Official Title of Study:

A Phase 2, Single-arm, Multi-center Trial to Determine the Efficacy and Safety of JCAR017 in Subjects With Relapsed or Refractory Diffuse Large B-Cell Lymphoma or With Other Aggressive B-Cell Malignancies

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A PHASE 2, SINGLE-ARM, MULTI-COHORT, MULTI-CENTER TRIAL TO DETERMINE THE EFFICACY AND SAFETY OF JCAR017 IN ADULT SUBJECTS WITH AGGRESSIVE B-CELL NON-HODGKIN LYMPHOMA (TRANSCEND WORLD)

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SPONSOR NAME/ ADDRESS:	Celgene Corporation 86 Morris Avenue Summit, NJ 07901

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TRANSCEND WORLD

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See appended electronic signature page
Signature of Celgene Therapeutic Area Head **dd mmm yyyy**
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Printed Name of Celgene Therapeutic Area Head and Title
By my signature, I indicate I have reviewed this protocol and find its content to be acceptable.

SITE PRINCIPAL INVESTIGATOR SIGNATURE PAGE

Signature of Site Principal Investigator	**dd mmm yyyy**
Printed Name of Site Principal Investigator **Institution Name:**_____ By my signature, I agree to personally supervise the conduct of this study at my study site and to ensure its conduct is in compliance with the protocol, informed consent, Institutional Review Board (IRB)/Ethics Committee (EC) procedures, instructions from Celgene representatives, the Declaration of Helsinki, International Council for Harmonisation (ICH) Good Clinical Practices Guidelines, and local regulations governing the conduct of clinical studies.	

PROTOCOL SUMMARY

Study Title

A Phase 2, Single-arm, Multi-cohort, Multi-center Trial to Determine the Efficacy and Safety of JCAR017 in Adult Subjects with Aggressive B-Cell Non-Hodgkin Lymphoma

Indication

Aggressive B-cell non-Hodgkin lymphoma (B-NHL)

Objectives

Primary Objectives

Cohorts 1, 2, 3, 4, and 5

- Determine the efficacy, defined as overall response rate (ORR), of JCAR017 in subjects with aggressive B-cell non-Hodgkin lymphoma

Cohort 7

- Evaluate the safety of JCAR017 treatment in subjects intended to be treated as outpatients

Secondary Objectives

- Evaluate the safety and feasibility of administering JCAR017 (Cohorts 1, 2, 3, 4, and 5)
- To determine the efficacy, defined as ORR of JCAR017 in subjects intended to be treated as outpatients (Cohort 7)
- Evaluate other measures of efficacy of JCAR017 (eg, complete response rate [CRR], event-free survival [EFS], progression-free survival [PFS], overall survival [OS], duration of response [DOR])
- Characterize the pharmacokinetic (PK) profile of JCAR017 in the peripheral blood measured using quantitative polymerase chain reaction (qPCR) detection for the JCAR017 vector sequence
- Describe changes in health-related quality of life (HRQoL) using global health/QoL, fatigue, physical and cognitive functioning subscales of the European Organisation for Research and Treatment of Cancer – Quality of Life C30 questionnaire (EORTC QLQ-C30) and the Functional Assessment of Cancer Therapy-Lymphoma "Additional concerns" subscale (FACT-LymS)

Study Design

Study JCAR017-BCM-001 is a single-arm, multi-cohort, multi-center, Phase 2 study to determine the efficacy and safety of JCAR017 in subjects with aggressive B-cell NHL (B-NHL).

Approximately 116 subjects will be enrolled into one of 6 cohorts as listed below:

- Cohort 1: Subjects with diffuse large B-cell lymphoma (DLBCL) not otherwise specified (NOS; de novo or transformed follicular lymphoma [tFL]), high-grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements with DLBCL

histology [HGBL]) and follicular lymphoma Grade 3B (FL3B) per World Health Organization (WHO) 2016 classification (Swerdlow, 2016), after ≥ 2 lines of therapy*, including an anthracycline and rituximab (or other CD20-targeted agent)

- Cohort 2: Transplant not eligible (TNE) subjects with DLBCL NOS (de novo or tFL), HGBL and FL3B per WHO 2016 classification, who failed first line therapy*, including an anthracycline and rituximab (or other CD20-targeted agent)
  - Transplant not eligible subjects will include those who are deemed ineligible for high-dose chemotherapy and HSCT due to age, performance status or comorbidity, while also having adequate organ function for CAR T cell treatment. At the very least, subjects have to meet one of the following criteria:
    a) Age ≥ 70 years
    b) ECOG performance status ≥ 2
    c) Impaired pulmonary function (diffusion capacity of carbon monoxide [DLCO] ≤ 60%, adjusted for hemoglobin concentration using the Dinakara equation)
    d) Impaired cardiac function (left ventricular ejection fraction [LVEF] < 50%)
    e) Impaired renal function (creatinine clearance [CrCl] < 60 mL/min)
    f) Impaired hepatic function (aspartate aminotransferase [AST] / alanine aminotransferase [ALT] > 2 x upper limit of normal [ULN], bilirubin ≥ 2 mg/dL or cirrhosis Child-Pugh B or C)
- Cohort 3 (Japan only): Subjects meeting eligibility criteria for either Cohort 1 or 2
- Cohort 4: Subjects with newly diagnosed HGBL. Subjects must be eligible for anthracycline and rituximab (or other CD20-targeted agent)-containing regimen as induction prior to consolidation with JCAR017**
- Cohort 5: Subjects with primary central nervous system lymphoma (PCNSL), who failed first line therapy with high-dose chemotherapy (HDCT) and autologous stem cell transplantation (ASCT), or who failed to proceed to HDCT and ASCT due to failure of Peripheral blood stem cell (PBSC) mobilization or insufficient response at the completion of induction therapy with high-dose methotrexate-based polychemotherapy regimen (eg, high dose methotrexate, high dose cytarabine, rituximab and thiotepa [MATRix regimen])
- Cohort 6: (REMOVED)
- Cohort 7: Subjects meeting eligibility criteria for Cohort 1 and suitable for outpatient treatment***

* For subjects with transformed disease, the subject should have had at least 2 lines of systemic therapy for his/her transformed disease (ie, DLBCL) for Cohort 1 and 1 line for Cohort 2 to be eligible. Lines of therapy do not include those given for a previously indolent condition (ie, follicular lymphoma). Subjects do NOT have to have anthracycline for their DLBCL if received for indolent disease.

** For subjects already undergoing anthracycline and rituximab-containing regimen, eligibility is to be discussed with the Medical Monitor. Subjects with complete metabolic response after 2 cycles of induction will proceed with JCAR017 infusion only at time of relapse, if applicable.

*** Subjects must meet the conditions for outpatient treatment and monitoring as outlined in the Outpatient Administration and Monitoring Guidance for Lisocabtagene Maraleucel.

Note: Subjects with secondary central nervous system (CNS) lymphoma involvement may enroll in Cohorts 1 to 4 and 7; subjects with PCNSL are eligible for Cohort 5. Subject selection must consider clinical risk factors for severe adverse events (AEs) and alternative treatment options. Subjects should only be enrolled if the Investigator considers the potential benefit outweighs the risk for the subject. For Cohort 5 and to not compromise safety, subject selection has been restricted to those fit enough to be considered for HDCT and ASCT as their prior therapy.

The first 3 subjects in Europe in Cohort 1 will be treated with a minimum interval of 14 days between JCAR017 infusions and assessed for acute safety 28 days after the third subject has received JCAR017 infusion. In addition, the product characteristics of the JCAR017 cell product manufactured with processing steps in Europe will be evaluated. If criteria for safety and feasibility are met, Cohort 1 will continue enrollment without gating and additional Cohorts 2, 4, 5 and 7 may be opened at Celgene's discretion. A minimum of 14 days treatment interval will also apply to all subjects treated in Cohort 5.

The first 10 subjects treated with JCAR017 in Europe must be hospitalized for a minimum of 14 days after JCAR017 infusion, unless otherwise recommended by a local authority. Experience to date with JCAR017 from the Juno TRANSCEND NHL 001 (017001) study suggests that outpatient administration of JCAR017 can be provided safely without compromising the subject's safety when appropriate education is provided and hospital admission is done upon symptoms of toxicity. Outpatient infusion of JCAR017 was associated with a 68% decrease in hospital length of stay (Palomba, 2018). Selected countries/sites will participate in the dedicated outpatient cohort. In order to enroll subjects in Cohort 7, sites must have treated at least 3 DLBCL subjects with CD19-targeted CAR T cell therapy, and must have a suitable infrastructure to allow for outpatient treatment and monitoring as outlined in the Outpatient Administration and Monitoring Guidance for Lisocabtagene Maraleucel.

Safety data will be reviewed on an ongoing basis. An early safety assessment will be performed 28 days after JCAR017 is administered to the 10th subject treated in Europe. Enrollment will be halted if the observed mortality rate is > 30%, irrespective of causality, or if > 50% of subjects who undergo leukapheresis fail to have a satisfactory cell product available for infusion.

In addition, an early safety assessment will be performed 28 days after JCAR017 is administered to the 10th subject treated in Cohort 2. Enrollment into Cohort 2 will be halted if the observed mortality rate within 28 days post infusion is > 30% (excluding death related to disease progression or relapse).

The first 3 subjects in Japan will be treated with a minimum interval of 14 days between JCAR017 infusions and assessed for acute safety 28 days after the third subject has received JCAR017 infusion. In addition, the first 10 subjects treated with JCAR017 in Japan must be hospitalized for a minimum of 14 days after JCAR017 infusion. The acute and subacute toxicity

profile of JCAR017 cell product manufactured entirely at the current manufacturing site in the United States (US) has already been established in subjects with relapsed/refractory (r/r) B-NHL with good tolerability observed in subjects with DLBCL (Abramson, 2018).

In addition, a staggered dosing approach will also be utilized for all new sites (Europe and Japan) without prior experience of administering CAR T cell therapies as follows:

- 1st subject infusion, wait 14 days
- 2nd subject infusion, wait 14 days

Following completion of the site-staggered enrollment approach for the first 2 subjects, the site may proceed with subject enrollment as communicated by Celgene.

Prior to initiation of any study procedure (screening period), subjects must provide informed consent. Once enrolled and during the pretreatment period, subjects will undergo leukapheresis to enable JCAR017 cell product generation. Upon successful JCAR017 cell product generation, subjects will enter the treatment period and receive lymphodepleting (LD) chemotherapy followed by infusion of JCAR017, 2 to 7 days after completion of LD chemotherapy. JCAR017 will be administered at a dose of 100 x 10^6 JCAR017-positive transfected viable T cells (CAR+ T cells).

After treatment with JCAR017, subjects will enter the post-treatment period. A first response assessment will be performed 28 days after JCAR017 infusion. Subjects will be followed for 2 years after their JCAR017 infusion for safety, disease status, survival and health-related quality of life and utility values measured using EORTC QLQ-C30 and EQ-5D-5L questionnaires and the FACT-LymS.

In addition, when feasible, all subjects will be invited to participate in interviews during their participation in the study to document their experience with JCAR017.

Delayed adverse events following exposure to gene modified T cells will be assessed and long-term persistence of these modified T cells, including vector integration sites as well as the generation of replication competent retrovirus will continue to be monitored under a separate Long-term follow-up (LTFU) protocol for up to 15 years after JCAR017 infusion as per competent authority guidelines.

The decision to discontinue a subject from the study is the responsibility of the Investigator or designee. Celgene will not delay or refuse this decision. However, prior to discontinuing a subject, the Investigator should contact the Medical Monitor and forward appropriate supporting documents for review and discussion.

Study Population

This study will enroll adult subjects in Europe and Japan with DLBCL NOS (de novo or tFL), HGBL, FL3B, and PCNSL. Subjects with secondary CNS involvement are allowed.

Length of Study

This study will enroll over approximately 40 months and will consist of 3 periods:

- The pretreatment period will consist of screening for eligibility, leukapheresis and a pretreatment evaluation (prior to LD chemotherapy)

- The treatment period will start with LD chemotherapy, followed by JCAR017 infusion 2 to 7 days after completion of LD chemotherapy. A first response evaluation will be performed at approximately 28 days after JCAR017 infusion
- The post-treatment period will consist of further efficacy and safety follow-up visits at approximately 2, 3 (at 4 months for Cohort 5), 6, 9, 12, 18 and 24 months after JCAR017 infusion

The End of Trial is defined as either the date of the last visit of the last subject completing the post-treatment follow-up of this study or the date when the last subject enters the LTFU study, or the date of receipt of the last data point from the last subject that is required for primary, secondary and/or exploratory analysis, as pre-specified in the protocol, whichever is the later date.

Study Procedures and Treatments

Following enrollment in the study, a leukapheresis collection will be performed on each subject to obtain a sufficient quantity of peripheral blood mononuclear cells (PBMCs) for the production of the JCAR017 cell product.

If necessary, anticancer treatment is allowed for disease control while JCAR017 is being manufactured (ie, after leukapheresis and prior to LD chemotherapy). After anticancer treatment the subject must continue to have positron emission tomography (PET)-positive disease and meet eligibility criteria pertaining to adequate organ function, active infections, pregnancy, and washout of prior therapy before initiation of LD chemotherapy.

Subjects will receive 3 days of fludarabine intravenously (IV) (30 mg/m^2/day) and cyclophosphamide IV (300 mg/m^2/day) for LD chemotherapy. Two to 7 days after completion of LD chemotherapy, JCAR017 will be administered by IV infusion at a dose of 100 x 10^6 JCAR017-positive transfected viable T cells (CAR+ T cells) as a single dose on Day 1. The JCAR017 investigational drug product is provided as 2 individually formulated CD8+CAR+ and CD4+CAR + frozen T cell suspensions in media containing dimethyl sulfoxide (DMSO) that are thawed and administered separately by IV infusion.

Subjects must be clinically stable and must have recovered from prior toxicities, to receive LD chemotherapy and proceed to JCAR017 infusion. Neither LD chemotherapy nor JCAR017 treatment should be administered if there is a worsening of performance status to ECOG 2, rapid clinical deterioration, or evidence of rapidly progressive disease. Note: subjects who are transplant not eligible or have PCNSL may have ECOG 2, however, must be clinically stable, recover from prior toxicities, and not have evidence of rapidly progressive disease or rapid clinical deterioration prior to receiving LD chemotherapy or JCAR017 infusion.

Overview of Key Efficacy Assessments

- DLBCL, FL3B: Efficacy response will be assessed according to the "Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification" (Cheson, 2014) based on radiographic tumor assessments. Subjects will have radiographic disease assessment by PET and/or computed tomography (CT)/ magnetic resonance imaging (MRI) scans at pretreatment evaluation and approximately 1, 3, 6, 9, 12, 18 and 24 months following JCAR017 infusion or until progressive disease or relapse

  - For subjects with secondary CNS involvement repeat cerebrospinal fluid (CSF) evaluation together with brain MRI and PET-CT when relevant

- PCNSL: Efficacy response will be assessed according to the "Report of an International Workshop to Standardize Baseline Evaluation and Response Criteria for Primary CNS Lymphoma" (Abrey, 2005) at pretreatment evaluation and approximately 1, 2, 4, 6, 9, 12, 18 and 24 months based on brain MRI and CSF examination. For subjects without CSF involvement, repeated evaluation is not required in absence of interval symptoms suggestive of leptomeningeal dissemination. PET-CT does not need to be repeated in the absence of systemic disease at baseline or suspicion of systemic PD. Ophthalmologic evaluation is completed at screening to exclude ocular lymphoma and does not need to be repeated unless symptoms occur.

Overview of Key Safety Assessments

Safety will be monitored via the following assessments at each visit:

- Physical examination, including performance status (PS)
- Laboratory evaluations
- Neurologic examination
- Adverse event (including serious adverse event [SAE]) monitoring and collection, including cytokine release syndrome (CRS) evaluation and neurotoxicity

Overview of Key Patient-Reported Outcome Assessments

Patient-reported outcomes (PROs) will be measured via the following assessments at each visit:

- EORTC QLQ-C30
- EQ-5D-5L
- FACT-LymS

All subjects will be required to complete the above questionnaires.

Where feasible, patient interviews will be used to capture the experience of JCAR017 therapy from a subject perspective.

Overview of Key Resource Use Data Capture

The time that subjects spend in hospital expressed in days spent in intensive care unit (ICU)/Non-ICU will be captured.

Statistical Methods

A formal interim analysis with the first 10 subjects treated with JCAR017 in Cohort 1 being followed for at least 3 months after JCAR017 infusion to test the superiority of JCAR017 will be performed.

Data from all sites will be combined for the final analysis for each cohort. Results will be presented using descriptive statistics.

Efficacy information will be summarized separately per cohort. Safety information will be analyzed per cohort and across cohorts. PK information will be combined for all subjects across cohorts.

The study will be conducted in compliance with International Council for Harmonisation (ICH) Good Clinical Practices (GCPs).

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1. INTRODUCTION

1.1. Disease Background

1.1.1. Non-Hodgkin Lymphoma

Non-Hodgkin lymphomas (NHL) comprise a heterogeneous group of malignancies. Within Europe, the incidence of NHL is approximately 49,533 with a mortality of 20,347 (Ferlay, 2015) and within the United States (US), the incidence and mortality is approximately 72,580 and 20,150, respectively (Siegel, 2016). Non-Hodgkin lymphomas are classified according to the current World Health Organization (WHO) classification (Swerdlow, 2016) into immature lymphoid neoplasms, mature B-cell neoplasms, T cell and natural killer (NK) cell neoplasms, and post-transplant lymphoproliferative disorders. Mature B-cell lymphomas are further classified into indolent lymphomas (eg, multiple myeloma, chronic lymphocytic leukemia [CLL]) and aggressive lymphomas (eg, diffuse large B-cell lymphoma [DLBCL]).

Diffuse large B-cell lymphoma is the most frequent lymphoma subtype, representing approximately 30% of all NHL. Diffuse large B-cell lymphoma can develop de novo or secondary to transformation of an indolent NHL. Estimated incidence in the European Union (EU) is 3 to 4/100,000/year, increasing with age from 0.3/100,000/year (35 to 39 years) to 26.6/100,000/year (80 to 84 years) (Tilly, 2012). About 10,000 deaths per year are due to DLBCL in the US (National Cancer Institute). Most patients with localized DLBCL can be cured with conventional combination immunochemo- or combined-modality therapy (Tilly, 2015). For patients with advanced-stage disease, the majority of patients can be cured with doxorubicin-based combination chemotherapy and rituximab (eg, rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, prednisone [R-CHOP]). Prognosis depends on individual risk factors. The International Prognostic Index (IPI) for aggressive NHL (diffuse large cell lymphoma) includes five significant risk factors prognostic of overall survival (OS): Patient age, serum lactate dehydrogenase (LDH) level, Eastern Cooperative Oncology Group (ECOG) performance status, disease stage, and extranodal involvement. Patients with ≥ 2 risk factors after age-adjustment have a poor prognosis with a 5-year OS-rate of 21% to 46%.

Despite overall improvement in outcomes of DLBCL, approximately one-third of patients will develop relapsed/refractory disease that remains a major cause of mortality. Refractory disease is defined as a < 50% decrease in lesion size or the appearance of new lesions. Relapsed disease reflects the (re)appearance of lesions after attainment of a partial or complete response (PR, CR) (Cheson, 2007). Relapsed/refractory patients have a poor prognosis due to lack of effective treatment options, particularly those who do not respond to second-line chemotherapy (median OS of 4.4 months) (Van Den Neste, 2016) and those who are transplant not eligible (TNE) after first line therapy. Elderly patients or patients with relevant organ dysfunction have typically been excluded in prospective trials exploring high-dose chemotherapy and stem cell transplant and evidence that this approach is better than conventional chemotherapy in this patient population remains to be demonstrated. The missing clear cut definitions of “not eligible for transplant” in the literature leads to highly individualized decision approaches among centers. To better describe nontransplant eligibility in this trial, Celgene and Juno jointly reached out to investigators in order to define criteria that are commonly used in the clinical setting to exclude patients from high-dose chemotherapy and stem cell transplant. These criteria are being included in the definition of the population to be enrolled in this study and study 017006 (PILOT), a study

being conducted in parallel in the US. Diffuse large B-cell lymphoma is a heterogeneous disease with several histological and molecular subtypes. The largest subgroup is DLBCL not otherwise specified (NOS). Molecular profiling by gene expression profiling (GEP) based on biologic similarity to normal stages of B-cell development (cell of origin [COO]) helped to further divide DLBCL into germinal center B-cell-like (GCB), activated B-cell-like (ABC) tumors, and primary mediastinal large B-cell lymphoma (PMBCL), a distinct clinical entity (Lenz, 2008). Immunohistochemistry (IHC) algorithms are clinically used to identify the COO and helped to identify ABC DLBCL as a high-risk subtype less likely to respond to standard immunochemotherapy.

Despite follicular lymphoma being an indolent lymphoma type, follicular lymphoma Grade 3B (FL3B) is regarded as aggressive lymphoma. Clinical behavior is very similar to DLBCL and FL frequently undergoes histological transformation into DLBCL. Consequently, current guidelines recommend treating FL3B according to the DLBCL treatment algorithm (National Comprehensive Cancer Network [National Comprehensive Cancer Network, 2019]). These patients are generally treated with an anthracycline-based chemotherapy combined with rituximab (eg, R-CHOP) and have a similar prognosis to that of de novo DLBCL.

1.1.1.1. High-grade B-cell Lymphoma with MYC and BCL2 and/or BCL6 Rearrangements with DLBCL Histology

High-grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements with DLBCL histology (HGBL) per WHO 2016 classification (Swerdlow, 2016) now encompass the entity previously referred to as double-hit or triple-hit lymphoma (DHL/THL). High-grade B-cell lymphoma represents approximately 7% to 10% of de novo cases of DLBCL with very poor OS of ≤ 12 months when treated with R-CHOP (Rosenthal, 2017).

This subset of HGBL has a poor prognosis when treated with standard chemoimmunotherapy and has increased risk of central nervous system (CNS) involvement and progression. Retrospective studies strongly suggest that aggressive induction regimens may confer a superior outcome. A multicenter retrospective analysis (Petrich, 2014) involving 311 patients with DHL treated with R-CHOP or intensive induction therapy, including dose-adjusted rituximab, etoposide, prednisolone, oncovin, cyclophosphamide, and hydroxydaunorubicin (R-EPOCH) regimen, fractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone (Hyper-CVAD) alternating with methotrexate and cytarabine (MA), or cyclophosphamide, vincristine, doxorubicin, high-dose methotrexate (CODOX-M)/ ifosfamide, etoposide and high-dose cytarabine (IVAC) showed the highest response rate for those treated with dose-adjusted R-EPOCH. Intensive induction was associated with improved progression free survival and improved overall survival in a multivariate analysis. The MD Anderson Cancer Center published a similar retrospective study involving 129 patients from their institution. In this study, CNS involvement occurred in 13% of patients. Patients with bone marrow involvement and poor performance status had the worst prognosis. Two-year event-free survival rates in patients who received R-CHOP, R-EPOCH, and R-HyperCVAD/MA were 25%, 67%, and 32%, respectively (Oki, 2014). Given the urgent need to improve prognosis for patients with HGBL, studies should embrace the concept of induction therapy followed by consolidation or maintenance therapy and explore novel treatment approaches in the front-line setting, a population with clear defined unmet medical need.

1.1.1.2. Primary Central Nervous System Lymphoma

Primary central nervous system lymphoma (PCNSL) is defined as lymphoma involving the cerebral parenchyma, leptomeninges, eyes or spinal cord without evidence of systemic disease that occurs in immunocompetent patients. PCNSL represents 2%–3% of all brain tumours, and less than 1% of all NHLs. Most of the cases are DLBCLs and 10%–20% develop intraocular lesions but rarely disseminate systemically (Deckert, 2011).

The International Extranodal Lymphoma Study Group (IELSG) has proposed a prognostic system for PCNSL based on the following prognostic factors:

- Age > 60 years
- Eastern Cooperative Oncology Group (ECOG) PS >1
- Elevated serum LDH
- Elevated cerebrospinal fluid (CSF) protein concentration
- Tumor localization within the deep regions of the brain

Based on the overall score, 3 categories have been defined as good risk (0–1), intermediate risk (2–3), and poor risk (4–5).

The Memorial Sloan-Kettering Cancer Center prognostic model for PCNSL (Abrey, 2006) only requires age and clinical performance status to build 3 different risk groups: good risk (patients < 50 years), intermediate risk (patients ≥ 50 years and Karnofsky performance score [KPS] ≥ 70) and high risk (patients ≥ 50; KPS < 70).

Historically, whole brain radiation therapy (WBRT) has been the standard treatment for PCNSL, and addition of immunochemotherapy to WBRT has improved significantly survival. Use of high-dose chemotherapy (HDCT) and autologous stem cell transplant (ASCT) has shown encouraging results in first line therapy of PCNSL with reduced neurotoxicity by avoiding WBRT and improving outcome (Illerhaus, 2016). Despite advances in initial treatment, up to half of patients relapse, and 10% to 15% of patients have primary refractory disease. Patients with primary refractory or relapsed PCNSL have a poor prognosis, with a median survival of 2 months without additional treatment (Grommes, 2017). The optimal salvage regimen for patients with recurrent or refractory PCNSL, especially those relapsing after prior HDCT, has not been established. No randomized trials have been conducted so far in this patient population.

For patients refractory to initial therapy or relapsing few treatment options are available, especially for patients failing HDCT and ASCT. While HDCT and ASCT plus consolidating WBRT may be an option in selected patients (Kasenda, 2017), most patients only have palliative options. Few agents have been investigated prospectively in patients with relapsed or refractory PCNSL. Prospective trials using single agents such as pemetrexed, topotecan, and temozolomide, as well as rituximab have demonstrated ORRs of 31% to 55% with limited median PFS of 1.6 to 5.7 months (Grommes, 2017).Unfortunately, none of these showed convincing activity sufficient to be established as standard therapy, and choice of salvage treatments depends on the clinical status, toxicities from previous treatments and duration of remission. Based on the limited evidence available so far, no treatment standard can be recommended (Vitolo, 2016).

