) | Provided by Miltenyi |
| **Lymphodepleting chemotherapy** | | |
| Cyclophosphamide | Auxiliary medicinal product (AxMP) | To be prescribed; any authorized merchandise may be used and must be prepared, handled and stored according to the applicable Summary of Product Characteristics (SmPC) and the institutional standards of practice. |
| Fludarabine | | |
| **Premedication** | | |
| Levetiracetam | AxMP | To be prescribed; any authorized merchandise may be used and must be prepared, handled and stored according to the applicable SmPC and the institutional standards of practice. |
| Allopurinol | | |
| Diphenhydramine | | |
| Acetaminophen | | |
| Antimicrobial prophylaxis | | |
| **Rescue medication** | | |
| Tocilizumab or biosimilar | AxMP | Mandatory to be available on site for the treatment of CRS; must be prepared, handled and stored according to the applicable SmPC and the institutional standards of practice. |

Abbreviations: AxMP = auxiliary medicinal product; CRS = cytokine release syndrome; IMP = investigational medicinal product; SmPC = summary of product characteristics

### 2.4.1 Lymphodepleting Chemotherapy Regimen

Lymphodepleting chemotherapy will be given to induce lymphopenia and facilitate engraftment and expansion of MB-CART2019.1 cells. Starting on Day -5, after approximately 5 days of initiation of cell culture, the 3-day conditioning chemotherapy regimen consisting of fludarabine and cyclophosphamide will be initiated, either inpatient or outpatient per investigator's discretion, according to institutional standard operating procedures (SOPs) for chemotherapy administration. The dose calculation for the chemotherapy administration will be based on participant weight, measured within the last 30 days, using participant total body weight (TBW) with any adjustment following site's standard practice. Chemotherapy may also be adjusted for creatinine clearance per the institution's standard practice. Lymphodepleting chemotherapy will be administered as follows:

- Cyclophosphamide 300 mg/m$^2$/day for 3 days infused IV according to institutional SoC on Day -5, -4, and -3.
- Fludarabine 30 mg/m$^2$/day for 3 days infused IV daily according to institutional SoC on Day -5, -4, and -3.

The criteria for initiating the conditioning regimen are as follows:

- No fever ≥101° F in 12 hours prior to first dose of chemotherapy, unless discussed with the protocol chair or protocol officer
- No evidence of uncontrolled infection
- No clinically significant cardiac dysfunction
- Creatinine clearance > 45 mL/min as defined in inclusion
- No acute neurological toxicity > Grade 1 (with the exception of peripheral sensory neuropathy).

Should an event exceed these criteria immediately prior to conditioning chemotherapy, conditioning chemotherapy must be delayed until the event resolves to baseline or ≤ Grade 1. Additionally, in order to initiate lymphodepletion, the in-process testing (Intermediate Results, Process Day 5) of the manufactured MB-CART2019.1 cells must meet the following criteria as stated in Table 3.

**Table 3: MB-CART2019.1: Intermediate Results, Process Day 5**

| Test Parameter | Acceptance Criteria |
|---|---|
| Cellular Composition (CD3+ cell concentration, percentage, and viability) | Determined and declared |
| Transduction Frequency | ≥1% CD3+CD20 CAR+ cells among viable CD3+ cells<br>≥3% CD3+CD19 CAR+ cells among viable CD3+ cells |
| Endotoxin | Determined and declared |
| Microbiological Examination | Negative |

Abbreviation: CAR = chimeric antigen receptor

Fluid support, antimicrobial prophylaxis, antiemetics, pre-medications and tumor lysis syndrome (TLS) prophylaxis will be administered prior to and during conditioning chemotherapy as per institutional standard of care practices.

Evaluations and procedures will be conducted as per Chapter 4.

### 2.4.2 Modified B Cell Chimeric Antigen Receptor T Cell 2019

#### 2.4.2.1 Cell Acquisition

Once the participant has met eligibility criteria, provided consent, and completed 2 cycles of induction therapy he/she will undergo a standard non-mobilized leukapheresis procedure for collection of peripheral blood MNC for MB-CART2019.1 manufacturing, according to SOPs of collection sites, with a target goal of collecting approximately 1-5 X $10^9$ MNC. Each participant must meet the criteria for proceeding to leukapheresis, which are listed in Section 4.2.2. The leukapheresis product is then transported to the central manufacturing facility according to sponsor's SOPs.

#### 2.4.2.2 Study Agent Formulation, Appearance, Packaging, and Labelling

Processing MNC products and subsequent MB-CART2019.1 cell manufacturing for this study will be performed at the central manufacturing site, which is compliant with federal regulations and regulatory standards for more than minimally manipulated cell products.

MB-CART2019.1 cells will be manufactured over a standard period of 12 days. The leukapheresis product will be collected from the participant and delivered to the central manufacturing facility. The Miltenyi Biotec CliniMACS Prodigy® will be utilized for closed system manufacture of MBCART2019.1 cells including selection, activation, transduction, and expansion. CD4+ and CD8+ will be enriched from the leukapheresis product using CliniMACS CD4 and CD8 reagents and analyzed by flow cytometry. Enriched CD4+ and CD8+ cells are then activated using the magnetic-activated cell sorting (MACS) Good Manufacturing Practice (GMP) CD3/CD28 TransAct kit (IL-7/IL-15) and are transduced with lentivirus vector that will introduce a CAR that externally express antibody binding regions to CD19 and CD20, with transmembrane signaling domains from 4-1BB and CD3ζ. Following transduction, the cells are expanded in the CliniMACS Prodigy® and analyzed for functional capacity and final formulation. Processing prior to the final preparation will be performed in a closed and sterile system using GMP grade reagents and materials obtained from Miltenyi Biotec. Cultures may be extended as needed for adequate cell growth. Cells will be required to meet standard release criteria (Appendix G).

The MB-CART2019.1 cells will be infused fresh without cryopreserving after release tests have been completed. In exceptional cases due to a deteriorating medical condition such that the participant cannot receive the fresh cells, their cells will be cryopreserved in the sponsor central manufacture facility. These participants will not be part of the per protocol analysis but of the safety analysis.

If manufacture of MB-CART2019.1 yields a cell dose that is higher than the planned weight-based dose plus the Quality Control (QC) retention vials, the extra cell product will be cryopreserved for research use or urgent medical use per Section 2.4.2.5.4.

#### 2.4.2.3 MB-CART2019.1 Cell Infusion

MB-CART2019.1 cells will be harvested after 12 days of manufacturing. The cells will be infused fresh after meeting criteria listed in Section 4.2.5 for cell infusion.

MB-CART2019.1 cell administration will NOT be delayed due to neutropenia, thrombocytopenia, or anemia which are all potential risks of lymphodepleting chemotherapy.

#### 2.4.2.4 Pre-medications and Supportive Concomitant Medications

- All participants will receive levetiracetam per institutional guideline or as medically indicated (recommended at 500 mg orally twice a day beginning before cell infusion (Day -1) for a minimum of 21 days after MB-CART2019.1 infusion).
- Participants at high risk of TLS, per investigator's discretion, will receive allopurinol per institutional guidelines.
- Participants will receive the following medications 30-60 minutes prior to cell infusion: diphenhydramine and acetaminophen. Dosing is per institutional guidelines.
- Supportive care with G-CSF can be administered per institutional standards of practice. Participants should not receive granulocyte-macrophage colony-stimulating factor (GM-CSF). Antimicrobial prophylaxis, fluid support, and transfusion support will be administered according to institutional standards of practice. See Appendix H for additional supportive care measures.

#### 2.4.2.5 MB-CART2019.1 Cell Dosage and Administration

Participants enrolled will be treated and observed as either inpatient or outpatient, following their institution's SoC, after the MB-CART2019.1 infusion. Patients should be hospitalized if they present with ongoing fever, hypotension, hypoxia, or ongoing central neurological toxicity Grade >1, or if deemed necessary by the treating investigator. Daily assessments for up to Day 7, either inpatient or outpatient, following MBCART2019.1 infusion are mandatory.

Given the possibility that a participant could develop CRS or ICANS/neurotoxicity after discharge from the hospital, participants will be asked to remain available for frequent visits to the clinic for the first 28 days post cell infusion (within 1 hour of the clinic through Day 14 and within 2 hours of the clinic through Day 28). Participants and their family members/caregivers will need to be educated on potential symptoms such as fever, dyspnea, confusion, aphasia, dysphasia, somnolence, encephalopathy, ataxia, or tremor. If participants develop these symptoms, they will be instructed to immediately contact the principal investigator or seek immediate medical attention.

Prior to infusion, the cell product identity label is double checked by 2 authorized staff (MD, NP, PA or RN), and identification of the product and documentation of administration are entered in the participant's medical record, as is done for blood banking protocols. Cell products should NOT be infused unless the product identification matches the participant's identification.

Cells will be administered at a dose of 2.5 x $10^6$ cells/kg +/-20% capped at 100 kg weight. The dose range would therefore be 2.0 – 3.0 x$10^6$ cells/kg capped at 100 kg. Target dose is therefore minimally 2.0x$10^6$. Cells are to be infused IV as a free-flowing infusion (or) via filtered tubing over 5-15 minutes, gently agitating the bag during infusion to prevent cell clumping. Documentation in the medical record (and electronic case report form [eCRF]) should include the volume of cell infusion, and cell product infusion time start/stop times. Administration within the shelf-life- must be ensured.

##### 2.4.2.5.1 Measures in Case of Dose Adjustments/Modifications/Delays

There are no planned dose modifications for chemotherapy or cell administration. If the administration must be interrupted, the remainder of the cell product can be administered within the shelf-life documented on the cell product at the investigator's discretion. If the participant is

unable to receive the entire MB-CART2019.1 product, they will be considered as receiving out-of-specification product as indicated in Section 2.4.2.5.2.

Participants who are enrolled and who subsequently become ineligible for cell infusion after leukapheresis product is collected (e.g., new end organ dysfunction, development of active infection) but prior to lymphodepletion will be taken off study and replaced. They will be followed for 30 days following the apheresis for safety and outcome. They will have their CAR T cell product cryopreserved for research use or potentially later infusion if they become eligible to receive the product in the future per protocol.

#### 2.4.2.5.2 Measures in Case of Out-of-Specification MB-CART2019.1 Product

In case of failure to manufacture the targeted cell dose, cell viability, or transduction efficiency, administration of MB-CART2019.1 may be allowed; however, these participants will be replaced on the study. In case they receive the product, these participants will undergo identical study procedures and will be followed for treatment-limiting toxicities (TLTs), AEs, and survival. Efficacy of this subset of participants will be analyzed within the CAR-T infused population per Chapter 5. In case the participant receives lymphodepletion but does not receive the product, it will be entered into the database and patients will be followed for 30 days after the lymphodepletion for safety monitoring.

#### 2.4.2.5.3 Measures in Case of Positive Microbial Testing in MB-CART2019.1 After Infusion

MB-CART2019.1 is administered prior to completion of the 14-day microbial (sterility) testing, so it is possible that a sterility test returns positive after administration. In that scenario, the MB-CART2019.1 product is considered out-of-specification and the site investigator will be notified immediately to follow site-specific procedure for positive cultures after infusion of cell therapy. These procedures should include appropriate infectious work-up and antimicrobial coverage as indicated based on the results of the sterility tests. The institutional principal investigator (PI) and sponsor will be responsible for either local or federal regulatory reporting. These participants will be treated as receiving out-of-specification investigational agents and will be replaced but followed up per protocol for TLTs and AEs, and included in the CAR-T infused population analyses.

#### 2.4.2.5.4 Measures When Subjects Cannot Receive MB-CART2019.1 After Lymphodepletion

Excess or unused MB-CART2019.1 cells not infused into participants will be cryopreserved at the central manufacturing facility. The infusion of these cryopreserved products should only be considered during urgent medical need as determined by the site PI and agreed upon by the sponsor, protocol chairs, and protocol officer. Participants who received cryopreserved product will be replaced but followed up per protocol for TLTs and AEs. They should also be enrolled in the LTFU gene therapy protocol.

### 2.4.2.6 Study Drug Disposal

Should MB-CART2019.1 cells require disposal, any unused MB-CART2019.1 cells and all associated infusion supplies must be disposed of according to local institutional SOPs. MB-CART2019.1 cells contain human cells genetically modified with a lentivirus; follow local biosafety guidelines for disposal of such products.

### 2.4.3 Concomitant Therapy

No concomitant disease-directed post MB-CART2019.1 therapy is allowed on this study outside clinical progression

Concomitant medications and treatments that are intended for the management of CAR T-cell toxicities (examples: tocilizumab, corticosteroids, anakinra) must be reviewed and recorded in the eCRF with any dose changes, new or discontinued medications recorded between MB-CART2019.1 infusion (day 0) and day 28. Other medications will only be recorded and reported with SAEs.

#### 2.4.3.1 Precautionary Medications, Treatments and Procedures

Supportive care will be administered as per institutional standards of care (see Appendix H, including the following:

- G-CSF may be administered per National Comprehensive Cancer Network (NCCN) guidelines or standard institutional practices
- Fluid and electrolyte support as per institutional standards of care
- Antimicrobial prophylaxis per institutional standards of care
- Transfusion support per institutional standards of care
- TLS prophylaxis per institutional standards of care

No prophylactic steroids or tocizliumab for CRS or ICANS prevention.

### 2.4.4 Risks and Toxicities

#### 2.4.4.1 General

The agents used in the study have well-defined toxicity profiles. These expected/anticipated toxicities are collected on a calendar-driven Toxicity Form, collected at regular intervals throughout the trial per Section 4.2.

#### 2.4.4.2 Cytokine Release Syndrome (CRS)

Given the unique presentation of CRS associated with CAR T cell therapy, a revised grading system has been recommended for appropriate classification of degree of toxicity. We will employ this revised grading system (Appendix F Table 15) when evaluating participants with CRS in this study [40, 41] in addition to Common Terminology Criteria for Adverse Events (CTCAE) version (v) 5.0 grading.

#### 2.4.4.3 Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)

Neurotoxicity (e.g., encephalopathy, somnolence, aphasia), which has been observed with CAR T cell therapies, is now grouped under ICANS and will be scored using ICE assessment tools (Appendix B) and American Society for Transplantation and Cellular Therapy (ASTCT) Consensus Grading (Appendix F Table 15 [42]) in addition to CTCAE v 5.0 grading. For seizure prophylaxis, participants will receive levetiracetam (Keppra) as per institutional guidelines or as medically indicated.

Identification and management of ICANS will follow institutional standards. Recommended assessment includes evaluation of the ICE score according to Appendix B. If ICANS is identified at Grade ≥ 1, staff should conduct an ICE assessment every shift and notify a physician

immediately with any changes in scores. Evaluation of any new onset of neurotoxicity should consider recommended interventions in Appendix F. These recommendations serve as guidance for toxicity management, but deviation from the guidance will not be considered a protocol deviation, as all toxicity management should be at the treating physician's discretion.

Medications with sedative properties should be avoided if possible unless required to manage seizures, i.e. benzodiazepines. Leukoencephalopathy has been observed on MRI in the setting of neurotoxicity. Follow-up MRI is recommended to monitor the course of leukoencephalopathy to potential resolution.

At the time of consent, participants and their families/caregivers should be warned of the risk of late neurotoxicity through Day 28 and told to seek immediate medical attention for any new symptoms of neurotoxicity. In addition, participants should be advised not to drive or operate heavy machinery for the first month after discharge and/or until 1 month after complete resolution of neurotoxicity symptoms.

#### 2.4.4.4 Immune Effector Cell-Associated Hemophagocytic Lymphohistiocytosis-Like Syndrome (IEC-HS)

Macrophage activation syndrome (MAS), hemophagocytic lymphohistiocytosis (HLH) and IEC-HS are closely related, hyperinflammatory syndromes characterized by uncontrolled activation of the immune system (T cells, natural killer [NK] cells, and macrophages) which lead to a cytokine storm resulting in hemophagocytosis and multi-organ dysfunction. While they all constitute hyperinflammatory conditions, they differ in their context and some specific characteristics. For grading of MAS and HLH please refer to Section 4.5.3. IEC-HS is a specific complication of CAR-T cell therapy, characterized by a delayed onset compared to CRS. Following CAR-T therapy, IEC-HS can manifest clinically as fever, cytopenias, abnormal liver function tests, hyperferritinemia, increased concentrations of pro-inflammatory cytokines, hepatosplenomegaly, coagulopathy, and neurologic symptoms, for definition and identification guidance please refer to Appendix F Table 18. Treatment considerations can be found in Appendix F.

#### 2.4.4.5 Treatment Limiting Toxicity Grading

In this study, AEs are graded according to the National Cancer Institute's (NCI's) CTCAE v 6.0 (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm) with the exception of CRS, ICANS, and IEC-HS, which will be graded using the criteria provided in Appendix F. In addition, infection grading refers to BMT CTN technical guideline grading, not CTCAE.

Only those AEs meeting one of the below criteria, that occur during the first 28 days after infusion, and are suspected to be possibly, probably, or definitely related to MB-CART2019.1 cells, will be used in the definition of TLT:

- Any duration Grade 4 CRS or ICANS or Grade 3 CRS or ICANS not resolving to ≤ Grade 2 within 72 hours
- IEC-HS ≥ Grade 3 not resolving to ≤Grade 2 within 1 week
- Any other Grade ≥3 clinically significant non-hematologic toxicity that does not resolve to ≤ Grade 2 in 7 days
- Grade 4 infections
- Any Grade 5 adverse event, excluding progression related deaths

Hematologic toxicities will not be considered in the definition of TLT, as pancytopenia is a common toxicity with this regimen. Non-clinically significant non-hematologic toxicities or laboratory abnormalities will also not be considered TLTs.

# CHAPTER 3

## 3 STUDY ENDPOINTS

### 3.1 Primary Endpoint

#### 3.1.1 Durable Overall Response Rate at 1-Year Post CAR T Infusion

The primary endpoint is the 1-year durable overall response rate following MB-CART2019.1 infusion, defined as the probability of having complete response or partial response at 1 year without post-infusion progression or death. Failures for 1-year durable overall response include clinical progression and death from any cause through 1 year post-infusion and stable disease at 1 year post-infusion. The time to durable overall response failure is defined as the time interval from CAR T cell infusion until a failure event occurs. Tests used for evaluation of disease status include physical examination, laboratory testing, bone marrow biopsy and aspirate, PET scans, and CT scans of neck, chest, abdomen and pelvis as indicated. The Lugano Classification will be used to assess response following MBCART2019.1 infusion.

### 3.2 Feasibility Endpoint

#### 3.2.1 Manufacturing Success of MB-CART2019.1

The feasibility endpoint is success of manufacturing MB-CART2019.1. The proportion of patients for whom CAR T cells are successfully manufactured will be described among all patients receiving leukapheresis and stratified by prior bendamustine use.

### 3.3 Secondary Endpoints

#### 3.3.1 Treatment Response

Treatment response will be assessed using Lugano Criteria [39]. Both best overall response and Day 90 response following MB-CART2019.1 infusion will be evaluated. The proportions of patients achieving a CR and an overall response (OR, consisting of CR and partial response) will be described [39].

#### 3.3.2 Overall Survival (OS)

Events for OS include deaths from any cause. OS is defined as the time interval from MB-CART2019.1 infusion until death. The OS probability will be assessed at 1-year post-infusion.

#### 3.3.3 Progression Free Survival (PFS)

Events for PFS include death from any cause and clinical progression. PFS is defined as the time interval from MB-CART2019.1 infusion until a PFS event occurs. The PFS probability with be assessed at 1-year post infusion.

#### 3.3.4 Duration of Complete Response (DOCR)

DOCR is defined as the time from a participant's first achieving a CR until either a disease progression occurs per 2014 Lugano or IPCG criteria or death, whichever occurs first. DOCR will be evaluated in the set of participants who achieve a CR. For participants who are in CR at MB-CART2019.1 infusion, their time of achieving CR will be the time of infusion.

### 3.3.5 Non-relapse Mortality (NRM)

Events for NRM include deaths without prior relapse/progression of the underlying malignancy. Relapse/progression is treated as a competing risk for NRM. The cumulative incidence of NRM will be described at 1-year post-infusion.