1.2. Compound Background

1.2.1. CD19 as a Therapeutic Target

CD19 is a 95-kDa glycoprotein present on B-cells from early development until differentiation into plasma cells (Stamenkovic, 1988). It is a member of the immunoglobulin superfamily and a component of a B-cell surface signal transduction complex that positively regulates signal transduction through the B-cell receptor (Brentjens, 2011; Stamenkovic, 1988). CD19 is an attractive therapeutic target because it is expressed by most B-cell malignancies, including B-cell NHL (B-NHL; [Davila, 2012]). Importantly, the CD19 antigen is not expressed on hematopoietic stem cells or on any normal tissue apart from those of the B-cell lineage.

1.2.2. CD19-Targeted Chimeric Antigen Receptors

CD19-specific chimeric antigen receptors (CARs) are single chain variable fragments (scFv) fused to a transmembrane domain and cytoplasmic signaling domains. Expression of the CD19-directed CAR in autologous T cells is achieved by ex vivo transfection using a recombinant retroviral or lentiviral vector. The CAR is expressed on the T cell surface and redirects the transfected T cells to CD19-expressing lymphoma cells, leading to CD19-specific tumor cell recognition, lysis, cytokine secretion, and T cell proliferation (Sadelain, 2013). In clinical studies, CD19-targeted CARs have demonstrated encouraging activity in adult and pediatric subjects with relapsed/refractory (r/r) B-cell acute lymphoblastic leukemia (ALL) and B-NHL (Davila, 2014; Kochenderfer, 2015; Lee, 2015; Maude, 2014; Porter, 2011; Turtle, 2016; Turtle, 2016).

Three CD19-directed CAR T therapies have been approved by the US Food and Drug Administration (FDA) and Japan Ministry of Health, Labour and Welfare (MHLW). In addition two of them were also approved by the European Medicines Agency (EMA):

- Tisagenlecleucel, approved for the treatment of patients up to age 25 years with B-cell precursor ALL that is refractory or in second or later relapse and for adult patients with relapsed or refractory (R/R) large B-cell lymphoma after 2 or more lines of systemic therapy including diffuse large B-cell lymphoma (DLBCL) not otherwise specified (NOS), high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma (Kymriah™ United States Product Insert [USPI], 2018; Kymriah, Summary of Product Characteristics [SmPC]).
- Axicabtagene ciloleucel, approved to treat adult patients with relapsed or refractory large B-cell lymphoma after 2 or more lines of systemic therapy, including DLBCL NOS, PMBCL, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma (Yescarta USPI, 2019; Yescarta, SmPC).
- Lisocabtagene maraleucel, approved for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified (including DLBCL arising from indolent lymphoma), high-grade B-cell lymphoma, primary mediastinal large B-cell lymphoma, and follicular lymphoma grade 3B (Breyanzi USPI, 2021).

1.2.3. JCAR017 Investigational Drug Product

The JCAR017 investigational drug product is a novel, CD19-targeted, genetically modified, autologous, defined composition, T cell immunotherapy. Lisocabtagene maraleucel has been accepted as the generic name for JCAR017. JCAR017 is manufactured from autologous peripheral blood mononuclear cells (PBMCs) that are obtained via standard leukapheresis collection procedures. The PBMCs undergo sequential positive selection for CD8+ and CD4+ T cells where the CD4 and CD8 purified T cell populations derived from the same starting material (leukapheresis) are separated, subsequently cryopreserved, transfected with CAR and expanded through parallel processing in order to ensure the final product is infused to the subjects in a defined cell composition. The CD19-specific CAR consists of an scFv binding domain derived from a murine CD19-specific monoclonal antibody (mAb; FMC63) and the 4-1BB and CD3ζ signaling domains. The truncated human epidermal growth factor receptor (EGFRt) protein is co-expressed with the CD19-specific CAR as a cell surface protein for analytical detection of transfected T cells.

The JCAR017 investigational drug product is provided as 2 individually formulated CD8+CAR+ and CD4+CAR+ T cell suspensions in media containing dimethyl sulfoxide (DMSO) that are thawed and administered separately by intravenous (IV) infusion. JCAR017 is administered intravenously.

Please refer to the Investigator's Brochure (IB) for detailed information concerning the available pharmacology, toxicology, clinical studies, and adverse event (AE) profile of JCAR017.

1.2.4. Clinical Experience with JCAR017 and Related CAR T Cell Products

JCAR017 is currently being evaluated in the Juno TRANSCEND NHL 001 (017001) study and a related CAR T cell product is being evaluated in the PLAT-02 study. In the PLAT-02 study, a first-in-human Phase 1 study of pediatric and young adult subjects with relapsed CD19+ B-cell ALL (PLAT-02 study; NCT02028455), a total of 43 subjects with relapsed CD19+ B-cell ALL were treated with JCAR017 at dose levels ranging from 5×10^5 to 10×10^6 CAR+ T cells/kg. All 43 infused subjects received lymphodepleting (LD) chemotherapy prior to T cell infusion (cyclophosphamide, n=27; cyclophosphamide and fludarabine, n=14; cyclophosphamide and etoposide, n=1; fludarabine, n=1). Thirty-nine of the 43 (91%) subjects received infusions at the desired 1:1 CD4:CD8 ratio and their infusions were well tolerated with only 1 related AE > Grade 2. A total of 93% (40/43) of the subjects had a documented minimal residual disease (MRD)-negative CR within 21 days following CAR T cell therapy. The 12-month event-free survival (EFS) is 50.8% (95% confidence interval [CI] 36.6, 69.9) and 12-month OS is 69.5% (95% CI 55.8, 86.5) (Gardner, 2017).

The TRANSCEND study is investigating JCAR017 in adult subjects with r/r B-cell NHL (Juno TRANSCEND NHL 001 (017001) study; NCT02631044) (Abramson, 2018). A total of 55 subjects had received JCAR017 at the time of data cutoff (May 4th, 2017). Preliminary data suggest promising antitumor activity of JCAR017 in these heavily pretreated, poor prognosis r/r subjects with aggressive NHL (median of 3 prior lines of therapy). The overall response rate (ORR) reported was 76% with a CR rate at 3 months of 51% and an acceptable safety profile. No dose-limiting toxicity (DLT) was observed at dose level DL2 (JCAR017 infusion of 100×10^6 viable CAR+ T cells) with a trend toward improved response rate at 3 months in patients treated at DL2 when compared to DL1: ORR 64% vs 46% and CR 46% vs 33% (trend maintained at the

July 04th data cut. Pharmacokinetic (PK) analyses showed that in vivo expansion of CAR+ T cells peaks around day 11 after infusion of JCAR017. This is consistent with the reported safety with most important toxicities (cytokine release syndrome [CRS] and neurotoxicity [NT]) occurring within the first 14 days after infusion.

Major safety findings include CRS, NT and hematological disorders, including neutropenia, thrombocytopenia and anemia. The most significant toxicities reported have been severe cytokine release syndrome (sCRS) and NT. Cytokine release syndrome was observed in 19 (35%) subjects treated, with only 1 subject developing sCRS (Grade 3-4). Neurotoxicity was observed in 12 (18%) subjects, of which 9 subjects (16%) developed severe NT (Grade 3-4). Median time to onset of CRS after JCAR017 infusion was 5 days, median time to onset of NT was 11 days. The median time to resolution to Grade 1 or better was 5 days for CRS and 7 days for NT. No unexpected early or late toxicities were reported. No cerebral edema, fatal CRS or NT were observed and symptoms were reversible and manageable with appropriate treatment intervention and close monitoring (Abramson, 2018).

The ability of CAR T cells to cross the blood-brain barrier has been reported (Kochenderfer, 2017) and has been observed in study 017001 (Abramson, 2018). At the time of data analysis, the subjects enrolled and experiencing NT had no evidence of CNS involvement. This supports the rationale to further investigate CAR T cell therapy in patients with primary CNS or secondary CNS involvement. Two subjects with secondary CNS involvement by DLBCL were included in study 017001. Both subjects experienced complete resolution of their CNS disease with no neurologic adverse events observed.

JCAR014, a CAR T cell product that expresses the same CD19-specific CAR as JCAR017 but is produced using a different manufacturing process, is currently being evaluated in a first-in-human Phase 1/2 trial in adult subjects with relapsed/refractory CD19+ ALL, CLL, and NHL (2639 study; NCT01865617). Data are available from 41 subjects with NHL, 39 of whom are evaluable for efficacy (Turtle, 2016). Among all 41 subjects with NHL, the rate of sCRS was 13% (4/32) and the rate of severe neurotoxicity was 25% (8/32). The dose of 2 x 10^7 CAR+ T cells/kg was determined to have unacceptable toxicity with two deaths from sCRS at that dose level. Fludarabine and cyclophosphamide LD chemotherapy was associated with a higher response rate than non-fludarabine regimens. The ORR and CR rate were 74% and 44%, respectively, in 27 subjects treated with the fludarabine-containing regimen versus 50% and 8%, respectively, in the 12 subjects treated with non-fludarabine-containing regimens. In the group of subjects treated with fludarabine-containing LD chemotherapy and a CAR+ T cell dose of 2 x 10^6 CAR+ T cells/kg, the ORR was 80% (16/20) and the CR rate was 50% (10/20).

Data are also available from 36 adult subjects with B-cell ALL treated with JCAR014 as part of the 2639 trial (Turtle, 2016). Twelve of the 36 subjects were post allogeneic hematopoietic stem cell transplantation (HSCT). CAR+ T cell doses were 2 x 10^5, 2 x 10^6, and 2 x 10^7 CAR+ T cells/kg. Lymphodepleting chemotherapy consisted of cyclophosphamide 60 mg/kg on Day 1 and fludarabine 25 mg/m^2 for 3 to 5 days in 23 subjects. The remainder received non-fludarabine-containing LD chemotherapy regimens. Use of fludarabine-containing LD chemotherapy was associated with increased expansion and persistence of the CAR+ T cells. Thirty-four subjects were evaluable for a response assessment: 34 (100%) achieved a morphologic bone CR, with 32 of 34 (94%) achieving a bone marrow CR. In 87 subjects evaluated for toxicity, the rates of sCRS and Grade ≥ 3 neurotoxicity were 16% and 31%,

respectively. Four subjects (4%) died of complications of CRS and one subject experienced irreversible neurotoxicity. See the JCAR017 Investigator's Brochure for further details.

1.3. Rationale

1.3.1. Study Rationale and Purpose

The purpose of this Phase 2 study is to evaluate the efficacy and safety of JCAR017 in adult subjects with aggressive B-NHL. Multiple recent reports in B-NHL have demonstrated encouraging activity of CD19-targeted CAR T cell investigational drug products that are unselected for T cell subsets (Kochenderfer, 2015; Schuster, 2016). JCAR017 differs from these products in that it consists of CD4+ and CD8+ CD19-targeted CAR+ T cells administered in a defined composition. It is known that CD4+ T cells enhance CD8+ effector T cell persistence, memory formation, and trafficking to antigen-rich tissues. Activated CD8+ T cells have also shown poor survival when CD4+ T cell help is absent, and CD4+ T cell help is required during recall expansion of memory CD8+ T cells (Bos, 2010; Toes, 1999). Likewise, CAR+ CD4+ T cells enhance CAR+ CD8+ cytolytic effector T cell function both in vitro and in vivo (Adusumilli, 2014). Thus, since JCAR017 has a defined ratio of CD4+ to CD8+ CD19-targeted CAR+ T cells, persistence, trafficking to the tumor, and antitumor activity may be improved compared with CAR T cell investigational drug products without a defined composition.

Emerging data indicates that in vivo expansion of CD19-targeted CAR T cells strongly correlates with antitumor response (Gardner, 2017; Kochenderfer, 2015; Schuster, 2016). The antitumor activity of CAR T cells in NHL has been lower than that observed in ALL subjects. The effect of the tumor microenvironment or bone marrow lymphoma involvement (ie, more accessible target antigen) on CAR T cell expansion and function may be important for antitumor activity in NHL. Biopsies will be required during this study to assess disease attributes that may affect expansion and activity of JCAR017.

The dose level to be used in this study was evaluated in the Juno TRANSCEND NHL 001 (017001) study (NCT02631044) being conducted in the US. Preliminary safety, PK and efficacy analyses of JCAR017 at dose level DL2 (100 x 10^6 viable CAR+ T cells) show a well-defined safety profile with low incidence of severe CRS or neurotoxicity and a favourable risk/benefit ratio. All these supporting the justification for the planned dose to be administered in the JCAR017-BCM-001 study (Abramson, 2018).

1.3.2. Lymphodepleting Chemotherapy Rationale

Data have been published for approximately 40 subjects with NHL who were treated with 3 different CD19-targeted CAR T cell products; however, there is no consensus on the optimal LD chemotherapy regimen to use prior to CD19-targeted CAR T cell therapy.

Encouraging antitumor activity has been observed in 11 subjects with NHL who received LD chemotherapy with a combination of high doses of cyclophosphamide (60 to 120 mg/kg) and fludarabine (25 mg/m^2/day x 5 days) (Kochenderfer, 2015). However, significant cardiac toxicity, neurotoxicity, and death were reported at the highest CAR T cell dose level (5 x 10^6 CAR+ T cells/kg). When the CAR T cell dose was reduced to 1 x 10^6 CAR+ T cells/kg and a lower dose regimen of cyclophosphamide (300 mg/m^2/day x 3 days) and fludarabine (30 mg/m^2/day x 3 days) was used, the severe cardiac and neurotoxicity was eliminated, and

although transient neurotoxicity (aphasia and ataxia) was still evident, encouraging antitumor activity was observed (Kochenderfer, 2014).

Data suggest that CAR T cell expansion, persistence, and antitumor activity are not as encouraging and retreatment is not as effective in JCAR014-treated subjects who were lymphodepleted with regimens other than fludarabine and cyclophosphamide (Turtle, 2016). When a high-dose cyclophosphamide (60 mg/kg) and fludarabine (25 mg/m^2/day x 3 to 5 days) lymphodepletion regimen was used, preliminary data suggest that cell expansion and antitumor activity of JCAR014 are improved; however, similar to the data presented by Kochenderfer et al., cardiac toxicity, neurotoxicity, and death were observed with high cell doses (20 x 10^6 CAR+ T cells/kg; see the JCAR017 IB for further details). Cellular expansion was also observed in a small number of subjects after retreatment with JCAR014 after fludarabine and cyclophosphamide LD chemotherapy, whereas no appreciable expansion was observed in subjects retreated with JCAR014 after LD chemotherapy with regimens other than fludarabine and cyclophosphamide (Turtle, personal communication).

The LD chemotherapy regimen employed in the current protocol is similar in intensity to the low-dose LD regimens described above. This regimen was selected to limit toxicity and retain antitumor activity, as well as to optimize cellular expansion and antitumor activity after retreatment and with multiple-dose schedules of JCAR017 infusion. Cyclophosphamide and fludarabine given in combination are now being uniformly used as lymphodepletion regimen in CAR T cell programs and are also used as standard combination regimen on Celgene's CAR T development programs. Cyclophosphamide and fludarabine will be administered at the same dose as in TRANSCEND NHL 001 (017001) study.

1.3.3. Rationale for JCAR017 Dose Selection

Promising results have been reported for different CD19-directed CARs in the treatment of adult (Kochenderfer, 2016; Schuster, 2016; Turtle, 2016) and pediatric (Park, 2016) CD19-positive lymphatic malignancies.

The Juno Phase 1 trial (TRANSCEND NHL 001 (017001), NCT02631044) is evaluating JCAR017 at several dose levels after LD chemotherapy with cyclophosphamide (300 mg/m^2/day x 3 days) combined with fludarabine (30 mg/m^2/day x 3 days). The initial dose level selected (DL1: 50 x 10^6 CAR+ T cells) was found to be tolerable, the dose was escalated to 100 x 10^6 CAR+ T cells (DL2) and additional dosing schedules were evaluated (Abramson, 2018). Preliminary analysis of safety and efficacy of 18 subjects treated at DL2 showed good tolerability and efficacy with a single JCAR017 infusion. Based on this data, a dose of 100 x 10^6 CAR+ T cells (DL2) was selected for this Phase 2 trial.

1.3.4. Rationale for Pharmacodynamics and Potential Predictive Biomarkers

The magnitude of CAR T cell expansion and persistence is, in some cases, a predictive biomarker that may correlate with response. Upon infusion, CAR T cells can expand > 1000-fold followed by a contraction phase and a persistence phase (Davila, 2014; Kalos, 2011). The second generation of CAR T cells containing a co-stimulatory domain, CD28 or 4-1BB (CD137) with enhanced proliferative capacity and persistence over the first generation of CAR T cells, showed marked antitumor effects in B-cell malignancies (Grupp, 2013; Kalos, 2011; Kochenderfer, 2010; Porter, 2011). Additionally, the administration of high-dose steroids ablated CAR T cell

expansion and was associated with recurrence of disease after initially achieving a complete response after CAR T cell infusion (Davila, 2014). These findings suggest that monitoring CAR T cells in a quantitative, sensitive and relevant manner is advantageous and thus both molecular and cellular methods will be used. A threshold for expansion or persistence that determines response or response duration remains to be identified.

An additional factor with the potential to limit CAR T cell persistence is the development of immunogenicity. The antigen receptor expressed on CAR T cells is comprised of a chimeric protein bearing regions of CD28, CD3, and the scFv derived from a mouse sequence against human CD19. The mouse derived sequence and the junctional regions could give rise to unique epitopes eliciting an immune response to inhibit CAR T cell persistence leading to CAR T cell loss and relapse. Humoral and/or cellular responses to CAR T cells have been reported (Kershaw, 2006; Lamers, 2011; Till, 2008) where limited CAR T cell persistence coincided with the detection of humoral and anti-CAR T cell immune responses (Lamers, 2011).

As the development of an immune response to CAR T cells could diminish efficacy, immunogenicity will be monitored during the course of the trial for correlation with loss of CAR T cell persistence and clinical outcome.

Severe cytokine release syndrome and neurotoxicity are toxicities observed with CAR T cell therapy. Increases in several cytokines such as interleukin (IL)-6, IL-5, IL-10, and interferon gamma (IFN-γ) have been observed although the pattern of elevated cytokines varies among subjects (Davila, 2014). Some degree of correlation may exist between the development of CRS and efficacy. While the severity of CRS has not been shown to be predictive of response, it has been associated with disease burden (Maude, 2014). Preliminary observations show a correlation of a subset of the aforementioned cytokines as well as additional cytokines such as IL-8, IL-15 and transforming growth factor alpha (TGF-α) may predict the severity of CRS and neurotoxicity. In addition, clinical markers of inflammation, C-reactive protein (CRP) and ferritin, are at elevated levels in subjects displaying CRS (Bonifant, 2016; Davila, 2014; Turtle, 2016). To understand the pathophysiology of potential CAR T cell mediated toxicity, an extensive soluble factor panel will be conducted on a multiplex assay platform.

Based on clinical data available from ALL studies, CD19 antigen loss has been associated with relapse in subjects treated with CD19-targeted CAR T cells. Initial estimates indicate 10% to 20% CD19 epitope loss in pediatric B-ALL while no CD19 antigen loss has been reported in adults with CLL after CAR T cell treatment suggesting subject population and/or disease indication may contribute to these differences (Grupp, 2013). The molecular characterization of CD19 antigen loss in B-ALL indicate a combination of aberrations at the deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) level (Ruella, 2016; Sotillo, 2015). While reports of CD19 antigen expression are preliminary in NHL patients, correlation between CD19 antigen loss and relapse have been noted. The expression of CD19 in tumor will be monitored by IHC for potential loss of antigen and correlated with relapse.

The prolonged persistence of CAR T cells and its relevance in efficacy may stem from the generation of memory CAR T cells. Based on multi-parameter flow cytometry to characterize the expression and phenotype of CD19 CAR T cells directly obtained from treated subjects, both CD4+ and CD8+ CAR T cell subsets displayed features associated with the central memory phenotype. Expression of CCR7 and higher levels of CD27, CD28 and CD127 were detected on the CAR T cells several months post infusion suggesting that persistence and perhaps clinical

response may be attributed to this T cell subtype (Kalos, 2011). However, the lack of persistence alone may not completely address CAR T cell treatment failure. A marker associated with T cell dysfunction, programmed cell death protein 1 (PD-1), was observed at high levels approximately one month post infusion and readily detected albeit at lower levels at five months. Therefore, a phenotypic analysis of the CAR T cells for various markers of exhaustion to understand features associated with persistence and function will be conducted. In addition, immune cells with suppressive activity such as T regulatory cells that may modulate CAR T cell function will be evaluated.

Exploratory assessments using tumor tissue, such as IHC, gene expression profiling, or whole exome sequencing will be correlated with disease features and JCAR017 efficacy. Additional correlative analyses will be conducted to understand features of JCAR017 PK, and characteristics of JCAR017 cells and circulating immune cells on JCAR017 persistence and function, clinical response, duration of response and toxicity.

2. STUDY OBJECTIVES AND ENDPOINTS

Table 1: Study Objectives

Primary Objectives
The primary objectives are: Cohorts 1, 2, 3, 4, and 5 • To determine the efficacy, defined as overall response rate (ORR) of JCAR017 in subjects with aggressive B-cell non-Hodgkin lymphoma Cohort 7 • To evaluate the safety of JCAR017 treatment in subjects intended to be treated as outpatients
Secondary Objectives
The secondary objectives are: • To evaluate the safety and feasibility of administering JCAR017 (Cohorts 1, 2, 3, 4, and 5) • To determine the efficacy, defined as ORR of JCAR017 in subjects intended to be treated as outpatients (Cohort 7) • To evaluate other measures of efficacy of JCAR017 (eg, complete response rate [CRR], event-free survival [EFS], progression-free survival [PFS], overall survival [OS], duration of response [DOR]) • To characterize the pharmacokinetic (PK) profile of JCAR017 in the peripheral blood measured using qPCR detection for the JCAR017 vector sequence • To describe changes in health-related quality of life (HRQoL) using the global health/QoL, fatigue, physical and cognitive functioning subscales of the European Organisation for Research and Treatment of Cancer – Quality of Life C30 questionnaire (EORTC QLQ-C30) and the Functional Assessment of Cancer Therapy-Lymphoma "Additional concerns" subscale (FACT-LymS)

Table 1: Study Objectives (Continued)

Exploratory Objectives
The exploratory objectives are: • To characterize the PK profile of JCAR017 in the peripheral blood using flow cytometry • To evaluate pharmacodynamic markers of JCAR017, including soluble factors such as chemokines and cytokines • To evaluate clinical outcomes versus histologies, disease characteristics and subject characteristics • To evaluate the tumor and tumor microenvironment for mechanisms of response and resistance to JCAR017 • To describe the effect of treatments directed at severe cytokine release syndrome (sCRS) and neurotoxicity on duration and severity of these events • To describe JCAR017 PK and pharmacodynamic effects on JCAR017 cell persistence and on the response of JCAR017 treatment of the disease under study • To characterize the prevalence and incidence of humoral immune responses to JCAR017 • To characterize the subject experience on JCAR017 using patient interviews • To measure hospital resource utilization, including hospitalization rate • To describe changes in the other domains of HRQoL using the rest of subscales in EORTC QLQ-C30 questionnaire (ie, those not specified in the secondary objectives) • To describe changes in health utility scores and global health using the European Quality of Life-5 Dimensions health state classifier to 5 Levels (EQ-5D-5L)

Table 2: Study Endpoints

Endpoint	Name	Description	Timeframe
Primary	Non-Hodgkin lymphoma (NHL; including secondary central nervous system [CNS] involvement): Overall Response Rate (ORR) *Cohorts 1, 2, 3, and 4*	Proportion of subjects achieving a complete response (CR) or partial response (PR) based on the Lugano classification (Cheson, 2014) (see Appendix C)	Up to 2 years after JCAR017 infusion
	Relapsed/refractory (r/r) primary central nervous system lymphoma (PCNSL): ORR *Cohort 5*	Proportion of subjects achieving a complete response (CR)/complete response unconfirmed (CRu) or PR based on the International Workshop to Standardize Baseline Evaluation and Response Criteria in Primary CNS Lymphoma (Abrey, 2005)	Up to 2 years after JCAR017 infusion
	Safety in subjects intended to be treated as outpatients *Cohort 7*	Type, frequency, and severity of all adverse events (AEs), including serious adverse events (SAEs) and laboratory abnormalities	Up to 2 years after JCAR017 infusion
Secondary	Safety	Type, frequency, and severity of AEs, including SAEs and laboratory abnormalities	Up to 2 years after JCAR017 infusion
	Safety in subjects treated as outpatients	Type, frequency, and severity of AEs, including SAEs and laboratory abnormalities	Up to 2 years after JCAR017 infusion
	ORR in subjects intended to be treated as outpatients *Cohort 7*	Proportion of subjects achieving a CR or PR based on the Lugano classification (Cheson, 2014) (see Appendix C)	Up to 2 years after JCAR017 infusion
	Complete response rate (CRR)	Proportion of subjects achieving a CR (or CR and CRu for subjects with PCNSL) following JCAR017 infusion	Up to 2 years after JCAR017 infusion
	Event-free survival (EFS)	Time from JCAR017 infusion to death from any cause, progressive disease (PD), or starting a new anticancer therapy, whichever occurs first	Up to 2 years after JCAR017 infusion

Table 2: Study Endpoints (Continued)

Endpoint	Name	Description	Timeframe
Secondary	Progression-free survival (PFS)	Time from JCAR017 infusion to the first documentation of PD, or death due to any cause, whichever occurs first	Up to 2 years after JCAR017 infusion
	Overall survival (OS)	Time from JCAR017 infusion to time of death due to any cause	Up to last subject last visit
	Duration of response (DOR)	Time from first response to progressive disease or death from any cause, whichever occurs first	Up to 2 years after JCAR017 infusion
	Pharmacokinetics (PK) by qPCR	Maximum concentration (C_{max}), time to peak concentration (T_{max}), area under the curve (AUC), and persistence of JCAR017 in peripheral blood as assessed by qPCR	Up to 2 years after JCAR017 infusion
	Health Related Quality of Life (domain of interest)	HRQoL using the global health/QoL, fatigue, physical and cognitive functioning subscales of the European Organisation for Research and Treatment of Cancer – Quality of Life C30 questionnaire (EORTC QLQ-C30) and the Functional Assessment of Cancer Therapy-Lymphoma "Additional concerns" subscale (FACT-LymS)	Up to 2 years after JCAR017 infusion
Exploratory	Blood biomarker	Analyses of soluble factors, including, but not limited to, cytokines and chemokines, immune cell subsets and gene expression analyses	Up to 6 months after JCAR017 infusion
	Immunogenicity assessments	Humoral immune response (anti-therapeutic antibody [ATA]). Cell mediated immune response may also be assessed	Up to 2 years after JCAR017 infusion
	Tumor biomarker	Cellular and molecular profiling of tumor tissue to explore potential efficacy and resistance mechanisms	Up to 2 years after JCAR017 infusion

Table 2: Study Endpoints (Continued)

Endpoint	Name	Description	Timeframe
Exploratory	PK by flow cytometry	Maximum concentration (C_{max}), time to peak concentration (T_{max}), area under the curve (AUC), and persistence of JCAR017 in peripheral blood as assessed by flow cytometry	Up to 2 years after JCAR017 infusion
	Safety	Response and time to resolution for severe cytokine release syndrome (sCRS) and/or neurotoxicity to interventions	Up to 2 years after JCAR017 infusion
	Hospital resource utilization	Number of inpatient intensive care unit (ICU) days, and outpatient visits	Up to 2 years after JCAR017 infusion
	HRQoL (other)	Other domains of HRQoL (not specified as secondary endpoints) measured by the rest of subscales of EORTC QLQ-C30	Up to 2 years after JCAR017 infusion
	Health Utility	Health utility scores and overall health as measured by EQ-5D-5L	Up to 2 years after JCAR017 infusion
	Subject experience on JCAR017	Qualitative data obtained from completion of patient interviews	Up to 2 years after JCAR017 infusion

3. OVERALL STUDY DESIGN

3.1. Study Design

This study is a single-arm, multi-cohort, multi-center, Phase 2 study to determine the efficacy and safety of JCAR017 in adult subjects with aggressive B-NHL.

Subjects will be enrolled into one of 6 cohorts as listed below (see Figure 1).

- Cohort 1: Subjects with DLBCL not otherwise specified (NOS; de novo or transformed follicular lymphoma [tFL]), high-grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements with DLBCL histology (HGBL) and follicular lymphoma Grade 3B (FL3B) per World Health Organization (WHO) 2016 classification (Swerdlow, 2016), after ≥ 2 lines of therapy*, including an anthracycline and rituximab (or other CD20-targeted agent)
- Cohort 2: Transplant not eligible (TNE) subjects with DLBCL NOS (de novo or tFL), HGBL and FL3B per WHO 2016 classification (Swerdlow, 2016), who failed first line therapy*, including an anthracycline and rituximab (or other CD20-targeted agent)
  - Transplant not eligible subjects will include those who are deemed ineligible for high-dose chemotherapy and HSCT due to age, performance status or comorbidity, while also having adequate organ function for CAR T cell treatment. At the very least, subjects have to meet one of the following criteria:
    a) Age ≥ 70 years
    b) ECOG performance status ≥ 2
    c) Impaired pulmonary function (diffusion capacity of carbon monoxide [DLCO] ≤ 60%, adjusted for hemoglobin concentration using the Dinakara equation
    d) Impaired cardiac function (left ventricular ejection fraction [LVEF] < 50%)
    e) Impaired renal function (creatinine clearance [CrCl] < 60 mL/min)
    f) Impaired hepatic function (aspartate aminotransferase [AST] / alanine aminotransferase[ALT] > 2 x upper limit of normal [ULN], bilirubin ≥ 2 mg/dL or cirrhosis Child-Pugh B or C)
  - Comorbidity will be assessed using Appendix G (HCT)-specific comorbidity index (HCT-CI) score (Sorror, 2005) to better describe the population in the analysis
- Cohort 3 (Japan only): Subjects meeting eligibility criteria for either Cohort 1 or 2
- Cohort 4: Subjects with newly diagnosed HGBL. Subjects must be eligible for anthracycline and rituximab (or other CD20-targeted agent) containing regimen as induction prior to consolidation with JCAR017**
- Cohort 5: Subjects with primary central nervous system lymphoma (PCNSL), who failed first line therapy with HDCT and ASCT, or who failed to proceed to HDCT and ASCT due to failure of PBSC mobilization or insufficient response at the

completion of induction therapy with high-dose methotrexate-based polychemotherapy regimen (eg high dose methotrexate, high dose cytarabine, rituximab and thiotepa [MATRix regimen])

- Cohort 6: (REMOVED)
- Cohort 7: Subjects meeting eligibility criteria for Cohort 1 and suitable for outpatient treatment***

* For subjects with transformed disease, the subject should have had at least 2 lines of systemic therapy for his/her transformed disease (ie, DLBCL) for Cohort 1 and 1 line for Cohort 2 to be eligible. Lines of therapy do not include those given for a previously indolent condition (ie, follicular lymphoma). Subjects do NOT have to have anthracycline for their DLBCL if received for indolent disease.

** For subjects already undergoing anthracycline and rituximab containing regimen, eligibility is to be discussed with Medical Monitor. Subjects with complete metabolic response after 2 cycles of induction will proceed with JCAR017 infusion only at time of relapse, if applicable.

*** Subjects must meet the conditions for outpatient treatment and monitoring as outlined in the Outpatient Administration and Monitoring Guidance for Lisocabtagene Maraleucel.

Note: Subjects with secondary CNS lymphoma involvement may enroll in Cohorts 1 to 4 and 7; subjects with PCNSL are eligible for Cohort 5. Subject selection must consider clinical risk factors for severe adverse events (AEs) and alternative treatment options. Subjects should only be enrolled if the Investigator considers the potential benefit outweighs the risk for the subject. For Cohort 5 and to not compromise safety, subject selection has been restricted to those fit enough to be considered for HDCT and ASCT as their prior therapy.

The first 3 subjects in Europe in Cohort 1 will be treated with a minimum interval of 14 days between JCAR017 infusions and assessed for acute safety 28 days after the third subject has received JCAR017 infusion. In addition, the product characteristics of the JCAR017 cell product manufactured with processing steps in Europe will be evaluated. If criteria for safety and feasibility are met, Cohort 1 will continue enrollment without gating and additional Cohorts 2, 4, 5 and 7 may be opened at Celgene's discretion. A minimum of 14 days treatment interval will also apply to all subjects treated in Cohort 5.

The first 10 subjects treated with JCAR017 in Europe must be hospitalized for a minimum of 14 days after JCAR017 infusion, unless otherwise recommended by a local authority. Experience to date with JCAR017 from the Juno TRANSCEND NHL 001 (017001) study suggests that outpatient administration of JCAR017 can be provided safely without compromising the subject's safety when appropriate education is provided and hospital admission is done upon symptoms of toxicity. Outpatient infusion of JCAR017 was associated with a 68% decrease in hospital length of stay (Palomba, 2018). Selected countries/sites will participate in the dedicated outpatient cohort. In order to enroll subjects in Cohort 7, sites must have treated at least 3 DLBCL subjects with CD19-targeted CAR T cell therapy, and must have a suitable infrastructure to allow for outpatient treatment and monitoring as outlined in the Outpatient Administration and Monitoring Guidance for Lisocabtagene Maraleucel.

Safety data will be reviewed on an ongoing basis. An early safety assessment will be performed 28 days after JCAR017 is administered to the 10th subject treated in Europe. Enrollment will be halted if the observed mortality rate is > 30%, irrespective of causality, or if > 50% of subjects who undergo leukapheresis fail to have a satisfactory cell product available for infusion.

In addition, an early safety assessment will be performed 28 days after JCAR017 is administered to the 10th subject treated in Cohort 2. Enrollment into Cohort 2 will be halted if the observed mortality rate within 28 days post infusion is > 30% (excluding death related to disease progression or relapse).

The first 3 subjects in Japan will be treated with a minimum interval of 14 days between JCAR017 infusions and assessed for acute safety 28 days after the third subject has received JCAR017 infusion. In addition, the first 10 subjects treated with JCAR017 in Japan will be hospitalized for a minimum of 14 days after JCAR017 infusion. The acute and subacute toxicity profile of JCAR017 cell product manufactured entirely at the current manufacturing site in the US has already been established in subjects with r/r B-NHL with good tolerability observed in subjects with DLBCL (Abramson, 2018).

In addition, a staggered dosing approach will also be utilized for all new sites (Europe and Japan) without prior experience of administering CAR T cell therapies as follows:

- 1st subject infusion, wait 14 days
- 2nd subject infusion, wait 14 days

Following completion of this site-staggered enrollment approach, the site may proceed with subject enrollment as communicated by Celgene. Calls will be scheduled at least monthly with all sites and their respective Investigators aiming to review and share all safety related events.

Prior to initiation of any study procedure (screening period), subjects must provide informed consent. Once enrolled and during the pretreatment period (see Figure 2), subjects will undergo leukapheresis to enable JCAR017 cell product generation. Upon successful JCAR017 cell product generation, subjects will enter the treatment period and receive LD chemotherapy followed by infusion of JCAR017, 2 to 7 days after completion of LD chemotherapy. JCAR017 will be administered at a dose of 100 x 10^6 JCAR017-positive transfected viable T cells (CAR+ T cells).

After treatment with JCAR017, subjects will enter the post-treatment period. A first response assessment will be performed 28 days after JCAR017 infusion. Subjects will be followed for 2 years after their JCAR017 infusion for safety, disease status, survival and health-related quality of life and utility values measured using European Organisation for Research and Treatment of Cancer – Quality of Life C30 questionnaire (EORTC QLQ-C30) and the European Quality of Life-5 Dimensions health state classifier to 5 Levels (EQ-5D-5L) and the Functional Assessment of Cancer Therapy-Lymphoma “Additional concerns” subscale (FACT-LymS).

In addition, when feasible, all subjects will be invited to participate in interviews during their participation in the study to document their experience with JCAR017.

Delayed adverse events following exposure to gene-modified T cells will be assessed and long-term persistence of these modified T cells, including vector integration sites as well as the generation of replication competent retrovirus will continue to be monitored under a separate

Long-term follow-up (LTFU) protocol for up to 15 years after JCAR017 infusion as per competent authority guidelines.

The decision to discontinue a subject from the study is the responsibility of the Investigator or designee. Celgene will not delay or refuse this decision. However, prior to discontinuing a subject, the Investigator should contact the Medical Monitor and forward appropriate supporting documents for review and discussion.

The study will be conducted in compliance with the International Council for Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use/Good Clinical Practice (GCP) and applicable regulatory requirements.

3.2. Stopping Rules

Adverse events and serious adverse events (SAEs) are expected to occur frequently in this study based on the subject population being accrued and on the nature of the advanced hematologic malignancy under study. Regular systematic review of SAEs will serve as the basis for pausing or prematurely stopping the study. Unexpected SAEs that are related to JCAR017 will be the primary criteria for pausing or stopping the study for all study cohorts except Cohort 7. Review of these SAEs, and any decision to pause enrollment or terminate the study, will be determined by the Data Safety Monitoring Board (DSMB) and Celgene. Decisions to pause enrollment or terminate a given cohort or the study will be communicated promptly to Investigators, to the Institutional Review Boards (IRBs)/Ethics Committees (ECs), Institutional Biosafety Committees (IBCs) (if applicable), and to the appropriate regulatory authorities.

3.2.1. Criteria for Pausing or Stopping the Study

A study cohort may be suspended or terminated for the following reasons:

- Any subject develops uncontrolled JCAR017 proliferation that is unresponsive to treatment
- Any subject develops detectable replication-competent lentivirus during the study
- Celgene, IRB/EC, or DSMB decides that subject safety may be compromised by continuing the study
- Celgene decides to discontinue/limit the development of JCAR017 in the indications under evaluation

3.2.2. Criteria for Pausing or Stopping Cohort 7

Safety monitoring boundaries based on Bayesian framework (Thall, 1994) have been included to help detect signals that may occur in Cohort 7. Safety monitoring boundaries are reported on Table 3. If the safety boundaries are crossed, Cohort 7 enrollment will be paused and ad hoc DSMB meetings will be held to review the data. Cohort 7 will remain paused for enrollment pending the DSMB recommendations.

Events occurring within 30 days of a JCAR017 cell product infusion defined for the safety boundaries are as follows:

- A Grade 3 or above, JCAR017-related, treatment-emergent neurological toxicity

- Prolonged Grade 4 and Grade 5 individual safety events
  - Life-threatening (Grade 4) toxicity attributable to JCAR017 that is unexpected, unmanageable (ie, does not resolve to Grade 3 or lower within 7 days), and unrelated to chemotherapy
  - Death related to JCAR017 therapy

Table 3: Safety Monitoring Boundaries for Cohort 7 Based on Thall and Simon (Thall, 1994)

Number of Subjects Treated in Cohort 7	Incidence
1-5	No Stopping
6-7	≥ 5
8-9	≥ 6
10-11	≥ 7
12-13	≥ 8
14-15	≥ 9
16-17	≥ 10
18-19	≥ 11
20-21	≥ 12
22-23	≥ 13
24-26	≥ 14

Note: No stopping boundaries for less than 6 subjects in Cohort 7. The enrollment will be paused if the boundaries are crossed, eg, out of 10 subjects treated in Cohort 7, at least 7 subjects experience specified toxicity events.

3.3. Study Duration for Subjects

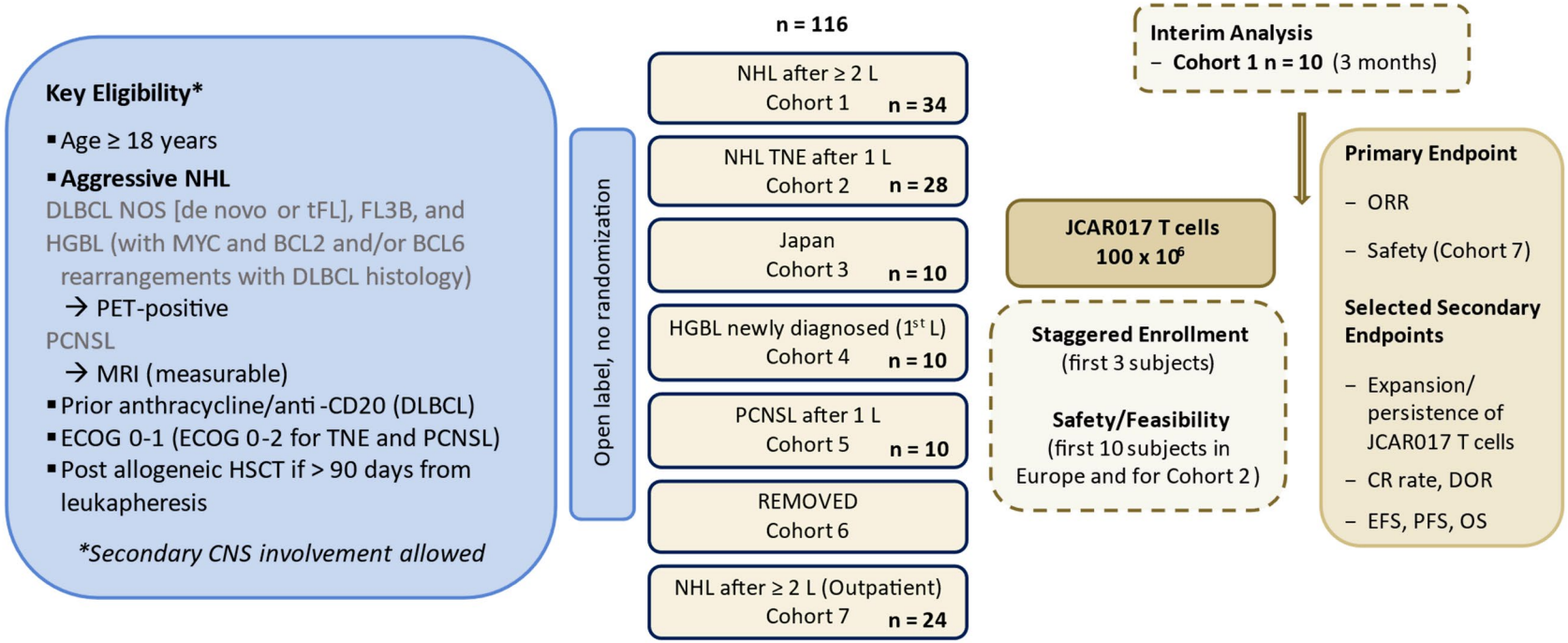
This study will enroll over approximately 40 months and will consist of 3 periods:

- The pretreatment period will consist of screening for eligibility, leukapheresis and a pretreatment evaluation (prior to LD chemotherapy)
- The treatment period will start with LD chemotherapy, followed by JCAR017 infusion 2 to 7 days after completion of LD chemotherapy. A first response evaluation will be performed at approximately 28 days after JCAR017 infusion.
- The post-treatment period will consist of further efficacy and safety follow-up visits at approximately 2, 3, (at 4 months for Cohort 5), 6, 9, 12, 18 and 24 months after JCAR017 infusion

3.4. End of Trial

The End of Trial is defined as either the date of the last visit of the last subject completing the post-treatment follow-up of this study or the date when the last subject enters the LTFU study, or the date of receipt of the last data point from the last subject that is required for primary, secondary and/or exploratory analysis, as pre-specified in the protocol, whichever is the later date.

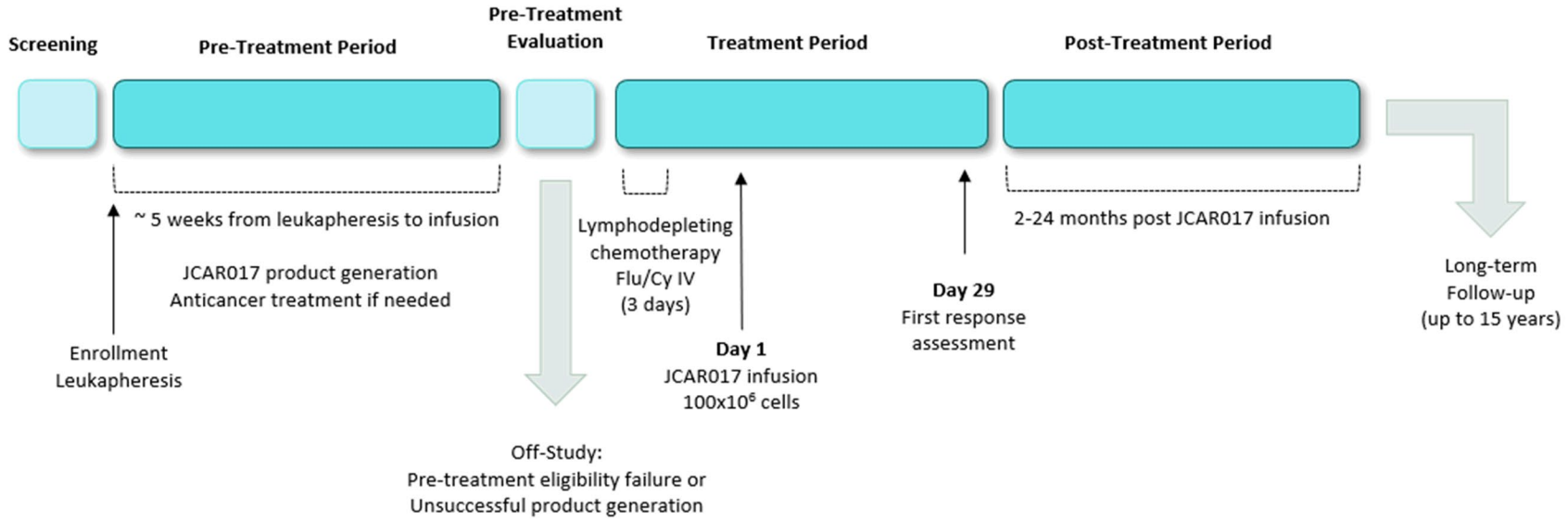
Figure 1: Overall Study Design



1

Abbreviations: CNS = central nervous system; CR = complete response; DLBCL = diffuse large B-cell lymphoma; DOR = duration of response; ECOG = Eastern Cooperative Oncology Group; EFS = event-free survival; FL3B = follicular lymphoma Grade 3B; HGBL = High-grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements with DLBCL histology; HSCT = hematopoietic stem cell transplantation; L = line(s) of therapy; max= maximum; MRI = magnetic resonance imaging; NHL = non-Hodgkin lymphoma; NOS = not otherwise specified; ORR = overall response rate; OS = overall survival; PCNSL = primary central nervous system lymphoma; PET = positron emission tomography; PFS = progression-free survival; tFL = transformed follicular lymphoma; TNE = transplant not eligible.

Figure 2: Study Schematic



Abbreviations: Flu/Cy = fludarabine/cyclophosphamide; IV = intravenous.

4. STUDY POPULATION

4.1. Number of Subjects

This study will enroll approximately 116 adult subjects in Europe and Japan.

4.2. Inclusion Criteria

Subjects must satisfy the following criteria to be enrolled in the study:

1. Subject is ≥ 18 years of age at the time of signing the informed consent form (ICF)
2. Subject must understand and voluntarily sign an ICF prior to any study-related assessments/procedures being conducted
3. Subject is willing and able to adhere to the study visit schedule and other protocol requirements
4. Investigator considers the subject is appropriate for adoptive T cell therapy
5. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Subjects not eligible for transplant (TNE) in Cohorts 2 and 3 and subjects in Cohort 5 may be enrolled with ECOG of 2 only if they meet all other inclusion/exclusion criteria.
6. Subjects with one of the following:
   - Cohort 1: Subjects with DLBCL NOS (de novo or tFL), HGBL and FL3B per WHO 2016 classification (Swerdlow, 2016), after ≥ 2 lines of therapy*, including an anthracycline and rituximab (or other CD20-targeted agent)
   - Cohort 2: Transplant not eligible subjects with DLBCL NOS (de novo or tFL), HGBL and FL3B per WHO 2016 classification (Swerdlow, 2016), who failed first line therapy*, including an anthracycline and rituximab (or other CD20-targeted agent)
     - Transplant not eligible subjects will include those who are deemed ineligible for high-dose chemotherapy and HSCT due to age, performance status or comorbidity, while also having adequate organ function for CAR T cell treatment. At the very least, subjects have to meet one of the following criteria:
       a) Age ≥ 70 years
       b) ECOG performance status ≥ 2
       c) Impaired pulmonary function (DLCO ≤ 60%, adjusted for hemoglobin concentration using the Dinakara equation)
       d) Impaired cardiac function (LVEF < 50%)
       e) Impaired renal function (CrCl < 60 mL/min)
       f) Impaired hepatic function (AST/ALT > 2 x ULN, bilirubin ≥ 2 mg/dL or cirrhosis Child-Pugh B or C)
     - Subjects must fulfill all other inclusion and exclusion criteria

- Cohort 3 (Japan only): Subjects meeting eligibility criteria for either Cohort 1 or 2
- Cohort 4: Subjects with newly diagnosed HGBL. Subjects must be eligible for anthracycline and rituximab (or other CD20-targeted agent) containing regimen as induction prior to consolidation with JCAR017**
- Cohort 5: Subjects with PCNSL who failed first line therapy with HDCT and ASCT, or who failed to proceed to HDCT and ASCT due to failure of PBSC mobilization or insufficient response at the completion of induction therapy with high-dose methotrexate-based polychemotherapy regimen (eg, high dose methotrexate, high dose cytarabine, rituximab and thiotepa [MATRix regimen])
- Cohort 6: (REMOVED)
- Cohort 7: Subjects meeting eligibility criteria for Cohort 1 and suitable for outpatient treatment***

* For subjects with transformed disease, the subject should have had at least 2 lines of systemic therapy for his/her transformed disease (ie, DLBCL) for Cohort 1 and 1 line for Cohort 2 to be eligible. Lines of therapy do not include those given for a previously indolent condition (ie, follicular lymphoma). Subjects do NOT have to have anthracycline for their DLBCL if received for indolent disease.

** For subjects already undergoing anthracycline and rituximab containing regimen, eligibility is to be discussed with Medical Monitor. Subjects with complete metabolic response after 2 cycles of induction will proceed with JCAR017 infusion only at time of relapse, if applicable.

*** Subjects must meet the conditions for outpatient treatment and monitoring as outlined in the Outpatient Administration and Monitoring Guidance for Lisocabtagene Maraleucel.

Note: Subjects with secondary CNS lymphoma involvement may enroll in Cohorts 1 to 4 and 7; subjects with PCNSL are eligible for Cohort 5. Subject selection must consider clinical risk factors for severe adverse events (AEs) and alternative treatment options. Subjects should only be enrolled if the Investigator considers the potential benefit outweighs the risk for the subject. For Cohort 5 and to not compromise safety, subject selection has been restricted to those fit enough to be considered for HDCT and ASCT as their prior therapy.

7. Histological confirmation of diagnosis at last relapse. Enough tumor material must be available for central confirmation of diagnosis, otherwise a new tumor biopsy is mandated.

   Note: If the subject did not experience CR since last biopsy, the most recent biopsy will be considered adequate to participate in the trial. For subjects with PCNSL, at a minimum, corresponding pathology report is required if archival tumor material is not available and repeated biopsy not feasible.