### 3.3.6 Relapse/progression

Relapse/progression events will be determined per Lugano criteria. NRM is treated as a competing risk for relapse/progression. The cumulative incidence of relapse/progression will be described at 1-year post-infusion.

### 3.3.7 IEC Related Toxicities

CRS, ICANS, and IEC-HS will be determined per ASTCT criteria [42, 43]. The incidence and severity of each of these toxicities within 28 days of CAR T cell infusion will be reported. The incidence and severity of Grade 3 or higher ICANS occurring after Day 28 post-CAR T cell infusion will be reported.

### 3.3.8 Event-free Survival (EFS)

Events for EFS include clinical progression, additional anti-lymphoma treatment initiation (oral therapy, radiation) in the absence of clinical progression, and death. EFS is defined as the time interval from MB-CART2019.1 infusion until an EFS event occurs. The EFS probability will be assessed at 1-year post-infusion.

## 3.4 Exploratory Endpoints

### 3.4.1 CAR T Cell Persistence

The proportion of patients for whom CAR T cells are present 1-year post-infusion will be described.

### 3.4.2 Out of Specification CAR T Cell Efficacy

Key clinical outcomes will be evaluated separately for patients who receive an out-of-specification MB-CART2019.1 product. These outcomes include durable overall response rate, OS, PFS, DOCR, and EFS at 1-year post-infusion as well as treatment response classification/best response by day 90 post-infusion and frequency of CRS, ICANS, and IEC-HS through Day 28 post-infusion.

### 3.4.3 Cytokine Levels

Levels of cytokines measured on the day of infusion and on Days 1, 4, 7, 10, 14, 21 and 28 will be described.

### 3.4.4 Subgroup Analyses of Clinical Outcomes

Key clinical outcomes will be evaluated separately by baseline characteristics including each of the high risk MCL criteria for eligibility, prior bendamustine use, MRD status, p53 mutation, CNS involvement, and CD19/CD20 expression. These outcomes include durable overall response rate, PFS, and OS at 1-year post-infusion as well as CR and OR at Day 90 post-infusion.

### 3.4.5 Infection

All Grade 2+ infections will be reported according to the Blood and Marrow Transplant Clinical Trials Network (BMT CTN) technical guidelines from Day 0 up to 1 year post- MB-CART2019.1 therapy. The incidence of viral, fungal and bacterial infections will be tabulated.

### 3.4.6 B-cell Recovery

The proportions of patients who have B-cell recovery (absolute B cell count ≥50/μL) after MB-CART2019.1 infusion will be described at 1 month, 3 months, 6 months, and 1-year post-infusion. The proportions of patients who received intravenous immunoglobulin (IVIG) replacement at these time points will also be described.

### 3.4.7 MRD Status

The proportions of patients with MRD at screening, Day 28, Month 3, Month 6, and 1 year will be described.

### 3.4.8 ICU hospitalization

The proportion of patients hospitalized in an intensive care unit (ICU) through Day 28 post CAR-T infusion will be reported.

### 3.4.9 Immune Effector Cell–Associated Hematotoxicity (ICAHT)

ICAHT will be graded per European Hematology Association (EHA)/European Society for Blood and Marrow Transplantation (EBMT) consensus grading [44] (Appendix F Table 15). The incidence and severity of ICAHT events through Month 6 post- MB-CART2019.1 infusion will be reported.

### 3.4.10 Immunosuppression Use

The proportions of patients who receive tocilizumab, corticosteroids, anakinra, and other immunosuppressives through Day 28 post MB-CART2019.1 infusion will be reported.

### 3.4.11 Patient-Reported Outcomes (PROs)

PROs will be measured at Baseline and at Days 14, 28, 90, 180, and 365 post- MB-CART2019.1 infusion using the following instruments/questionnaires: Patient-Reported Outcomes Measurement Information System (PROMIS) domains for global quality of life, physical function, fatigue, cognitive function, depression, and anxiety; Comprehensive Score of Financial Toxicity (COST); return to work items; sociodemographic/social determinants of health items; and Patient-Reported Caregiver Assessment (PRCA). The scales will be scored according to the recommendations of the developers. Participants who are able to read and speak in English or Spanish are eligible to participate in the PRO component of this trial.

# CHAPTER 4

## 4 PATIENT ENROLLMENT AND EVALUATION

### 4.1 Enrollment

Screening studies and evaluations will be used to determine the eligibility of each participant for study inclusion. All evaluations must be completed within the 42-day screening window and prior to leukapheresis, unless stated otherwise in Appendix C.

Consented participants will be registered using the Advantage eClinical Electronic Data Capture System. The following procedures should be followed:

1. Interested participants will sign a study informed consent form which will include consent for screening assessments, study procedures, and follow up.
2. Following pre-screening for potential eligibility and signing of informed consent, the potential participant will be enrolled into Segment 0 in Advantage eClinical, a web based electronic data collection system, by an authorized user. A unique study Patient identifier (ID) # will be generated.
3. After the participant is enrolled into Segment 0, the authorized user should complete the screening forms to ensure that all the information is compiled to confirm eligibility (per Section 2.3) for Segment A. Sites can set a tentative apheresis date with Miltenyi.
4. After filling out the Screening Forms and ensuring the patient meets all eligibility criteria, the authorized user will be able to enroll the patient in Segment A. **The patient may not undergo apheresis or begin study treatment until they are enrolled in Segment A.**

#### 4.1.1 Co-Enrollment

Participants may be co-enrolled into observational studies. Co-enrollment in interventional studies may be permitted after discussion with protocol chairs and officer.

### 4.2 Study Monitoring

As this is a cellular therapy clinical trial, the treatment period will include the lymphodepletion regimen (starting on Day -5), followed by the MB-CART2019.1 cell infusion (Day 0), with subsequent follow-up, including the initial safety monitoring period (Day 1 to Day 28) and the response and survival observation period (Day 28 and beyond). The trial observation period for TLTs will conclude on Day 28 (approximately 4 weeks after MB-CART2019.1 cell infusion), while the trial follow-up will conclude 12 months after the MB-CART2019.1 cell infusion. The study windows are ± 1 day for Days 10 and 14, ± 2 days for Day 21, and ± 3 days through Day 28 visits. The study window for visits Day 90 (Month 3) is ± 7 days, and Day 180 (Month 6) to end of Year 1 (Month 12) are ± 14 days. Pre-treatment and post-treatment investigations are summarized in The Schedule of Assessments (Appendix C).

#### 4.2.1 Screening Evaluations

The screening period begins on the date the participant signs the Institutional Review Board (IRB)-approved informed consent form (ICF). and continues through confirmation of enrollment into Segment A. Procedures that are to be performed as part of the practice of medicine and which would be done whether or not study entry was contemplated, such as for diagnosis or treatment of a disease or medical condition, may be performed and the results subsequently used

for determining study eligibility without first obtaining consent. On the other hand, informed consent must be obtained prior to initiation of any clinical screening procedures that are performed solely for the purpose of determining eligibility for research, i.e., withdrawal from medication (wash-out period).

Screening studies and evaluations will be used to determine the eligibility of each participant for study inclusion. All evaluations must be completed within the 42-day screening window unless otherwise stated below:

- History and physical examination
  - Diagnostic history, previous treatment, pregnancy risks (if applicable), recent chemotherapy, previous treatment complications, central venous access, review of any high-risk infectious behaviors and adverse event assessment
  - Physical examination including vital signs, height, weight, and body surface area
  - ECOG performance status
  - Assessment of need for venous access
- Neurologic examination including ICE assessment
- Safety laboratory assessments
  - Complete blood count (CBC) with differential
  - Comprehensive Metabolic Panel and LDH
  - Prothrombin time (PT)/international normalized ratio (INR), partial thromboplastin time (PTT), D-Dimer, and Fibrinogen
  - Ferritin, CRP, and Uric Acid
  - Creatinine Clearance
- Infectious disease evaluation per institutional cellular therapy SOP within 6 months of MCL diagnosis and prior to leukapheresis, at a minimum to include:
  - Anti-HIV-1, Anti-HIV-2, HIV-1-nucleic acid test (NAT)
  - HBsAg
  - Anti-HBc
  - Anti-HCV
- Serum or urine pregnancy test for females of childbearing potential
- Quantitative Serum Immunoglobulins
- Electrocardiogram (ECG)
- Trans-thoracic ECHO or MUGA (can be completed within 3 months of apheresis unless the patient has had subsequent anthracycline exposure in which case this must be repeated).
- Lugano 2014 disease status evaluations specific to the participant's type and location of disease following completion of Cycle 2 Induction Therapy:
  - PET-CT or CT imaging for all participants within 6 weeks of apheresis and after the second cycle of induction treatment
  - MRI brain with and without contrast for participants with history of CNS lymphoma
  - Lumbar puncture for collection of cerebrospinal fluid (CSF) samples for all participants with CSF involvement, history of CNS involvement or ongoing CNS lymphoma
  - Bone marrow biopsy and aspirate
  - Participants must have a baseline tumor biopsy sample (at least 5 unstained slides or tissue or tissue block) from the most recent collection available prior to MB-CART2019.1 infusion. If archival tissue is not available, patient may be enrolled after discussion with the protocol chair and/or protocol officer

- Acquire samples for correlative/complementary research:
  - Baseline tumor sample
  - Immune Research Studies
  - MRD assessment
  - Samples collected for future research, if patient signed the future research portion of the informed consent form.

### 4.2.2 Pre-apheresis

Participants who complete screening, meet the eligibility criteria listed in Section 2.3, and are enrolled into Segment A can confirm their scheduled leukapheresis and undergo the subsequent lymphodepletion regimen. Within 7 days of apheresis, participants will complete baseline PRO questionnaires and must meet the following criteria to proceed with leukapheresis:

- No evidence of a clinically significant uncontrolled infection
- No evidence of clinical progression
- CBC with differential within 7 days of procedure; must meet criteria outlined in Section 2.3
- Comprehensive Metabolic Panel and LDH within 7 days of procedure; must meet criteria outlined in Section 2.3
- Renal Function tests within 7 days of procedure; must meet criteria outlined in Section 2.3
- ALC ≥ 100/µL within 7 days of procedure
- For corticosteroids doses > 10 mg/day of prednisone equivalent, a washout of at least 7 days prior to leukapheresis
- For systemic therapy or radiation therapy, at least 2 weeks or 5 half-lives, whichever is shorter, must have elapsed at the time of scheduled leukapheresis
  - BTKis can be continued through apheresis until one day prior to start of lymphodepletion
- Negative coronavirus disease 2019 (COVID-19) test within 7 days of procedure (If testing positive, the site should delay apheresis for a minimum of 10 days. If the patient is asymptomatic after 10 days, the site may proceed.)
- QoL/PRO

### 4.2.3 Leukapheresis Procedure

The participating sites' leukapheresis program SOPs will govern the collection of MNC. The goal is to collect approximately 1-5 X $10^9$ MNCs during leukapheresis.

### 4.2.4 Lymphodepleting Chemotherapy

Lymphodepleting chemotherapy will be given to induce lymphopenia to facilitate engraftment and expansion of MB-CART2019.1 cells according to administration procedures outlined in Section 2.4.1. Should an event exceed these criteria immediately prior to lymphodepleting chemotherapy, chemotherapy must be delayed until the event resolves to ≤ Grade 1 or baseline.

The following procedures will be completed on Day -5, Day -4, and Day -3 (fludarabine and cyclophosphamide) with abnormalities managed as per institution specific guidelines for administration of chemotherapy:

- Physical examination: Vital signs, body weight, and applicable concomitant medications
- Safety laboratory assessments (local laboratory, each day of lymphodepletion)
  - CBC with differential

  - Uric Acid (Day -5 only)
  - Comprehensive Metabolic Panel and LDH
- Must meet eligibility criteria listed in Section 2.4.1

### 4.2.5 MB-CART2019.1 Cell Infusion

Participants must meet the following criteria for cells to be infused (based on labs obtained within 24 hours of cell infusion):

- The participant's MB-CART2019.1 cells must meet release criteria
- No new medical complication that would unduly increase risk of infusion
  - No new requirement for continuous supplemental oxygen therapy >2L by nasal cannula to keep saturation >90%
- No active cardiac arrhythmias not controlled with medical management
- No hypotension requiring pressor support, except hypotension caused by underlying disease
- No uncontrolled active infectious complications
  - No fever ≥101°F in 12 hours prior to cell infusion unless discussed with protocol officer or protocol chairs.
- Corticosteroid therapy at a pharmacologic dose (>10 mg/day of prednisone or equivalent doses of other corticosteroids) and other immunosuppressive drugs must be avoided for 5 days prior to MB-CART2019.1 administration with the exception of antiemetic or other exceptional needs for prophylaxis or treatment.

The following procedures will be completed at the time points outlined:

#### 4.2.5.1 Evaluations Prior to Cell Infusion

Within 24 hours prior to cell infusion on Day 0:

- Safety laboratory assessment
  - CBC with differential
  - Ferritin, CRP
  - Comprehensive Metabolic Panel and LDH
- Samples for correlative/complementary research to be obtained prior to MB-CART2019.1 infusion and sent to central laboratory
  - Immune Research Studies (to accommodate this sample collection on weekdays they may be drawn Day -1)
  - Cytokine studies

Within 12 hours prior to MB-CART2019.1 infusion on Day 0:

- Physical examination: vital signs and body weight
- ECOG performance status

Prior to cell infusion on Day 0 at 0 hours ± 10 min:

- Concomitant medications documentation

#### 4.2.5.2 Evaluations Post Cell Infusion Day 0

The infusion should be performed following standard institutional guidelines for CAR-T infusions. Following the infusion the patient should be monitored for a minimum of 2 hours, per local institutional guidelines. At the end of the monitoring period the site should record the patient's vital signs and any AEs or SAEs.

### 4.2.6 Post Infusion Follow-up Schedule

The follow-up schedule for study visits after MB-CART2019.1 infusion are outlined below and in the Table of Assessments in Appendix C. A detailed description of each of the case report forms and the procedures required for forms completion and submission can be found in the BMT CTN 2501 forms guide.

#### 4.2.6.1 Evaluations from Day +1 to Day +7

The following procedures will be completed daily (unless otherwise specified):

- Physical examination: vital signs, applicable concomitant medications
- Neurologic examination, including daily ICE assessment should be conducted to identify early signs of neurotoxicity.
    - If neurotoxicity is identified at Grade ≥2, nursing staff should conduct an ICE assessment (Appendix B) every shift and notify physician immediately with any changes in score.
- Safety laboratory assessment:
    - CBC with differential,
    - Comprehensive Metabolic Panel and LDH
    - PT/INR, PTT, D-Dimer, and Fibrinogen ferritin (Days 1, 4, and 7)
    - Ferritin and CRP (Days 1, 4, and 7)
    - Uric Acid
- Samples for correlative/complementary research (central laboratory):
    - Cytokine studies
    - Immune Research Studies

#### 4.2.6.2 Evaluations at Day +10 (±1 day), Day +14 (±1 day), and Day 21 (± 2 days)

The following procedures will be completed at each visit (unless otherwise specified):

- Physical examination: vital signs and applicable concomitant medications
- Neurologic examination including ICE assessment (Days 14 and 21)
    - If neurotoxicity is identified at Grade ≥ 2, nursing staff should notify physician immediately with any changes in score (Appendix B)
- Safety laboratory assessment:
    - CBC with differential,
    - Comprehensive Metabolic Panel and LDH
    - PT/INR, PTT, D-Dimer, Fibrinogen
    - Ferritin, CRP (Days 10 and 14)
    - Uric Acid
- QoL/PRO (Day 14)
- Samples for correlative/complementary research (central laboratory):

- Cytokine studies
- Immune Research Studies

#### 4.2.6.3 Evaluations at Day 28 (± 3 days)

All participants will undergo the following evaluations on Day +28. Day +28 will be the primary assessment for safety of TLT.

- Physical examination: vital signs and applicable concomitant medications
- ECOG performance status
- Neurologic examinations, including ICE assessment
  - If neurotoxicity is identified at Grade ≥ 2, nursing staff should notify physician immediately with any changes in score (Appendix B)
- Safety laboratory assessment:
  - CBC with differential
  - Comprehensive Metabolic Panel and LDH
  - PT/INR, PTT, D-Dimer, and Fibrinogen ferritin
  - Ferritin and CRP
- Quantitative Serum Immunoglobulins
- QoL/PRO
- Response assessment
  - PET/CT for FDG-avid lymphomas
  - Gadolinium- enhanced MRI brain and spine for CNS lymphoma cohort
  - CSF evaluation**:** For participants with history of CNS lymphoma at baseline and to confirm response and/or if new abnormalities cause clinical suspicion of relapse in CNS (if feasible and other location tissue biopsy not feasible).
- Samples for correlative/complementary research (central laboratory):
  - Cytokine studies
  - Immune Research Studies
  - MRD assessment
  - Samples collected for future research, if patient signed the future research portion of the informed consent form.

#### 4.2.6.4 Evaluations at Month +3/Day +90 (± 7 days)

- Physical examination: vital signs and concomitant medications
- Safety laboratory assessment:
  - CBC with differential,
  - Comprehensive Metabolic Panel and LDH
- Quantitative Serum Immunoglobulins
- Response assessment
  - PET/CT
  - Bone marrow biopsy
- Samples for correlative/complementary research (central laboratory):
  - Immune Research Studies
  - MRD assessment
  - Samples collected for future research, if patient signed the future research portion of the informed consent form.
- QoL/PRO

#### 4.2.6.5 Evaluations at Month +6/Day +180 (± 14 days), Month +9/Day +270 (± 14 days), and Month +12/Day +365 (± 14 days)

The following procedures will be completed at each of these visits (unless otherwise specified):

- Physical examination: vital signs and concomitant medications
- Safety laboratory assessment:
  - CBC with differential,
  - Comprehensive Metabolic Panel and LDH
- QoL/PRO, at Month 6 and Month 12 only
- Quantitative Serum Immunoglobulins
- Response assessment, at Month 6 and Month 12 only
  - PET/CT
  - MRI brain for participants with history of CNS involvement
- Samples for correlative/complementary research (central laboratory):
  - Immune Research Studies, Month 6 and Month 12 only
  - MRD assessment, at Month 6 and Month 12 only
  - Samples collected for future research (if patient signed the future research portion of the informed consent form), at Month 6 and Month 12 only
- Enroll into LTFU (for details see Section 4.4), Month 12 only

### 4.2.7 Data Capture Forms

**Criteria for Forms Submission**: Criteria for timeliness of submission for all study forms are detailed in the study forms guide. Forms that are not entered into the data capture system within the specified time will be considered delinquent. A missing form will continue to be requested either until the form is entered into the data capture system and integrated into the Data Coordinating Center (DCC)'s master database, or until an exception is granted.

### 4.2.8 Patient Reported Outcomes

The CIBMTR Survey Research Group (SRG) centrally coordinates all Patient Reported Outcome (PRO) survey assessments. At the time a participant is enrolled in Segment 0, the SRG receives an email notification and adds that participant to CIBMTR's electronic Patient Reported Outcomes (ePRO) system for data collection tracking. Transplant Centers provide participant contact information securely to the SRG upon participant enrollment. PRO surveys will be completed at the timepoints indicated in Table 4.

Baseline PRO surveys will be collected by the center electronically or on paper forms. Baseline PRO surveys should be collected within 7 days before apheresis, although between apheresis and lymphodepletion will be accepted. SRG will provide centers a set of unique electronic survey links in both English and Spanish for Baseline PRO administration.

Day 14 and Day 28 PRO surveys will also be collected by the center. SRG will provide centers with electronic links unique to the patient and time point. Electronically collected PRO surveys are directly entered into the ePRO system via unique links. PDFs of paper surveys will be available for centers on the study website. Centers will scan and securely email any completed paper PRO surveys to the SRG for data entry.

The SRG will centrally collect all post-treatment PRO surveys starting on Day 90. At Day 90, the SRG will attempt to contact the participant by phone to confirm contact information, remind them of survey assessment time points and confirm how they want to complete PRO surveys (paper or

electronic). After speaking by phone with the participant, or if they are unreachable by phone, the SRG will send the Day 90 PRO survey by email and/or mail.