8. **For subjects with NHL (except Cohort 5):** Subjects must have positron emission tomography (PET)-positive disease as per Lugano Classification (Cheson, 2014)

9. **For subjects with PCNSL:** Subjects must have disease that is objectively measurable by International Workshop to Standardize Baseline Evaluation and Response Criteria in Primary Central Nervous System Lymphoma (Abrey, 2005). Cerebrospinal fluid (CSF) cytology will be repeated to monitor leptomeningeal disease.
10. Adequate organ function, defined as:
    - Adequate bone marrow function to receive LD chemotherapy as assessed by the Investigator
    - Serum creatinine < 1.5 x ULN or creatinine clearance > 30 mL/min (estimated glomerular filtration rate [eGFR] by Cockroft-Gault)
    - Alanine aminotransferase (ALT) ≤ 5 x ULN and total bilirubin < 2.0 mg/dL (or < 3.0 mg/dL for subjects with Gilbert's syndrome or lymphomatous infiltration of the liver)
    - Adequate pulmonary function, defined as ≤ Grade 1 dyspnea according to Common Terminology Criteria for Adverse Events (CTCAE) and oxygen saturation (SaO_2) ≥ 92% on room air
    - Adequate cardiac function, defined as LVEF ≥ 40% as assessed by echocardiogram or multigated acquisition (MUGA) scan performed within 4 weeks prior to leukapheresis
11. Adequate vascular access for leukapheresis procedure
12. Subjects must agree to not donate blood, organs, sperm or semen, and egg cells for usage in other individuals after the JCAR017 infusion
13. Female subjects of childbearing potential (FCBP) must:
    a. Have two negative pregnancy tests as verified by the Investigator (one negative serum beta human chorionic gonadotropin [ß-hCG] pregnancy test result at screening and one negative serum pregnancy test within 48 hours prior to the first dose of LD chemotherapy). This applies even if the subject practices true abstinence* from heterosexual contact
    b. Either commit to true abstinence* from heterosexual contact (which must be reviewed on a monthly basis and source documented) or agree to use, and be able to comply with, effective contraception without interruption. Contraception methods must include 1 highly effective (barrier) method of contraception from screening until at least 12 months following LD chemotherapy

       Note: Highly effective methods are defined as those that result in a low failure rate (ie, less than 1% per year) when used consistently and correctly. The following are examples of contraception:

       Highly effective methods:

       – Intrauterine device (IUD)
       – Hormonal (birth control pill, injections, implants)
       – Tubal ligation

- Partner's vasectomy

c. Agree to abstain from breastfeeding during study participation and for at least 12 months following LD chemotherapy
d. There is insufficient exposure data to provide any recommendation concerning the duration of contraception and the abstaining from breastfeeding following treatment with JCAR017. Any decision regarding contraception and breastfeeding after JCAR017 infusion should be discussed with the treating physician

14. Male subjects must:

a. Practice true abstinence* (which must be reviewed on a monthly basis and source documented) or agree to use a condom during sexual contact with a pregnant female or a female of childbearing potential while participating in the study and until at least 12 months following LD chemotherapy even if he has undergone a successful vasectomy
b. There is insufficient exposure data to provide any recommendation concerning the duration of contraception following treatment with JCAR017. Any decision regarding contraception after JCAR017 infusion should be discussed with the treating physician.

* True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. In contrast, periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

4.3. Exclusion Criteria

The presence of any of the following will exclude a subject from enrollment:

1. Subject has any significant medical condition, laboratory abnormality, or psychiatric illness that would prevent the subject from participating in the study
2. Subject has any condition including the presence of laboratory abnormalities, which would place the subject at unacceptable risk if participating in the study
3. Subject has any condition that confounds the ability to interpret data from the study
4. Subjects with T cell rich/histiocyte rich large B-cell lymphoma (THRBCL), primary cutaneous large B-cell lymphoma, primary mediastinal B-cell lymphoma (PMBCL), Epstein-Barr virus (EBV) positive DLBCL of the elderly, Burkitt lymphoma, and intraocular lymphoma
5. Subjects with prior history of malignancies, other than aggressive r/r NHL, unless the subject has been in remission for ≥ 2 years with the exception of the following non-invasive malignancies:

- Basal cell carcinoma of the skin
- Squamous cell carcinoma of the skin
- Carcinoma in situ of the cervix
- Carcinoma in situ of the breast

- Incidental histologic finding of prostate cancer (T1a or T1b using the TNM [tumor, nodes, metastasis] clinical staging system) or prostate cancer that is curative
- Other completely resected stage 1 solid tumor with low risk for recurrence

6. Treatment with any prior gene therapy product
7. Subjects who have received previous CD19-targeted therapy
8. Human immunodeficiency virus (HIV) infection, hepatitis B, or hepatitis C:
   - Subjects with a history of or active HIV are excluded
   - Subjects with active hepatitis B, or active hepatitis C are excluded
     – Subjects with a negative polymerase chain reaction (PCR) assay for viral load for hepatitis B or C are permitted. Subjects positive for hepatitis B surface antigen and/or anti-hepatitis B core antibody with negative viral load are eligible and should be considered for prophylactic antiviral therapy
9. Subjects with uncontrolled systemic fungal, bacterial, viral or other infection (including tuberculosis) despite appropriate antibiotics or other treatment at the time of leukapheresis or JCAR017 infusion
10. Presence of acute or chronic graft-versus-host disease (GVHD)
11. Active autoimmune disease requiring immunosuppressive therapy
12. History of any one of the following cardiovascular conditions within the past 6 months:
    - Heart failure class III or IV as defined by the New York Heart Association (NYHA)
    - Cardiac angioplasty or stenting
    - Myocardial infarction
    - Unstable angina
    - Other clinically significant cardiac disease
13. History or presence of clinically relevant CNS pathology not related to disease under study such as epilepsy, seizure, aphasia, stroke, cerebral edema, severe brain injuries, dementia, Parkinson's disease, cerebellar disease, organic brain syndrome, or psychosis
14. Pregnant or nursing women
15. Treatment with alemtuzumab within 6 months of leukapheresis, or treatment with fludarabine or cladribine within 3 months of leukapheresis
16. Use of the following (see Section 8.2 for full details):
    - Therapeutic doses of corticosteroids (defined as > 20 mg/day prednisone or equivalent) within 7 days prior to leukapheresis or 72 hours prior to JCAR017 infusion. Physiologic replacement, topical, and inhaled steroids are permitted.
    - Low-dose chemotherapy (eg, vincristine, rituximab, cyclophosphamide ≤ 300 mg/m^2) given after leukapheresis to maintain disease control must be stopped ≥ 7 days prior to LD chemotherapy

- Cytotoxic chemotherapeutic agents that are not considered lymphotoxic within 1 week prior to leukapheresis. Oral anticancer agents, including lenalidomide and ibrutinib, are allowed if at least 3 half-lives have elapsed prior to leukapheresis
- Lymphotoxic chemotherapeutic agents (eg, cyclophosphamide > 300 mg/m^2, ifosfamide, bendamustine) within 2 weeks prior to leukapheresis
- Experimental agents within 4 weeks prior to leukapheresis unless no response or progressive disease (PD) is documented on the experimental therapy and at least 3 half-lives have elapsed prior to leukapheresis
- Immunosuppressive therapies within 4 weeks prior to leukapheresis and JCAR017 infusion (eg, calcineurin inhibitors, methotrexate or other chemotherapeutics, mycophenolate, rapamycin, thalidomide, immunosuppressive antibodies such as anti-tumor necrosis factor [TNF], anti-IL-6, or anti-IL-6R)
- Donor lymphocyte infusions (DLI) within 6 weeks prior to JCAR017 infusion
- Radiation within 6 weeks prior to leukapheresis. Subjects must have progressive disease in irradiated lesions or have additional non-irradiated, PET-positive lesions to be eligible. Radiation to a single lesion, if additional non-irradiated, measurable PET-positive lesions are present, is allowed up to 2 weeks prior to leukapheresis. Prior WBRT for subjects enrolled in Cohort 5 is not allowed
- Allogeneic HSCT within 90 days prior to leukapheresis
- Prior hematopoietic stem cell transplant (only applicable to Cohort 2)
- Systemic immunostimulatory agents (including but not limited to interferon and IL-2) within 6 weeks or 5 half-lives of the drug, whichever is shorter, prior to JCAR017 infusion

17. Progressive vascular tumor invasion, thrombosis, or embolism
18. Venous thrombosis or embolism not managed on a stable regimen of anticoagulation
19. Known severe hypersensitivity to DMSO or Dextran

5. TABLE OF EVENTS

Table 4: Table of Events

	Pretreatment Period			Treatment Period										Post-Treatment Period							Survival Follow-up
	Screening	Leukapheresis	Pre-Treatment Evaluation	LD Chemotherapy	JCAR017 Infusion	Follow-Up															
Study Day	Up to 14 days before leukapheresis[dd]	Approximately 35 days before Day 1	Within 7 days before LD chemotherapy	Start 5 to 10 days before Day 1[ee]	1	2	3	4	8	11	15	22	29	60	90/ 120[jj]	180	270	365	545	730 (EOS) or ET	q3m
Visit Window (Days)	-	-	-	-	-	-	-	+1	±1	±1	±2	±2	±2	+14	+14	+35	+35	+35	+35	+35	±30
STUDY PROCEDURES																					
Informed consent	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Eligibility criteria	x	-	x[y]	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Medical history	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
ECOG	x	x	x	x	x	-	-	-	x	-	x	x	x	x	x[a, jj]	x[a]	x[a]	x[a]	x[a]	x[a]	-
HCT-CI[x]	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Frailty index score[x]	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Pulmonary function test (DLCO and FEV_1)[x]	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Height	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Weight	x	-	x	-	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Physical examination[b]	x[aa]	-	x[aa]	-	x	x	x	x	x	x	x	x	x	x[a]	x[a, jj]	x[a]	x[a]	x	-	x	-
Routine neurologic examination	x	-	x	-	x	-	-	x	x	x	x	x	x	x[ii]	x[jj]	x[a, ii]	x[a, ii]	x[a, ii]	x[a, ii]	x[a, ii]	-
Ophthalmologic examination[ii, kk]	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Table 4: Table of Events (Continued)

	Pretreatment Period			Treatment Period										Post-Treatment Period							Survival Follow-up
	Screening	Leukapheresis	Pre-Treatment Evaluation	LD Chemotherapy	JCAR017 Infusion	Follow-Up															
Study Day	Up to 14 days before leukapheresis[dd]	Approximately 35 days before Day 1	Within 7 days before LD chemotherapy	Start 5 to 10 days before Day 1[ee]	1	2	3	4	8	11	15	22	29	60	90/ 120[ii]	180	270	365	545	730 (EOS) or ET	q3m
Visit Window (Days)	-	-	-	-	-	-	-	+1	±1	±1	±2	±2	±2	+14	+14	+35	+35	+35	+35	+35	±30
IPI	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
MMSE[hh]	-	-	x	-	x	-	-	x	x	-	x	-	x	-	x[ii]	-	-	-	-	-	-
Vital signs[d]	x	x[e]	x	x	x[f]	x	x	x	x	x	x	x	x	-	-	-	-	-	-	-	-
12-lead ECG	x	-	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
MUGA scan/ECHO	x[z]	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Viral serology	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Serum pregnancy	x	-	x[g]	-	-	-	-	-	-	-	-	-	-	-	x[ii]	x	x	x	-	-	-
HLA typing and donor chimerism[h]	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Urinalysis	x	-	-	-	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Leukapheresis	-	x[i]	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
LD chemotherapy	-	-	-	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
JCAR017 infusion[gg]	-	-	-	-	x[j]	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Table 4: Table of Events (Continued)

	Pretreatment Period			Treatment Period										Post-Treatment Period							Survival Follow-up
	Screening	Leukapheresis	Pre-Treatment Evaluation	LD Chemotherapy	JCAR017 Infusion									Follow-Up							
Study Day	Up to 14 days before leukapheresis[dd]	Approximately 5 weeks before Day 1	Within 7 days before LD chemotherapy	Start 5 to 10 days before Day 1 [ee]	1	2	3	4	8	11	15	22	29	60	90/ 120[jj]	180	270	365	545	730 (EOS) or ET	q3m
Visit Window (Days)	-	-	-	-	-	-	-	+1	±1	±1	±2	±2	±2	+14	+14	+35	+35	+35	+35	+35	±30
Adverse events and concomitant medications[b]	AEs related to protocol-mandated procedures and associated concomitant medications			All AEs and associated concomitant medications[cc]												AEs related to JCAR017 and/or LD chemotherapy and associated concomitant medications						-
CT/MRI	x	-	x[k, l]	-	-	-	-	-	-	-	-	-	x[m]	x[ii]	x[a, jj]	x[a]	x[a]	x[a]	x[a]	x[a]	-
Brain MRI[ll]	x	-	x[k, l]	-	-	-	-	-	-	-	-	-	x[c]	x[ii]	x[a, c, jj]	x[a, c]	x[a, c]	x[a, c]	x[a, c]	x[a, c]	-
CSF assessment[c]	x	-	x	-	-	-	-	-	-	-	-	-	x	x[a, o, ii]	x[a, o, jj]	x[a, o]	x[a, o]	x[a, o]	x[a, o]	x[a, o]	-
PET	x[n]	-	x[k, l]	-	-	-	-	-	-	-	-	-	x[m]	x[ii, p]	x[p, jj]	x[p]	x[p]	x[p]	x[p]	x[p]	-
Tumor biopsy	x[q, z]	-	-	-	-	-	-	-	-	-	x	-	-	At progression							-
BMA/BMB	x	-	-	-	-	-	-	-	-	-	-	-	-	At time of CR in subjects with previous bone marrow involvement							-
Hematology	x	x	x	x	x	-	-	x	x	x	x	x	x	x	x[jj]	x	x	x	x	x	-
Coagulation	-	-	x	-	x	-	-	x	x	x	x	x	x	-	-	-	-	-	-	-	-
Chemistry	x	x	x	x	x	-	-	x	x	x	x	x	x	-	-	-	-	-	-	-	-
Creatinine clearance	x	-	-	x[s]	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Inflammatory markers	-	-	x	-	x	-	-	x	x	x	x	x[t]	x[t]	-	-	-	-	-	-	-	-
Immunoglobulins	-	-	x	-	-	-	-	-	-	-	x	x	x	x[u]	x[u]	x[u]	x[u]	x[u]	x[u]	x[u]	-

Table 4: Table of Events (Continued)

	Pretreatment Period			Treatment Period										Post-Treatment Period							Survival Follow-up
	Screening	Leukapheresis	Pre-Treatment Evaluation	LD Chemotherapy	JCAR017 Infusion									Follow-Up							
Study Day	Up to 14 days before leukapheresis[dd]	Approximately 5 weeks before Day 1	Within 7 days before LD chemotherapy	Start 5 to 10 days before Day 1 [ee]	1	2	3	4	8	11	15	22	29	60	90/120[ii]	180	270	365	545	730 (EOS) or ET	q3m
Visit Window (Days)	-	-	-	-	-	-	-	+1	±1	±1	±2	±2	±2	+14	+14	+35	+35	+35	+35	+35	±30
EORTC QLQ-C30	x	-	x	-	x	-	-	-	-	-	-	-	x	x	x	x	x	x	x	x	-
EQ-5D-5L	x	-	x	-	x	-	-	-	-	-	-	-	x	x	x	x	x	x	x	x	-
FACT-LymS	x	-	x	-	x	-	-	-	-	-	-	-	x	x	x	x	x	x	x	x	-
Hospital resource utilization	-	-	-	at all time																	-
Survival status	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	x
RESEARCH SAMPLES																					
Peripheral blood sample for soluble factors[ff] (plasma)	x	-	x	-	x[v]	-	-	x	x	x	x	x	x	-	-	-	-	-	-	-	-
Peripheral blood sample for immunogenicity (serum)	x	-	-	-	-	-	-	-	-	-	x	-	x	x	x	x	x	x	x	x	-
Peripheral blood sample for immunogenicity (PBMC)	x	-	-	-	-	-	-	-	-	-	x	-	x	x	-	-	-	-	-	-	-
Peripheral blood sample for PK by flow cytometry[bb]	x	-	-	-	x[v]	-	-	x	x	x	x	x	x	x	x[ii]	x	x	x	x	x	-
Peripheral blood sample for viral vector sequence PK by qPCR[w]	x	-	-	-	x[v]	-	-	x	x	x	x	x	x	x	x[ii]	x	x	x	x	x	-

Table 4: Table of Events (Continued)

	Pretreatment Period			Treatment Period										Post-Treatment Period							Survival Follow-up
	Screening	Leukapheresis	Pre-Treatment Evaluation	LD Chemotherapy	JCAR017 Infusion	Follow-Up															
Study Day	Up to 14 days before leukapheresis[dd]	Approximately 5 weeks before Day 1	Within 7 days before LD chemotherapy	Start 5 to 10 days before Day 1 [ee]	1	2	3	4	8	11	15	22	29	60	90/ 120[jj]	180	270	365	545	730 (EOS) or ET	q3m
Visit Window (Days)	-	-	-	-	-	-	-	+1	±1	±1	±2	±2	±2	+14	+14	+35	+35	+35	+35	+35	±30
Peripheral blood sample for biomarkers (PBMC)	x	-		-	-	-	-	-	-	-	x	-	x	x	-	x	-	-	-	-	-
Peripheral blood sample for biomarkers (Immunophenotyping)	x	x	-	-	-	-	-	-	x	-	x	x	x	x	-	x	-	-	-	-	-
Peripheral blood sample for RCL testing	-	x	-	-	-	-	-	-	-	-	-	-	-	-	x	x	-	x	-	x	-

Abbreviations: AE = adverse event; BMA = bone marrow aspirate; BMB = bone marrow biopsy; CNS = central nervous system; CR = complete response CRF = case report form; CSF = cerebrospinal fluid; CT = computed tomography; DLCO = diffusion capacity of carbon monoxide; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer – Quality of Life C30 questionnaire; EOS = end of study; EQ-5D-5L = European Quality of Life-5 Dimensions health state classifier to 5 Levels; ET = early termination; FACT-LymS = Functional Assessment of Cancer Treatment-Lymphoma "Additional concerns" subscale; FEV_1 = forced expiratory volume in one second; GVHD = graft-versus-host disease; HCT = hematopoietic cell transplantation; HCT-CI = HCT-specific comorbidity index; HLA = human leukocyte antigen; HSCT = hematopoietic stem cell transplantation; ICF = informed consent form; IPI = International Prognostic Index; IV = intravenous; LD = lymphodepleting; MMSE = Mini Mental State Examination; MRI = magnetic resonance imaging; MUGA = multigated acquisition; PBMC = peripheral blood mononuclear cell; PCNSL = primary central nervous system lymphoma; PCR = polymerase chain reaction; PD = progressive disease; PET = positron emission tomography; PK = pharmacokinetic; q3m = every 3 months; qPCR = quantitative polymerase chain reaction; RCL = replication-competent lentivirus; TNE = transplant not eligible.

[a] Not required after PD/relapse or subsequent anticancer treatment.

[b] Please refer to Section 6.3 for the assessments that will be performed in subjects who have received subsequent anticancer treatment.

[c] For Cohort 1, 2, 3, 4, and 7: Required at screening for subjects with suspected or confirmed CNS involvement. Subsequent assessments are only required for subjects with confirmed CNS involvement. For Cohort 5: Required at screening and at time of pre-treatment evaluation unless medically contraindicated. For subjects without CSF involvement, repeated evaluation is not required in absence of interval symptoms suggestive of leptomeningeal dissemination.

[d] Subjects who require hospitalization should have vital signs assessed daily. Minimum and maximum values within a 24-hour period should be recorded on the appropriate CRF.

[e] Vital signs should be taken before and after leukapheresis.

[f] Measured within 15 minutes prior to the first JCAR017 administration and approximately every 15 minutes thereafter for the first hour, and hourly for the next 2 hours. If the subject's vital signs are not stable 4 hours following the final IV administration, vital signs should be monitored as clinically indicated until stable.

[g] Within 48 hours prior to starting LD chemotherapy.

[h] Data from local testing will be collected for those subjects with prior allogeneic HSCT.
[i] Should be scheduled as soon as possible after meeting eligibility criteria.
[j] 2 to 7 days after completion of LD chemotherapy.
[k] For subjects who receive anticancer treatment for disease control while JCAR017 is being manufactured, restaging must be performed after completion of the intervening anticancer treatment and as close as possible to the start of lymphodepleting chemotherapy (recommended within 7 to 14 days prior to start). For Cohort 4, restaging is mandatory after 2 cycles of induction to check for complete metabolic response.
[l] Recommended within 14 days prior to start of LD chemotherapy. Not required if intervening anticancer treatment was not given and if scans were done at the study site for screening or within 6 weeks prior to the start of LD chemotherapy.
[m] Once between Days 29 to 35. Not required for subjects in Cohort 5 without systemic involvement at screening.
[n] PET scan to confirm the presence of PET-positive lymphoma or, for Cohort 5, to assess potential systemic involvement in subjects with PCNSL. PET scan may be performed more than 30 days prior to screening if no intervening anticancer treatments have been performed or if the Investigator confirms continued disease presence
[o] CSF assessment not required for subjects in CR unless suspicion for CNS relapse.
[p] Not required for subjects in Cohort 5 without systemic involvement at screening, subjects in CR, subjects who have progressed, or after institution of additional anticancer treatment. A PET scan should be performed to verify PD.
[q] Collection of tissue from latest archived tumor biopsy (block or slides) for tumor evaluation. If archival sample is before most recent relapse, a new tumor biopsy is mandated to confirm diagnosis. Note: If the subject did not experience CR since last biopsy, the most recent biopsy will be considered adequate to participate in the trial. For subjects with PCNSL, at a minimum, corresponding pathology report is required if archival tumor material is not available and repeated biopsy not feasible.
[r] For subjects with accessible disease.
[s] First day of LD chemotherapy only.
[t] If clinically indicated.
[u] Not required for subjects with documented B-cell recovery without recent use of intravenous immunoglobulin.
[v] Pre-infusion.
[w] At any time point ≥ 12 months after JCAR017 infusion, if persistence vector sequence is detected in ≥ 1% of cells, the pattern for vector integration sites will be analyzed. If integration pattern suggests a predominant integration site, a repeat analysis will be conducted within 3 months and further studies including insertion site analysis will be performed.
[x] For TNE subjects in Cohorts 2 and 3 only.
[y] The subject must continue to meet pretreatment eligibility criteria pertaining to adequate organ function, active infections, pregnancy, and washout of prior therapy before initiation of LD chemotherapy.
[z] Performed within 4 weeks prior to leukapheresis.
[aa] Including GVHD assessment (if applicable).
[bb] Not required at Japanese sites.
[cc] For subjects receiving LD chemotherapy but not JCAR017, all AEs and associated concomitant medications will be collected for 30 days following the last dose of LD chemotherapy.
[dd] Screening procedure as standard of care within 30 days prior to signing the ICF may be used to evaluate study eligibility based on discussion with Celgene.
[ee] Assessments to be performed each day before administration of LD chemotherapy (refer to Section 6.2.1).
[ff] Soluble factors, such as cytokines and chemokines.
[gg] Prior to dose, it must be confirmed that the subject meets criteria for JCAR017 infusion (refer to Section 6.2.2).
[hh] If subjects develop neurologic symptoms suspicious of and/or diagnosed as neurologic toxicity, subjects will have daily MMSE exams (see Appendix D) until resolution of symptoms, unless the subject is medically incapacitated and/or medically unable to complete the MMSE. If exceptional circumstances preclude the continued administration of outcome measures using planned modalities, then alternate administration methods (eg, abbreviated version of the MMSE questionnaire) may be used. If immune effector cell-associated encephalopathy (ICE) scores are taken per institutional practice, those scores should be recorded as well.
[ii] For PCNSL subjects in Cohort 5 only (refer to Section 6.5).
[jj] For PCNSL subjects in Cohort 5 only: all efficacy assessments should be performed at Day 120 instead of Day 90 (refer to Section 6.5) and only other study procedures and research samples marked with [jj] are repeated at Day 90 and at Day 120.
[kk] Only to be repeated after screening if new symptom(s) or suspicion occurs.

[ll] For Cohort 1, 2, 3, 4, and 7, brain MRI is required at screening for subjects with suspected or confirmed CNS involvement. Subsequent assessments are only required for subjects with confirmed CNS involvement.

6. PROCEDURES

Any questions regarding the protocol should be directed to the Medical Monitor(s) or designee.

6.1. Pretreatment Period

6.1.1. Screening

Screening may begin up to 14 days prior to leukapheresis when the subject signs the IRB/EC-approved informed consent form and continues until enrollment (ie, meeting eligibility requirements; or screen failure is determined). Where applicable, institutional decision boards (eg, multidisciplinary tumor boards, Réunion de concertation pluridisciplinaire [RCP]) should be involved in subject selection. If a subject has had a screening procedure as standard of care within 30 days prior to signing the ICF, it may be used to evaluate study eligibility based on discussion with Celgene. The following assessments will be performed during the screening period, prior to enrollment:

- Obtain informed consent
- Assess eligibility per inclusion/exclusion criteria. All inclusion/exclusion criteria must be met in order for subjects to enroll in the study
- Obtain medical history, including: Disease diagnosis and history, HSCT history, chemotherapy, radiation and surgical history, history of prior gene therapy. May include history of toxicities related to prior treatments and allergies
- Physical examination, including routine neurologic examination, height, weight, and vital signs (blood pressure, body temperature, respirations, heart rate, and oxygen saturation via pulse oximetry) and GVHD assessment (if applicable)
- ECOG performance status assessment
- IPI status
- For TNE subjects in Cohorts 2 and 3 only: HCT-CI score (Sorror, 2005) (see Appendix G) and Frailty Scale (Larocca, 2016) (see Appendix H)
- For TNE subjects in Cohorts 2 and 3 only: Pulmonary function test to assess DLCO (adjusted for hemoglobin concentration using the Dinakara equation) and forced expiratory volume in one second (FEV_1)
- MUGA scan or cardiac echocardiogram (ECHO) (performed within 4 weeks prior to leukapheresis) for LVEF
- 12-lead electrocardiogram (ECG)
- Ophthalmologic examination (for subjects with PCNSL only)
- Collection of peripheral blood samples for clinical laboratory evaluations:
  - Chemistry
  - Hematology
  - Viral serology
  - Serum ß-HCG pregnancy test on women of child-bearing potential

  - Determination of creatinine clearance (eGFR by Cockcroft-Gault, see Appendix F)
- Urinalysis
- PET scan to confirm the presence of PET-positive lymphoma or for Cohort 5, to assess potential systemic involvement in subjects with PCNSL. PET scan may be performed more than 30 days prior to screening if no intervening anticancer treatments have been performed or if the Investigator confirms continued disease presence
- Computed tomography (CT)/magnetic resonance imaging (MRI) (chest, neck, abdomen, pelvis)
- Brain MRI required only for subjects with suspected or confirmed CNS involvement
- Lumbar puncture or Ommaya reservoir tap for CSF assessment required only for subjects with suspected or confirmed CNS involvement
- Collection of tissue from latest archived tumor biopsy (block or slides) for tumor evaluation. If archival sample is before most recent relapse, a new tumor biopsy is mandated to confirm diagnosis for subjects with accessible disease
- Bone marrow aspirate and biopsy
- Administration of EQ-5D-5L and EORTC QLQ-C30 questionnaires and FACT-LymS
- Research samples (see the JCAR017-BCM-001 laboratory manual for details):
  - Immunogenicity
  - Pharmacokinetics (PK) by flow cytometry (not required at Japanese sites)
  - Viral vector sequence PK by qPCR
  - Biomarkers
- Local laboratory assessments (see Appendix E)
  - Human leukocyte antigen (HLA) typing and donor chimerism for subjects who had previous allogeneic HSCT (not required if HLA typing results are available from previous testing)
- Record all AEs related to protocol-mandated procedures and associated concomitant medications

6.1.2. Leukapheresis (approximately 35 days prior to JCAR017 infusion)

Leukapheresis should be scheduled in coordination with the Celgene as soon as possible after the subject has completed screening and eligibility requirements are met. Prior to leukapheresis, appropriate protocol mandate washout periods are to be followed (see Table 5). Venous access is required for leukapheresis and should be determined according to institutional practice. Should a technical issue arise during the procedure or in the immediate

processing of the product such that it cannot be used for JCAR017 production, a second collection procedure may be performed.

The following assessments will be conducted prior to leukapheresis:

- Chemistry
- Hematology. CBC with differential on the day of leukapheresis (or within 24 hours prior)
- Vital signs (blood pressure, body temperature, respirations, heart rate, and oxygen saturation via pulse oximetry) (also after leukapheresis)
- ECOG performance status assessment
- Research samples (see the JCAR017-BCM-001 laboratory manual for details):
  - Biomarkers (Immunophenotyping)
  - RCL testing
- Record all AEs related to protocol-mandated procedures and associated concomitant medications
- Patient interview (see Table 7)

Table 5: Washout Periods Prior to Leukapheresis and Prior to Lymphodepleting Chemotherapy

Treatment	**Washout**	
	Prior to Leukapheresis	**Prior to Lymphodepleting Chemotherapy**
Systemic Therapy		
Alemtuzumab	6 months	
Fludarabine	3 months	7 days
Cladribine	3 months	7 days
Experimental agents	4 weeks/3 half-lives (whichever is greater)	Not applicable
Lymphotoxic chemotherapeutic agents (eg, cyclophosphamide , ifosfamide, bendamustine)	2 weeks	7 days
Therapeutic doses of corticosteroids (defined as > 20 mg/day prednisone or equivalent)	7 days	Not applicable
Cytotoxic chemotherapeutic agents not considered lymphotoxic (eg, doxorubicin, vincristine, gemcitabine, oxaliplatin, carboplatin, etoposide)	7 days	
Rituximab	7 days	
Oral chemotherapeutic agents (eg, lenalidomide and ibrutinib)	3 half-lives	

Table 5: Washout Periods Prior to Leukapheresis and Prior to Lymphodepleting Chemotherapy (Continued)

Treatment	Washout	
	Prior to Leukapheresis	**Prior to Lymphodepleting Chemotherapy**
Intrathecal		
Dexamethasone, methotrexate, cytosine arabinoside	7 days	
Radiation Therapy		
Radiation, multiple lesions	6 weeks	7 days (not allowed for Cohort 5)
Radiation, single lesion, if additional non-irradiated PET-positive lesions are present	2 weeks	

6.1.3. Anticancer Treatments between Leukapheresis and Lymphodepleting Chemotherapy

If necessary, anticancer treatment is allowed for disease control while JCAR017 is being manufactured (ie, after leukapheresis and prior to LD chemotherapy). Low-dose chemotherapy (eg, vincristine, rituximab, cyclophosphamide ≤ 300 mg/m^2) is allowed if completed at least 7 days prior to the start of LD chemotherapy. If other agents are used, the washout periods noted in the exclusion criteria (see Table 5) must be met. The use of therapeutic agents with little/no evidence in the scientific literature for NHL should be discussed with Celgene. Except for Cohort 5 (PCNSL), local radiation is allowed to a single lesion or subset of lesions if other non-irradiated PET-positive lymphoma lesions are present. If anticancer treatment is necessary during this time, the pretreatment PET and CT/MRI assessments and other pretreatment study procedures (see Section 6.1.4) must be performed after the anticancer treatment has been completed. The subject must continue to have PET-positive disease and meet pretreatment eligibility criteria pertaining to adequate organ function, active infections, pregnancy, and washout of prior therapy before initiation of LD chemotherapy.

6.1.4. Pretreatment Evaluation (following enrollment and within 7 days prior to lymphodepleting chemotherapy)

The following assessments will be conducted:

- For subjects who receive anticancer treatment for disease control while JCAR017 is being manufactured:

  Restaging CT/MRI (chest, neck, abdomen, pelvis) and PET must be performed after completion of the intervening anticancer treatment and as close as possible to the start of LD chemotherapy (recommended within 7 to 14 days prior to start). For Cohort 4, restaging is mandatory after 2 cycles of induction to check for complete metabolic response.

- For subjects who did not receive anticancer treatment control while JCAR017 is being manufactured:

If no scans were done at the study site for screening and within 6 weeks prior to the start of LD chemotherapy, CT/MRI and PET scans must be performed (recommended within 14 days prior to start of LD chemotherapy).

- Brain MRI required only for subjects with confirmed CNS involvement
- Lumbar puncture or Ommaya reservoir tap for CSF assessment required only for subjects with confirmed CNS involvement (Cohort 5 subjects must repeat CSF assessment at time of pre-treatment evaluation unless medically contraindicated)

The following assessments will be conducted within 7 days prior to starting LD chemotherapy and after any anticancer treatment received for tumor control:

- Confirm inclusion/exclusion (as defined in Section 4.2 and Section 4.3) and study pretreatment eligibility criteria:
  - PET positive disease
  - Adequate organ function
  - Washout of prior therapy
  - No uncontrolled bacterial, viral or fungal infection

  In case of suspected infection, subject should be treated and LD chemotherapy postponed until the active infection has resolved.

  Physical examination, including routine neurologic examination, weight, and vital signs (blood pressure, body temperature, respirations, heart rate, and oxygen saturation via pulse oximetry) and GVHD assessment (if applicable)
- ECOG performance status assessment
- Mini Mental State Examination (MMSE; see Appendix D) and ICE score (if performed)
- 12-lead ECG
- Research samples (see the JCAR017-BCM-001 laboratory manual for details):
  - Biomarkers (Soluble factors)
- Collection of peripheral blood samples for clinical laboratory evaluations:
  - Chemistry
  - Hematology
  - Coagulation
  - Inflammatory markers
  - Immunoglobulins
  - Serum ß-HCG pregnancy test on all women of child-bearing potential (within 48 hours prior to starting LD chemotherapy)
- Record all AEs related to protocol-mandated procedures and associated concomitant medications
- Administration of EQ-5D-5L and EORTC QLQ-C30 questionnaires and FACT-LymS

- Patient interview (see Table 7)

6.2. Treatment Period

Subjects must be clinically stable and must have recovered from prior toxicities, to receive LD chemotherapy and proceed to JCAR017 infusion. Neither LD chemotherapy nor JCAR017 treatment should be administered if there is a worsening of performance status compared to initial eligibility criteria, rapid clinical deterioration, or evidence of rapidly progressive disease. Note: Subjects who are transplant not eligible or have PCNSL may have ECOG 2, however, must be clinically stable, recover from prior toxicities, and not have evidence of rapidly progressive disease or rapid clinical deterioration prior to receiving LD chemotherapy or JCAR017 infusion.

6.2.1. Lymphodepleting Chemotherapy (start 5 to 10 days prior to JCAR017 infusion)

Upon notification from Celgene that JCAR017 will be available, LD chemotherapy should be initiated so as to finish at least two days prior to JCAR017 infusion. Lymphodepleting chemotherapy can start 5 to 10 days prior to JCAR017 infusion. Please see Section 7.3.1 for the recommended administration. Subjects must be evaluated for evidence of ongoing infections prior to the LD chemotherapy to be started. In case of suspicion of infection, subject should be treated accordingly and LD chemotherapy postponed until infection resolution.

Subjects should not experience a significant worsening in clinical status compared to the initial eligibility criteria that would, in the opinion of the treating physician, increase the risk of adverse events associated with lymphodepleting chemotherapy or exclude them from treatment with JCAR017 (see Section 6.2.2).

The following assessments will be performed on each day before administration of LD chemotherapy:

- Vital signs
- ECOG performance status assessment
- Collection of peripheral blood samples for clinical laboratory evaluations:
  - Determination of creatinine clearance (eGFR by Cockcroft-Gault, see Appendix F) (required only on first day of LD chemotherapy)
  - Chemistry
  - Hematology
- Record all AEs and associated concomitant medications
- Hospital resource utilization

6.2.2. JCAR017 Administration: Day 1

Subjects will receive JCAR017 infusion 2 to 7 days after completion of LD chemotherapy.

The first 10 subjects treated with JCAR017 respectively in Europe and in Japan must be hospitalized for a minimum of 14 days after JCAR017 infusion.

Subjects who do not have adequate social support outside of the hospital or do not have reliable transportation to the clinic for scheduled evaluations or emergencies post-therapy should be considered for hospitalization for the first 14 days of treatment.

Subjects should not experience a significant worsening in clinical status compared to initial eligibility criteria that would, in the opinion of the treating physician, increase the risk of adverse events associated with JCAR017 infusion. Subjects who meet at least one of the following criteria on the day of scheduled JCAR017 infusion should have JCAR017 administration delayed:

- Suspected or active systemic infection
- Onset of fever ≥ 38°C/100.4°F, not related to underlying disease
- Presence of progressive radiographic abnormalities on chest x-ray, or requirement for supplemental oxygen to keep saturation greater than 91%
- Cardiac arrhythmia not controlled with medical management
- Hypotension requiring vasopressor support
- New-onset or worsening of other non-hematologic organ dysfunction ≥ Grade 3
- Taking any of the prohibited medications as described in Section 8.2
- Progressive vascular tumor invasion, thrombosis, or embolism
- Venous thrombosis or embolism not managed on a stable regimen of anticoagulation

Subjects with active infection must have JCAR017 infusion postponed until the active infection has resolved (subjects with suspected/ active infection must have negative culture for at least 24 hours on appropriate antibiotics or negative rapid viral panel). Subjects with organ toxicities may not receive JCAR017 until the organ toxicities have recovered to ≤ Grade 2. In case of delayed infusion, lymphodepleting chemotherapy may need to be repeated after discussion with the Sponsor (see Section 6.2.1).

In the event that a subject experiences any of the above, the Sponsor must be contacted and discussion regarding delay of treatment must occur.

The following assessments are to be performed prior to the JCAR017 infusion:

- Physical examination
- Weight
- Vital signs (measured within 15 minutes prior to the first JCAR017 administration)
- ECOG performance status assessment
- Routine neurologic examination
- MMSE (see Appendix D) and ICE score (if performed).
- Record all AEs and associated concomitant medications
- Collection of peripheral blood samples for clinical laboratory evaluations:
  - Chemistry
  - Hematology

  - Coagulation
  - Inflammatory markers
- Urinalysis
- Research samples (pre-infusion; see the JCAR017-BCM-001 laboratory manual):
  - PK by flow cytometry (not required at Japanese sites)
  - Viral vector sequence PK by qPCR
  - Biomarkers (Soluble factors)
- Administration of EQ-5D-5L and EORTC QLQ-C30 questionnaires and FACT-LymS
- Patient interview (see Table 7)
- JCAR017 premedication (see Section 7.3.2)
- Hospital resource utilization

Treatment administration will be registered in the interactive response technology (IRT) system.

- After infusion, vital signs will be repeated approximately every 15 minutes for the first hour, and hourly for the next 2 hours. If the subject's vital signs are not stable 4 hours following the final IV administration, vital signs should be monitored as clinically indicated until stable.

6.2.3. Days 2 and 3

- Vital signs
- Physical examination
- Record all AEs and associated concomitant medications
- Hospital resource utilization

6.2.4. Day 4 (+1 day)

- Vital signs
- Routine neurologic examination
- Physical examination
- MMSE (see Appendix D and Section 6.4.4) and ICE score (if performed)
- Record all AEs and associated concomitant medications
- Collection of peripheral blood samples for clinical laboratory evaluations:
  - Chemistry
  - Hematology
  - Coagulation
  - Inflammatory markers
- Research samples (see the JCAR017-BCM-001 laboratory manual):

  - PK by flow cytometry (not required at Japanese sites)
  - Viral vector sequence PK by qPCR
  - Biomarkers (Soluble factors)
- Hospital resource utilization

6.2.5. Day 8 (±1 day)

- Physical examination
- Vital signs
- ECOG performance status assessment
- Routine neurologic examination
- MMSE (see Appendix D and Section 6.4.4) and ICE score (if performed)
- Record all AEs and associated concomitant medications
- Collection of peripheral blood samples for clinical laboratory evaluations:
  - Chemistry
  - Hematology
  - Coagulation
  - Inflammatory markers
- Research samples (see the JCAR017-BCM-001 laboratory manual):
  - PK by flow cytometry (not required at Japanese sites)
  - Viral vector sequence PK by qPCR
  - Biomarkers (Soluble factors, immunophenotyping)
- Hospital resource utilization

6.2.6. Day 11 (±1 day)

- Vital signs
- Physical examination
- Routine neurologic examination
- Record all AEs and associated concomitant medications
- Collection of peripheral blood samples for clinical laboratory evaluations:
  - Chemistry
  - Hematology
  - Coagulation
  - Inflammatory markers
- Research samples (see the JCAR017-BCM-001 laboratory manual):
  - PK by flow cytometry (not required at Japanese sites)

  - Viral vector sequence PK by qPCR
  - Biomarkers (Soluble factors)
- Hospital resource utilization

6.2.7. Days 15, 22, and 29 (±2 days)

- Physical examination
- Vital signs
- ECOG performance status assessment
- Routine neurologic examination
- Brain MRI for subjects with confirmed CNS involvement is required on Day 29
- MMSE required on Days 15 and 29 (see Appendix D and Section 6.4.4) and ICE score (if performed)
- Administration of EQ-5D-5L and EORTC QLQ-C30 questionnaires and FACT-LymS required on Day 29
- Record all AEs and associated concomitant medications
- Collection of peripheral blood samples for clinical laboratory evaluations:
  - Chemistry
  - Hematology
  - Coagulation
  - Inflammatory markers required on Day 15 (required on Days 22 and 29 if clinically indicated)
  - Immunoglobulins
- Research samples (see the JCAR017-BCM-001 laboratory manual):
  - Immunogenicity required on Days 15 and 29
  - PK by flow cytometry (not required at Japanese sites)
  - Viral vector sequence PK by qPCR
  - Biomarkers (PBMC required on D15 and D29, Soluble factors and Immunophenotyping required on D15, 22 and 29)
- Response evaluation by PET scan and CT/MRI (once between Days 29 to 35). PET-CT does not need to be repeated in the absence of systemic disease at baseline or suspicion of systemic PD for subjects in Cohort 5.
- Tumor biopsy for subjects with accessible disease required on Day 15
- Lumbar puncture or Ommaya reservoir tap for CSF assessment for subjects with confirmed CNS involvement at pre-treatment is required on Day 29
- Patient interview required on Day 29 (see Table 7)
- Hospital resource utilization

6.3. Post-Treatment Period (Follow-up)

All subjects who received any JCAR017 infusion, including subjects with progressive disease, should complete the post-treatment period visits at approximately 2, 3 (4 month for subjects with PCNSL), 6, 9, 12, 18, and 24 months (end of study [EOS]) after JCAR017 infusion for disease status and survival, unless otherwise specified.

The following assessments will be performed in subjects who have not received subsequent anticancer treatment following JCAR017 infusion:

- Physical examination required on Months 2, 3 (and on month 4 for subjects with PCNSL only), 6, 9, 12, and 24 (after PD/relapse: required on Months 12 and 24)
- Routine neurologic examination required for all subjects on Month 3 (except for subjects with PCNSL). For subjects with PCNSL required on Months 2, 4, 6, 9, 12, 18, and 24 (after PD/relapse: required on Month 2)
- Brain MRI for subjects with confirmed CNS involvement is required on Months 3, 6, 9, 12, 18 and 24 (not required after PD/relapse). For subjects with PCNSL required on Months 2, 4, 6, 9, 12, 18, and 24 (not required after PD/relapse)
- PET scan required on Months 3, 6, 9, 12, 18, and 24 or to verify PD (not required for subjects in CR or after PD/relapse). For subjects with PCNSL required on Months 2, 4, 6, 9, 12, 18, and 24 (not required for subjects without systemic involvement at screening, subjects in CR or after PD/relapse)
- CT/MRI scan required on Months 3, 6, 9, 12, 18, and 24 (not required after PD/relapse). For subjects with PCNSL required on Months 2, 4, 6, 9, 12, 18, and 24 (not required after PD/relapse)
- Lumbar puncture or Ommaya reservoir tap for CSF assessment for subjects with confirmed CNS involvement is required on Months 3, 6, 9, 12, 18, and 24 (not required for subjects in CR if no suspicion of CNS relapse and after PD/relapse). For subjects with PCNSL required on Months 2, 4, 6, 9, 12, 18, and 24 (not required for subjects with negative CSF at pre-treatment visit, in CR if no suspicion of CNS relapse and after PD/relapse).
- MMSE and ICE score (if performed) required on Month 3 (and on Month 4 for subjects with PCNSL only) (see Appendix D and Section 6.4.4)
- ECOG performance status assessment required on Months 2, 3 (and on month 4 for subjects with PCNSL only), 6, 9, 12, 18, and 24 (not required after PD/relapse)
- Administration of EQ-5D-5L and EORTC QLQ-C30 questionnaires and FACT-LymS
- Collection of peripheral blood samples for clinical laboratory evaluations:
  - Hematology required on Months 2, 3 (and on month 4 for subjects with PCNSL only), 6, 9, 12, 18, and 24
  - Immunoglobulins required on Months 2, 3, 6, 9, 12, 18, and 24 (not required if B-cell recovery documented without recent administration of intravenous immunoglobulins [IVIG])
  - Serum ß-HCG pregnancy test on all women of child-bearing potential required on Month 3, 6, 9 and 12 (and on Month 4 only for subjects with PCNSL)

- Research samples (see the JCAR017-BCM-001 laboratory manual for details):
  - RCL sample collection required on Months 3, 6, 12, and 24
  - Immunogenicity
  - PK by flow cytometry (not required at Japanese sites)
  - Viral vector sequence PK by qPCR sample collection
  - Biomarkers (PBMC and Immunophenotyping) required on Months 2 and 6
- Record all AEs and associated concomitant medications until 90 days after JCAR017 infusion and afterwards all AEs related to JCAR017 and/or LD chemotherapy and associated concomitant medications
- Patient interview (see Table 7)
- Hospital resource utilization

The following assessments will be performed in subjects who have received subsequent anticancer treatment:

- Collection of all anticancer treatment since JCAR017 infusion
- Physical examination required on Months 12 and 24
- Immunoglobulins required on Months 3, 6, 9, 12, 18, and 24 (not required if B-cell recovery documented without recent administration of IVIG)
- RCL sample collection required on Months 3, 6, 12, and 24
- Viral vector sequence PK by qPCR sample collection
- Pregnancy test at Month 3, if applicable
- Record AEs and associated concomitant medications according to Section 10.1
- Patient interview (see Table 7)
- Hospital resource utilization

Note: Subjects who receive HSCT post-JCAR017 (but no other anticancer treatment) should continue to undergo scans, unless they have demonstrated PD prior to transplant. A PET scan should be performed to verify PD.

6.3.1. Unscheduled Evaluations

If the Investigator feels that a subject needs to be evaluated at a time other than the protocol-specified visit, the subject may be asked to come in to the clinic for an unscheduled evaluation. The following assessments may be performed, as appropriate:

- Physical examination
- Vital signs
- ECOG performance status assessment
- MMSE (see Appendix D and Section 6.4.4) and ICE score (if performed)
- Clinical laboratory evaluations
- PET scan

- CT/MRI scan
- Tumor biopsy (see the JCAR017-BCM-001 laboratory manual)
- Bone marrow aspirate and biopsy
- CSF assessment
- Ophthalmologic examination
- RCL peripheral blood
- Research samples (see the JCAR017-BCM-001 laboratory manual):
  - Immunogenicity
  - PK by flow cytometry. If a subject has received additional non-lymphotoxic anticancer treatment, radiation, or surgery after progressive disease PK samples may be collected every 1 to 2 weeks (not applicable at Japanese sites).
  - Viral vector sequence PK by qPCR
  - Biomarkers
- Hospital resource utilization

Additionally, if the Investigator requests any of the following procedures, research samples may be collected, when possible:

- Lumbar puncture or Ommaya reservoir tap for CSF assessment
- Pleural, peritoneal, or other relevant fluid sampling
- Tissue sampling
- Autopsy

6.3.2. Assessments upon Progressive Disease

The following assessments will be performed as soon as possible after progressive disease:

- Tumor biopsy, if clinically feasible (see the JCAR017-BCM-001 laboratory manual)
- Research samples (see the JCAR017-BCM-001 laboratory manual):
  - Immunogenicity
  - PK by flow cytometry (not required at Japanese sites)
  - Viral vector sequence PK by qPCR
  - Biomarkers

6.3.3. Assessment upon Complete Response

For subjects with previous bone marrow involvement, a bone marrow aspirate and biopsy will be performed upon achieving of a complete response.

6.3.4. Assessments at Time of Death

In case an autopsy is performed and there is a safety concern for which a tissue analysis is needed, pertinent tissue samples will be collected if feasible, for central analysis of markers

related to safety when consent has been obtained from the subject and as allowed by local regulation.

6.3.5. Early Withdrawal

If a subject voluntarily withdraws prematurely from the study, a visit will be scheduled as soon as possible, and all of the assessments listed for the 24 month (EOS) visit will be performed.

6.3.6. Survival Follow-Up

After EOS visit or time of withdrawal, all enrolled subjects will be followed for survival every 3 months (± 30 days) until last subject last visit. Additional survival follow-up information will be collected in the context of the LTFU protocol for all subjects who received JCAR017.

6.3.7. Long-Term Follow-Up

Because this protocol involves gene transfer, long-term follow-up for lentiviral vector safety, disease status, and survival will continue on this protocol until 24 months after last infusion of JCAR017, regardless of disease status, and rolled over to a separate LTFU protocol thereafter for up to 15 years after JCAR017 infusion.

All subjects who either complete the primary follow-up period specified in this protocol or who prematurely withdraw after JCAR017 infusion will be asked to enroll in the LTFU protocol at the EOS visit or at the time of withdrawal, respectively. A separate informed consent form will be provided for the LTFU protocol. Subjects who do not consent to participate in the LTFU protocol will be followed for survival through public record if permitted by local regulations.

6.4. Safety Assessments

6.4.1. Physical Examination

A physical examination should include assessments of the following body parts/systems: abdomen, extremities, heart, lungs, and neurologic. In addition, symptom-directed exams should be performed.

6.4.2. Vital Signs

Vital signs include temperature, respiratory rate, heart rate and blood pressure. SaO_2 will be assessed by pulse oximetry. Refer to Table 4, and Sections 6.2.2 and Section 7.3.4 for more details.

6.4.3. Height and Weight

Height in centimeters (cm) or inches (in) and body weight to the nearest kilogram (kg) in indoor clothing, but without shoes will be measured according to Table 4.

6.4.4. Routine Neurologic and Mini Mental State Examinations

A routine neurologic examination should include, at minimum, a physical examination to assess cranial nerves, motor and sensory skills, coordination and balance. The MMSE (see Appendix D) may be administered by an appropriately trained provider (ie, physician, nurse); a neurologist is not required. If exceptional circumstances preclude the continued

administration of outcome measures using planned modalities, then alternate administration methods (eg, abbreviated version of the MMSE questionnaire) may be used. Efforts should be made to have the same provider perform the MMSE on a given subject to maintain consistency of assessment. If subjects develop neurologic symptoms suspicious of and/or diagnosed as neurologic toxicity, subjects will have a daily MMSE until resolution of symptoms, unless the subject is medically incapacitated and/or medically unable to complete the MMSE. If immune effector cell-associated encephalopathy (ICE) scores are taken per institutional practice, those scores should be recorded as well.

6.4.5. Cerebrospinal Fluid Assessment and Central Nervous System Symptom Assessment

For Cohort 1, 2, 3, 4 and 7, Cerebrospinal fluid assessments should be performed for subjects with suspected or confirmed CNS involvement (if CNS involvement is suspected CNS imaging should also be performed) at screening. Repeat CSF at pretreatment evaluation and after JCAR017 administration is only required for subjects with confirmed CNS involvement, and should be performed until complete response. Thereafter, repeat CSF only in subjects with suspicion of CNS relapse (Table 4). For Cohort 5 CSF is required at screening and at time of pre-treatment evaluation, unless medically contraindicated. For subjects without CSF involvement, repeated evaluation is not required in the absence of interval symptoms suggestive of leptomeningeal dissemination.

Cerebrospinal fluid will be analyzed for cell count and differential cytology (see the JCAR017-BCM-001 laboratory manual for instructions on sending a sample for JCAR017 testing). Cerebrospinal fluid cultures (bacterial, fungal, viral) should be performed as clinically indicated for suspicion of infection.

6.4.6. Eastern Cooperative Oncology Group Performance Status

Eastern Cooperative Oncology Group performance status (see Appendix B) will be used to evaluate subject eligibility at screening and will be assessed throughout the study at timepoints specified in Table 4.

6.4.7. Echocardiogram and Multigated Acquisition Scan

An assessment of LVEF will be performed by ECHO or MUGA scan to assess the cardiac function of the subject and to confirm study eligibility.

6.4.8. Electrocardiogram

A standard 12-lead ECG should be obtained at timepoints indicated in Table 4. Electrocardiogram tracings should be labelled with the study number, subject number, date, and Investigator's signature, and kept in the source documents at the study site.

6.4.9. Replication-Competent Lentivirus Testing

Replication-competent lentivirus testing will be performed on genomic DNA obtained by a peripheral blood draw and, if positive, confirmed on PBMC. Details regarding sample collection and processing are provided in the JCAR017-BCM-001 laboratory manual. Testing for RCL will utilize a polymerase chain reaction based assay.

Samples for RCL testing will be collected at timepoints indicated in Table 4. If all samples collected within the first year after the dose of JCAR017 are negative, subsequent samples will be collected and archived. However, if any of the samples are positive, the test will be

repeated to confirm the result. If the repeat test is also positive, further analysis of the RCL will be undertaken in order to ascertain the nature of the RCL and potential effects. Subjects with detectable RCL are expected to continue to have blood samples collected and tested until RCL is undetectable. If RCL is detected, further analysis of the RCL will be performed and more extensive follow-up measures will be undertaken as appropriate until RCL becomes undetectable. Any confirmed positive result from RCL testing will be reported as an SAE within 24 hours and as an adverse experience in the form of an Investigational New Drug (IND) safety report. In addition, the relevant health authorities will be notified of the detected RCL.