The SRG will continue to contact the participants via email, phone and/or mail to collect PRO surveys on Day 180 and Day 365. The SRG will follow up by phone and e-mail with non-responders up to approximately six contact attempts or until the visit window closes, to minimize missing surveys. If participants do not respond, SRG may request that local study coordinators remind participants or administer the PRO surveys at clinical visits. The SRG may also administer surveys verbally by phone if needed. The SRG will record participant responses in the electronic version of the survey contemporaneously while reading questions and response choices to the patient.

PRO surveys will be available in English and Spanish languages. Participants who are unable to complete PRO surveys in English and Spanish are still eligible for the study and will complete all non-PRO assessments.

#### 4.2.8.1 Patient Reported Outcomes Measurement Information System (PROMIS) Domains

Five PROMIS domains will be used to measure detailed functioning and symptom burden for participants. PROMIS measures utilize T-score metrics, with higher scores indicating more of the concept (i.e., physical function or depression). Scores are normalized to 50 with a standard deviation of 10, and scores greater than 0.5 times standard deviation (i.e., <45 or >55, compared to the general population) are considered clinically meaningful.

The PROMIS domains are Physical Function, Fatigue, Cognitive Function, Depression, and Anxiety. Additionally, two global quality of life and health status items will be included.

#### 4.2.8.2 Financial Impact Scales

The Comprehensive Score for Financial Toxicity (COST), Patient-Reported Economic and items about income and insurance measure the impacts of treatment on finances and economic status of the patient households.

#### 4.2.8.3 Patient Reported Caregiver Assessment (PRCA)

The Patient Reported Caregiver Assessment (PRCA) measures the type of support provided by caregivers, and the economic burden to patient caregivers.

**Table 4: Schedule of PRO Assessments**

| | Items (Minutes) | Baseline Pre-apheresis | Day 14 ± 3 days | Day 28 ± 3 days | Day 90 ± 14 days | Day 180 ± 14 days | Day 365 ± 14 days |
|---|---|---|---|---|---|---|---|
| PROMIS Global QoL | 2 (<1) | X | X | X | X | X | X |
| PROMIS Physical Function | 8 (2) | X | X | X | X | X | X |
| PROMIS Fatigue | 4 (1) | X | X | X | X | X | X |
| PROMIS Cognitive Function | 4 (1) | X | X | X | X | X | X |
| PROMIS Depression | 4 (1) | X | X | X | X | X | X |

| | Items (Minutes) | Baseline Pre-apheresis | Day 14 ± 3 days | Day 28 ± 3 days | Day 90 ± 14 days | Day 180 ± 14 days | Day 365 ± 14 days |
|---|---|---|---|---|---|---|---|
| PROMIS Anxiety | 4 (1) | X | X | X | X | X | X |
| FACIT-COST | 12 (3) | X | | | | X | X |
| Return to Work items | 2 (<1) | | | | X | X | X |
| Sociodemo/SDOH | 12 (3) | X | | | | | X |
| Patient-Reported Caregiver Assessment | 1-6 (2) | X | | | X | | X |
| Totals (Minutes) | | 51-56 (14) | 26 (6) | 26 (6) | 40-45 (11) | 40 (10) | 53-58 (15) |

Abbreviations: FACIT-COST = Functional Assessment of Chronic Illness Therapy–Comprehensive Score for Financial Toxicity; PROMIS = Patient-Reported Outcomes Measurement Information System; QoL = quality of life; SDOH = Social Determinants of Health

#### 4.2.8.4 PRO Compensation

To compensate participants for their effort and time and ensure high compliance on PRO surveys, gift cards will be distributed to study participants for PRO survey completion. Participants will receive one gift card for each completed PRO survey timepoint. Each pre-paid visa gift card will be valued at $20 and will be mailed to the address provided by the participant. The SRG will track all completed surveys, distribute gift cards to recipients and manage gift card inventory.

### 4.3 Reporting Participant Deaths

Recipient death information must be entered into the data capture system within 24 business hours of knowledge of the participant's death. If the cause of death is unknown at that time, it does not need to be recorded at that time. However, once the cause of death is determined, the Death Form must be updated in the data capture system.

### 4.4 Long-Term Follow-up

Participants will be consented for a separate long-term follow-up study. This study will track participant outcomes annually from years 2-15 post-infusion.

### 4.5 CIBMTR Data Reporting

Centers participating in BMT CTN trials must register pre- and post-infusion outcomes on all consecutive infusions done at their institution during their time of participation to the Center for International Blood and Marrow Transplant Research (CIBMTR). Registration is done using procedures and forms from the CIBMTR. (Note: Federal legislation requires submission of these forms for all United States [US] allotransplant recipients.) Enrollment on BMT CTN 2501 must be indicated on the CIBMTR Pre-Cellular Therapy Essential Data (Pre-CTED/F4000) form. Additionally, CIBMTR pre- and post- cellular therapy infusion CRFs must also be submitted for all participants enrolled on this trial. CIBMTR forms and data will be provided at the standard CIBMTR data collection timepoints.

## 4.6 Adverse Experience Reporting

### 4.6.1 Definitions

**Adverse Event**: An AE is any undesirable sign, symptom or medical condition or experience that develops or worsens in severity after starting the first dose of study treatment or any procedure specified in the protocol, even if the event is not considered to be related to the study. Events occurring after informed consent but before leukapheresis will not be considered or reported as AEs unless the event was possibly, probably or definitely related to research procedures. Laboratory abnormalities occurring prior to leukapheresis will not be considered AEs.

An AE is considered a continuation of the same AE if it represents the same underlying medical condition that never truly resolved, even if it temporarily improved. It is considered a new incident if there is a documented resolution and clinically meaningful interval before recurrence.

**Serious Adverse Event:** An SAE, as defined in 21 Code of Federal Regulations (CFR) 312.32, is any AE that results in one of the following outcomes, regardless of causality and expectedness:

- **Results in death**.
- **Is life-threatening**. Life-threatening means that the person was at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction which hypothetically might have caused death had it occurred in a more severe form.
- **Requires or prolongs inpatient hospitalization** (i.e., the event required at least a 24-hour hospitalization or prolonged a hospitalization beyond the expected length of stay). Hospitalization admissions and/or surgical operations scheduled to occur during the study period, but planned prior to study entry, are not considered SAEs if the illness or disease existed before the person was enrolled in the trial, provided that it did not deteriorate in an unexpected manner during the trial (e.g., surgery performed earlier than planned). Hospitalization planned for lymphodepletion or initial monitoring after CAR-T therapy is not considered an SAE unless inpatient hospitalization is prolonged.
- **Results in persistent or significant disability/incapacity**. Disability is defined as a substantial disruption of a person's ability to conduct normal life functions.
- **Is a congenital anomaly or birth defect** in a neonate/infant born to a mother exposed to study drug
- **Is an important medical event** when, based upon appropriate medical judgment, it may jeopardize the participant and require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias and convulsions that do not result in inpatient hospitalization, and the development of drug dependency or drug abuse.

Medical and scientific judgment should be exercised in deciding whether expected reporting is also appropriate in situations other than those listed above. For example, important medical events may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require intervention to prevent one of the outcomes listed in the definition above (e.g., suspected transmission of an infectious agent by a medicinal product is considered an SAE). Any event is considered an SAE if it is associated with clinical signs or symptoms judged by the investigator to have a significant clinical impact.

**Anticipation:**

- **Anticipated AEs** are those that are listed in the protocol, the informed consent document, package inserts, or have been previously identified as resulting from the underlying disease or the CAR T therapy process.
- **Unanticipated AEs** would include those that have not been listed in the protocol, the informed consent document, package inserts, or have not been previously identified as resulting from the underlying disease or the CAR T therapy process. Unanticipated events also include events that would normally be anticipated, but vary in nature, intensity, or frequency, as determined by the investigator.

**Expectedness**:

- **Expected AEs** are those that have been previously identified as resulting from administration of the study therapy. For the purposes of this study, an AE is considered expected when it appears in the IB as a known safety risk.
- **Unexpected AEs** are those that are not listed as a known risk in the IB or vary in nature, intensity, or frequency from those known risks.

### 4.6.2 Definition of Treatment Emergent Adverse Events (TEAEs)

TEAEs are undesirable events that are not present prior to medical treatment, or an already present event that worsens either in intensity or frequency following the introduction of the investigational therapy. A TEAE will be defined as any AE with onset on or after the date of leukapheresis, and including the lymphodepletion chemotherapy, the MB-CART2019.1 cell infusion, the 28-day post-infusion follow-up period, and up to 90 days post-infusion period.

### 4.6.3 Classification of Adverse Events by Severity

The severity refers to the intensity of the reported event. The Investigator must categorize the severity of each reportable SAE according to the NCI CTCAE v6.0. CTCAE guidelines can be referenced at the following website: https://dctd.cancer.gov/research/ctep-trials/for-sites/adverse-events/ctcae-v6.pdf. For any term that is not specifically listed in the CTCAE scale, intensity will be assigned a grade of 1 through 5 using the following CTCAE guidelines:

- **Grade 1**: Mild; asymptomatic or mild symptoms, clinical or diagnostic observations only; intervention not indicated.
- **Grade 2**: Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate- instrumental activities of daily living.
- **Grade 3**: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living.
- **Grade 4**: Life-threatening consequences; urgent intervention indicated.
- **Grade 5**: Death related to AE.

In this study, AEs are graded according to NCI's CTCAE v6.0 with the exception of CRS, ICANS, and IEC-HS, which will be graded using the criteria provided in Appendix F and are classified by ASTCT Consensus Criteria [42, 43]. In addition, infection grading refers to BMT CTN technical guideline grading, not CTCAE.

### 4.6.4 Classification of Adverse Events by Relationship to Study Intervention

The relationship of each reported event to the study treatment will be assessed by the Investigator after careful consideration of all relevant factors such as (but not limited to) the underlying study indication, coexisting disease, concomitant medication, relevant history, pattern of the SAE, temporal relationship to any study treatment interventions and de-challenge or re-challenge according to the following guidelines:

- **Possibly, Probably, or Definitely Related:** there is a reasonable possibility that the study treatment caused the event. A relationship of possibly, probably, or definitely related to the investigational product is considered related for the purposes of regulatory authority reporting.
- **Unlikely, or Not Related:** There is no reasonable possibility that the investigational product caused the event. An unlikely or not related relationship to the investigational product is not considered related for the purposes of regulatory authority reporting

### 4.6.5 Reporting of Laboratory Abnormalities

The diagnosis associated with any clinically significant laboratory abnormalities should be recorded as an AE on the eCRF, per direction of reporting requirements in Section 4.6.5. The reported AE should indicate the underlying abnormality or diagnosis (e.g., renal insufficiency) as opposed to the observed deviation in laboratory results (e.g., elevated creatinine) if in fact the underlying abnormality or diagnosis is known.

Please note that laboratory values that meet criteria for reporting and are a Grade 4 by CTCAE may have different criteria and may not be considered life-threatening with urgent intervention indicated. If the laboratory abnormality itself meets SAE criteria (i.e. results in hospitalization), it will be considered an SAE regardless of grading.

A treatment-emergent abnormal laboratory result is considered to be clinically significant and hence, reportable as an AE, if it meets one or more of the following conditions:

- Induces clinical signs or symptoms.
- Requires active intervention
- The abnormality or investigational value is clinically significant in the opinion of the investigator.

In the event of clinically significant abnormal laboratory test values, the tests should be repeated and followed up until they have returned to the normal range and/or the abnormality is adequately explained or accounted for.

Laboratory abnormalities occurring prior to leukapheresis will not be considered AEs.

### 4.6.6 BMT CTN Adverse Event Reporting Guidelines

AE reporting will be consistent with BMT CTN procedures (BMT CTN Administrative Manual of Procedures [MOP], Chapter 6), although the specifics of this section should be followed per protocol, as MOP procedures are more general. Events meeting reporting requirements as described below must be reported even if the Investigator is unsure whether a relationship exists between the adverse event and the use of study treatment.

Pre-existing conditions do not need to be reported as AEs unless they worsen during the study. All AEs and SAEs should be followed until the event has resolved or stabilized.

**Anticipated Event Collection**

Many anticipated AEs will be reported from time of leukapheresis at regular intervals as defined on the Form Submission Schedule, including calendar-driven case report forms (CRFs) (e.g., Toxicity) or event-driven CRFs (e.g., Relapse/Progression, Infection, Hospitalization/Re-admission, and Death). Events of relapse and infection will not be reported as AEs, but on their designated forms, as these are part of the study endpoints (the exception to this is grade 3 or higher infections meeting Adverse Event of Special Interest (AESI) criteria per AESI section below, which will be collected on the AE form set. Any anticipated life-threatening SAE not collected on another study form must be reported on the AE CRF set.

**AEs Reported on the AE Form**

All unanticipated SAEs, non-serious CTCAE grade 3-4 events not captured on another form, and all CTCAE grade 3-4 events at least possibly related to the study product (even if reported on another form) will be reported through an expedited AE reporting system via the Advantage eClinical data capture system from signature of study consent until the end of study or until patient discontinues trial participation and completes safety follow-up procedures, whichever occurs first. **Any unanticipated life-threatening and fatal SAEs must be reported within 24 hours of knowledge of the event. All other SAEs must be reported within 3 business days of knowledge of the event.** If the SAE is also a suspected unexpected serious adverse reaction (SUSAR), the Sponsor or its designee may urgently require further information from the investigator for expedited reporting to health authorities. Investigator safety letters (ISLs) must be prepared for SUSARs according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary. The Sponsor or its designee may issue an Investigator Notification to inform all investigators involved in any study with the same drug that this SUSAR has been reported.

For non-serious and non-AESI events that require collection, a simplified Adverse Event form will collect basic information.

If there are network outages, a paper copy of the AE forms must be completed and emailed to Emmes to initiate review. Once the system is available, the event information must be entered into the system.

The National Heart, Lung, and Blood Institute (NHLBI)/Data and Safety Monitoring Board (DSMB) will receive reports of all Suspected Unexpected Serious Adverse Reactions (SUSARs) within two business days of the time they are sent to the FDA (FDA submission guidelines are 7 regulatory days for life-threating and fatal events and 15 regulatory days for all other SUSARs). They will receive reports of AESIs within 7 days of Medical Monitor review. The DSMB will also review summary reports of all reported events on at least an annual basis.

### 4.6.7 Reporting of Special Situations and Adverse Events of Special Interest (AESIs)

Pregnancy will be reported as a special situation for this trial and will follow reporting guidelines per Section 4.6.8.

This trial will also have AESIs. If any of these AESIs occur, this event should be reported on the AE CRFs, whether it is considered a non-serious event or an SAE, and regardless of anticipation assessment. All AESIs are to be collected until the end of study or until patient discontinues trial participation and completes safety follow-up procedures, whichever occurs first. In this study, AEs are graded according to NCI's CTCAE v6.0 with the exception of CRS, ICANS, and IEC-HS, which will be graded using the criteria provided in Appendix F and are classified by ASTCT Consensus Criteria [42, 43]. In addition, infection grading refers to BMT CTN technical guideline grading, not CTCAE. All AESIs should be reported within 24 hours of knowledge of the event.

AESIs include the following:

- CAR-T infusion reactions (Grade 3 or greater), defined as events that occur within 24 hours of CAR-T infusion
- CRS (Grade 3+)
- ICANS (Grade 3+)
- IEC-HS / MAS / HLH (any grade)
- TLS (Grade 3 or greater)
- Prolonged cytopenias (Grade ≥ 3), defined as neutropenia, anemia, or thrombocytopenia present at Day 28 visit or new onset (Grade 3 or greater) cytopenias after Day 28
- Infections (only Grade 3 or greater)
- Secondary malignancies (new onset events)
- Death due to any cause
- Hypogammaglobulinemia will be assessed as an AE, as well as laboratory value of immunoglobulin G (IgG) < 400 mg/dL. AEs of hypogammaglobulinemia should be reported throughout the study.

  TLS ≥ Grade 3 will be summarized based on the Adverse Events report and grading by the investigator. TLS should be reported similar to all other AEs/SAE for the 90 days from the time of CAR-T infusion.

### 4.6.8 Procedure in Case of Pregnancy

If a female participant becomes pregnant during the study intervention period or within 30 days from the study intervention, the Investigator should report the information through an expedited AE reporting system via the EDC system within 1 business day. The expected date of delivery or expected date of the end of the pregnancy, last menstruation, estimated conception date, pregnancy result, neonatal data, and other related information will be requested.

The Investigator will follow the medical status of the mother, as well as the fetus, as if the pregnancy is an SAE and will report the outcome. Additional information regarding the outcome of a pregnancy (which is categorized as an SAE) is mentioned below.

- “Spontaneous abortion” includes miscarriage, abortion, and missed abortion.
- Death of an infant within 30 days after birth should be reported as an SAE regardless of its relationship with the study intervention.
- If an infant dies more than 30 days after birth, it should be reported if a relationship between the death and intrauterine exposure to the study intervention is judged as “possible” by the Investigator.
- In the case of a delivery of a living newborn, the “normality” of the infant is evaluated at the birth.
- Unless a congenital anomaly is identified prior to spontaneous abortion or miscarriage, the embryo or fetus should be assessed for congenital defects by visual examination.

Information will be collected at the time of delivery/birth and 180 and 360 days after birth.

### 4.6.9 AE Reporting Form Guidance

The forms to be completed for each type of event are shown in Table 5.

**Table 5: AE Reporting Form Guidance**

| Type of Event | Form(s) to be Completed |
|---|---|
| Death | AE Form |
| AESI | AE Form |
| Unanticipated SAE | AE Form |
| Infections | Infection Form<br>AE Form also (if Grade 3 or higher) |
| Deaths (Grade 5 event) | Death Form<br>AE Form |
| Grade 3-4 AE not captured on another form | AE Form |
| Grade 3-4 Anticipated AE captured on Toxicity Form, but also related to study product | Toxicity Form<br>AE Form |
| Grade 3-4 Anticipated AE captured on Toxicity Form, but not related to study product | Toxicity Form |

Abbreviations: AE = adverse event; AESI = adverse event of special interest; SAE = serious adverse event

# CHAPTER 5

## 5 STATISTICAL CONSIDERATIONS

### 5.1 Study Overview

This study is a Phase II, multicenter, single arm trial to assess the efficacy and safety of CAR20.19 T cells as a consolidation therapy for high risk MCL. The accrual goal is 52 participants who have enrolled and received an infusion of the MB-CART2019.1 that is within specification and non-cryopreserved. Enrolled participants who do not receive an MB-CART2019.1 infusion that is within specification and non-cryopreserved will be replaced to meet this enrollment target.

#### 5.1.1 Accrual Duration

It is estimated that 24 months of accrual will be necessary to enroll the targeted sample size.

#### 5.1.2 Primary Objective, Endpoint, and Hypothesis

The primary endpoint is the 1-year durable overall response rate, defined as the probability of having complete response or partial response at 1 year without post-infusion progression or death. The primary objective is to evaluate the 1-year durable overall response rate. The primary hypothesis is that the 1-year durable overall response rate for high risk MCL patients who receive CAR20.19 T-cell infusion is higher than 55%. The null hypothesis is that this rate equals 55% or less. This hypothesis will be tested using a one-sided significance level of 2.5%.

#### 5.1.3 Randomization and Blinding

This is a single arm trial; therefore, no randomization or blinding will be performed.

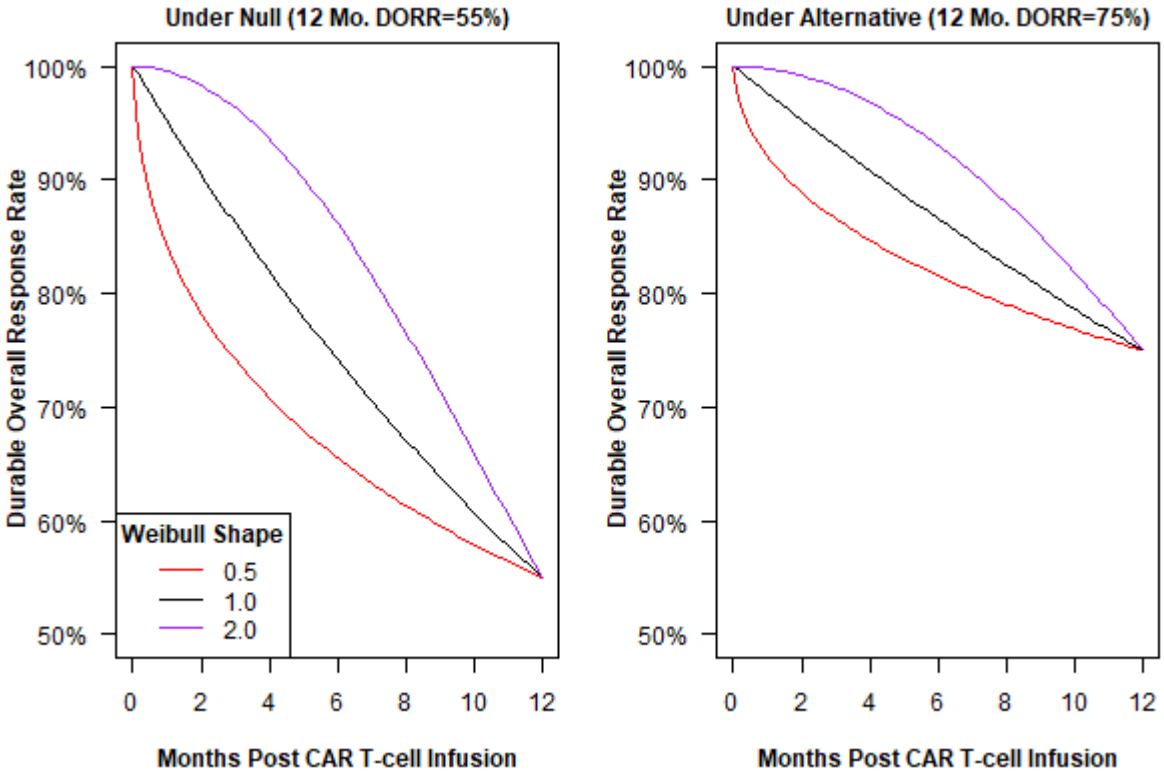
### 5.2 Sample Size and Power Considerations

For a one-sided 2.5% significance level, a sample size of 52 participants was determined to provide at least 80% power if the true 1-year durable overall response rate is at least 75%, an improvement of at least 20% over the null rate of 55%. To account for potential missing data due to censoring of follow-up, this rate will be estimated using the Kaplan-Meier estimator. The sample size was based on an approximate normal test of a binomial proportion, adjusted for an expected dropout rate of 10%. If dropout is present, the Kaplan-Meier estimator can incorporate available partial follow-up information on censored patients who dropped out and so a Kaplan-Meier-based test is expected also to have at least 80% power for this sample size. The test statistic used is the standardized, log transformed Nelson-Aalen estimate at 1 year, which is approximated better by a normal distribution than the standardized Kaplan-Meier estimate for small samples [45, 46]; for large samples, both test statistics follow a standard normal distribution if the true durable overall response rate is 55%. A Z test will be applied to the transformed statistic for hypothesis testing.

For the modest sample size of this study, the type I error rate and power were estimated using simulations in settings where the durable overall response failure time distribution is a Weibull distribution with shape parameter values of 0.5, 1.0, and 2.0. These correspond to respective situations where most events occur early, between months 0 – 3; the events are approximately equally distributed across months 0 – 12; and most events occur late, between months 9 – 12. Figure 4 displays their corresponding durable overall response failure curves under the null and targeted alternative 1-year durable overall response rates of 55% and 75%, respectively. These patterns comprise a range of plausible event patterns that may arise in trial settings and will serve

to evaluate the robustness of the test in achieving its intended type I error and power levels across potential event distributions.

**Figure 4: Possible Weibull Distributions for Durable Overall Response Failures Under the Null and Targeted Alternative Hypotheses**




Abbreviations: CAR = chimeric antigen receptor; Mo = months; DORR = durable overall response rate

Table 6 shows the empirical type I error rates and power from these simulations with random censoring times generated from an exponential distribution that produces a 10% dropout rate by 1 year; 100,000 Monte Carlo replicates were generated per scenario. The type I error rates range from 1.9 – 2.1% and the power to detect a true 1-year durable overall response rate of 75% is 80.2 – 81.8%, showing that the test meets its type I error and power specifications for all scenarios considered.

**Table 6: Probability of Rejecting the Null Hypothesis that 1-Year Durable Overall Response Rate Does Not Exceed 55% Under Various True Rates and Event Distributions**

| True 1 Year DORR Rate | Weibull Distribution for DORR Event Time | | |
|---|---|---|---|
| | Shape=0.5 | Shape=1.0 | Shape=2.0 |
| 55% (Null Hypothesis) | 2.1% | 1.9% | 2.0% |
| 65% | 26.0% | 25.4% | 25.2% |
| 70% | 54.0% | 53.3% | 52.5% |
| 75% (Targeted Alternative Hypothesis) | 81.8% | 80.8% | 80.2% |
| 80% | 96.2% | 95.9% | 95.6% |

* Rejection probabilities were estimated using 100,000 Monte Carlo simulations per scenario.
Abbreviation: DORR = durable overall response rate

## 5.3 Interim Analysis and Pausing Guidelines

Interim analyses will be performed for safety only, not for efficacy or futility. Participants will be monitored for key safety endpoints on a daily basis for evidence of excess risk. Safety outcomes to be monitored include NRM within 100 days post MB-CART2019.1 infusion and TLT within 28 days post infusion. If rates significantly exceed pre-set thresholds, the NHLBI will be notified in order that the DSMB can be advised. The policies and composition of the DSMB are described in the BMT CTN MOP. The monitoring guidelines serve as a trigger for a temporary pause of enrollment and a consultation with the DSMB for additional review; they are not formal stopping rules that mandate automatic closure of study enrollment. Upon review of the pausing guidelines data, the DSMB will make recommendations to the National Heart, Lung, and Blood Institute (NHLBI) on whether a study status change should be made. The NHLBI will make the final determination on action to be taken if the pausing guidelines are met.

### 5.3.1 Non-relapse Mortality by Day 100 Post MB-CART2019.1 Infusion

A safety pausing rule will monitor NRM through 100 days post MB-CART2019.1 infusion. Relapse/progression is treated as a competing risk for NRM. The analysis population for this monitoring consists of all patients who receive a MB-CART2019.1 infusion, regardless of whether the MB-CART2019.1 is within specification and non-cryopreserved. The Day 100 NRM rate is not expected to exceed 10%. A safety monitoring boundary for NRM was developed using a time-to-event-sequential probability ratio test (TITE-SPRT) [47] that contrasts a 10% null rate to a 25% targeted excessive rate. Unlike monitoring approaches that treat toxicity data as binary outcomes, the TITE-SPRT uses a time-to-event analysis approach that can incorporate available data from patients who have not completed full follow-up for the 100-day evaluation period, expediting the detection of excess risk. The nominal type I error rate for this procedure is 5%, corresponding to a critical value of 13.021 for the probability ratio and a rejection boundary with intercept 2.336 and slope 0.166 for the number of events versus effective sample size.

At each examination, the effective sample size (ESS) is computed, defined as

$$\text{ESS} = \text{patients whose Day 100 NRM status is known} + \frac{\text{total days follow up in patients whose Day 100 NRM status is pending}}{100 \text{ days}}.$$

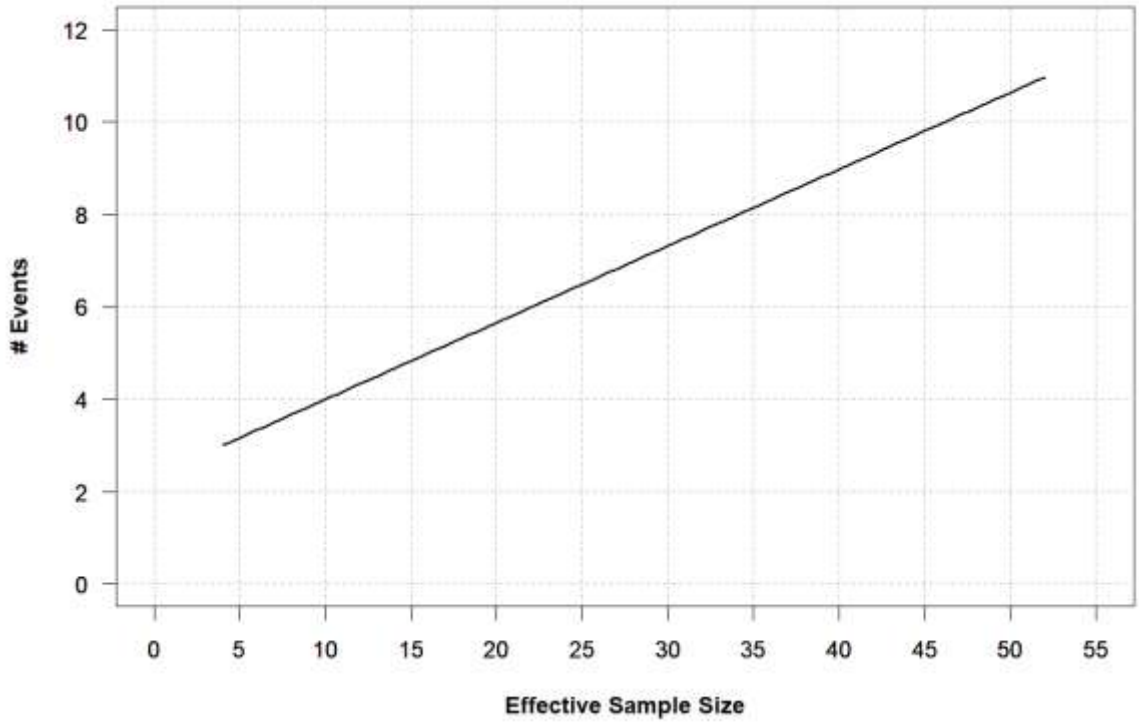
The ESS counts each patient whose status is known (either because an NRM or relapse was observed before Day 100 or they completed 100 days of follow up without relapse/NRM) as a full participant, whereas a patient who is event-free and has not reached 100 days is counted as a fractional participant, the fraction being determined by the portion of the 100 day period completed. The ESS can be viewed as the total exposure of trial patients to the investigational therapy and can equivalently be described as the total person-days of evaluation among MB-CART2019.1 infused patients, which equals 100 x ESS days. Table 7 displays the pausing guideline for NRM. The ESS is compared to the rejection boundary value for the number of Day 100 NRM events. At least 3 events must be observed in order to trigger review. Figure 5 displays the pausing boundary graphically.

**Table 7: Pausing Guideline for Day 100 NRM in a 52 Participant Cohort**

| Effective Sample Size | Total Person-days Evaluated | Rejection Boundary for # NRM Events |
|---|---|---|
| 3.00 – 4.00 | 300 – 400 | 3 |
| 4.01 – 10.02 | 401 – 1002 | 4 |
| 10.03 – 16.05 | 1003 – 1605 | 5 |
| 16.06 – 22.07 | 1606 – 2207 | 6 |
| 22.08 – 28.10 | 2208 – 2810 | 7 |
| 28.11 – 34.12 | 2811 – 3412 | 8 |
| 34.13 – 40.15 | 3413 – 4015 | 9 |
| 40.16 – 46.17 | 4016 – 4617 | 10 |
| 46.18 – 52.00 | 4618 – 5200 | 11 |

Abbreviation: NRM = non-relapse mortality

**Figure 5: Rejection Boundary for Day 100 NRM and Day 28 TLT Pausing Guidelines**




Abbreviations: NRM = non-relapse mortality; TLT = treatment-limiting toxicity

Table 8 shows the operating characteristics of this test over a range of true NRM rates. Uniform accrual of 52 participants over a 2-year period is assumed. The operating characteristics were computed using 100,000 Monte Carlo simulations under the assumption that NRM events are uniformly distributed over the first 100 days post MB-CART2019.1 infusion. This procedure rejects the null hypothesis 4.5% of the time when the true Day 100 NRM rate is 10% and 84.4% of the time when the rate is 25%. If the true rate is 25%, the trial will be paused and the DSMB will be consulted at approximately 14 months after opening on average, when 7 events have been observed in 30 enrolled participants.

**Table 8: Operating Characteristics of Sequential Monitoring Procedure for Day 100 NRM in a 52 Participant Cohort**

| True Day 100 NRM Rate | 10% | 15% | 20% | 25% | 30% |
|---|---|---|---|---|---|
| Probability of Early Pausing | 0.045 | 0.244 | 0.579 | 0.844 | 0.963 |
| Mean Month Paused | 26.6 | 23.8 | 19.0 | 14.1 | 10.5 |
| Mean # Events | 5.1 | 6.8 | 7.3 | 6.8 | 5.9 |
| Mean # Participants Enrolled | 50.8 | 46.4 | 38.3 | 29.7 | 22.8 |

* Operating characteristics were estimated using 100,000 Monte Carlo simulations per scenario.
Abbreviation: NRM = non-relapse mortality

### 5.3.2 Treatment Limiting Toxicity by Day 28 Post MB-CART2019.1 Infusion

The frequency of TLTs occurring through 28 days post MB-CART2019.1 infusion will be monitored. Death is treated as a competing risk for TLT. The analysis population for this monitoring consists of patients who receive a MB-CART2019.1 infusion, regardless of whether the MB-CART2019.1 is within specification and non-cryopreserved. The Day 28 TLT rate is not expected to exceed 10%. A safety monitoring boundary for TLT was developed using a TITE-

SPRT that contrasts a 10% null rate to a 25% targeted excessive rate. The nominal type I error rate for this procedure is 5%, corresponding to a critical value of 13.021 for the probability ratio and a rejection boundary with intercept 2.336 and slope 0.166 for the number of events versus effective sample size.

At each examination, the ESS is computed, defined as

$$\text{ESS} = \text{patients whose Day 28 TLT status is known} + \frac{\text{total days follow up in patients whose Day 28 TLT status is pending}}{28 \text{ days}}.$$

The ESS counts each patient whose status is known (either because a TLT or death was observed before Day 28 or they completed 28 days of follow up without TLT/death) as a full participant, whereas a patient who is event-free and has not reached 28 days is counted as a fractional participant. The ESS can be viewed as the total exposure of trial patients to the investigational therapy and can equivalently be described as the total person-days of evaluation among MB-CART2019.1 infused patients, which equals 28 x ESS days. Table 9 displays the pausing guideline for TLT. The ESS is compared to the rejection boundary value for the number of Day 28 TLT events. At least 3 events must be observed in order to trigger review. Figure 5 displays the pausing boundary graphically.

**Table 9: Pausing Guideline for Day 28 TLTs in a 52-Participant Cohort**

| Effective Sample Size | Total Person-days Evaluated | Rejection Boundary for # TLT Events |
|---|---|---|
| 3.00 – 4.00 | 84 – 112 | 3 |
| 4.01 – 10.02 | 113 – 280 | 4 |
| 10.03 – 16.05 | 281 – 449 | 5 |
| 16.06 – 22.07 | 450 – 618 | 6 |
| 22.08 – 28.10 | 619 – 786 | 7 |
| 28.11 – 34.12 | 787 – 955 | 8 |
| 34.13 – 40.15 | 956 – 1124 | 9 |
| 40.16 – 46.17 | 1125 – 1293 | 10 |
| 46.18 – 52.00 | 1294 – 1456 | 11 |

Abbreviation: TLT = treatment-limiting toxicity

Table 10 shows the operating characteristics of this test over a range of true TLT rates. Uniform accrual of 52 participants over a 2-year period is assumed. The operating characteristics were computed using 100,000 Monte Carlo simulations under the assumption that TLT events are uniformly distributed over the first 28 days post MB-CART2019.1 infusion. This procedure rejects the null hypothesis 4.7% of the time when the true Day 28 TLT rate is 10% and 84.5% of the time when the rate is 25%. If the true rate is 25%, the trial will be paused and the DSMB will be consulted at approximately 13 months after opening on average, when 7 events have been observed in 27 enrolled participants.

**Table 10: Operating Characteristics of Sequential Monitoring Procedure for Day 28 TLT in a 52-Participant Cohort**

| True Day 28 TLT Rate | 10% | 15% | 20% | 25% | 30% |
|---|---|---|---|---|---|
| Probability of Early Pausing | 0.047 | 0.249 | 0.583 | 0.845 | 0.963 |
| Mean Month Paused | 24.2 | 21.7 | 17.2 | 12.6 | 9.2 |
| Mean # Events | 5.1 | 6.8 | 7.2 | 6.7 | 5.8 |
| Mean # Participants Enrolled | 50.6 | 45.6 | 36.7 | 27.4 | 20.2 |

* Operating characteristics were estimated using 100,000 Monte Carlo simulations per scenario.
Abbreviation: TLT = treatment-limiting toxicity

## 5.4 Demographic and Baseline Characteristics

Demographics and baseline characteristics will be described for all enrolled participants. Characteristics to be examined are age, sex, race/ethnicity, ECOG performance status core, HEMATOTOX score, bendamustine use, p53 mutation, CNS involvement of lymphoma, and CD19/CD20 expression levels.

## 5.5 Statistical Analysis Strategy

### 5.5.1 Analysis Populations

#### 5.5.1.1 Primary Analysis Population

The primary analysis population will consist of all participants who receive an infusion of within specification, non-cryopreserved MB-CART2019.1.

#### 5.5.1.2 CAR T Infused Population

The CAR T infused population will consist of all patients who receive the MB-CART2019.1 infusion, regardless of whether the cells are within specification and non-cryopreserved.

#### 5.5.1.3 Leukapheresis Population

The leukapheresis population will consist of patients who undergo leukapheresis with the goal of obtaining a minimum of 1 x $10^9$ MNC for manufacture of MB-CART2019.1 cells.

#### 5.5.1.4 Enrolled Population

The enrolled population will consist of all participants who provide informed consent and enroll (meet eligibility criteria described in Section 2.3) in BMT CTN 2501.

### 5.5.2 Analysis of the Primary Endpoint

The primary endpoint, the durable overall response rate at 1-year post infusion, is the probability of having complete response or partial response at 1 year without post-infusion progression or death. Failures for 1-year durable overall response rate include clinical progression and death from any cause through 1 year post-infusion and stable disease at 1 year post-infusion. The time of durable overall response failure is defined as the time interval from MB-CART2019.1 infusion until the first failure event occurs. Participants who are event-free and withdraw, are lost to follow-up, or complete study follow-up without experiencing an event will be censored at their last contact date. Participants who receive additional anti-lymphoma therapy will be censored at the date of therapy initiation. Kaplan-Meier curves will be used to display durable overall response rate from MB-CART2019.1 infusion to 1 year post infusion. A point estimate and 95% confidence interval

(CI) of the 1-year durable overall response rate will be reported using Kaplan-Meier estimates. The durable overall response rate will be analyzed using the primary analysis population.

The hypothesis that the 1-year durable overall response rate exceeds 55% will be tested at a 2.5% one-sided significance level using a Z test of the standardized, log transformed Nelson-Aalen estimate at 1 year.

### 5.5.3 Analysis of Feasibility Endpoint

The feasibility endpoint is success of manufacturing MB-CART2019.1. The counts and proportions of patients for whom MB-CART2019.1 is successfully manufactured will be described in the leukapheresis population among all patients and stratified by prior bendamustine use.

### 5.5.4 Analysis of Secondary Endpoints

#### 5.5.4.1 Treatment Response

Treatment response will be analyzed using the primary analysis population. The counts and percentages of participants with complete response, partial response, stable disease, and progressive disease will be described at Day 90 post MB-CART2019.1 infusion. The best response for patients through Day 90 will be similarly tabulated.

The proportions of patients with complete response and overall response (partial or complete) will be estimated using sample proportions and 95% Wilson score CIs. Best overall response, defined as a patient achieving a complete or partial response at any time, will be estimated similarly.

#### 5.5.4.2 Overall Survival (OS)

OS is defined as the time interval from MB-CART2019.1 infusion until death. Participants who withdraw, are lost to follow-up, or complete study follow-up alive will be censored at their last contact date. Kaplan-Meier curves will be used to display OS from MB-CART2019.1 infusion to 1 year post infusion. A point estimate and 95% CI of 1-year OS will be reported using Kaplan-Meier estimates. OS will be analyzed using the primary analysis population.