Samples will be archived with appropriate safeguards to ensure long-term stability and an efficient system for the prompt linkage and retrieval of the stored samples with the subject's study records and the production lot records. Archived samples will be destroyed as outlined in the separate LTFU protocol.

If a subject develops a secondary malignancy, Celgene will request a sample for detection of CAR T sequence. An unscheduled blood draw may also be collected for RCL testing.

6.4.10. Persistent Vector Sequence Monitoring

Persistence of JCAR017 vector sequence will be monitored at timepoints indicated in Table 4. Details regarding sample collection and processing are provided in the JCAR017-BCM-001 laboratory manual. The presence of vector sequences will be determined by evaluation of blood samples for the JCAR017 transgene by qPCR. If more than 1% of cells in test samples collected at the Day 365 visit or later tested positive for vector sequences, the pattern of vector integration sites was then to be analyzed. If integration pattern suggests a predominant integration site, a repeat analysis will be conducted within 3 months and further studies including insertion site analysis will be performed.

6.4.11. Clinical Laboratory Evaluations

Screening and other laboratory evaluations (see Appendix E) will be performed according to Table 4. Additional assessments should be performed between scheduled study visits as clinically required in order to diagnose and monitor AEs/SAEs or expected events. Clinical management of study subjects will be based on local assessments.

6.5. Efficacy Assessment

- DLBCL, FL3B: Efficacy response will be assessed according to the "Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and non-Hodgkin lymphoma: The Lugano Classification" (Cheson, 2014) (see Appendix C) based on radiographic tumor assessments. Subjects will have radiographic disease assessment by PET and/or CT/MRI scans at pretreatment evaluation and approximately 1, 3, 6, 9, 12, 18 and 24 months following JCAR017 infusion or until progressive disease or relapse
  - For subjects with secondary CNS involvement: Brain MRI and repeat CSF assessments by flow cytometry
- PCNSL: Efficacy response will be assessed according to the "Report of an International Workshop to Standardize Baseline Evaluation and Response Criteria for Primary CNS Lymphoma" (Abrey, 2005) at pretreatment evaluation and approximately 1, 2, 4, 6, 9, 12, 18 and 24 months following treatment based on the following assessments:

- Brain MRI
- CSF assessment (if positive at pre-treatment or suspicion of relapse)
- PET-CT mandatory at screening to assess for potential systemic involvement. Thereafter, PET-CT does not need to be repeated in the absence of systemic disease at baseline or suspicion of systemic PD

6.5.1. Pseudoprogression

If a subject demonstrates early tumor progression (defined as occurring prior to/at 3 months after JCAR017 infusion), the Investigator is responsible for evaluating whether the subject is experiencing a possible pseudoprogression (ie, tumor flare, which is a local inflammatory reaction indicating early tumor response at sites of disease such as lymph nodes; (Cheson, 2016).

6.5.2. Independent Review Committee

An independent review committee (IRC) will be established to review radiographic and pertinent clinical data (as appropriate) and to determine response and progression status on an ongoing basis. The details of the IRC processes and review methods will be described in an IRC charter. Clinical management of study subjects will be based upon Investigator's assessment. The findings of the IRC will be considered primarily for analyses of efficacy endpoints.

6.6. Pharmacokinetics

Assessment of JCAR017 PK will be determined by qPCR to detect the JCAR017 transgene and by flow cytometry to enumerate the number and immunophenotype of JCAR017 cells. Pharmacokinetics by flow cytometry will not be done at Japanese sites. Peripheral blood will be collected as indicated in Table 4.

Detailed information regarding the collection, handling, and shipment of PK assessment samples is provided in the JCAR017-BCM-001 laboratory manual.

6.7. Biomarkers, Pharmacodynamics, Pharmacogenomics

6.7.1. Immunogenicity Assessments

Immune responses to JCAR017 will be evaluated with an anti-therapeutic antibody (ATA) assay to detect the presence of serum antibodies that bind to the extracellular region of JCAR017. Additional methods, such as ELISpot, may also be used to evaluate cellular immune responses to JCAR017 using peripheral blood mononuclear cells (PBMCs). Peripheral blood will be collected for these studies at the timepoints indicated in Table 4.

Detailed information regarding the collection, handling, and shipment of immunogenicity assessment samples is provided in the JCAR017-BCM-001 laboratory manual.

6.7.2. Biomarker Assessments

Exploratory biomarker assessments will include, but are not limited to, immunophenotypic and genomic evaluation of JCAR017 and circulating cells in peripheral blood, characterization of tumor and tumor microenvironment, and analysis of plasma cytokines.

Sample specimens will be collected for these studies at the timepoints indicated in Table 4 and Table 6 for exploratory biomarkers.

Table 6: Exploratory Biomarkers Sampling

Biomarker Assessment Type	Sample Type	Timepoint
Pharmacokinetics (PK) by flow cytometry	Peripheral blood	Screening, D1, D4, D8, D11, D15, D22, D29, D60, D90, D180, D270, D365, D545, D730
Immunophenotyping (circulating T cell subset and JCAR017)	Peripheral blood	Screening, leukapheresis (prior), D8, D15, D22, D29, D60, D180
Soluble factors	Plasma	Screening, pretreatment evaluation, D1 (pre-infusion), D4, D8, D11, D15, D22, D29
PBMC isolation	Peripheral blood	Screening, D15, D29, D60, D180
Disease characterization	Tumor biopsy	Screening, D15 and at progression

Abbreviations: D = day; PBMC = peripheral blood mononuclear cells.

Tumor tissue biopsy will be collected to investigate cellular elements within the tumor and the tumor microenvironment for biomarkers related to clinical efficacy and association with disease features (eg, cell of origin, cytogenetics). In addition, tumor biopsy specimens will be analyzed for expression of various markers. Characterization of the tumor specimen may provide insights into the pathways operative in the tumor microenvironment that may influence the fate and function of adoptively transferred JCAR017.

The tumor biopsy will be collected by either tumor excision, incision or multiple core needles (4 passages preferred) and processed for formalin fixed paraffin embedding. In addition to standard clinical histology, genetic mutation analysis and expression of various markers of resistance and efficacy will be performed.

It is strongly recommended to submit to the central laboratory any archival tumor biopsy samples collected prior to study entry or during the study at timepoints other than described above for biomarker analysis.

Peripheral blood and plasma will be collected to evaluate the following:

- Immunophenotyping will be done to characterize JCAR017 and circulating immune cell subsets to identify protein and nucleic acid markers correlated with JCAR017 activation, persistence and possible regulation of JCAR017 cells by circulating immune cells
- Soluble factors from plasma will be measured as a marker of immune activation and to determine potential correlations between cytokine production, efficacy and severity of CRS and neurotoxicity
- Gene expression profiling (eg, ribonucleic acid-sequencing [RNA-Seq]) and various analyses at the nucleotide level may be conducted on JCAR017 cells and immune cells in order to identify markers or gene signatures correlating with clinical response

The data collected in these biomarker assessments will be used in aggregate to elucidate relationship with CAR T cell function, persistence, molecules present in the tumor/tumor microenvironment, and peripheral blood to clinical response and toxicity.

Detailed information regarding the collection, handling, and shipment of biomarker samples is provided in the JCAR017-BCM-001 laboratory manual.

6.8. Patient-Reported Outcomes

Patient-reported quality-of-life outcomes will be administered according to Table 4.

If the subject withdraws from the study prematurely, all attempts should be made to obtain a final quality-of-life questionnaire prior to subject discontinuation. EQ-5D-5L and EORTC QLQ-C30 and the FACT-LymS will be used to assess the subject's health as well as physical, social, emotional, and functional well-being.

The questionnaires will be completed by the subjects before any clinical assessments are performed at any given visit. If subjects refuse to complete all or any part of a questionnaire, this will be documented in the case report form (CRF). Questionnaires should be completed in the language most familiar to each subject, and subjects should be given adequate time and space to complete the questionnaires. Site personnel should review questionnaires for completeness and ask subjects to complete any missing responses. The reasons for any missing questionnaires will be documented (eg, subjects too sick to complete questionnaire, subject unwilling to complete questionnaire and questionnaire not administered to subject due to administrative error).

Where feasible, patient interviews will be used to capture the experience of JCAR017 therapy from a subject perspective.

6.8.1. EORTC QLQ-C30

The EORTC QLQ-C30 questionnaire will be used as a measure of health-related quality of life. The QLQ-C30 is composed of both multi-item scales and single item measures. These include five functional scales (physical, role, emotional, cognitive and social), 3 symptom scales (fatigue, nausea/vomiting, and pain), a global health status/health-related quality of life (HRQoL) scale, and six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). Each of the multi-item scales includes a different set of items – no item occurs in more than one scale.

The QLQ-C30 questionnaire employs a week recall period for all items and a 4-point scale for the functional and symptom scales/items with response categories "Not at all", "A little", "Quite a bit" and "Very much". The 2 items assessing global health status/HRQoL utilize a 7-point scale ranging from 1("Very Poor") to 7 ("Excellent") (Aaronson, 1993) (see Appendix I).

6.8.2. EQ-5D-5L

EQ-5D is a standardized measure of health status developed by the EuroQol Group in order to provide a simple, generic measure of health for clinical and economic appraisal. The EQ-5D-5L consists of the EQ-5D-5L descriptive system and the EQ visual analogue scale (EQ VAS). The descriptive system comprises dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression). Each dimension has 5 levels (no problems, slight problems, moderate problems, severe problems, extreme problems).

In 2005, a Task Force was established within the EuroQol Group to investigate methods to improve the instrument's sensitivity and to reduce ceiling effects. After much discussion, the Task Force decided that there should be no change in the number of dimensions for a new version of EQ-5D.

However, previously published studies by EuroQol Group members showed that experimental 5-level versions of EQ-5D could significantly increase reliability and sensitivity (discriminatory power) while maintaining feasibility and potentially reducing ceiling effects.

The EQ-5D-5L still consists of 2 pages – the EQ-5D-5L descriptive system (page 1) and the EQ Visual Analogue Scale (page 2). The descriptive system comprises the same 5 dimensions as the EQ-5D-3L (mobility, self-care, usual activities, pain/discomfort, anxiety/depression).

However, each dimension now has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The respondent is asked to indicate his/her health state by ticking (or placing a cross) in the box against the most appropriate statement in each of the 5 dimensions. This decision results in a 1-digit number expressing the level selected for that dimension. The digits for 5 dimensions can be combined in a 5-digit number describing the respondent's health state. It should be noted that the numerals 1 to 5 have no arithmetic properties and should not be used as a cardinal score.

The EuroQol Group had received feedback over the years that respondents sometimes found it difficult to draw a line from the box to the scale. It was also cumbersome for administrators to record their scores. The EQ-5D-5L now asks respondents to simply 'mark an X on the scale to indicate how your health is TODAY' and then to 'write the number you marked on the scale in the box below'.

This should make the task easier for both respondents and users (EuroQol, 1990; Herdman, 2011) (see Appendix J).

6.8.3. FACT-LymS

The Functional Assessment of Cancer Treatment-Lymphoma "Additional concerns" subscale (FACT-LymS) consists of the FACT-General scale and a 15-item lymphoma-specific additional concerns subscale (LYM). This scale addresses symptoms and functional limitations that are important to lymphoma patients. Only the LYM subscale will be administered in this study. The LYM items are scored on a 0 ("Not at all") to 4 ("Very much") response scale. Items are aggregated to a single score on a 0-60 scale (see Appendix K).

6.8.4. Patient Interviews

Standardized measures of HRQoL have not been widely used in evaluations of CAR T cell therapies and due to the novelty of JCAR017 much has yet to be learned about its impact on HRQoL, which may currently be missed by these standard HRQoL measures. For this reason, subjects will be invited to be interviewed during the study; the aim being to provide an opportunity for subjects to share their experiences of JCAR017 therapy in their own words, capturing insights not usually recorded via the established patient-reported outcomes (PRO) scales and questionnaires.

Where feasible, subjects will be requested to participate in a series of interviews over the 2-year study period according to Table 7. The interviews will be structured by a discussion guide.

The first interview will last up to one hour and will be conducted in-person or via telephone. The remainder of the interviews will be shorter in duration, lasting approximately 30 minutes, and may be conducted either over the telephone or in-person. Interviews will be scheduled at a time convenient to the subjects.

During the interviews, subjects may be asked about:

- Their experience of B-cell NHL, including symptoms and how the condition affects their life
- Their experience with JCAR017 therapy
- Their decision to participate in the study
- Their experiences during the study

The patient interviews will include a combination of closed and open-ended items, but will predominantly provide qualitative data. Any quantitative data will be presented descriptively. Robust qualitative methods will be applied to the development of all materials and analysis, in line with gold standard PRO practices such as those required by the Food and Drug Administration (FDA) for PRO instrument development and industry good research practice publications (Patrick, 2011).

Table 7: Table of Events, Patient Interviews

	Pretreatment Period			Treatment Period										Post-Treatment Period						
	Screening	Leukapheresis	Pretreatment Evaluation	LD Chemotherapy	JCAR017 Infusion									Follow-Up						
Study Day	**7 to 14 days before leukapheresis**	**Within time from screening to leukapheresis**	**Within 7 days before LD chemotherapy**	**Start 5 to 10 days before Day 1**	**1**	**2**	**3**	**4**	**8**	**11**	**15**	**22**	**29**	**60**	**90**	**180**	**270**	**365**	**545**	**730 (EOS) or ET**
Visit Window (Days)	**-**	**-**	**-**	**-**	**+2**	**-**	**-**	**+1**	**±1**	**±1**	**±2**	**±2**	**±2**	**+14**	**+14**	**+35**	**+35**	**+35**	**+35**	**+35**
Patient interviews[a] for subjects enrolled under Protocol Amendment 1, 2	-	x[b]	x	-	x[c]	-	-	-	-	-	-	-	x	x	x	x	x	x	x	x
Patient interviews[a] for subjects enrolled under Protocol Amendment 3	-	x[d]	-	-	-	-	-	-	-	-	-	-	-	-	x[e]	-	x[e]	-	-	-

Abbreviations: EOS = end of study; ET = early termination; LD = lymphodepleting.
[a] Patient interviews will be performed by an external organization with specialist expertise in conducting patient interviews.
[b] Interview is to be performed before the leukapheresis.
[c] A window of 72-hours post-JCAR017 infusion is allowed.
[d] If missed, interview is to be performed at Pretreatment Evaluation.
[e] Interview is to be performed from study visit until 28 days after study visit.

6.9. Hospital Resource Utilization

Hospital resource utilization will be assessed based on the numbers of ICU inpatient days and non-ICU inpatient days in addition to outpatient visits. Dates of admission and discharge to the hospital and to the ICU will be collected together with the reasons for the hospitalization(s).

7. DESCRIPTION OF STUDY TREATMENTS

7.1. Lymphodepleting Chemotherapy

See Section 1.3.2 for a description of fludarabine and cyclophosphamide.

7.2. Description of Investigational Product

7.2.1. JCAR017

See Section 1.2.3 for a description of JCAR017.

See the JCAR017 Product Administration Manual for details of packaging and labeling, product request and shipment, product preparation and administration, and product disposal and destruction.

7.3. Treatment Administration and Schedule

7.3.1. Lymphodepleting Chemotherapy

Subjects will be treated with fludarabine IV (30 mg/m^2/day for 3 days) and cyclophosphamide IV (300 mg/m^2/day for 3 days) prior to JCAR017 infusion. Except for Japan, fludarabine and cyclophosphamide will be sourced locally by the clinical site. Refer to the most recent package inserts for further details on the administration of these agents (Cyclophosphamide, 2017; Fludarabine, 2019).

Lymphodepleting chemotherapy can start 5 to 10 days before JCAR017 infusion and must be completed at least 2 days before JCAR017 infusion. If side effects from the LD chemotherapy occur, JCAR017 infusion may be delayed for up to 14 days after LD chemotherapy upon discussion with Celgene. If the delay is more than 14 days, some of the screening procedures as well as LD chemotherapy may need to be repeated. Refer to Section 6.2.1 for the assessments that will be performed on each day of LD chemotherapy.

Serum creatinine will be measured on the first day of LD chemotherapy; LD chemotherapy should be withheld if serum creatinine is > 1.5 times the ULN OR calculated creatinine clearance (eGFR by Cockcroft-Gault, see Appendix F) or radioisotope glomerular filtration rate (GFR) is ≤ 30 mL/min.

The recommended administration is as follows:

- The IV hydration is 1 L of 0.9% NaCl given at 500 mL/hr starting 2 hours prior to cyclophosphamide
- Fludarabine IV 30 mg/m^2 over 30 minutes
  - If CrCl 50 to 70 mL/min: Reduce dose by 20% for each daily dose
  - If CrCl 30 to 49 mL/min: Reduce dose by 40% for each daily dose
  - If CrCl < 30 mL/min: Do not administer fludarabine
- Cyclophosphamide IV 300 mg/m^2 over 60 minutes

- Additional 1 L of 0.9% NaCl given at 500 mL/hr

Antiemetic therapy may be given prior to LD chemotherapy per institutional practice. Mesna may be used for subjects with a history of hemorrhagic cystitis per institutional practice.

7.3.2. JCAR017 Premedication

Subjects should be premedicated with 500 to 650 mg acetaminophen oral (PO) and 25 to 50 mg diphenhydramine hydrochloride (PO or IV) 30 to 60 minutes prior to JCAR017 infusion. In case the diphenhydramine hydrochloride is not available in a country, it is acceptable to use another H1 antihistamine.

These medications may be repeated every 6 hours as needed based on the Investigator's assessment of symptoms. Premedication with steroids should be avoided.

7.3.3. JCAR017 Preparation and Cell Thawing

See the JCAR017-BCM-001 Product Administration Manual for details.

7.3.4. JCAR017 Administration

JCAR017 will be infused at a dose of 100 x 10^6 JCAR017-positive transfected viable T cells (50×10^6 CD8+ CAR+ T cells and 50×10^6 CD4+ CAR+ T cells), on Day 1 (2 to 7 days after completion of LD chemotherapy). Each JCAR017 dose consists of CD4+ CAR+ T cells and CD8+ CAR+ T cells. The subject must be continuously monitored during IV administration of JCAR017. Vital signs (temperature, respiratory rate, heart rate, blood pressure, and SaO_2 by pulse oximetry) will be measured within 15 minutes prior to the first JCAR017 administration, and approximately every 15 minutes thereafter for the first hour, and hourly for the next 2 hours. If the subject's vital signs are not stable 4 hours following the final IV administration, vital signs should be monitored as clinically indicated until stable.

See the JCAR017-BCM-001 Product Administration Manual for complete information.

7.3.5. Protocol Product Deviation Plan

The JCAR017 Protocol Product Deviation Plan (PPDP) addresses the use of the non-conforming investigational product in global clinical trials. The JCAR017 PPDP defines an assessment and decision-making process that permits release to the investigator and clinical site of drug product that does not meet the specification for certain non-safety related attributes (non-conforming product). In this process, the Celgene Medical Monitor and the Primary Investigator at the clinical site agree that the health of the subject and the risk/benefit profile is acceptable for the subject to receive treatment with the non-conforming investigational product. Development Quality Assurance then assesses the recommendation and is ultimately responsible for the drug product lot disposition. The JCAR017 PPDP is a standalone document.

7.3.6. Exception Use of Non-conforming Product

Once a decision is made for the exception use of non-conforming product, country-specific requirements will be followed for the release of the non-conforming product to treat a subject enrolled in a JCAR017 clinical trial. For example, approval from the local health authorities and/or IRBs/ECs will be obtained where required. In the EU, requirements provided in Section

11.54 of the EU Guideline on good manufacturing practice specific to advanced therapy medicinal products (European Commission, 2017) will be followed. Any subject will need to provide consent prior to receiving the non-conforming product. While subjects treated with the non-conforming product will be followed as per the Table of Events (Table 4) listed in the protocol, their data will be excluded from the primary safety/efficacy evaluable analysis. Their data will be analyzed separately.

Subjects treated with non-conforming product will be replaced for the purposes of study enrollment of per protocol evaluable subjects.

7.3.7. Overdose

Overdose, as defined for this protocol, refers to fludarabine (IV), cyclophosphamide (IV) or JCAR017 (IV). On a per-dose basis, an overdose is defined as the following amount over the protocol-specified dose of these drug(s) assigned to a given subject, regardless of any associated AEs or sequelae:

- IV: 10% over the protocol-specified dose

On a schedule or frequency basis, an overdose is defined as anything more frequent than the protocol required schedule or frequency. On an infusion rate basis, an overdose is defined as any rate faster or slower than the protocol-specified infusion time reflected as infusion time (±50%).

Complete data about drug administration, including any overdose, regardless of whether the overdose was accidental or intentional, should be reported in the CRF (see Section 10 for the reporting of AEs associated with overdose).

7.4. Method of Treatment Assignment

Interactive response technology will be employed to manage cohort assignments.

7.5. Packaging and Labeling

7.5.1. Product Tracking

The identity of the JCAR017 cell product will be checked and verified at each critical step of cell processing as part of the chain of identity. Procedures will be in place to address product tracking requirements and will encompass all process steps including collection of the leukapheresis product, receipt of the leukapheresis product, JCAR017 manufacturing and testing, in-process labeling, and JCAR017 labeling and packaging for shipment.

7.5.2. Product Packaging and Labeling

The label(s) for the JCAR017 cell product will include, but may not be limited to, Sponsor name, address and telephone number, the protocol number, cell product name, dosage form and strength (where applicable), amount of JCAR017 cell product per container, lot number, expiry date (where applicable), medication identification/kit number, dosing instructions, storage conditions, and required caution statements and/or regulatory statements as applicable. Additional information may be included on the label as applicable per local regulations

These same identifiers are maintained from leukapheresis collection throughout the manufacturing process and are used on the final JCAR017 cell product. These unique identifiers should be verified per the Chain of Identity procedures listed in the JCAR017 Product Administration Manual.

The final JCAR017 cell product is provided frozen and packaged to the study site per the dosing regimen specified in the protocol.

Prior to the JCAR017 infusion, two trained individuals will verify all unique identifier information in the presence of the subject to confirm that the information is correctly matched to the subject.

7.5.3. Cell Product Supply and Storage

Detailed instructions on the storage, handling, and preparation of JCAR017 cell product will be provided in the JCAR017 Product Administration Manual.

7.6. Investigational Product Accountability and Disposal

7.6.1. Accountability Procedures

An inventory must be performed and a product receipt log filled out and signed by the person accepting the shipment of JCAR017 cell product.

7.6.2. Drug Disposal and Destruction

Celgene (or designee) will review with the Investigator and relevant site personnel the process for JCAR017 cell product return, disposal, and/or destruction including responsibilities for the site versus Celgene (or designee).

7.7. Investigational Product Compliance

For the IV medication of JCAR017, the administered dosage will be recorded in the source documents. The Investigator(s) or designee is responsible for taking an inventory of each JCAR017 cell product received and comparing it with the accompanying shipping order/packaging slip. The Investigator(s) will verify the accuracy of the information on the shipping order/packaging slip.

At the study site, the JCAR017 cell product will be stored in a locked, safe area to prevent unauthorized access and should be stored as directed on the product label.

An accurate accounting of the dispensing and return of JCAR017 cell product for each study subject will be maintained in source documents on an ongoing basis by a member of the study site staff. Additionally, the JCAR017 cell product is lost or damaged, this information should be documented in the study subject's CRF and source documents.

Celgene will instruct the Investigator on the return, disposal, and/or destruction of unused cell product.

8. CONCOMITANT MEDICATIONS AND PROCEDURES

8.1. Permitted Concomitant Medications and Procedures

Medications taken by the subject at the time of an AE related to protocol-mandated procedures will be recorded from informed consent until initiation of LD chemotherapy. All medications will be recorded from the time of initiation of LD chemotherapy until 90 days after last dose of JCAR017. From 91 days post last dose of either LD chemotherapy or JCAR017 until the EOS visit, concomitant medications ongoing at the time of JCAR017 or LD chemotherapy-related AEs will be recorded. For subjects receiving lymphodepleting chemotherapy but not JCAR017, concomitant medications associated with AEs will be recorded for 30 days following the last dose of lymphodepleting chemotherapy.

Subjects should be discouraged from use of illicit drugs, herbal remedies, self-prescribed drugs, tobacco products, or excessive alcohol at any time during the clinical study.

If necessary, anticancer treatment is allowed for disease control while JCAR017 is being manufactured (see Section 6.1.3).

Due to the large amount of data generated during hospitalizations, a targeted concomitant medication collection approach will be utilized for the CRF. Therefore, the following medications should NOT be entered on the CRF during inpatient and Intensive Care Unit (ICU) stays:

- IV fluids (with the exception of IV fluids administered for treatment of hypotension associated with CRS, which should be recorded)
- Heparin flushes
- Stool softeners
- Vitamins, minerals, health supplements
- Saline flushes
- Lotions

The following treatments should be reported during inpatient and ICU stays:

- Vasopressors
- Oxygen use
- Antibiotics
- Growth factors

8.2. Prohibited Concomitant Medications and Procedures

Immunosuppressive medications including, but not limited to systemic corticosteroids at doses exceeding 20 mg/day of prednisone or equivalent, methotrexate, azathioprine, and tumor necrosis factor alpha (TNF-α) blockers.

The following medications are prohibited until lack of response, subsequent therapy for lymphoma, or 1 year following JCAR017 infusion, whichever comes first:

- Steroids: therapeutic doses (> 20 mg/day of prednisone or equivalent) unless used for treatment of sCRS. Therapeutic doses may be used in life-threatening situations, for other medical conditions when indicated, or after loss of detectable JCAR017 cells. Pretreatment containing steroids may be given for necessary medications (eg, IVIG) after discussion with Celgene. Premedication with steroids for JCAR017 infusion is not allowed. Physiologic replacement dosing of steroids is allowed. Topical steroids, inhaled steroids, and intrathecal steroids for CNS relapse prophylaxis are permitted

The following medications are prohibited during the treatment and follow-up periods unless used as an anticancer agent after lack of adequate response to JCAR017 or progression of lymphoma:

- Donor lymphocyte infusions
- Immunosuppressive therapies (eg, calcineurin inhibitors, methotrexate or other chemotherapeutics, mycophenolate, rapamycin, thalidomide, immunosuppressive antibodies such as anti-TNF, anti-IL-6, or anti-IL-6R), unless needed for treatment of GVHD
- Non-protocol-specified anticancer agents. Lymphocytic cytotoxic chemotherapy may be administered as an extraordinary measure to treat AEs of uncontrolled JCAR017 proliferation, or CRS or neurotoxicity unresponsive to other therapeutic interventions
- Cetuximab, or other anti-EGFR treatments, unless intended for treatment of uncontrolled JCAR017 proliferation
- Experimental agents
- Radiation, unless needed for local control of a single tumor lesion in the presence of other non-irradiated PET-positive lesions

8.3. Concomitant Medications and Procedures

Prophylactic treatment/measures are strongly recommended for subjects at risk for tumor lysis syndrome (TLS), per institutional or clinical standards.