#### 5.5.4.3 Progression Free Survival (PFS)

PFS is defined as the time interval from MB-CART2019.1 infusion until death or clinical progression, whichever happens first. Participants who are event-free and withdraw, are lost to follow-up, or complete study follow-up alive will be censored at their last contact date. Kaplan-Meier curves will be used to display PFS from MB-CART2019.1 infusion to 1 year post infusion. A point estimate and 95% CI of 1-year PFS will be reported using Kaplan-Meier estimates. PFS will be analyzed using the primary analysis population.

#### 5.5.4.4 Duration of Complete Response (DOCR)

DOCR will be analyzed using the subset of primary analysis population patients who achieve a CR. DOCR is defined as the time interval from first achieving a CR until progressive disease or death, whichever occurs first. For participants who are in CR at MB-CART2019.1 infusion, their time of achieving CR will be the time of infusion. Kaplan-Meier curves will be used to display DOCR through 1 year post infusion. A point estimate and 95% CI of 1-year DOCR will be reported using Kaplan-Meier estimates. An estimate and 95% CI for the median DOCR time will be reported.

#### 5.5.4.5 Non-relapse Mortality (NRM)

NRM will be analyzed using the primary analysis population. The time interval from MB-CART2019.1 infusion until NRM will be described using the Aalen-Johansen estimator, with relapse/progression treated as a competing risk. Estimates and 95% CIs of the cumulative incidence of NRM will be provided at 1 year post MB-CART2019.1 infusion.

#### 5.5.4.6 Relapse/progression

Relapse/progression will be analyzed using the primary analysis population. The time interval from MB-CART2019.1 infusion until relapse/progression will be described using the Aalen-Johansen estimator, with NRM treated as a competing risk. Estimates and 95% CIs of the cumulative incidence of relapse/progression will be provided at 1 year post MB-CART2019.1 infusion.

#### 5.5.4.7 Immune Effector Cell Related Toxicities

CRS, ICANS, and IEC-HS will be analyzed using the primary analysis population. The counts and percentages of participants experiencing CRS, ICANS, and IEC-HS through Day 28 post MB-CART2019.1 infusion will be described for each toxicity overall and by grade. The counts and percentages of participants experiencing ICANS after Day 28 post MB-CART2019.1 infusion will also be described overall and by grade.

#### 5.5.4.8 Event-free Survival (EFS)

EFS is defined as the time interval from MB-CART2019.1 infusion until clinical progression, additional anti-lymphoma treatment initiation (including oral therapy, IV, or radiation) in the absence of clinical progression, and death. Participants who are event-free and withdraw, are lost to follow-up, or complete study follow-up without experiencing an event will be censored at their last contact date. Kaplan-Meier curves will be used to display EFS from MB-CART2019.1 infusion to 1 year post infusion. A point estimate and 95% confidence interval (CI) of 1-year EFS will be reported using Kaplan-Meier estimates. EFS will be analyzed using the primary analysis population.

### 5.5.5 Analysis of Exploratory Endpoints

#### 5.5.5.1 CAR T Cell Persistence

The proportion of patients for whom CAR T cells remain present at 1 year post-infusion will be described using the sample proportion and a 95% Wilson score confidence interval. CAR T cell persistence will be analyzed using the primary analysis population.

#### 5.5.5.2 Out of Specification CAR T Cell Efficacy

The efficacy of CAR-T infusion will be described in patients who receive an out-of-specification MB-CART2019.1 product. The durable overall response rate, OS, PFS, DOCR, and EFS at 1 year post CAR T infusion will be estimated using the Kaplan-Meier estimator, while 1-year cumulative incidences of NRM and relapse/progression will be estimated by the Aalen-Johansen estimator. The counts and percentages for treatment response classification at Day 90 post infusion and for best response will be provided. The counts and percentages of participants experiencing CRS, ICANS, and IEC-HS through Day 28 post MB-CART2019.1 infusion will be described.

#### 5.5.5.3 Cytokine Levels

The levels of IFN-g, IL10, IL6, and TNF-a on the day of MB-CART2019.1 infusion and at Days 1, 4, 7, 10, 14, 21, and 28 will be described using the sample mean, median, quartiles, minimum, and maximum. Cytokine levels will be analyzed using the primary analysis population.

#### 5.5.5.4 Subgroup Analyses of Clinical Outcomes

The durable overall response rate, PFS, and OS at 1 year post-infusion will be evaluated using Kaplan-Meier point estimates and 95% CIs separately for subgroups determined by baseline prior bendamustine use, MRD status, p53 mutation, CNS involvement, and CD19/20 expression levels. CD19/20 expression levels will be dichotomized using the median for this analysis. CR and OR rates at Day 90 post-infusion will be estimated using sample proportions and 95% Clopper-Pearson CIs in these subgroups. These analyses will be conducted using the primary analysis population and will be performed only for subgroups having at least 5 patients.

#### 5.5.5.5 Infection

The number of Grade 2 or higher infections (graded per the BMT CTN Infectious Diseases Technical Document) and number of participants infected from the time of MB-CART2019.1 infusion to 1 year post-infusion will be summarized by type and severity in the primary analysis population.

#### 5.5.5.6 B-cell Recovery

The proportions of patients who have B-cell recovery after MB-CART2019.1 infusion will be described at 1 month, 3 months, 6 months, and 1 year post-infusion using sample proportions and 95% Wilson score CIs. The proportions of patients who received IVIG replacement after infusion will be described similarly. B-cell recovery and IVIG replacement will be analyzed using the primary analysis population.

#### 5.5.5.7 MRD Status

The proportions of patients with MRD at screening, Day 28, Month 3, Month 6, and 1 year will be described using sample proportions and 95% Wilson score CIs. MRD status will be analyzed using the primary analysis population.

#### 5.5.5.8 ICU hospitalization

The proportion of patients who are hospitalized to an ICU through Day 28 post MB-CART2019.1 infusion will be described using the sample proportion and a 95% Wilson score CI. ICU hospitalization will be analyzed using the primary analysis population.

#### 5.5.5.9 ICAHT

The counts and percentages of patients having ICAHT post- MB-CART2019.1 infusion will be reported overall, by grade, and by time period (Days 0-28 and after Day 28). ICAHT will be analyzed using the primary analysis population.

#### 5.5.5.10 Immunosuppression Use

The proportions of patients who receive tocilizumab, corticosteroids, anakinra, and other immunosuppressive therapies through Day 28 post MB-CART2019.1 infusion will be described using sample proportions and 95% Wilson score CIs. Immunosuppression use will be analyzed using the primary analysis population.

#### 5.5.5.11 Patient Reported Outcomes

The distributions of scores for the PROMIS domains and COST will be described by descriptive statistics at each assessment time point. Responses to return to work, sociodemographic/social determinants of health, and PRCA items will be tabulated by frequency and percentages at each assessment time. These instruments will be analyzed using the primary analysis population.

Changes in scores from baseline to each follow-up assessment time will be evaluated for the PROMIS domains and COST. A linear mixed model will be used for each PRO measure to assess changes over time, with fixed effects for assessment times and random effects to account for correlations of scores within participants.

### 5.5.6 Analysis of Safety Endpoints

The frequency of Grade 3-5 AEs per CTCAE version 6.0 occurring from the time of leukapheresis until 1 year post MB-CART2019.1 infusion will be tabulated by system organ class (SOC) and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA®) dictionary. The frequency and proportion of participants having at least one Grade 3-5 AE will be summarized by SOC and preferred term. Detailed listings of unanticipated SAEs, including grade and relationship to treatment, will be presented. Adverse events will be summarized separately for the primary analysis, MB-CART2019.1 infused, and leukapheresis populations.

# APPENDIX A: HUMAN SUBJECTS

## 1. Participant Consent

Candidates for the study will be identified as described in Chapter 4 of the protocol. The Prinicipal Investigator or his/her designee at each transplant center will contact the candidates, provide the participant with information about the purpose of the study, and obtain consent. The BMT CTN will provide a template of the consent form to each center. Each center will customize the template according to their local requirements and submit it for review by the NMDP IRB. The DCC will verify the adequacy of the consent forms prior to submission to the IRB. Each center must provide evidence of IRB approval to the DCC.

## 2. Confidentiality

Confidentiality will be maintained by individual names being masked and assigned a participant ID code. The code relaying the participant's identity with the ID code will be kept separately at the center. The ID code will be generated by and kept on file at the BMT CTN DCC upon enrollment.

## 3. Participation of Women and Minorities

Women, ethnic minorities, and other populations will be included in this study. Accrual of women and minorities at each center will be monitored to determine whether their rates of enrollment are reflective of the distribution of potentially eligible women and minorities expected from data reported to the CIBMTR and from published data on incidence of MCL in these groups. Centers will be notified if their rates differ significantly from those expected and asked to develop appropriate recruitment reports.

# APPENDIX B: IMMUNE EFFECTOR CELL-ASSOCIATED ENCEPHALOPATHY (ICE) ASSESSMENT

**Directions:** Answer whether each task was performed correctly (Not Done/Yes/No). If you answer YES put **1** in the Score column; If you answer NO (or Not Done) put **0** in the Score column.

**Table 11: ICE Assessment**

| Tasks | Performed correctly? | Score |
|---|---|---|
| 1. What is the current year? | | **0** |
| 2. What is the current month? | | **0** |
| 3. What is the current city? | | **0** |
| 4. What hospital are you in? | | **0** |
| 5. Name this object (*point to an object in the room)* | | **0** |
| 6. Name this object (*point to an object in the room)* | | **0** |
| 7. Name this object (*point to an object in the room)* | | **0** |
| 8. Following commands: (e.g. Show me 2 fingers) | | **0** |
| 9. Write a simple sentence (*provide paper and pencil)* | | **0** |
| 10. Count backward from 100 in 10's. | | **0** |
| **Total Score** | | **0** |

| Signature of Individual Conducting the Assessment: | Date: |
|---|---|
| Printed Name: | |

**Scoring ICE**
Score 10: No impairment
Score 7-9: Grade 1 ICANS
Score 3-6: Grade 2 ICANS
Score 0-2: Grade 3 ICANS
Score 0 due to participant unarousable and unable to perform ICE assessment: Grade 4 ICANS

# APPENDIX C: SCHEDULE OF ASSESSMENTS

## Table 12: Schedule of Assessments

| | Pre-infusion | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Assessments and Procedures** | **Screening (Within 42 Days of Apheresis)** | **Within 7 Days Prior to Apheresis** | **Apheresis** | **Lymphodepletion Days -5, -4, -3** | **Day 0 – MB-CART2019.1 Infusion** | **Days +1-7 (Week 1 Daily Visits** | **Days +10, 14 (Week 2)** | **Day 21 (Week 3)** | **Day +28 or Month +1** | **Month +3 (Day 90)** | **Month +6 (Day 180)** | **Month +9 (Day 270)** | **Month +12 (Day 365)** |
| | | | | | | | ±1 day | ±2 days | ±3 days | ±7 days | ±14 days | ±14 days | ±14 days |
| **Screening** | | | | | | | | | | | | | |
| Informed Consent and Patient Registration | X | | | | | | | | | | | | |
| Demographics and Medical History | X | | | | | | | | | | | | |
| ECG[1] | X | | | | | | | | | | | | |
| ECHO/MUGA | X | | | | | | | | | | | | |
| Pregnancy Test[2] | X | X | | | | | | | | | | | |
| **TREATMENT** | | | | | | | | | | | | | |
| Leukapheresis | | | X | | | | | | | | | | |
| Lymphodepletion[3] | | | | X[3] | | | | | | | | | |
| Central Line[4] | | | | | X | | | | | | | | |
| MB-CART2019.1 Infusion[5] | | | | | X | | | | | | | | |
| **CLINICAL PROCEDURES** | | | | | | | | | | | | | |
| Physical Examination[6] | X | X | | X[3] | X[7] | X[8] | X | X | X | X | X | X | X |
| ECOG Performance Status | X | | | | X | | | | X | | | | |
| Bone Marrow Biopsy and Aspirate[9] | X | | | | | | | | | X | | | |
| CT, PET/CT[10] | X | | | | | | | | X | X | X | | X |
| MRI Brain (if h/o CNS involvement)[11] | X | | | | | | | | X | | X | | X |
| CSF analysis via Lumbar Puncture[12] | X | | | | | | | | X | | | | |

| | Pre-infusion | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Assessments and Procedures** | **Screening (Within 42 Days of Apheresis)** | **Within 7 Days Prior to Apheresis** | **Apheresis** | **Lymphodepletion Days -5, -4, -3** | **Day 0 – MB-CART2019.1 Infusion** | **Days +1-7 (Week 1 Daily Visits** | **Days +10, 14 (Week 2)** | **Day 21 (Week 3)** | **Day +28 or Month +1** | **Month +3 (Day 90)** | **Month +6 (Day 180)** | **Month +9 (Day 270)** | **Month +12 (Day 365)** |
| | | | | | | | ±1 day | ±2 days | ±3 days | ±7 days | ±14 days | ±14 days | ±14 days |
| CBC with Differential | X | X | | X[3] | X | X[8] | X | X | X | X | X | X | X |
| Comprehensive Metabolic Panel[13] and LDH | X | X | | X[3] | X | X[8] | X | X | X | X | X | X | X |
| Uric Acid | X | | | X[3] | X | X[8] | X | X | | | | | |
| Ferritin, CRP[14] | X | | | | X | X[14] | X | | X | | | | |
| PT/INR, PTT, D-Dimer, Fibrinogen[15] | X | | | | X | X[15] | X | X | X | | | | |
| Infectious Disease Markers[16] | X | X[17] | | X[17] | | | | | | | | | |
| Creatinine Clearance[18] | X | X | | | | | | | | | | | |
| Quantitative Serum Immunoglobulins (IgG, IgA, IgM) | X | | | | | | | | X | X | X | X | X |
| ICE Assessment[19] | X | | | | | X[8] | X | X | X | | | | |
| **CORRELATIVE STUDIES** | | | | | | | | | | | | | |
| Tumor Biopsy Sample[20] | X | | | | | | | | | | | | |
| Immune Research Studies[21] | X | | | | X | X | X | X | X | X | X | | X |
| Minimal Residual Disease (MRD)[22] | X | | | | | | | | X | X | X | | X |
| Cytokine Studies[23] | | | | | X | X | X | X | X | | | | |
| Patient-reported Outcomes[24] | | X | | | | | X | | X | X | X | | X |
| Future Research Collections[25] | X | | X | | | | | | X | X | X | | X |

Abbreviations: CAR = chimeric antigen receptor; CBC = complete blood count; CNS = central nervous system; CRP = C-reactive protein; CSF = cerebrospinal fluid; CT = computed tomography; DNA = deoxyribonucleic acid; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; h/o = history of; ICE = immune effector cell-associated encephalopathy; IgA = immunoglobulin A; IgG = immunoglobulin G; IgM = immunoglobulin M; INR = international normalized ratio; LDH = lactate dehydrogenase; MRI = magnetic resonance imaging; MUGA = multigated acquisition scan; PET = positron emission tomography; PT = prothrombin time; PTT = partial thromboplastin time

**Footnotes**

[1] ECG will be done at baseline and repeat as clinically indicated

[2] Women of childbearing potential must have a negative serum or urine pregnancy test to participate in the study as per eligibility criteria

[3] Assessments should be completed each day of lymphodepletion chemotherapy unless otherwise specified. Start date of lymphodepletion chemotherapy will be determined on the date of MB-CART2019.1 infusion.

[4] A central line is required for MB-CART2019.1 infusion

[5] Patients will receive a full dose of MB-CART2019.1 as a single infusion on Day 0. MB-CART2019.1 is to be given fresh after manufacturing without cryopreservation. For those unable to receive immediate administration of MB-CART2019.1, cryopreserved cells can be given later per protocol guidance.

[6] History and height are only required at screening. Weight should be collected during Screening, at apheresis, and prior to and on each day of lymphodepletion. Physical examinations should occur per institutional guidelines ensuring that concomitant medications noted in Section 2.4.3 are captured.

[7] Vitals should include blood pressure, temperature, respiratory rate, pulse, and pulse oximetry. On the day of MB-CART2019.1 infusion, vitals should be done prior to infusion, at the end of infusion, and at 2-hours post-infusion.

[8] Assessments should be completed each day from Days +1 through +7

[9] Bone Marrow Biopsy and Aspirate will be performed in all patients pre-infusion of MB-CART2019.1 and again at Day 90 in responding patients. Patients with PD prior to day 90 will not require repeat bone marrow biopsy

[10] For screening either CT neck/chest/abd/pelvis with IV contrast OR PET/CT are adequate. For response assessment, PET/CT at day 28, 90 and 365. If not approved by insurance, then CT neck/chest/abd/pelvis with IV contrast is acceptable. For other time points, either is acceptable

[11] MRI Brain is required in patients with history or clinical symptoms of CNS involvement by MCL at screening and in follow-up

[12] CSF analysis including flow cytometry and cytology is required in patients with history or clinical symptoms of CNS involvement by MCL

[13] Comprehensive metabolic panel: albumin, alkaline phosphatase (ALP), aspartate aminotransferase (AST), bicarbonate, bilirubin, calcium, chloride, creatinine, glucose, potassium (K), sodium (Na), total protein, blood urea nitrogen (BUN), alanine aminotransferase (ALT).

[14] Ferritin and CRP should be assessed at Screening and on Days 0, +1, +4, +7, +10, +14, and Day +28.

[15] DIC panel including PT/INR, PTT, D-Dimer, Fibrinogen should be assessed at Screening, at Day +7, Day +10, Day +14, Day +21, and Day +28

[16] Patients must be tested for HIV, Hepatitis B surface antigen/antibody and core antibody and HCV within 6 months of MCL diagnosis. If the HCV antibody is positive, a screening HCV ribonucleic acid (RNA) by any reverse transcriptase-PCR (RT-PCR) or branched DNA (bDNA) assay must be performed. Repeat testing is not required.

[17] COVID-19 testing will be done according to institutional guidelines for cell therapy treatments (for example, prior to apheresis and prior to lymphodepletion).

[18] Creatinine clearance will be calculated according to 24 Hour Urine Collection, CKD-EPI equation, OR Cockcroft-Gault equation at screening. Should be done as part of screening and may need to be repeated prior to apheresis if there is more than a week gap.

[19] Given concern for neurotoxicity with CAR T cells, neurological evaluation (ICE) will be done at Screening and on Day +1 through Day +7, Day +14, Day +21, and Day +28. Additional ICE testing can be performed as clinically indicated.

[20] Participants must have a baseline tumor biopsy sample (at least 5 unstained slides or tissue or tissue block) available prior to MB-CART2019.1 infusion. If archival tissue is not available, patients may be enrolled after discussion with the protocol chair and/or protocol officer. If a tumor biopsy occurs post infusion, per standard of care, the site should collect and submit.

[21] Blood for the Immune Research Studies (Appendix D) will be collected at Screening, prior to infusion on Day 0, then on Days 4, 7, 14, 21, 28, 90, 180, and 365.

[22] MRD testing can be done by SoC (e.q., ClonoSEQ ®) using next generation sequencing, but will also be done at screening (for ID) and disease burden (MRD) and at Day +28 (for assessment), then at Month +3, Month +6, Month +12, and relapse centrally. Specimen type and collection information can be found in Appendix D.

[23] At minimum, will include assays for the following cytokines: IFN-g, IL10, IL6 and TNF-a. Cytokines will be checked prior to CAR T infusion, Day 0, and then on Days +4, +7, +14, +21, and +28.

[24] PROs see Table in Section 4.2.8.3 for details on assessments

[25] Only for patients who consented to participate in future research. See Appendix D for sample details.

# APPENDIX D: RESEARCH LABORATORY PROCEDURES

**Collection of MANDATORY Samples for Immunologic Endpoints and Additional Future Correlative Laboratory Studies**

Peripheral blood, tumor tissue, and buccal swabs will be collected for patients who consent to the BMT CTN 2501 study. Sample collection will be performed periodically throughout the study for correlative laboratory testing associated with critical immunologic study endpoints.