Lymphodepleting regimens accompany JCAR017 administration and utilize cyclophosphamide and fludarabine. Please refer to the currently approved cyclophosphamide and fludarabine phosphate Summary of Product Characteristics (SmPC) (Cyclophosphamide, 2017; Fludarabine, 2019).

To minimize the risk of infusion reactions, all subjects should be premedicated with acetaminophen and diphenhydramine prior to JCAR017 infusion (see Section 7.3.2).

Supportive care for the management of CRS is detailed in Appendix M. In some cases, tocilizumab, an anti-IL-6R-antibody, may be required to treat toxicities such as severe cytokine release syndrome. Please refer to currently approved RoActemra® SmPC (RoActemra®, 2019). As per the approved EU SmPCs for CAR T cell therapy, the EMA is expecting a minimum of 4 doses of tocilizumab to be available prior to infusion for the management of CRS. For CAR T site in the EU, the recommendation is to follow the labeled guidance from the EMA. However, it is important to understand that the JCAR017 Management Guidelines for Cytokine Release Syndrome and Neurotoxicity and the recommended use of tocilizumab is different from the CRS management algorithms of the approved CAR Ts. Hence, Celgene requires that all JCAR017

global sites (eg, US, EU, Japan) must have at least 2 doses of tocilizumab available prior to infusion per a given subject. It is recommended to resupply in case tocilizumab is given.

The preferred dose to intervene in subjects with sCRS is 8 mg/kg. Other anti-IL-6 antagonist, if available in the country concerned, should be considered in the event of sCRS not responding to tocilizumab. Dosing of any other anti-IL-6 agent should be per prescribing information.

The use of red blood cells and platelet transfusions, and/or colony-stimulating factors is permitted per institutional or clinical standards.

The use of prophylactic or empiric anti-infective agents (eg, trimethoprim/sulfamethoxazole for pneumocystis pneumonia [PCP] prophylaxis, broad spectrum antibiotics, antifungals, or antiviral agents for febrile neutropenia) is permitted per institutional standards.

9. STATISTICAL CONSIDERATIONS

9.1. Overview

This is a single-arm, multi-cohort, multi-center, Phase 2 study to determine the efficacy and safety of JCAR017 in adult subjects with r/r DLBCL or with other advanced B-cell malignancies including FL3B and CNS lymphoma.

Data from all sites will be combined for the final analysis for each cohort. Results will be presented using descriptive statistics.

Efficacy information will be summarized separately per cohort. Safety information will be analyzed per cohort and across cohorts. PK information will be combined for all subjects across cohorts.

The data generated from Cohort 2 will complement the data from Study 017006 (PILOT) enrolling a similar population in the US.

9.2. Study Population Definitions

In this study the following analysis populations will be defined for the analysis and presentation of the data.

9.2.1. Screened Set

The Screened set will include all subjects who have signed informed consent.

9.2.2. Enrolled Set

The Enrolled set will include all subjects who have signed informed consent, who pass all eligibility criteria at screening and undergo leukapheresis.

9.2.3. Leukapheresed Set

The Leukapheresed set will include all subjects who have undergone leukapheresis.

9.2.4. JCAR017-Treated Set

The JCAR017-treated set will include all subjects who have received JCAR017 cell product.

9.2.5. Efficacy Evaluable Set

The Efficacy Evaluable set will include all subjects who have received the JCAR017 cell product in accordance with drug product release specifications, and who had a baseline assessment and at least one post-JCAR017 infusion disease assessment.

9.2.6. qPCR Pharmacokinetic Analysis Set

The qPCR PK Analysis set includes subjects in the JCAR017-treated set who have both baseline and on study PK measurements as assessed by qPCR.

9.2.7. Flow Cytometry Pharmacokinetic Analysis Set

The flow cytometry PK Analysis set includes subjects in the JCAR017-treated set who have both baseline and on study PK measurements as assessed by flow cytometry.

9.2.8. Patient-Reported Outcome Analysis Set

The PRO Analysis set will include all subjects who complete their baseline PRO questionnaires and have at least one post-baseline measurement in the JCAR017-treated set.

9.2.9. Population Analyses

Primary efficacy analysis will be based on the JCAR017-treated set. The Enrolled set and Efficacy Evaluable set will be used for supportive analyses when applicable. Safety analysis will be based on the JCAR017-treated set. The PK analysis will be based on the PK analysis set. Patient-reported outcomes will be analyzed based on the PRO Analysis set.

9.3. Sample Size and Power Considerations

Sample size and power were calculated using EAST® Version 6.4 software system.

9.3.1. Cohort 1

A sample size of 34 subjects treated with JCAR017 provides at least 90% power to reject the null hypothesis of response rate less than 40% assuming the target response rate of 70% using an exact binomial test with an overall two-sided significance level of 0.05 considering a formal interim analysis with the first 10 subjects treated with JCAR017 being followed for at least 3 months after JCAR017 infusion to test the superiority of JCAR017.

An interpolated spending function will be used as efficacy boundary for the interim analysis with a significance level of 0.01. The significance level for efficacy for the interim and primary analyses will be 0.01 and 0.017 (both one-sided), respectively. The calculation was performed using EAST 6.4 (Cytel Inc.).

The primary analysis for Cohort 1 is planned after at least 34 subjects have been treated with JCAR017 and the last subject has been followed for at least 6 months or until death, progressive disease, or withdrawal from study.

9.3.2. Cohort 2

Approximately 28 subjects will be treated with JCAR017 in Cohort 2. A sample size estimate of 28 subjects treated with JCAR017 would provide at least 80% power to reject the null hypothesis of response rate less than 40% assuming the target response rate of 70% using an exact binomial test with two-sided significance level 0.05.

The original null hypothesis had been defined based on a preliminary estimate from the literature for 2L populations. A retrospective patient Real-World data cohort will be used as a more comparable external/synthetic control to provide the reference rate for the null hypothesis testing of ORR $\leq$ p0% in the primary analysis. Generation of the external control will be described in the Real-World Evidence (RWE) Study CA082-014 Statistical Analysis Plan (SAP). The primary analysis for Cohort 2 is planned after approximately 28 subjects have been treated with

JCAR017 and have been followed for at least 6 months after first response (either CR or PR) or until death, progressive disease, or withdrawal from study.

9.3.3. Cohort 3 (Japan only)

At least 10 subjects treated with JCAR017 will be enrolled to evaluate preliminary efficacy and safety.

In Japan, analysis will be conducted by combining Cohorts 1, 2 and 3. The primary efficacy analysis will be performed after at least 10 Japanese subjects in Cohort 3 have been treated with JCAR017 and have been followed for at least 3 months or until death, progressive disease, or withdrawal from study, and at the time when the number of subjects, who are eligible for the Efficacy Evaluable Set, has reached at least 34 subjects when combining Cohorts 1, 2 and 3. The primary efficacy analysis and safety analysis will be based on the JCAR017-Treated Set.

The primary efficacy endpoint is ORR. A sample size of 34 subjects provides at least 90% power to reject the null hypothesis of a response rate less than 40% assuming a target response rate of 70% with a one-sided significance level of 0.025 using an exact binomial test. Hence, we can formally test for statistical significance of the results with at least 34 subjects.

Other efficacy endpoints such as complete response rate, event-free survival, progression-free survival, overall survival and duration of response will also be analyzed for these subjects. Another objective will be to observe whether there is a consistent trend in the efficacy results for the at least 10 Japanese subjects in Cohort 3 (Japan only) compared to the efficacy results in the subjects in Cohort 1 and 2.

With regards to safety, the type, frequency, severity, and causality of AEs, including SAEs and laboratory abnormalities, will be reported for these subjects.

9.3.4. Cohort 7

Cohort 7 is for subjects intended to be treated as outpatients. Subjects will be considered outpatients if they leave the clinic or are discharged from the hospital on the day of JCAR017 infusion.

This cohort is designed for estimation of incidence of safety events and does not include formal hypothesis testing or adjustment for multiplicity. For any individual incidence rate (eg, AEs), 24 subjects would provide a precision of ± 20.9% to estimate each endpoint assuming a CI of 95%. This is based on an event rate of 50% using the exact Clopper-Pearson method.

An analysis will be conducted when all treated subjects have been followed for at least 6 months after first response. In the Juno Study 017001, treatment with JCAR017 in subjects with r/r aggressive B-cell NHL resulted in observed incidence rates for Grade ≥ 3 CRS or NT, infections, and prolonged cytopenias of 12%, 9%, and 38%, respectively (data on file). If similar rates are observed in this study, this would provide sufficient precision for meaningful interpretation of the observed rates. Example rates and associated 95% CI are given in Table 8.

Table 8: Example Rates (± 95% Confidence Intervals)

Rate	Sample Size	Expected Count	Lower 95% CI*	Upper 95% CI*
70%	24	17	48.9%	87.4%
50%	24	12	29.1%	70.9%
38%	24	9	18.8%	59.4%
12%	24	3	2.7%	32.4%
8%	24	2	1%	27%

Abbreviation: CI = Confidence Interval.
* Based on exact Clopper-Pearson method.

9.3.5. Gated Cohorts

Cohorts 4 and 5 may be opened at Celgene's discretion (see Section 3.1):

- Cohort 4: A target of 10 subjects for which JCAR017 has been manufactured will be enrolled to evaluate preliminary efficacy and safety
- Cohort 5: A target of 10 subjects treated with JCAR017 will be enrolled to evaluate preliminary efficacy and safety
- Cohort 6 (REMOVED)

9.4. Background and Demographic Characteristics

Subject's age, height, weight, and baseline characteristics will be summarized using descriptive statistics, while sex, race and other categorical variables will be provided using frequency tabulations for both JCAR017-treated set and Enrolled set for each cohort. Medical history data will be summarized using frequency tabulations by Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and preferred term (PT) for both the JCAR017-treated set and Enrolled set for each cohort.

9.5. Subject Disposition

Summaries of subject disposition will be provided for both JCAR017-treated set and Enrolled set. The number and percentage of subjects who are eligible for study treatment but not able to successfully generate a JCAR017 cell product, along with the reason(s) for manufacturing failure, will be summarized per cohort.

9.6. Efficacy Analysis

9.6.1. General Consideration

The primary efficacy analysis will be based on the JCAR017-treated set. The Leukapheresed set, Enrolled set and Efficacy Evaluable set will be used as supportive analysis when applicable.

For binary endpoints, such as ORR, the frequency distribution (n, %) will be provided. The point estimate together with two-sided exact 95% CI will be provided.

For time-to-event endpoints such as EFS, PFS and OS, the Kaplan-Meier product limit method will be used to estimate the survivorship function. Event rates at specific timepoints will be estimated from the Kaplan-Meier curves. Medians together with two-sided 95% CI will be calculated.

9.6.2. Primary Endpoint

The primary efficacy endpoint for Cohorts 1, 2, 3, 4 and 5 is ORR determined by an IRC (Cohorts 1, 2 and 3) or by Investigator assessment (Cohorts 4, and 5) after JCAR017 infusion. For subjects with NHL (including subjects with secondary CNS involvement) the ORR is defined as the proportion of subjects with a best overall response (BOR) of either CR or PR from JCAR017 infusion until disease progression, end of study, the start of another anticancer therapy, or HSCT. For subjects with PCNSL the ORR is defined as the proportion of subjects with BOR of either CR, complete response unconfirmed (Cru) or PR from JCAR017 infusion until disease progression, end of study, the start of another anticancer therapy, or HSCT.

Subjects with unknown or missing response will be included in the analysis counted as non-responders (JCAR017-treated set, Leukapheresed set, and Enrolled set).

Of note, the primary endpoint for Cohort 7 is safety (type, frequency, and severity of all AEs, including SAEs and laboratory abnormalities).

An exact binomial test with 1-sided significance level 0.025 will be used for hypothesis testing of ORR. The ORR will be calculated along with the two-sided 95% exact Clopper-Pearson CI.

9.6.3. Secondary Efficacy Endpoints

Secondary endpoints analyses will be performed to further assess the efficacy of JCAR017.

Complete Response Rate

Complete response rate is defined as percentage of subjects achieving a BOR of CR/CRu following JCAR017 infusion until disease progression, end of study, the start of another anticancer therapy, or HSCT.

Subjects with unknown or missing response will be included in the analysis counted as non-responder (JCAR017-treated set, Leukapheresed set, and Enrolled set).

Event-free Survival

Event-free survival is defined as the interval from the date of JCAR017 infusion to the earliest of the following events: death from any cause, progressive disease, or starting a new anticancer therapy.

In case a subject does not have an EFS event prior to data cutoff date, EFS will be censored at the date of the last adequate disease assessment.

Progression-free Survival

Progression-free survival is defined as the interval from the date of JCAR017 infusion to progressive disease or death due to any cause, whichever occurs first.

Subjects who did not experience progressive disease and who did not die before the data cutoff date will be censored at the time of the last visit with adequate response assessment when the subjects were known not to have progressed.

Overall Survival

Overall survival is defined as the interval from the date of JCAR017 infusion to the date of death due to any reason.

Data from surviving subjects will be censored at the last time that the subject is known to be alive.

Duration of Response

Duration of response is defined as the interval from the first documentation of response to progressive disease or death from any cause, whichever occurs first. Duration of response will be evaluated for subjects who achieve a response.

Subjects who did not experience progressive disease and who did not die before the data cutoff date will be censored at the time of the last visit with adequate response assessment when the subjects were known not to have progressed.

Pharmacokinetics

Maximum concentration, time to peak concentration, area under the curve, and persistence of JCAR017 will be analyzed based on the PK analysis sets for qPCR and flow cytometry.

Health-Related Quality of Life

Patient-reported outcomes as measured by EORTC QLQ-C30, EQ-5D-5L and the FACT-LymS will be analyzed based on the PRO analysis set.

Overall Response Rate

Secondary efficacy endpoints for Cohort 7 will also include ORR defined as the proportion of subjects with a BOR of either CR or PR from JCAR017 infusion until disease progression, end of study, the start of another anticancer therapy, or HSCT.

9.6.4. Subgroup Analyses

Efficacy subgroup analyses will be performed on the following variables:

- Age: < 40, ≥ 40 to < 65, ≥ 65 years at screening (additional age categories per cohorts are defined in the SAP)
- Performance status: ECOG 0 versus 1 versus 2
- Sex: male versus female
- Ethnicity: Hispanic or Latino versus not Hispanic or Latino
- Race: white versus other races
- Prior hematopoietic stem cell transplantation status: yes versus no
- Prior response status: The status is refractory if a subject achieved less than a CR to last prior therapy; otherwise the status is relapsed

  - Refractory versus relapsed
  - Refractory or relapsed disease < 12 months (defined as a CR lasting no more than 12 months) versus relapsed ≥ 12 months to first-line therapy (for Cohort 2)
- Prior chemotherapy response status: chemorefractory versus chemosensitive to last therapy. The status is chemorefractory if a subject achieved stable disease or PD to last chemotherapy-containing regimen or relapsed < 12 months after autologous stem cell transplantation; otherwise the status is chemosensitive
- CNS disease status: known as CNS disease versus no known CNS disease at screening
- Cell of origin: ABC versus GCB
- Molecular subtype: HGBL versus DLBCL without MYC and BCL2 and/or BCL6 rearrangements

Subgroup analyses will only be performed if there are enough subjects in each subgroup. Some grouping of classes will be considered if there are too few subjects in some subgroups. Other subgroup analyses may be performed if deemed appropriate, as described in the SAP.

9.7. Safety Analysis

Safety analysis including treatment-emergent adverse events (TEAE) and laboratory findings will be based on JCAR017-treated set aggregated for all cohorts as well as separately for each cohort.

Treatment-emergent adverse events ≥ Grade 3 in subjects infused with JCAR017 in a clinical trial setting include neurologic toxicities, such as encephalopathy, hypotension, cytokine release syndrome, febrile neutropenia, and hypoxia. These events will be carefully monitored during JCAR017 infusion and during follow-up. The following safety assessments will also be monitored:

- The timing and length of inpatient hospitalization
- Physical examination
- MMSE and ICE score (if performed)
- Laboratory evaluations to monitor closely for neurologic changes, CRS, and fever
- Expected cytopenia and potential infections attributable to the LD chemotherapy

9.7.1. Adverse Events

- Adverse events will be coded using MedDRA SOC and PT
- The severity of each adverse event will be graded by the Investigator using CTCAE Version 4.03, unless otherwise specified in the protocol. If CTCAE criteria do not exist for a given event, the Investigator should use one of the following: Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life-threatening), or Grade 5 (fatal) to describe the maximum intensity of the adverse event

- Related AEs are those for which the Investigator selects "Related" to JCAR017 or LD therapy on the AE CRF. Relatedness will always default to the Investigator's choice, not that of the Medical Monitor
- Adverse events will be identified and captured as SAEs if they meet the definition for SAE

9.7.2. Definition of Treatment-emergent Adverse Event

A JCAR017 TEAE is defined as below:

- Any AE that occurs from start of JCAR017 infusion and up to 90 days after JCAR017 infusion

9.7.3. Summary of Adverse Events

All AEs will be listed. The focus of AE summarization will be on JCAR017 TEAEs.

Adverse event summaries will provide the number and percentage of subjects with TEAEs by SOC and PT, based on the JCAR017-treated set as follows (a brief high-level summary will also be provided):

- All AEs
- All AEs by severity grade
- Grade ≥ 3 AEs
- Grade 5 AEs
- All SAEs
- All JCAR017-related AEs
- JCAR017-related Grade ≥ 3 AEs
- JCAR017-related Grade 5 AEs
- All JCAR017-related SAEs
- LD chemotherapy-related AEs
- All AEs occurring after 90 days following the infusion of JCAR017
- All AEs recorded between signing informed consent and the infusion of JCAR017

Multiple occurrence of the same events will be counted only once per subject in each summary.

Adverse events will be summarized and listed first by SOC in descending order of incidence and then by PT (within each SOC), also in descending order of incidence. In summaries by severity grade, the most severe grade will be used for those AEs that occur more than once for an individual subject during the study.

In addition to the above summary tables, all TEAEs and SAEs will be summarized by SOC only and by PT only in order of descending incidence.

9.8. Laboratory Evaluations

The focus of the laboratory data summarization will be on the JCAR017 treatment-emergent laboratory abnormalities using the JCAR017-treated set. JCAR017 treatment-emergent laboratory abnormalities are defined as an abnormality that, compared to baseline, worsens by at least one grade after JCAR017 infusion and up to 90 days after JCAR017 infusion. The baseline value is defined as the last available recorded value on or prior to the date of JCAR017 infusion.

All laboratory data will be listed with a variable indicating whether the event is treatment-emergent.

9.8.1. Numeric Laboratory Results

Summaries of laboratory data will be based on observed data and will be reported using standard international units. Baseline, raw values, and changes from baseline will be summarized using descriptive statistics for each laboratory test specified in the study protocol.

Median (Q1, Q3) values for each laboratory parameter will be plotted over time using a box plot. Mean ± SE of the observed values and changes from baseline for each laboratory parameter will be plotted over time using line plots.

9.8.2. Graded Laboratory Values

Applicable hematological and serum biochemistry laboratory data will be programmatically graded according to CTCAE, Version 4.03 severity grade: mild (Grade 1), moderate (Grade 2), severe (Grade 3), or life threatening (Grade 4). Grade 0 includes all non-missing values that do not meet criteria for an abnormality of at least Grade 1. Some laboratory tests have criteria for both increased and decreased levels; analyses for each direction (ie, increased, decreased) will be presented separately.

9.8.3. Summaries of Laboratory Abnormalities

All laboratory data will be listed. The focus of laboratory data summarization will be on JCAR017 treatment-emergent laboratory abnormalities. Summaries (number and percentage of subjects) of baseline, post-baseline at each visit, and worst post-baseline treatment-emergent laboratory abnormalities will be provided. Subjects will be categorized according to the most severe abnormality grade. All summaries of laboratory abnormalities will be based on the JCAR017-treated set.

Shift tables will be presented by showing the change in CTCAE severity grade from baseline to each post-baseline visit and to the maximum post-baseline grade. For parameters for which a CTCAE severity scale does not exist, shift tables will be presented showing change in results from the baseline value (low, normal, and high) to each post-baseline visit and to the worst post-baseline value (low, normal, and high).

9.9. Other Topics

9.9.1. Data Safety Monitoring Board

An independent DSMB will review cumulative study data over the course of the study to evaluate safety, protocol conduct, and scientific validity and integrity of the trial. The DSMB,

composed of a statistician and select physicians with experience in hematology/oncology and/or T cell therapy, will be assembled under a dedicated charter specifically developed for safety oversight of the study. DSMB members will not be actively involved in the study design, conduct, or subject accrual and must not have financial, proprietary, professional, or other interests that may affect impartial, independent decision making.

The DSMB will be convened prior to enrollment of the first subject on the protocol and will meet approximately twice a year throughout the trial and as needed to address any safety issues that may arise. Subject safety will be evaluated as specified in the Data Safety and Monitoring Plan (DSMP) or DSMB charter. The DSMB will provide advice to Celgene as outlined in the DSMB charter. The effectiveness of the risk mitigation plan will be reviewed by the DSMB at each meeting. After each DSMB meeting, a statement summarizing the outcome of the review will be provided to Celgene. If the DSMB recommends continuing the study, no details from the review will be revealed. Celgene will provide this statement from the DSMB review to the study Investigators for submission to the site's IRB/EC within 10 working days after receipt of the statement.

9.9.2. Scientific Steering Committee

The conduct of this trial will be overseen by a scientific steering committee (SSC), presided over by the coordinating Principal Investigator and if possible the representative Regional Investigators from countries participating in this study. The SSC will serve in an advisory capacity to the Sponsor. Operational details for the SSC will be detailed in a separate SSC charter.

Note: The SSC is separate from the DSMB.

9.9.3. Exploratory Analysis

The PK by flow cytometry, pharmacodynamic (Pd) and biomarker analyses as well as the health technology assessment analyses will be specified exploratory analyses. The exploratory endpoints of the study are listed in Section 2. Detailed information regarding the collection, handling, and shipment of biomarker samples is provided in the JCAR017-BCM-001 laboratory manual. Further details of the exploratory analyses are provided in the statistical analysis plan.

Planned exploratory analyses will include:

- Characterization of the PK profile of JCAR017 as assessed by flow cytometry to enumerate and immunophenotype JCAR017 cells
- Pharmacodynamic biomarker effects of JCAR017 by assessment of B-cell aplasia, immunoglobulins, soluble biomarkers and markers of inflammation (CRP and ferritin)
- Flow cytometry immunophenotyping of JCAR017 cells and resident immune cells in the blood
- Cellular and genomic profiling of tumor biopsy samples to investigate the tumor and tumor microenvironment for mechanisms of response and relapse

- To characterize the prevalence and incidence of humoral immune responses to JCAR017. Cellular immunogenicity may also be evaluated by testing PBMC for the presence of anti-JCAR017 cytotoxic T cell
- Replication-competent lentivirus safety testing will be performed on DNA obtained from peripheral blood, the presence of viral vector envelope sequences will be assessed using a qPCR based assessment
- Safety: The effect of treatments directed at sCRS and neurotoxicity on duration and severity of sCRS and neurotoxicity
- Hospital resource utilization: Number of inpatient days, ICU days, and outpatient visits
- Subject experience on JCAR017: Qualitative data obtained from completion of patient interviews

10. ADVERSE EVENTS

10.1. Monitoring, Recording and Reporting of Adverse Events

An AE is any noxious, unintended, or untoward medical occurrence that may appear or worsen in a subject during the course of a study. It may be a new intercurrent illness, a worsening concomitant illness, an injury, or any concomitant impairment of the subject's health, including laboratory test values (as specified by the criteria in Section 10.3), regardless of etiology. Any worsening (ie, any clinically significant adverse change in the frequency or intensity of a pre-existing condition) should be considered an AE.

Abuse, withdrawal, sensitivity or toxicity to an investigational product (IP) should be reported as an AE. Overdose, accidental or intentional, whether or not it is associated with an AE should be reported on the overdose CRF (see Section 7.3.7 for the definition of overdose). Any sequela of an accidental or intentional overdose of an investigational product should be reported as an AE on the AE CRF. If the sequela of an overdose is an SAE, then the sequela must be reported on an SAE report form and on the AE CRF. The overdose resulting in the SAE should be identified as the cause of the event on the SAE report form and CRF but should not be reported as an SAE itself.

In the event of overdose, the subject should be monitored as appropriate and should receive supportive measures as necessary. There is no known specific antidote for JCAR017, fludarabine or cyclophosphamide overdose. Actual treatment should depend on the severity of the clinical situation and the judgment and experience of the treating physician.

All subjects will be monitored for AEs during the study. Assessments may include monitoring of any or all of the following parameters: the subject's clinical symptoms, laboratory, pathological, radiological or surgical findings, physical examination findings, or findings from other tests and/or procedures.

Adverse events must be recorded as shown in Table 9. If they meet the seriousness criteria, they will be reported to Drug Safety as provided in Section 10.5.

Table 9: Recording Periods for Adverse Events

Start	End	Required Recording
Signing of informed consent	Start of LD chemotherapy	Only AEs related to any study procedure, and any toxicity change to ongoing AEs will be recorded in the CRF as a separate AE record Conditions unrelated to study procedures should be reported in the medical history CRF
Start of LD chemotherapy	Day 90, after JCAR017 infusion	All AEs, irrespective of causality, and any toxicity change to ongoing AEs will be recorded in the CRF as a separate AE record
Day 91, after JCAR017 infusion	End of study	Only AEs related to any study procedure or JCAR017 will be collected; changes in toxicity grade will be recorded as a single event with the highest toxicity grade experienced at any time during the event recorded
Start of LD chemotherapy	End of Study	The following clinical conditions should be reported as SAEs, regardless of relatedness to JCAR017: • Second Primary Malignancies • New onset or exacerbation of pre-existing neurologic disorder • New onset of rheumatologic disorder or other autoimmune disorder • New onset of hematologic disorder Rare and unexpected disorder with an unknown etiology (eg, Guillain Barre, Stevens Johnsons Syndrome

If a subject receives lymphodepleting therapy but not JCAR017, all AE/SAEs should be recorded/reported for 30 days following the last dose of lymphodepleting chemotherapy.