- **Research Samples for Laboratory Correlatives Associated with Immunologic Endpoints and Additional Future Correlative Laboratory Studies:** Required research samples for study-specific immunologic correlatives include the collection of peripheral blood samples as summarized in Table 13 below (and in Table 12 in Appendix C). The correlative studies include (1) Persistence and Phenotype of Infused CAR T cells, (2) qPCR for Integrated DNA Vector, (3) Presence of Replication Competent (RCL) virus by qPCR for VSV-g, (4) cytokine studies, (5) immune reconstitution, and (6) Minimal Residual Disease (MRD) testing. Participants must also have a baseline tumor biopsy sample from the most recent collection available prior to MB-CART2019.1 infusion. Once the samples are collected at specified time points, all but the cytokine study samples will be shipped on the day of collection (for tumor tissue, would be shipped following receipt from the pathology lab) directly to the BMT CTN Biorepository for processing and long-term research aliquot storage and future batch testing. Cytokine study samples will be frozen on site and batch shipped to the BMT CTN Repository at the request of the BMT CTN DCC. All samples will be tracked through GlobalTrace. Detailed procedures regarding specimen collection schedules, procedures, and shipping instructions will be found in the BMT CTN 2501 Research Sample Information Guide.

**Collection of OPTIONAL BMT CTN Biorepository Samples Supporting Future Research:**

Bone marrow aspirate, peripheral blood, cerebral spinal fluid, and apheresis product will be collected and stored to support future research. Once the samples are collected at the transplant center at specified time points, they will be shipped on the day of collection to the BMT CTN Biorepository for final processing and long-term storage. The collection, processing, and shipping of these biospecimens are summarized in Table 14 (and in Table 12 in Appendix C). These samples will be tracked through GlobalTrace. Detailed procedures regarding specimen collection schedules, procedures, and shipping instructions will be found in the BMT CTN 2501 Research Sample Information Guide.

**Table 13: Mandatory Research Samples**

| MANDATORY Research Samples Associated with Immunologic Study Endpoints and Future Correlative Laboratory Studies | | | | | |
|---|---|---|---|---|---|
| **Purpose** | **Sample Type** | **Sample Collection Summary** | **Dates Samples Obtained** | **Shipping Specifications** | **Shipping Location** |
| **Immune Research Studies** (Persistence and Phenotype of Infused CAR T cells, qPCR for Integrated DNA Vector, Presence of Replication Competent (RCL) virus by qPCR for VSV-g, and Immune Reconstitution) | 20 mL Peripheral Blood (EDTA) | Collect blood sample and place it into lavender top plastic BD Vacutainer® tube(s), containing EDTA anticoagulant. Gently mix sample by inversion 8-10 times to mix sample well with anticoagulant. | **Screening, Day 0 Pre-CAR-T Infusion, post-treatment D4, D7, D14, D21, D28, D90, D180, and D365** | Samples will be shipped at ambient temperature on the day of collection to the BMT CTN Biorepository for PBMC storage by priority overnight FED EX delivery. | BMT CTN Repository |
| **Cytokine Studies** | 4 mL Peripheral Blood (SST) | Collect blood sample and place it into an SST Vacutainer® tube. Allow blood to clot 30-60 minutes and centrifuge per manufacturer's instructions. Serum will need to be aliquoted into cryovials and frozen at -70° C within 3 hours of blood collection. Detailed sample processing information will be found in the BMT CTN 2501 Laboratory Sample Guide. | **Day 0 Pre-CAR-T Infusion, post-treatment D4, D7, D14, D21, and D28** | Samples will be batch shipped (upon request of the BMT CTN DCC staff) on dry ice to the BMT CTN Biorepository for serum storage by priority overnight FED EX delivery. | BMT CTN Repository |
| **Tumor Biopsy Sample** | 5 unstained FFPE slides | Labeled unstained FFPE slides should be placed in slide box. | **Screening** | Samples will be shipped at ambient temperature to the BMT CTN Biorepository for storage by priority overnight FED EX delivery. | BMT CTN Repository |

| MANDATORY Research Samples Associated with Immunologic Study Endpoints and Future Correlative Laboratory Studies | | | | | |
|---|---|---|---|---|---|
| **Purpose** | **Sample Type** | **Sample Collection Summary** | **Dates Samples Obtained** | **Shipping Specifications** | **Shipping Location** |
| **Minimal Residual Disease (MRD)** | 6-10 unstained FFPE slides (10µm thick) + H&E slide[1] | Labeled unstained FFPE + H&E slides should be placed in slide box. | **Screening** | Samples will be shipped at ambient temperature to the BMT CTN Biorepository for storage by priority overnight FED EX delivery. | BMT CTN Repository |
| | 10 mL Peripheral Blood (Streck tube) | Collect blood sample and place it into provided Streck tube. Gently mix sample by inversion 8-10 times to mix sample well with anticoagulant. | **Screening, Day 0 Pre-CAR-T Infusion, post-treatment D28, M3, M6, M12 and relapse.** | Samples will be shipped at ambient temperature on the day of collection to the BMT CTN Biorepository for plasma storage by priority overnight FED EX delivery. | BMT CTN Repository |
| | 2 mL Peripheral Blood (EDTA) | Collect blood sample and place it into lavender top plastic BD Vacutainer® tube, containing EDTA anticoagulant. Gently mix sample by inversion 8-10 times to mix sample well with anticoagulant. | **Screening** | Samples will be shipped at ambient temperature on the day of collection to the BMT CTN Biorepository for storage by priority overnight FED EX delivery. | BMT CTN Repository |
| | Buccal swab | Utilize buccal swab collection kit provided by study. See Research Sample Information Guide for sampling instructions. | **Screening** | Samples will be shipped at ambient temperature on the day of collection to BMT CTN Biorepository for storage by priority overnight FED EX delivery. | BMT CTN Repository |

Abbreviations: BMT CTN = Blood and Marrow Transplant Clinical Trials Network; CAR-T = Chimeric Antigen Receptor T Cell; D = day; DNA = deoxyribonucleic acid; EDTA = ethylenediaminetetraacetic acid; FFPE = formalin fixed paraffin embedded; M = month; qPCR = quantitative polymerase chain reaction; RCL = replication competent lentivirus; VSV-G = vesicular stomatitis virus-G

Footnote

1 See Research Sample Information Guide for additional sample options.

**Table 14: Optional Biorepository Samples**

| OPTIONAL BMT CTN Biorepository Samples Supporting Future Research | | | | | |
|---|---|---|---|---|---|
| **Purpose** | **Sample Type** | **Sample Collection Summary** | **Dates Samples Obtained** | **Shipping Specifications** | **Shipping Location** |
| **Future Research PBMCs and Plasma** | 10 mL Peripheral Blood (EDTA) | Collect blood sample and place it into lavender top plastic BD Vacutainer® tube(s), containing EDTA anticoagulant. Gently mix sample by inversion 8-10 times to mix sample well with anticoagulant. | **Screening, post-treatment D28, D90, D180, and D365** | Samples will be shipped at ambient temperature on the day of collection to the BMT CTN Biorepository for PBMC and plasma storage by priority overnight FED EX delivery. | BMT CTN Repository |
| **Future Research Serum** | 4 mL Peripheral Blood (SST) | Collect blood sample and place it into an SST Vacutainer® tube. Allow blood to clot 30-60 minutes and centrifuge per manufacturer's instructions. | **Screening, post-treatment D28, D90, D180, and D365** | Samples will be shipped at ambient temperature on the day of collection to the BMT CTN Biorepository for storage by priority overnight FED EX delivery. | BMT CTN Repository |
| **Future Research Whole Blood** | 5 mL Peripheral Blood (EDTA) | Collect blood sample and place it into lavender top plastic BD Vacutainer® tube(s), containing EDTA anticoagulant. Gently mix sample by inversion 8-10 times to mix sample well with anticoagulant. | **Screening, post-treatment D28, D90, D180, and D365** | Samples will be shipped at ambient temperature on the day of collection to the BMT CTN Biorepository for storage by priority overnight FED EX delivery. | BMT CTN Repository |
| **Future Research Bone Marrow Aspirate** | 5 mL Bone Marrow Aspirate (EDTA) | Collect blood sample and place it into lavender top plastic BD Vacutainer® tube(s), containing EDTA anticoagulant. Gently mix sample by inversion 8-10 times to mix sample well with anticoagulant. | **Screening and D90** | Samples will be shipped at ambient temperature on the day of collection to the BMT CTN Biorepository for storage by priority overnight FED EX delivery. | BMT CTN Repository |

| OPTIONAL BMT CTN Biorepository Samples Supporting Future Research | | | | | |
|---|---|---|---|---|---|
| **Purpose** | **Sample Type** | **Sample Collection Summary** | **Dates Samples Obtained** | **Shipping Specifications** | **Shipping Location** |
| **Future Research Cerebral Spinal Fluid** | 2-3 mL | Collect CSF in flow media (RPMI). See Research Sample Information Guide for processing instructions | **Screening and D28 (when clinically indicated)** | Samples will be batch shipped (upon request of the BMT CTN DCC staff) on dry ice to the BMT CTN Biorepository for storage by priority overnight FED EX delivery. | BMT CTN Repository |
| **Future Research Apheresis Product** | 3 mL | Collect apheresis sample and place into specimen transport tube. | **Time of apheresis** | Samples will be shipped at refrigerated temperature on the day of collection to the BMT CTN Biorepository for storage by priority overnight FED EX delivery. | BMT CTN Repository |

Abbreviations: BMT CTN = Blood and Marrow Transplant Clinical Trials Network; CSF = cerebrospinal fluid; D = day; DCC= data coordinating center; EDTA = ethylenediaminetetraacetic acid; RPMI = Roswell Park Memorial Institute; SST = serum separator tube

# APPENDIX E: PRO QUESTIONNAIRES

Following are the Patient Reported Outcome (PRO) survey items for this study. These are presented by assessment, with notes about when each assessment is included on the PRO surveys. Patient-facing PRO documents (paper versions of survey and screenshots of electronic versions) will be created and approved by the NMDP IRB before PRO collection begins.

## PROMIS Global Quality of Life

**Note**: This assessment is included at all PRO time points – baseline, Day 14, Day 28, Day 90, Day 180, Day 365

**Please respond to each question or statement by marking one box per row**

| | Excellent | Very good | Good | Fair | Poor |
|---|---|---|---|---|---|
| In general, would you say your health is: | □ | □ | □ | □ | □ |
| In general, would you say your quality of life is: | □ | □ | □ | □ | □ |

## PROMIS Physical Function – Short Form 8c, v2.0

**Note**: This assessment is included at Day 180 and Day 365 time points. Exclude at Day 14 and Day 28 time points.

**Please respond to each question or statement by marking one box per row**

| | Without any difficulty | With a little difficulty | With some difficulty | With much difficulty | Unable to do |
|---|---|---|---|---|---|
| Are you able to bend down and pick up clothing from the floor? | □ | □ | □ | □ | □ |
| Are you able to stand up from an armless straight chair? | □ | □ | □ | □ | □ |
| Are you able to dress yourself, including tying shoelaces and buttoning your clothes? | □ | □ | □ | □ | □ |
| Are you able to go up and down stairs at a normal pace? | □ | □ | □ | □ | □ |
| Are you able to wash and dry your body? | □ | □ | □ | □ | □ |
| Are you able to go for a walk of at least 15 minutes | □ | □ | □ | □ | □ |

| | Not at all | Very little | Somewhat | Quite a lot | Cannot do |
|---|---|---|---|---|---|
| Does your health now limit you in doing vigorous activities, such as running, lifting heavy objects, participating in strenuous sports? | □ | □ | □ | □ | □ |

| | No difficulty at all | A little bit of difficulty | Some difficulty | A lot of difficulty | Can't do because of health |
|---|---|---|---|---|---|
| How much difficulty do you have doing your daily physical activities, because of your health? | □ | □ | □ | □ | □ |

**PROMIS Physical Function – Short Form 8c 7-day, v2.0**

**Note**: This assessment is included at Day 14 and Day 28 time points. Exclude at Baseline, Day 90, Day 180 and Day 365 time points.

**Please respond to each question or statement by marking one box per row**

| In the past 7 days… | Without any difficulty | With a little difficulty | With some difficulty | With much difficulty | Unable to do |
|---|---|---|---|---|---|
| Are you able to bend down and pick up clothing from the floor? | □ | □ | □ | □ | □ |
| Are you able to stand up from an armless straight chair? | □ | □ | □ | □ | □ |
| Are you able to dress yourself, including tying shoelaces and buttoning your clothes? | □ | □ | □ | □ | □ |
| Are you able to go up and down stairs at a normal pace? | □ | □ | □ | □ | □ |
| Are you able to wash and dry your body? | □ | □ | □ | □ | □ |
| Are you able to go for a walk of at least 15 minutes | □ | □ | □ | □ | □ |

| In the past 7 days… | Not at all | Very little | Somewhat | Quite a lot | Cannot do |
|---|---|---|---|---|---|
| Does your health now limit you in doing vigorous activities, such as running, lifting heavy objects, participating in strenuous sports? | □ | □ | □ | □ | □ |

| In the past 7 days… | No difficulty at all | A little bit of difficulty | Some difficulty | A lot of difficulty | Can't do because of health |
|---|---|---|---|---|---|
| How much difficulty do you have doing your daily physical activities, because of your health? | □ | □ | □ | □ | □ |

**PROMIS Fatigue – Short Form 4a, v1.0**

**Note**: This assessment is included at all PRO time points – baseline, Day 14, Day 28, Day 90, Day 180,Day 365

**Please respond to each question or statement by marking one box per row**

| During the past 7 days… | Not at all | A little bit | Somewhat | Quite a bit | Very much |
|---|---|---|---|---|---|
| I feel fatigued | □ | □ | □ | □ | □ |
| **In the past 7 days…** | | | | | |
| How fatigued were you on average? | □ | □ | □ | □ | □ |
| How run-down did you feel on average? | □ | □ | □ | □ | □ |
| **During the past 7 days…** | | | | | |
| I have trouble starting things because I am tired | □ | □ | □ | □ | □ |

**PROMIS Cognitive Function – Short Form 4a, v2.0**

**Note**: This assessment is included at all PRO time points – baseline, Day 14, Day 28, Day 90, Day 180,Day 365

**Please respond to each question or statement by marking one box per row**

| In the past 7 days… | Never | Rarely (Once) | Sometimes (Two or three times) | Often (About once a day) | Very often (Several times a day) |
|---|---|---|---|---|---|
| My thinking has been slow | □ | □ | □ | □ | □ |
| It has seemed like my brain was not working as well as usual | □ | □ | □ | □ | □ |
| I have had to work harder than usual to keep track of what I was doing | □ | □ | □ | □ | □ |
| I have had trouble shifting back and forth between different activities that require thinking | □ | □ | □ | □ | □ |

**PROMIS Depression – Short Form 4a, v1.0**

**Note**: This assessment is included at all PRO time points – baseline, Day 14, Day 28, Day 90, Day 180,Day 365

**Please respond to each question or statement by marking one box per row**

| In the past 7 days… | Never | Rarely | Sometimes | Often | Always |
|---|---|---|---|---|---|
| I felt worthless | □ | □ | □ | □ | □ |
| I felt helpless | □ | □ | □ | □ | □ |
| I felt depressed | □ | □ | □ | □ | □ |
| I felt hopeless | □ | □ | □ | □ | □ |

**PROMIS Anxiety – Short Form 4a, v1.0**

**Note**: This assessment is included at all PRO time points – baseline, Day 14, Day 28, Day 90, Day 180,Day 365

**Please respond to each question or statement by marking one box per row**

| In the past 7 days… | Never | Rarely | Sometimes | Often | Always |
|---|---|---|---|---|---|
| I felt fearful | □ | □ | □ | □ | □ |
| I found it hard to focus on anything other than my anxiety | □ | □ | □ | □ | □ |
| My worries overwhelmed me | □ | □ | □ | □ | □ |
| I felt uneasy | □ | □ | □ | □ | □ |

**Comprehensive Score for financial toxicity (COST)**

**Note**: This assessment is included Baseline, Day 180, and Day 365. Excluded at Day 14, Day 28 and Day 90.

**Below is a list of statements that other people with your illness have said are important. Please mark one response per line to indicate your response as it applies to the past 7 days.**

| | Not at all | A little bit | Somewhat | Quite a bit | Very much |
|---|---|---|---|---|---|
| I know that I have enough money in savings, retirement, or assets to cover the cost of my treatment. | □ | □ | □ | □ | □ |
| My out-of-pocket medical expenses are more than I thought they would be. | □ | □ | □ | □ | □ |
| I worry about the financial problems I will have in the future as a result of my illness or treatment. | □ | □ | □ | □ | □ |

| | | | | | |
|---|---|---|---|---|---|
| I feel I have no choice about the amount of money I spend on care. | ☐ | ☐ | ☐ | ☐ | ☐ |
| I am frustrated that I cannot work or contribute as much as I usually do. | ☐ | ☐ | ☐ | ☐ | ☐ |
| I am satisfied with my current financial situation. | ☐ | ☐ | ☐ | ☐ | ☐ |
| I am able to meet my monthly expenses. | ☐ | ☐ | ☐ | ☐ | ☐ |
| I feel financially stressed. | ☐ | ☐ | ☐ | ☐ | ☐ |
| I am concerned about keeping my job and income, including work at home. | ☐ | ☐ | ☐ | ☐ | ☐ |
| My cancer or treatment has reduced my satisfaction with my present financial situation. | ☐ | ☐ | ☐ | ☐ | ☐ |
| I feel in control of my financial situation. | ☐ | ☐ | ☐ | ☐ | ☐ |
| My illness has been a financial hardship to my family and me. | ☐ | ☐ | ☐ | ☐ | ☐ |



**Return to Work Item**

**Note**: This assessment is included at Day 90, Day 180, Day 365. Exclude at Baseline, Day 14, Day 28

**Since your CAR T infusion, have you returned to work?** *(Select one response that most closely matches your situation)*

- ☐ Yes, I have returned to working, at a similar schedule as before my transplant.
- ☐ Yes, I have returned to working, at a reduced schedule than before my transplant.
- ☐ No, I have not returned to work, but aim to in the future.
- ☐ Not applicable, I do not aim to work after my transplant (e.g., I am retired).

**If yes, approximately when did you return to work after your transplant?**

Month _____ Year _____

**Sociodemographic/Occupational Function items**

**Note** These items are included at Baseline and Day 365. Exclude at Dy 14, Day 28, Day 90, Day 180, Day 365

**Which of the following best describes your current job status?** *(Select all that apply)*

- ☐ Working full-time (30 or more hours per week)
- ☐ Working part-time (less than 30 hours per week)
- ☐ Caring for home or family (not seeking paid work)
- ☐ Unemployed and looking for work (including laid off or furloughed)
- ☐ Unable to work due to illness or disability
- ☐ Retired
- ☐ Student
- ☐ Option not listed, please specify: _____

**What is your zip code? _____**

**What is your ancestry or ethnic origin? When defining your background, consider your family history and which regions of the world your ancestors were born in before they arrived in the United States.** *(Select one or more options that closest identifies your background.)*

<table>
<tr>
<td>☐ White<br>☐ Eastern European (e.g. Bulgarian, Georgian, Polish, Romanian, Ukrainian, etc.)<br>☐ Northern European (e.g. Finnish, Norwegian, Swedish, etc.)<br>☐ Russian or former Soviet Union<br>☐ Southern European (e.g. Greek, Italian, Portuguese, Spanish, etc.)<br>☐ Western European (e.g. British, French, German, Irish, Scottish, etc.)<br>☐ White Caribbean<br>☐ White South or Central American<br>☐ Not otherwise specified White</td>
<td>☐ Black or African<br>☐ African American<br>☐ Black Caribbean (e.g. Haitian, Jamaican, etc.)<br>☐ Black South or Central American<br>☐ East African (e.g. Ethiopian, Kenyan, Somali, Tanzanian, etc.)<br>☐ South African (e.g. Angolan, Botswana, Mozambican, Zambian, Zimbabwean, etc.)<br>☐ West African (e.g. Ghanian, Malian, Nigerian, Senegalese, etc.)<br>☐ Not otherwise specified Black/African</td>
<td>☐ Hispanic or Latino<br>☐ Brazilian<br>☐ Caribbean Hispanic (Dominican, Guatemalan, Salvadoran, etc.)<br>☐ Cuban<br>☐ Mexican<br>☐ Puerto Rican<br>☐ South or Central American Hispanic<br>☐ Not otherwise specified Hispanic or Latino</td>
</tr>
<tr>
<td rowspan="2">☐ Asian<br>☐ Caribbean Indian<br>☐ Chinese<br>☐ Filipino<br>☐ Indian<br>☐ Japanese<br>☐ Korean<br>☐ Malaysian<br>☐ Mongolian<br>☐ Pakistani</td>
<td>☐ Indigenous American<br>☐ Alaska Native<br>☐ Indigenous Caribbean<br>☐ Indigenous North American<br>☐ Indigenous South or Central American<br>☐ Not otherwise specified Indigenous American</td>
<td>☐ Jewish<br>☐ Ashkenazi<br>☐ Mizrahi<br>☐ Sephardi<br>☐ Not otherwise specified Jewish</td>
</tr>
<tr>
<td>☐ Pacific Islander<br>☐ Melanesian (e.g. Fijian, Papua New Guinean, etc.)</td>
<td>☐ Middle Eastern or North African<br>☐ Arab Peninsula (e.g. Emirati, Kuwaiti, Saudi, Yemeni, etc.)</td>
</tr>
</table>

| | | |
|---|---|---|
| ☐ Taiwanese<br>☐ Thai<br>☐ Vietnamese<br>☐ Other Indian Subcontinent *(e.g. Bangladeshi, Nepali, Sri Lankan, etc.)*<br>☐ Other Southeast Asian *(e.g. Cambodian, Indonesian, Singaporean, etc.)*<br>☐ Not otherwise specified Asian | ☐ Micronesian *(e.g. Chamorro, Guamanian, Marshallese, etc.)*<br>☐ Native Hawaiian<br>☐ Polynesian *(e.g. Maori, Samoan, Tongan, etc.)*<br>☐ Not otherwise specified Pacific Islander | ☐ Central Asian *(e.g. Afghan, Iranian, Kazakhstani, Turkish, etc.)*<br>☐ East Mediterranean *(e.g. Iraqi, Jordanian, Lebanese, Syrian, etc.)*<br>☐ North African *(e.g. Algerian, Egyptian, Moroccan, etc.)*<br>☐ Not otherwise specified Middle Eastern or North African |
| ☐ Not otherwise specified: _____ | | ☐ Don't know |

**What is your current relationship status?** *(Select the one response that best describes your current relationship status)*

☐ Married or living with a partner
☐ Never married
☐ Separated / Divorced
☐ Widowed
☐ Option not listed, please describe: _____

**What is the highest degree or level of school that you have completed?** *(Select one response)*

☐ Up to 8th grade
☐ 9th - 12th grade (no diploma)
☐ High school diploma or equivalent (GED)
☐ Some college, no degree
☐ Vocational or Associate's degree
☐ College degree (B.A./B.S.)
☐ Advanced degree (e.g., Master's or Doctorate program)
☐ Don't know

**What type of health insurance coverage do you have?** *(Select all that apply)*

☐ Private health insurance (including through your employer)
☐ National Health Insurance (Non-US Government-sponsored)
☐ Medicare
☐ Medigap
☐ Medicaid
☐ Children's Health Insurance Program (CHIP)
☐ Military-related healthcare (TRICARE (CHAMPUS) / VA health care / CHAMP-VA)
☐ Indian Health Service

- ☐ State-sponsored health plan
- ☐ Disability insurance
- ☐ Other government program (please describe): _____
- ☐ Other health insurance coverage (please describe): _____
- ☐ No insurance
- ☐ Don't know

**What is your total yearly HOUSEHOLD income from all sources, before taxes?** *(Select one response)*

*This includes money from jobs, disability benefits, social security payments, pensions or retirement, dividends and any other income received by ALL members of your household.*

- ☐ Less than $10,000
- ☐ $10,000 to $19,999
- ☐ $20,000 to $29,999
- ☐ $30,000 to $39,999
- ☐ $40,000 to $49,999
- ☐ $50,000 to $59,999
- ☐ $60,000 to $69,999
- ☐ $70,000 to $79,999
- ☐ $80,000 to $89,999
- ☐ $90,000 to $99,999
- ☐ $100,000 to $149,999
- ☐ $150,000 to $199,999
- ☐ $200,000 or more
- ☐ Don't know

**What is your total yearly PERSONAL income from all sources, before taxes?** *(Select one response)*
*This includes money YOU personally earned from jobs, disability benefits, social security payments, pensions or retirement, dividends and any other income. Do not include income from other household members.*

- ☐ Less than $10,000
- ☐ $10,000 to $19,999
- ☐ $20,000 to $29,999
- ☐ $30,000 to $39,999
- ☐ $40,000 to $49,999
- ☐ $50,000 to $59,999
- ☐ $60,000 to $69,999
- ☐ $70,000 to $79,999
- ☐ $80,000 to $89,999
- ☐ $90,000 to $99,999
- ☐ $100,000 to $149,999
- ☐ $150,000 to $199,999
- ☐ $200,000 or more
- ☐ Don't know

**Including yourself, how many people live in your household at least 50% of the time?**

Adults (age 18 and older): _____

Children (age 17 and younger): _____

**How much have your disease and treatment experiences impacted your goals concerning work or school?** *(Select one response)*

- ☐ Very negative impact

☐ Somewhat negative impact

- ☐ Transportation (eg, driving to doctor's appointments, driving for errands)
- ☐ Homemaking (eg, shopping, cleaning, preparing meals)
- ☐ Personal care assistance (eg, feeding, bathing, toileting, dressing, grooming)
- ☐ Healthcare assistance (eg, help with medications, wound care)
- ☐ Managing finances (eg, paying bills, managing budget)
- ☐ Mobility assistance (eg, walking)
- ☐ None of the above

**Please answer the following questions if your caregiver was a spouse/partner or any family member.**

**In the last 3 months, has your caregiver reduced their hours at work?** *(Select one response)*

- ☐ Yes
- ☐ No
- ☐ Not applicable

**In the last 3 months, has your caregiver ever quit their job?** *(Select one response)*

- ☐ Yes
- ☐ No
- ☐ Not applicable

**In the last 3 months, has your caregiver taken early retirement?** *(Select one response)*

- ☐ Yes
- ☐ No
- ☐ Not applicable

# APPENDIX F: TOXICITY GRADING AND CARE GUIDELINES

## Cytokine Release Syndrome (CRS)

### Table 15: ASTCT CRS Consensus Grading[#]

| CRS Parameter | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|
| **Fever[†]** | Temperature ≥38°C | Temperature ≥38°C | Temperature ≥38°C | Temperature ≥38°C |
| **With either:** | | | | |
| **Hypotension** | None | Not requiring vasopressors | Requiring one vasopressor with or without vasopressin | Requiring multiple vasopressors (excluding vasopressin) |
| **And/or[‡]** | | | | |
| **Hypoxia** | None | Requiring low-flow nasal cannula[^] or blow-by | Requiring high-flow nasal cannula[^], facemask, non- rebreather mask, or Venturi mask | Requiring positive pressure (e.g.: CPAP, BiPAP, intubation and mechanical ventilation) |

Source: ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells; Lee, Daniel W. et al.; Biology of Blood and Marrow Transplantation, Volume 25, Issue 4, 625 - 638
Abbreviations: BiPAP = bilevel positive airway pressure; CPAP: continuous positive airway pressure
[#] Organ toxicities associated with CRS may be graded according to CTCAE v5.0 but they do not influence CRS grading
[†] Fever is defined as temperature ≥38°C not attributable to any other cause. In participants who have CRS then receive antipyretics or anti-cytokine therapy such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.
[‡] CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. For example, a participant with temperature of 39.5°C, hypotension requiring one vasopressor and hypoxia requiring low- flow nasal cannula is classified as having Grade 3 CRS.
Organ toxicities associated with CRS may be graded according to CTCAE v5.0 but they do not influence CRS grading.
^ Low-flow nasal cannula is defined as oxygen delivered at ≤ 6 liters/minute. Low-flow also includes blow-by oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula is defined as oxygen delivered at > 6 liters/minute.

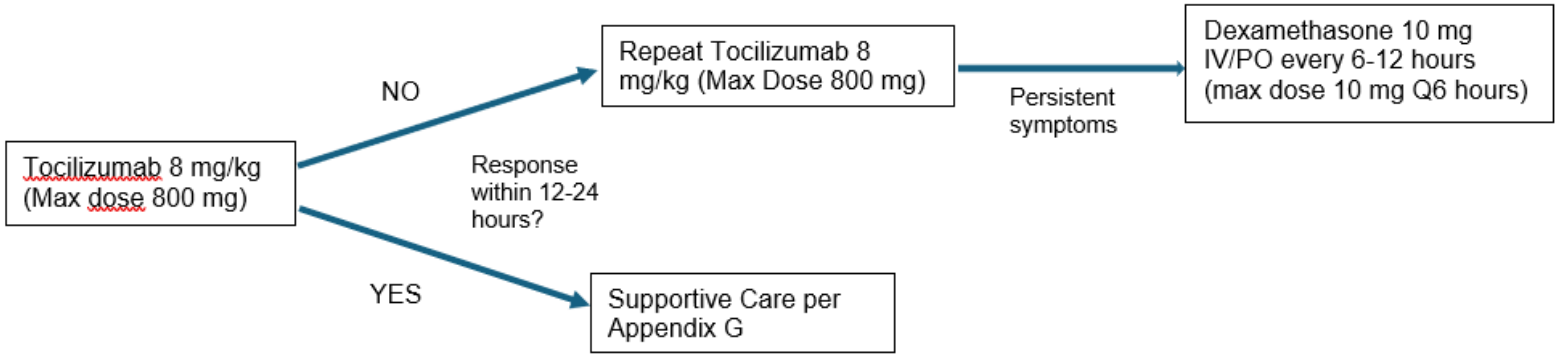
**Table 16: CRS Symptoms, Evaluation, Management, Response**

| CRS assessed via ASBMT consensus criteria | Grade 1 toxicities | Grade 2 toxicities[1] | Grade 3 or Grade 4 toxicities |
|---|---|---|---|
| **Evaluation & Management** | Infectious work-up, initiation/escalation of antibiotics per institutional standards. IV fluids, anti-pyretic therapy as indicated with cooling blankets and acetaminophen (avoid NSAIDs). Supportive care measure[2] | Admission to hospital (if not admitted). IV fluids, infectious work-up, supportive care measures | Admission to hospital, intensive care unit transfer as indicated. IV fluids, infectious work-up, respiratory support, and renal replacement therapy as indicated |
| **Response & Escalation** | Tocilizumab 8 mg/kg x 1 +/- Dexamethasone | Tocilizumab 8 mg/kg x 1 + Dexamethasone 10 mg IV/PO Q6-Q12H | Tocilizumab 8 mg/kg x 1 + Dexamethasone 10 mg IV/PO Q6-Q12H<br>Additional agents as indicated: pulse solumedrol, anakinra |

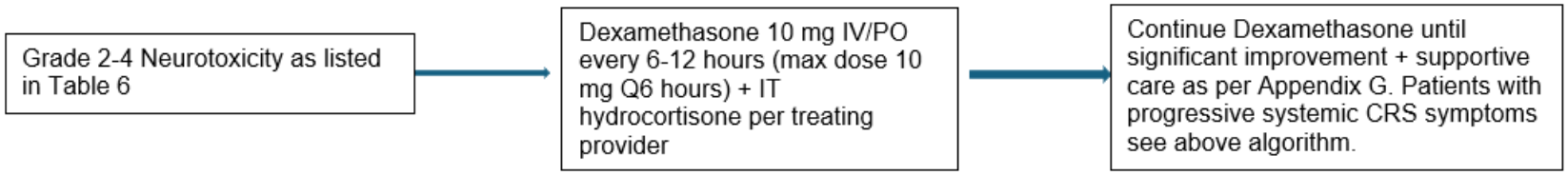
3-CRS Directed Treatment Algorithm is on the following page [41].
Abbreviations: ASBMT = American Society for Blood and Marrow Transplantation; CRS = cytokine release syndrome; IV = intravenous; NSAID = non-steroidal anti-inflammatory drug; PO = *per os* (by mouth); Q = *quaque* (every)

# Cytokine Release Syndrome Directed Treatment

## Without Neurological Toxicities




## With Neurological Toxicities[1]




*1-Patients with neurological toxicities can be treated with dexamethasone with or without the presence of systemic CRS.*

Abbreviations: CRS = cytokine release syndrome; IT = intrathecal; IV = intravenous; Max = maximum; PO = *per os* (by mouth); Q = *quaque* (every)

## Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)

### Table 17: Neurotoxicity Evaluation and Management

| Neurotoxicity assessed ASTCT Consensus Grading | | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|---|
| GRADING | **ICE Score** | 7-9 | 3-6 | 0-2 | 0 (unarousable and unable to perform ICE) |
| | **Depressed Level of Consciousness** | Awakens Spontaneously | Awakens to Voice | Awakens to tactile stimulus | Unarousable ore requires vigorous or repetitive stimuli to arouse. Stupor or Coma |
| | **Seizure** | N/A | N/A | Any clinical seizure focal or generalized that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention | Life-threatening prolonged seizure (>5 min); or Repetitive clinical or electrical seizures without return to baseline in between |
| | **Motor findings** | N/A | N/A | | Deep focal motor weakness such as hemiparesis or paraparesis |
| | **Elevated ICP/Cerebral Edema** | N/A | N/A | Focal/local edema on neuroimaging | Diffuse cerebral edema on neuroimaging; decerebrate or decorticate posturing; or cranial nerve VI palsy; or papilledema; or Cushing's triad |
| **Evaluation** | | Neurological Exam, additional work-up as indicated | Neurological Examination, MRI Brain +/- lumbar puncture and EEG as indicated. Neurological consultation. | | |
| **Management** | | Clinical vigilance, monitoring, supportive care | Admit to hospital (if not hospitalized). Start Dexamethasone 10 mg IV/PO every 6-12 hours (max dose 10 mg Q6 hours) and strongly consider one dose of IT hydrocortisone (100 mg) alone or with chemotherapy. | | |

Abbreviations: ASTCT = American Society for Transplantation and Cellular Therapy; EEG = electroencephalogram; ICE = immune effector cell-associated encephalopathy; ICP = intracranial pressure; IT = intrathecal; IV = intravenous; MRI = magnetic resonance imaging; N/A = not applicable; PO = *per os* (by mouth); Q = *quaque* (every)

Notations:

1) ICANS grade is determined by the most severe event (ICE score, level of consciousness, seizure, motor findings, raised ICP/cerebral edema) not attributable to any other cause; for example, a patient with an ICE score of 3 who has a generalized seizure is classified as Grade 3 ICANS.
2) N/A indicates not applicable.
3) A patient with an ICE score of 0 may be classified as Grade 3 ICANS if awake with global aphasia, but a patient with an ICE score of 0 may be classified as Grade 4 ICANS if unarousable.
4) Depressed level of consciousness should be attributable to no other cause (e.g., no sedating medication).
5) Tremors and myoclonus associated with iIEC therapies may be graded according to CTCAE v5.0, but they do not influence ICANS grading.
6) Intracranial hemorrhage with or without associated edema is not considered a neurotoxicity feature and is excluded from ICANS grading. It may be graded according to CTCAE v5.0.

## Immune Effector Cell-Associated Hemophagocytic Lymphohistiocytosis-Like Syndrome (IEC-HS)

**Table 18: Immune effector cell associated HLH-like syndrome (IEC-HS): Definition and Identification**

| | |
|---|---|
| **Most common manifestations[$]** | REQUIRED: Elevated ferritin (> 2 x ULN or baseline [at time of infusion] and/or rapidly rising (per clinical assessment) |
| | Onset with resolving/resolved CRS or worsening inflammatory response after initial improvement with CRS directed therapy* |
| | Hepatic transaminase elevation** (> 5 x ULN (if baseline was normal) or > 5 x baseline if baseline was abnormal) |
| | Hypofibrinogenemia (< 150 mg/dL or < LLN)^^ |
| | Hemophagocytosis in bone marrow or other tissue^^ |
| | Cytopenias (new onset, worsening, or refractory[&]) |
| **Other manifestations that may be present** | Lactate dehydrogenase elevations (> ULN) |
| | Other coagulation abnormalities (e.g., elevated PT/PTT) |
| | Direct hyperbilirubinemia |
| | New onset splenomegaly |
| | Fevers (new[#] or persistent)^^ |
| | Neurotoxicity |
| | Pulmonary manifestations (e.g., hypoxia, pulmonary infiltrates, pulmonary edema) |
| | Renal insufficiency (new onset) |
| | Hypertriglyceridemia (fasting level, >265 mg/dL^^) |

Abbreviations: CRS = cytokine release syndrome; HLH = hemophagocytic lymphohistiocytosis; IEC-HS = immune effector cell associated hemophagocytic lymphohistiocytosis-like syndrome; LLN = lower limit of normal; PT = prothrombin time; PTT = partial thromboplastin time; ULN = upper limit of normal

^Diagnosis is made only when it is not attributable to alternative etiologies, including CRS, infection and/or disease progression;
[*]Although most cases of IEC-HS have been seen with antecedent CRS, this may not always be the case and emerging experience will shed light on how IEC-HS may present;
[&]Generally at least one lineage will be a Grade 4 cytopenia (platelets, neutrophils, hemoglobin).
[#]As distinguished from CRS onset or recrudescence of CRS;
[$]Constellation of findings typically simultaneously (e.g., all within 72 hours);
**consistent with Grade 3 hepatic transaminase elevations as per CTCAE v 5.0;
^^as per HLH-2004
Source: [43]

**Table 19: IEC-HS Management per Hines et al ASTCT [43].**

| | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|
| **Grading** | Asymptomatic or mild symptoms, requires observation and/or clinical and diagnostic evaluation. Intervention not indicated | Mild to moderate symptoms, with intervention indicated (e.g., immunosuppressive agents directed at IEC-HS, transfusions for asymptomatic hypofibrinogenemia) | Severe or medically significant but not immediately life-threatening (e.g., coagulopathy with bleeding requiring transfusion support, or hospitalization required for new-onset acute kidney injury, hypotension, or respiratory distress) | Life threatening consequences: urgent intervention indicated (e.g.. life-threatening bleeding or hypotension, respiratory distress requiring intubation, dialysis indicated for acute kidney injury) |
| **Supportive Care Measures** | Observation | Cryoprecipitate for hypofibrinogenemia<br>Transfusion support for cytopenia. Infectious prophylaxis (consider anti-mold coverage in neutropenic patients on steroids)<br>Viral monitoring (HHV6, EBV, CMV) | As Grade 2 and other support as clinically indicated (renal replacement therapy, pressor support). | As Grade 2 and other support as clinically indicated (renal replacement therapy, pressor support). |
| **Response & Escalation** | Observation | Anakinra 100-200 mg SC/IV TID and/or Dexamethasone 10 mg IV/PO Q6-Q12H | Anakinra 100-200 mg SC/IV TID and/or Dexamethasone 10 mg IV/PO Q6-Q12H<br><br>Alternative agents<br>Ruxolitinib<br>Low-dose Etoposide<br>Emapalumab | Anakinra 100-200 mg SC/IV TID and/or Dexamethasone 10 mg IV/PO Q6-Q12H<br><br>Alternative agents<br>Ruxolitinib<br>Low-dose Etoposide<br>Emapalumab |

Abbreviations: ASTCT = American Society for Transplantation and Cellular Therapy; CMV = cytomegalovirus; EBV = Epstein-Barr virus; HHV6 = human herpesvirus 6; IEC-HS = immune effector cell associated hemophagocytic lymphohistiocytosis-like syndrome; IV = intravenous; PO = *per os* (by mouth); Q = *quaque* (every); SC = subcutaneous; TID = ter in die (3 times a day)

**Table 20: EHA/EBMT Consensus Grading for Immune Effector Cell–associated Hematotoxicity (ICAHT)**

| Grading | 1 | 2 | 3 | 4 |
|---|---|---|---|---|
| **Early ICAHT (day 0-30)** | | | | |
| ANC ≤500/μL | <7 d | 7-13 d | ≥14 d | Never above 500/μL |
| ANC ≤100/μL | — | — | ≥7 d | ≥14 d |
| **Late ICAHT (after day +30)**∗ | | | | |
| ANC | ≤1500/μL | ≤1000/μL | ≤500/μL | ≤100/μL |

Abbreviations: ANC = absolute neutrophil count; d = days; EBMT = European Society for Blood and Marrow Transplantation; EHA = European Hematology Association; ICAHT = immune effector cell-associated hematotoxicity

# APPENDIX G: MB-CART2019.1 T CELL PRODUCT RELEASE SPECIFICATIONS

**Table 21: Product Information for Fresh Drug Product**

| | | | |
|---|---|---|---|
| **Manufacturer Name** | Miltenyi Biotec, Inc. | **Client Code** | M003A |
| **Unit Packaging** | CryoMACS Bag | **Expiration** | 36 hours |
| **Product Configuration** | Volume (mL) per bag equals to patient weight in kg (max 100 mL +/- 5%) | **Storage Requirement** | 2°C to 8°C |

Abbreviation: max = maximum

**Table 22: Release Specification – Rapid Release for Fresh Drug Product**

| Test Parameter | Analytical Method | Acceptance Criterion |
|---|---|---|
| Appearance (Fresh Drug Product: Day 12) | Visual Inspection SV-SOP-A-000179 SV-ATT-A-000146 SV-ATT-A-000229 (1) | Slightly turbid infusion dispersion / Primary package integrity |
| CD3+ Cell Viability (Fresh Drug Product: Day 12) | Flow Cytometry, CD19 Flow Panel A SV-SOP-A-000058 SV-ATT-A-000004 | ≥ 80% viable cells among $CD45^+CD3^+$ cells |
| CD3+ Cell Percentage (Fresh Drug Product: Day 12) | Flow Cytometry, CD19 CAR Flow Panel A SV-SOP-A-000058 SV-ATT-A-000004 | ≥ 80% $CD3^+$ cells among viable $CD45^+$ cells |
| CD3+ Cell Concentration (Fresh Drug Product: Day 12) | Flow Cytometry, CD19 CAR Flow Panel A SV-SOP-A-000058 SV-ATT-A-000004 | Determined and declared |
| Transduction Frequency (Fresh Drug Product: Day 12) | Flow Cytometry, CD19 Flow Panel B SV-SOP-A-000055 SV-ATT-A-000003 | ≥ 7% $CD3^+CD19$ $CAR^+$ cells among viable $CD3^+$ cells |
| Dose: CD3+CAR+ cells/mL (Fresh Drug Product: Day 12) | Flow Cytometry, CD19 Flow Panel A SV-SOP-A-000058 SV-ATT-A-000004<br><br>Flow Cytometry, CD19 Flow Panel B SV-SOP-A-000055 SV-ATT-A-000003 | $2.5 \times 10^6$ $CD3^+CAR^+$ cells/mL ± 20% or<br><br>$1.0 \times 10^6$ $CD3^+CAR^+$ cells/mL ± 20% |

| Test Parameter | Analytical Method | Acceptance Criterion |
|---|---|---|
| Identity / Potency by CAR detection reagent binding Fresh Drug Product: Day 12) | Flow Cytometry, CD20-CD19 CAR Flow Panel B<br>SV-SOP-A-000117<br>SV-ATT-A-000017 | Conforms [2] |
| | Flow Cytometry, CD19 Flow Panel B<br>SV-SOP-A-000055<br>SV-ATT-A-000003 | Conforms [3] |
| Potency by IFN-γ Secretion (In-Process: Day 11) | IFN-γ secretion assay<br>SV-SOP-A-000118<br>SV-ATT-A-000018 | Absolute IFN-γ secretion for CD19 and CD20: > 0 pg/mL |
| Vector Copy Number (VCN) (In-Process: Day 9 or 10 or 11) | qPCR<br>SV-SOP-A-000060<br>SV-ATT-A-000007 | 0.5 - 5 copies per transduced cell |
| Bacterial Endotoxin (In-Process: Day 5) | Endosafe-PTS<br>SV-SOP-A-000016<br>SV-ATT-A-000035<br>(Samples Dilution: 1:20) [5] | ≤ 5 EU/mL [4] |
| Bacterial Endotoxin (Fresh Drug Product: Day 12) | Endosafe-PTS<br>SV-SOP-A-000016<br>SV-ATT-A-000035<br>(Samples Dilution: 1:100) [5] | ≤ 5 EU/mL [4] |
| Sterility: Gram Stain (Fresh Drug Product: Day 12) | Gram Stain<br>SV-SOP-A-000013<br>SV-ATT-A-000078 | Negative |
| Sterility<br>BacT Rapid Sterility Testing MBI (7 days) or USP <71> (14 days)<br><br>(In-Process: Day 8 or 9 or 10 or 11) For all applicable fields | BacT Rapid Sterility Testing (7 days)<br>SV-SOP-A-000199<br>SV-ATT-A-000206<br>or<br>USP <71> (14 days) | Negative to date |
| Mycoplasmas (In-Process: Day 8 or 9 or 10 or 11) | qPCR<br>SV-SOP-A-000238<br>SV-ATT-A-000236<br>Or<br>MycoSEQ PCR<br>Element: CM-297-002 | Negative |

Abbreviations: CAR = chimeric antigen receptor; CD = cluster of differentiation; EU = endotoxin unit; IFN-γ = interferon-gamma; PCR = polymerase chain reaction; qPCR = quantitative polymerase chain reaction; USP = United States Pharmacopeia; VCN = vector copy number

[1] To be completed if container integrity defect(s) or particulate(s) were observed.
[2] Refers to a measured value equal to or above the threshold of 50% CD20 scFv CAR+/ CD19 scFv CAR+ cells
[3] Refers to a measured value equal to or above the threshold of 7% CD19 scFv CAR+ cells
[4] Represents ≤ 5 EU/per kilogram body weight.
[5] Any dilution up to the MVD of 1:1000 may be used for retest (for both In-process: Day 5 and Fresh Drug Product: Day 12).

**Table 23: Release Specification – Full Release for Fresh Drug Product**

| Test Parameter | Analytical Method | Acceptance Criterion |
|---|---|---|
| CoA – Rapid Release | N/A | Pass |
| Sterility<br>BacT Rapid Sterility Testing (7 days)<br>or<br>USP <71> (14 days)<br>(Fresh Drug Product: Day 12) | BacT Rapid Sterility Testing (7 days)<br>SV-SOP-A-000199<br>SV-ATT-A-000206<br>or<br>USP <71> (14 days) | Negative |
| Mycoplasmas<br>(Fresh Drug Product: Day 12) | qPCR<br>SV-SOP-A-000238<br>SV-ATT-A-000236<br>Or<br>MycoSEQ PCR<br>Element: CM-297-002 | Negative |
| Potency by IFN-γ Secretion<br>(Fresh Drug Product:<br>Day 12) | IFN-γ secretion assay<br>SV-SOP-A-000118<br>SV-ATT-A-000018 | Report Result |

Abbreviations: CoA = certificate of analysis; IFN-γ = interferon-gamma; PCR = polymerase chain reaction; qPCR = quantitative polymerase chain reaction; USP = United States Pharmacopeia

# APPENDIX H: SUPPORTIVE CARE MEASURES FOR CAR T CELL TREATMENT

Guidelines developed and adapted from [48].

## Supportive Care Recommendations for Subjects Receiving CAR T cells

| | |
|---|---|
| Constitutional | • Administer acetaminophen for symptomatic management of fevers in participants with normal hepatic function<br>• Provide cooling blankets for fevers >40°C<br>• Avoid corticosteroids and NSAIDs<br>• Avoid meperidine |
| Cardiovascular | • Minimize anti-hypertensives prior to cell infusion<br>• Monitor vital signs at least every 4 hours for up to 48 hours post MB-CART2019.1 cell infusion<br>• Monitor vital signs Q2H in participants with fevers and tachycardia<br>• Initiate replacement of IV fluids for participants with poor oral intake or high insensible losses to maintain net even fluid balance<br>• IV fluid boluses for participants with SBP less than their pre-infusion baseline or those with hypotension SBP<90 mmHg<br>• Persistent hypotension not responsive to fluids should be initiated on vasopressors and participants transferred to intensive care unit<br>• For participant on vasopressors evaluate cardiac function with troponin and ECG. Echocardiogram can be performed as indicated. |
| Infectious disease | • Prophylactic antibiotics as per institutional guidelines<br>• Neutropenic Fever management as per institutional guidelines with broad spectrum antibiotics. Appropriate fever work-up with chest x-ray, urinalysis, and blood cultures |
| Hematologic | • Initiate Allopurinol for TLS prevention as per institutional guidelines<br>• Transfuse RBCs for Hgb <8 g/dL<br>• Transfuse platelets for platelets<20 k/μL<br>• Monitor ANC as per schedule of events and administer G-CSF if needed.<br>• Transfuse fresh frozen plasma in participants with PTT prolongation >2.0-fold upper limit of normal<br>• Transfuse cryoprecipitate to maintain fibrinogen ≥100 mg/dL |
| Neurologic | • Neuro checks Q4H by nursing staff in participants with ≥Grade 2 ICANS<br>• MRI Brain +/- lumbar puncture and EEG in participants with ≥Grade 2 ICANS<br>• Neurological consultation for participants with ≥ Grade 2 ICANS<br>• ICE assessment as in Appendix B<br>• Dexamethasone treatment for ≥ Grade 3 ICANS |

Abbreviations: ANC = absolute neutrophil count; ECG = electrocardiogram; EEG = electroencephalogram; G-CSF = granulocyte colony-stimulating factor; Hgb = hemoglobin; ICANS = immune effector cell-associated neurotoxicity syndrome; ICE = immune effector cell-associated encephalopathy; IV = intravenous; NSAID = non-steroidal anti-inflammatory drug; PTT = partial thromboplastin time; Q = quaque (every); RBC = red blood cell; SBP = systolic blood pressure; TLS = tumor lysis syndrome

# APPENDIX I: ABBREVIATIONS

| Terms | Definitions |
|---|---|
| AE | Adverse Event |
| AESI | Adverse Event of Special Interest |
| ALC | Absolute Lymphocyte Count |
| ALP | Alkaline Phosphatase |
| ALT | Alanine Aminotransferase |
| ANC | Absolute Neutrophil Count |
| AST | Aspartate Aminotransferase |
| ASBMT | American Society for Blood and Marrow Transplantation |
| ASCT | Autologous Stem Cell Transplant |
| ASTCT | American Society for Transplantation and Cellular Therapy |
| AxMP | Auxiliary Medicinal Product |
| bDNA | Branched Deoxyribonucleic Acid |
| BiPAP | Bilevel Positive Airway Pressure |
| BITE | Bispecific T Cell Engaging |
| BMT CTN | Blood and Marrow Transplant Clinical Trials Network |
| BR | Bendamustine and Rituximab |
| BTK | Bruton Tyrosine Kinase |
| BTKi | Bruton Tyrosine Kinase Inhibitor |
| BUN | Blood Urea Nitrogen |
| CAR | Chimeric Antigen Receptor |
| CAR-T | Chimeric Antigen Receptor T Cell |
| CBC | Complete Blood Count |
| CD | Cluster of Differentiation |
| CFR | Code of Federal Regulations |
| CI | Confidence Interval |
| CIBMTR | Center for International Blood and Marrow Transplant Research |
| CK | Complex Karyotype |

| Terms | Definitions |
|---|---|
| CKD-EPI | Chronic Kidney Disease Epidemiology Collaboration |
| CM | Central Memory |
| CMV | Cytomegalovirus |
| CNS | Central Nervous System |
| CoA | Certificate of Analysis |
| COVID-19 | Coronavirus Disease 2019 |
| CPAP | Continuous Positive Airway Pressure |
| CR | Complete Response |
| CRP | C-reactive protein |
| CRS | Cytokine Release Syndrome |
| CSF | Cerebrospinal Fluid |
| CT | Computed Tomography |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CVA | Cerebral Vascular Accident |
| d | Days |
| D | Day |
| DCC | Data Coordinating Center |
| DLBCL | Diffuse Large B Cell Lymphoma |
| DNA | Deoxyribonucleic Acid |
| DOCR | Duration of Complete Response |
| DOR | Duration of Response |
| DORR | Durable Overall Response Rate |
| DSMB | Data Safety Monitoring Board |
| EBMT | European Society for Blood and Marrow Transplantation |
| EBV | Epstein-Barr Virus |
| ECG | Electrocardiogram |
| ECHO | Echocardiogram |
| ECOG | Eastern Cooperative Oncology Group |

| Terms | Definitions |
|---|---|
| eCRF | Electronic Case Report Form |
| EDTA | Ethylenediaminetetraacetic Acid |
| EEG | Electroencephalogram |
| EF | Ejection Fraction |
| EHA | European Hematology Association |
| EMRA | Effector Memory |
| ESS | Effective Sample Size |
| EU | Endotoxin Unit |
| FDG | 18F-Fluorodeoxyglucose |
| FFPE | Formalin Fixed Paraffin Embedded |
| FFS | Failure-free Survival |
| GCP | Good Clinical Practice |
| G-CSF | Granulocyte Colony-Stimulating Factor |
| GM-CSF | Granulocyte-Macrophage Colony-Stimulating Factor |
| GMP | Good Manufacturing Practice |
| HBc | Hepatitis B Core |
| HBsAg | Hepatitis B Surface Antigen |
| HCT | Hematopoietic Cell Transplantation |
| HCV | Hepatitis C Virus |
| Hgb | Hemoglobin |
| HHV6 | Human Herpesvirus 6 |
| HIV | Human Immunodeficiency Virus |
| HLH | Hemophagocytic Lymphohistiocytosis |
| h/o | History of |
| ICAHT | Immune Effector Cell–Associated Hematotoxicity |
| ICANS | Immune Effector Cell-Associated Neurotoxicity Syndrome |
| ICE | Immune Effector Cell-Associated Encephalopathy |
| ICF | Informed Consent Form |

| Terms | Definitions |
|---|---|
| ICP | Intracranial Pressure |
| ICU | Intensive Care Unit |
| ID | Identifier |
| IEC | Immune Effector Cell |
| IEC-HS | Immune Effector Cell-Associated Hemophagocytic Lymphohistiocytosis |
| IFN-g | Interferon-gamma |
| IgA | Immunoglobulin A |
| IgM | Immunoglobulin M |
| IHC | Immunohistochemistry |
| IL | Interleukin |
| IMP | Investigational Medicinal Product |
| IND | Investigational New Drug |
| INR | International Normalized Ratio |
| IRB | Institutional Review Board |
| IT | Intrathecal |
| IV | Intravenous |
| IVIG | Intravenous Immunoglobulin |
| JCO | Journal of Clinical Oncology |
| K | Potassium |
| LDH | Lactate Dehydrogenase |
| LFT | Liver Function Test |
| LLN | Lower Limit of Normal |
| LTFU | Long-term Follow-up |
| M | Month |
| MACS | Magnetic-Activated Cell Sorting |
| MAS | Macrophage Activation Syndrome |
| Max | Maximum |
| MB-CART2019 | Modified B Cell Chimeric Antigen Receptor T Cell 2019 |

| Terms | Definitions |
|---|---|
| MB-CART2019.1 | Multispecific Bispecific Chimeric Antigen Receptor T Cells |
| MCL | Mantle Cell Lymphoma |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mEFS | Median Event-free Survival |
| MIPI | Mantle Cell Lymphoma International Prognostic Index |
| MIPI-c | Mantle Cell Lymphoma International Prognostic Index Combined |
| MNC | Mononuclear Cell(s) |
| Mo | Months |
| MOP | Manual of Procedures |
| mOS | Median Overall Survival |
| mPFS | Median Progression-free Survival |
| MRD | Minimal Residual Disease |
| MRI | Magnetic Resonance Imaging |
| MUGA | Multigated Acquisition Scan |
| mut | Mutation |
| Na | Sodium |
| N/A | Not Applicable |
| NAT | Nucleic Acid Test |
| NCCN | National Comprehensive Cancer Network |
| NCI | National Cancer Institute |
| NEJM | New England Journal of Medicine |
| NHL | Non-Hodgkins Lymphoma |
| NHLBI | National Heart, Lung, and Blood Institute |
| NK | Natural Killer |
| NR | Not Reached |
| NSAID | Non-Steroidal Anti-Inflammatory Drug |
| OR | Overall Response |
| ORR | Overall Response Rate |

| Terms | Definitions |
|---|---|
| PCR | Polymerase Chain Reaction |
| PET | Positron Emission Tomography |
| PFS | Progression-Free Survival |
| PO | *Per Os* (by mouth) |
| PRO | Patient-Reported Outcome |
| PROMIS | Patient-Reported Outcomes Measurement Information System |
| PT | Prothrombin Time |
| PTT | Partial Thromboplastin Time |
| Q | *Quaque* (every) |
| QC | Quality Control |
| QoL | Quality of Life |
| qPCR | Quantitative Polymerase Chain Reaction |
| RBC | Red Blood Cell |
| R-CHOP | Rituximab, Cyclophosphamide, Doxorubicin Hydrochloride (Hydroxydaunomycin), Vincristine Sulfate (Oncovin), and Prednisone |
| RCL | Replication-Competent Lentivirus |
| R-DHAP | Rituximab, Dexamethasone, High-dose Arabinose C, and Platinol |
| R-FC | Rituximab, Fludarabine, and Cyclophosphamide |
| R-HDAC | Rituximab and High-dose Cytosine Arabinoside |
| RNA | Ribonucleic Acid |
| RPMI | Roswell Park Memorial Institute |
| R/R | Relapsed/Refractory |
| RT-PCR | Reverse Transcriptase-Polymerase Chain Reaction |
| SAE | Serious Adverse Event |
| SBP | Systolic Blood Pressure |
| SC | Subcutaneous |
| SCM | Stem-Cell Memory |
| sIL-2R | soluble interleukin-2 receptor |

| Terms | Definitions |
|---|---|
| SmPC | Summary of Product Characteristics |
| SoC | Standard of Care |
| SOC | System Organ Class |
| SOP | Standard Operating Procedure |
| SST | Serum Separator Tube |
| TBW | Total Body Weight |
| TEAE | Treatment-Emergent Adverse Event |
| TID | *Ter In Die* (3 times a day) |
| TITE-SPRT | Time-to-Event-Sequential Probability Ratio Test |
| TLS | Tumor Lysis Syndrome |
| TLT | Treatment-Limiting Toxicity |
| TNF-a | Tumor Necrosis Factor-alpha |
| TP53 | Tumor Protein 53 |
| ULN | Upper Limit of Normal |
| US | United States |
| USP | United States Pharmacopeia |
| v | Version |
| VCN | Vector Copy Number |
| VSV-g | Vesicular Stomatitis Virus-G |
| y | Year(s) |

# APPENDIX J: REFERENCES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# BMT CTN 2501 CAR-T for MCL_Protocol_v1.0

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Challenge: The user opened the agreement.

2026-08-27 - 8:29:19 PM GMT

michael.jain@moffitt.org authenticated with Email OTP by verifying one-time code sent via email

Challenge: The user completed the signing ceremony.

2026-08-27 - 8:30:57 PM GMT

Document e-signed by Michael Jain (michael.jain@moffitt.org)

Signing reason: I am Approving this document

Signature Date: 2026-08-27 - 8:30:58 PM GMT - Time Source: server- IP address: 47.203.30.151 - Signature Appearance Selected: TYPE

Email viewed by Nirav Shah (nishah@mcw.edu)

2026-08-27 - 9:51:05 PM GMT- IP address: 141.106.128.44

nishah@mcw.edu authenticated with Email OTP by verifying one-time code sent via email

Challenge: The user opened the agreement.

2026-08-27 - 9:51:28 PM GMT

nishah@mcw.edu authenticated with Email OTP by verifying one-time code sent via email

Challenge: The user completed the signing ceremony.

2026-08-27 - 9:53:15 PM GMT

Document e-signed by Nirav Shah (nishah@mcw.edu)

Signing reason: I am Approving this document

Signature Date: 2026-08-27 - 9:53:15 PM GMT - Time Source: server- IP address: 141.106.128.44 - Signature Appearance Selected: TYPE

Agreement completed.

2026-08-27 - 9:53:15 PM GMT