Serious Adverse Events made known to the Investigator at any time thereafter that are suspected of being related to IP and/or to any study procedure will be recorded as well. Documentation must be supported by an entry in the subject's source document.

A diagnosis or syndrome should be recorded on the AE page of the CRF rather than the individual signs or symptoms of the diagnosis or syndrome. In addition to recording CRS and neurotoxicity as a diagnosis, the signs and symptoms of CRS and neurotoxicity will be recorded on separate CRFs. Any medical condition already present prior to first LD chemotherapy should not be reported as an AE unless the medical condition is related to any study procedure and increases in severity. In this case, it should be reported as an AE and indicated as a worsening event.

Inpatient or ICU stays, while anticipated, are not scheduled protocol-defined visits. In addition, inpatient or ICU admissions can generate large amounts of clinical data (eg, multiple concomitant medications, frequent concomitant medication dose changes, laboratory values, and vital sign assessments). Therefore, targeted collection of data from inpatient or ICU stays, as well as a separate CRF for detailing specific adverse events of special interest (AESI; ie, signs

and symptoms of CRS and neurotoxicity), will be utilized for the purpose of adequately describing the expected risks of JCAR017 and the recommendations for managing these risks.

Adverse Events and SAEs will be recorded on the AE page of the CRF and in the subject's source documents. All SAEs meeting the criteria described in Table 9 must be reported to Celgene Drug Safety within 24 hours of the Investigator's knowledge of the event by facsimile, or other appropriate method, using the SAE Report Form, or approved equivalent form.

10.2. Evaluation of Adverse Events

A qualified Investigator will evaluate all adverse events as to:

10.2.1. Seriousness

An SAE is defined as any AE occurring at any dose that:

- Results in death;
- Is life-threatening (ie, in the opinion of the Investigator, the subject is at immediate risk of death from the AE);
- Requires inpatient hospitalization or prolongation of existing hospitalization (hospitalization is defined as an inpatient admission, regardless of length of stay).
- Results in persistent or significant disability/incapacity (a substantial disruption of the subject's ability to conduct normal life functions);
- Is a congenital anomaly/birth defect;
- Constitutes an important medical event;

  Important medical events are defined as those occurrences that may not be immediately life-threatening or result in death, hospitalization, or disability, but may jeopardize the subject or require medical or surgical intervention to prevent one of the other outcomes listed above. Medical and scientific judgment should be exercised in deciding whether such an AE should be considered serious.

Events **not considered** to be SAEs are hospitalizations for:

- A standard procedure for protocol therapy administration. However, hospitalization or prolonged hospitalization for a complication of therapy administration will be reported as an SAE
- Routine treatment or monitoring of the studied indication not associated with any deterioration in condition
- The administration of blood or platelet transfusion as routine treatment of studied indication. However, hospitalization or prolonged hospitalization for a complication of such transfusion remains a reportable SAE
- A procedure for protocol/disease-related investigations (eg, surgery, scans, endoscopy, sampling for laboratory tests, bone marrow sampling). However, hospitalization or prolonged hospitalization for a complication of such procedures remains a reportable SAE

- Hospitalization or prolongation of hospitalization for technical, practical, or social reasons, in absence of an AE
- A procedure that is planned (ie, planned prior to start of treatment on study); must be documented in the source document and the CRF. Hospitalization or prolonged hospitalization for a complication remains a reportable SAE
- An elective treatment of or an elective procedure for a pre-existing condition, unrelated to the studied indication, that has not worsened from baseline
- Emergency outpatient treatment or observation that does not result in admission, unless fulfilling other seriousness criteria above

If an AE is considered serious, both the AE page/screen of the CRF and the SAE Report Form must be completed.

For each SAE, the Investigator will provide information on severity, start and stop dates, relationship to LD chemotherapy and/or JCAR017, action taken regarding LD chemotherapy and/or JCAR017, and outcome.

10.2.2. Severity and Intensity

For both AEs and SAEs, the Investigator must assess the severity/intensity of the event.

The severity/intensity of AEs will be graded based upon the subject's symptoms according to the Common Terminology Criteria for Adverse Events (CTCAE, Version 4.03);

Adverse Events that are not defined in the CTCAE should be evaluated for severity/intensity according to the following scale:

- Grade 1 = Mild – transient or mild discomfort; no limitation in activity; no medical intervention/therapy required
- Grade 2 = Moderate – mild to moderate limitation in activity, some assistance may be needed; no or minimal medical intervention/therapy required
- Grade 3 = Severe – marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalization is possible
- Grade 4 = Life-threatening – extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable
- Grade 5 = Death – the event results in death

The term "severe" is often used to describe the intensity of a specific event (as in mild, moderate or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This criterion is not the same as "serious" which is based on subject/event outcome or action criteria associated with events that pose a threat to a subject's life or functioning.

Seriousness, not severity, serves as a guide for defining regulatory obligations.

10.2.3. Causality

The Investigator must determine the relationship between the administration of LD chemotherapy and JCAR017 and the occurrence of an AE/SAE as Not Suspected or Suspected as defined below:

- Not suspected:A causal relationship of the adverse event to either LD chemotherapy or JCAR017 administration is **unlikely or remote**, or other medications, therapeutic interventions, or underlying conditions provide a sufficient explanation for the observed event
- Suspected: There is a **reasonable possibility** that the administration of LD chemotherapy or JCAR017 caused the adverse event. 'Reasonable possibility' means there is evidence to suggest a causal relationship between the LD chemotherapy or JCAR017 and the adverse event

Causality should be assessed and provided for every AE/SAE based on currently available information. Causality is to be reassessed and provided as additional information becomes available.

If an event is assessed as suspected of being related to a comparator, ancillary or additional LD chemotherapy or JCAR017 that has not been manufactured or provided by Celgene, please provide the name of the manufacturer when reporting the event.

10.2.4. Duration

For both AEs and SAEs, the Investigator will provide a record of the start and stop dates of the event.

10.2.5. Action Taken

The Investigator will report the action taken with investigational products as a result of an AE or SAE, as applicable (eg, discontinuation, interruption, or dose reduction of investigational products, as appropriate) and report if concomitant and/or additional treatments were given for the event.

10.2.6. Outcome

The Investigator will report the outcome of the event for both AEs and SAEs.

Serious adverse events will be followed until they return to baseline, the event stabilizes or is no longer considered clinically significant by the Investigator; the subject dies or withdraws consent; or study closure.

10.3. Abnormal Laboratory Values

An abnormal laboratory value is considered to be an AE if the abnormality:

- Results in discontinuation from the study;
- Requires treatment, modification/interruption of LD chemotherapy or JCAR017 cell product dose, or any other therapeutic intervention (including transfusions or growth factors); or

- Is judged to be of significant clinical importance, eg, one that indicates a new disease process and/or organ toxicity, or is an exacerbation or worsening of an existing condition.

Regardless of severity grade, only laboratory abnormalities that fulfill a seriousness criterion need to be documented as a serious adverse event.

If a laboratory abnormality is one component of a diagnosis or syndrome, then only the diagnosis or syndrome should be recorded on the AE page/screen of the CRF. If the abnormality was not a part of a diagnosis or syndrome, then the laboratory abnormality should be recorded as the AE. If possible, the laboratory abnormality should be recorded as a medical term and not simply as an abnormal laboratory result (eg, record thrombocytopenia rather than decreased platelets).

10.4. Pregnancy

All pregnancies and suspected pregnancies (including elevated β-hCG or positive pregnancy test in a female subject of childbearing potential regardless of disease state) occurring any time after receipt of LD chemotherapy or infusion of JCAR017, in either a female subject of childbearing potential or a partner of childbearing potential of a male subject are immediately reportable events. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Celgene Drug Safety immediately by email, phone or facsimile, or other appropriate method, using the Pregnancy Initial Report Form, or approved equivalent form.

10.4.1. Females of Childbearing Potential

The Investigator will follow the female subject until completion of the pregnancy and afterwards up to 1 year of the newborn baby, and must notify Celgene Drug Safety immediately about the outcome of the pregnancy (either normal or abnormal outcome) using the Pregnancy Follow-up Report Form, or approved equivalent form.

If the outcome of the pregnancy was abnormal (eg, spontaneous abortion), the Investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE to Celgene Drug Safety by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 28 days that the Investigator suspects is related to the in utero exposure to the LD chemotherapy or JCAR017 should also be reported to Celgene Drug Safety by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

10.4.2. Male Subjects

If a female partner of a male subject who has received LD chemotherapy and/or JCAR017 becomes pregnant, the male subject should notify the Investigator, and the pregnant female partner should be advised to call their healthcare provider immediately. The pregnant partner will be asked for consent (if permitted by local regulations) for follow-up by the Investigator until completion of the pregnancy and afterwards up to 1 year of the newborn baby.

10.5. Reporting of Serious Adverse Events

Any AE that meets any criterion for an SAE requires the completion of an SAE Report Form in addition to being recorded on the AE page/screen of the CRF. All SAEs must be reported to Celgene Drug Safety within 24 hours of the Investigator's knowledge of the event by facsimile, or other appropriate method (eg, via email), using the SAE Report Form, or approved equivalent form. This instruction pertains to initial SAE reports as well as any follow-up reports.

The Investigator is required to ensure that the data on these forms is accurate and consistent. This requirement applies to all SAEs (regardless of relationship to LD chemotherapy or JCAR017) recorded in the CRF as described in Section 10.1.

The SAE report should provide a detailed description of the SAE and include a concise summary of hospital records and other relevant documents. If a subject died and an autopsy has been performed, copies of the autopsy report and death certificate are to be sent to Celgene Drug Safety as soon as these become available. Any follow-up data should be detailed in a subsequent SAE Report Form, or approved equivalent form, and sent to Celgene Drug Safety.

Progressive disease is considered as a study endpoint and will not be reported as an SAE. However, any sign, symptom, or manifestation of progressive disease that meet any of the seriousness criteria will be reported as individual SAE.

Where required by local legislation, the Investigator is responsible for informing the Institutional Review Board/Ethics Committee (IRB/EC) of the SAE and providing them with all relevant initial and follow-up information about the event. The Investigator must keep copies of all SAE information on file including correspondence with Celgene and the IRB/EC.

10.5.1. Safety Queries

Queries pertaining to SAEs will be communicated from Celgene Drug Safety to the site via facsimile or electronic mail. The response time is expected to be no more than five (5) business days. Urgent queries (eg, missing causality assessment) may be handled by phone.

10.5.2. Death Reports

Deaths due to progressive disease will not be reported as an SAE unless considered related to LD chemotherapy or JCAR017 (ie, if assessed as lack of efficacy by the Investigator). Any sign, symptom, or manifestation of progressive disease that meet any of the seriousness criteria and result in death will be reported as individual SAEs. Any other AEs leading to death should be reported as an SAE according to Table 9.

10.6. Expedited Reporting of Adverse Events

For the purpose of regulatory reporting, Celgene Drug Safety will determine the expectedness of events suspected of being related to JCAR017 based on the Investigator's Brochure.

For countries within the European Economic Area (EEA), Celgene or its authorized representative will report in an expedited manner to Regulatory Authorities and Ethics Committees concerned, suspected unexpected serious adverse reactions (SUSARs) in accordance with Directive 2001/20/EC and the Detailed Guidance on collection, verification and

presentation of adverse reaction reports arising from clinical trials on investigational products (IPs) for human use (ENTR/CT3) and also in accordance with country-specific requirements.

Celgene or its authorized representative shall notify the Investigator of the following information:

- Any AE suspected of being related to the use of JCAR017 in this study or in other studies that is both serious and unexpected (ie, SUSAR);
- Any finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.

Where required by local legislation, the Investigator shall notify his/her IRB/EC promptly of these new serious and unexpected AE(s) or significant risks to subjects.

The Investigator must keep copies of all pertinent safety information on file including correspondence with Celgene and the IRB/EC (see Section 14.3 for record retention information).

Celgene Drug Safety Contact Information:

For Celgene Drug Safety contact information, please refer to the Serious Adverse Event Report Form Completion Guidelines or to the Pregnancy Report Form Completion Guidelines.

10.7. Adverse Event of Special Interest

An adverse event of special interest (AESI) is one of scientific and medical interest specific to understanding of the Investigational Product and may require close monitoring and rapid communication by the Investigator to the Sponsor. An AESI may be serious or nonserious. The rapid reporting of AESIs allows ongoing surveillance of these events in order to characterize and understand them in association with the use of this investigational product.

Adverse events of special interest for JCAR017 include but are not limited to:

- Infusion reaction
- Cytokine release syndrome (CRS)
- Neurological toxicity (NT)
- Macrophage activation syndrome (MAS)
- Tumor lysis syndrome (TLS)

Further information regarding the list of AESI can be found in the statistical analysis plan (SAP).

10.8. Potential Risks and Management of Treatment Toxicities

A summary of potential risks and management of treatment toxicity is provided below.

Expected toxicities are described in the Reference Safety Information (RSI) in the Investigator's Brochure (IB). These toxicities include, but are not limited to, Grade 4 CRS, neurotoxicity (eg, encephalopathy and/or seizures), and hypotension. The expected toxicities may also result in secondary toxicities of Grade 4 renal toxicity, hepatic toxicity, or other organ involvement. Consistent with the RSI in the JCAR017 IB all life-threatening or fatal events will be considered

unexpected for the purpose of reporting SUSARs to regulatory authorities, and if considered related to JCAR017 treatment will be reported in expedited fashion.

See the IB for a complete discussion of potential risks associated with JCAR017.

10.8.1. Management of Toxicities Associated with JCAR017

Cytokine release syndrome and NT are associated with CAR T cell therapies. Celgene has developed specific toxicity management guidelines for CRS and NT associated with Celgene cellular products based on current clinical experience across the clinical development programs (Appendix M). These recommendations are based on the CRS revised grading system (Lee, 2014) and the CTCAE and need to be used for grading of CRS and NT to guide management in this trial.

If available and adopted as per site standard practice, CRS and NT grading according to the American Society for Transplantation and Cellular Therapy Consensus Grading System (Lee, 2019) should also be recorded in the CRF to inform future modifications of the management guidelines.

10.8.1.1. Cytokine Release Syndrome

Administration of JCAR017 is associated with CRS. Cytokine release syndrome is characterized by fever, fatigue, nausea, headache, dyspnea, tachycardia, rigors, hypotension, hypoxia, myalgia/arthralgia, anorexia, and neurologic abnormalities (eg, altered mental status, aphasia, altered level of consciousness, and seizures or seizure-like activity). Cytokine release syndrome generally occurs within 2 weeks after CAR T cell infusion and in severe cases may be life-threatening.

Subjects at high risk of developing sCRS include those who develop the following (Davila, 2014):

- Fever (≥ 38 ºC) for at least 3 days
- Changes in 2 different cytokines of at least 75-fold or a maximum change in 1 cytokine of at least 250-fold
- One or more clinical signs of toxicity such as:
  - Hypotension (requiring vasopressor support)
  - Hypoxia (pO2 < 90%)
  - Neurologic disorders (including mental status changes, obtundation, and seizures)

Elevated CRP (≥ 20 mg/dL) and ferritin levels (> 5000 ng/mL) are also reliable indicators of sCRS. Thus, close observation of these subjects is strongly recommended.

Please refer to Appendix M for detailed description of CRS, grading and treatment recommendations. Note: Cetuximab is not indicated for the treatment of CRS.

10.8.1.2. Fever

The possibility of CRS should be considered for all subjects with fever (≥ 38.5°C) following JCAR017 infusion. Subjects should be monitored closely for hemodynamic instability and

changing neurologic status. Febrile subjects, neutropenic or otherwise, should be evaluated promptly for infection and managed per institutional or standard clinical practice.

10.8.1.3. Cytopenias

Severe (Grade ≥ 3) cytopenias, including anemia, leukopenia, neutropenia, and thrombocytopenia, can occur with both JCAR017 and lymphodepleting chemotherapy, and delayed recovery has been observed. Complete blood counts (CBCs) should be monitored after JCAR017 infusion until count recovery. Institutional guidelines should be followed in the event of Grade ≥ 3 cytopenias.

10.8.1.4. Infections

Life-threatening and fatal infections have been observed. Severe infections may include bacterial, fungal (including pneumocystis jirovecii), and viral infections (eg, cytomegalovirus [CMV], hepatitis B virus [HBV], respiratory viruses, and other viruses). A high index of suspicion is warranted in the event of prolonged or recurrent cytopenias, especially in conjunction with hypogammaglobulinemia, severe lymphopenia, and/or recent use of corticosteroids. Viral reactivation and other serious opportunistic infections should be considered in these settings, and prophylactic, pre-emptive, or symptomatic treatment with antimicrobial, antifungal, anti-pneumocystic, and/or antiviral therapies should be considered per local institutional guidelines.

10.8.1.5. Neurologic Toxicities

CAR T cell therapy is associated with neurologic toxicities. Neurologic symptoms can vary and may include altered mental status, aphasia, altered level of consciousness, and seizures or seizure-like activity. Neurologic toxicities can accompany CRS (precede or follow other CRS symptoms) or can occur in isolation. Neurologic symptoms generally occur within 3 weeks after CAR T cell infusion and in severe cases may be life-threatening.

Please refer to Appendix M for detailed description of neurologic toxicities, grading and treatment recommendations. Note: Cetuximab is not indicated for the treatment of neurologic toxicities.

10.8.1.6. Macrophage Activation Syndrome

Macrophage activation syndrome (MAS) is a serious disorder potentially associated with uncontrolled activation and proliferation of CAR T cells and subsequent activation of macrophages. MAS is typically characterized by high-grade, non-remitting fever, cytopenia, and hepatosplenomegaly. Laboratory abnormalities found in MAS include elevated inflammatory cytokine levels, serum ferritin, soluble IL-2 receptor (sCD25), triglycerides, and decreased circulating NK cells. Other findings include variable levels of transaminases, signs of acute liver failure, coagulopathy, and disseminated intravascular coagulopathy. There are no definitive diagnostic criteria for MAS; it is typically diagnosed using published criteria for hemophagocytic lymphohistiocytosis (Schulert, 2015). While there is considerable overlap in clinical manifestations and laboratory findings between MAS and CRS, other distinguishing MAS physical findings such as hepatosplenomegaly and lymphadenopathy are not common in adult subjects treated with activated T cell therapies.

Subjects treated with JCAR017 should be monitored for MAS, and cytokine-directed therapy should be considered as clinically indicated.

10.8.1.7. Infusion Reactions

Administration of JCAR017 may cause infusion reactions, such as fever, rigors, rash, urticaria, dyspnea, hypotension, and/or nausea.

To minimize the risk of infusion reactions, all subjects should be premedicated with acetaminophen and diphenhydramine prior to JCAR017 infusion (see Section 7.3.2). Mild infusion reactions should be managed expectantly with antipyretics, antihistamines, and anti-emetics. Corticosteroids should be avoided because of the potential impact on efficacy of infused JCAR017 cells. Rigors may be treated with meperidine.

The following guidelines should be followed for infusion reactions:

- Grade 1: administer symptomatic treatment; continue JCAR017 infusion of both CD8+ and CD4+ components at the same dose and rate
- Grade 2: stop administration of JCAR017; administer symptomatic treatment, and resume JCAR017 administration of both CD8+ and CD4+ components at a reduced rate of administration only after symptoms resolution
- Grade 3: stop administration of JCAR017, administer symptomatic treatment, and resume at a reduced rate of administration only after symptoms resolve. If Grade 3 reaction recurs, discontinue JCAR017 infusion; no further CD8+ or CD4+ components of JCAR017 should be administered
- Grade 4: discontinue administration of JCAR017 and administer symptomatic treatment as necessary; no further CD8+ or CD4+ components of JCAR017 should be administered.

10.8.1.8. Tumor Lysis Syndrome

Both LD chemotherapy and JCAR017 may cause TLS in subjects with high disease burden. Subjects should be closely monitored for laboratory evidence of TLS (hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia; see Appendix L), and subjects at high risk for developing TLS, such as those with high disease burden and high cell turnover, should receive prophylactic treatment including administration of allopurinol and hydration, per standard clinical practice, per institutional standards.

10.8.1.9. B-Cell Aplasia

B-cell aplasia is an expected potential off-tumor, on-target toxicity. Prolonged B-cell aplasia has been observed in other CD19-directed CAR T cell programs (Davila, 2014; Grupp, 2013). Serum immunoglobulin levels will be obtained from all subjects prior to and at various timepoints following JCAR017 infusion. Hypogammaglobulinemic subjects (serum immunoglobulin G [IgG] < 500 mg/dL) should be considered for intravenous immunoglobulin replacement therapy per institutional guidelines.

10.8.1.10. Graft-Versus-Host Disease

The likelihood of GVHD occurring with CAR T cell therapy is low, but it remains a theoretical risk. Subjects who have undergone allogeneic HSCT and who have active, acute or chronic GVHD at screening are excluded from enrolling in this protocol. However, due to residual donor engraftment, some or all T cells of JCAR017 may be of donor origin. Subjects who received a previous allogeneic HSCT will be assessed for donor chimerism at screening and will be monitored closely throughout the study for signs of GVHD.

10.8.1.11. Uncontrolled T Cell Proliferation

JCAR017 could theoretically proliferate out of control. If uncontrolled JCAR017 proliferation occurs, subjects may be treated with high-dose steroids (eg, methylprednisolone 1-3 mg/kg/day, tapered over 7 days) or LD doses of cyclophosphamide (1 to 3 g/m^2 IV). If an Investigator suspects uncontrolled JCAR017 proliferation, Celgene should be contacted immediately. In an animal model the EGFR antibody cetuximab was used to ablate EGFRt-expressing CAR T cells in vivo (Wang, 2011). Currently, there is no data available on use of cetuximab or other EGFR-directed antibodies for depletion of JCAR017 CAR T cells in humans.

10.8.1.12. Replication-Competent Lentivirus, Clonality and Insertional Oncogenesis

Lentiviral vectors used in gene transfer are engineered to be replication-defective; however, generation of RCL during manufacturing is still a possibility. Modern vector production systems have been improved to reduce the risk of RCL generation. To date, there have been no reports of RCL generated during lentiviral vector manufacturing, which may be due, at least in part, to the use of self-inactivating vectors such as the lentiviral vector used in the production of JCAR017 (Rothe, 2013).

Concerns for possible vector integration into the host genome have arisen due to preclinical studies that have shown retrovirus-mediated malignant transformation in mice (Li, 2002; Modlich, 2005) and monkeys (Donahue, 1992), and a single clinical study reporting development of leukemia in subjects with X-linked severe combined immunodeficiency (SCID) who received retroviral-modified CD34+ hematopoietic stem cells (Hacein-Bey-Abina, 2003) including one subject who died (Couzin, 2005). Of note, no instances of RCL generation during production or lentivirus-mediated malignant transformation in animals or subjects have been reported to date.

Data has recently been published on the integration sites of retroviral and lentiviral vectors used for T cell modification in clinical trials (McGarrity, 2013; Scholler, 2012; Wang, 2009). No clonality of integration sites was observed. In addition, there did not appear to be enrichment of integration sites near genes involved in clonal expansion or persistence.

10.8.1.13. Risks Associated with Lymphodepleting Chemotherapy

Subjects will receive fludarabine and cyclophosphamide prior to treatment with JCAR017 to facilitate LD chemotherapy and CAR T cell engraftment. Refer to the SmPC for specific details surrounding the risks of fludarabine phosphate and cyclophosphamide.

10.8.1.14. New Malignancies

New malignancies must be reported as SAEs. This includes any second primary malignancy, regardless of causal relationship to IP (study drug[s]), occurring at any time for the duration of the study, from the time of signing the ICF until study end. These events must also be documented in the appropriate page(s) of the CRF and subject's source documents. Documentation on the diagnosis of the new malignancy must be provided at the time of reporting as a serious adverse event (eg, any confirmatory histology or cytology results, x-rays, CT scans, etc.). Celgene will request a sample of the neoplastic tissue for causality analysis related to use of integrating vector to determine if insertional oncogenesis is suspected.

11. DISCONTINUATIONS

11.1. Treatment Discontinuation

The following events are considered sufficient reasons for discontinuing a subject from the LD chemotherapy or JCAR017:

- Adverse event
- Subject withdrawal of consent
- Manufacturing failure
- Death
- Lost to follow-up
- Other (to be specified on the CRF)

The reason for discontinuation of treatment should be recorded in the CRF and in the source documents.

The decision to discontinue a subject from treatment remains the responsibility of the treating physician, which will not be delayed or refused by Celgene. However, prior to discontinuing a subject, the Investigator may contact the Medical Monitor and forward appropriate supporting documents for review and discussion.

11.2. Study Discontinuation

The following events are considered sufficient reasons for discontinuing a subject from the study:

- Screen failure
- Adverse event
- Subject withdrawal of consent
- Death
- Lost to follow-up
- Study termination by Sponsor
- Other (to be specified on the CRF)

The reason for study discontinuation should be recorded in the CRF and in the source documents.

12. EMERGENCY PROCEDURES

12.1. Emergency Contact

In emergency situations, the Investigator should contact the responsible Clinical Research Physician/Medical Monitor or designee by telephone at the number(s) listed on the Emergency Contact Information page of the protocol (after title page).

In the unlikely event that the Clinical Research Physician/Medical Monitor or designee cannot be reached, please contact the global Emergency Call Center by telephone at the number listed on the Emergency Contact Information page of the protocol (after title page). This global Emergency Call Center is available 24 hours a day and 7 days a week. The representatives are responsible for obtaining your call-back information and contacting the on-call sponsor/contract research organization Medical Monitor, who will then contact you promptly.

Note: The back-up 24-hour global emergency contact call center should only be used if you are not able to reach the Clinical Research Physician(s) or Medical Monitor or designee for emergency calls.

12.2. Emergency Identification of Investigational Products

This is an open-label study; therefore, the JCAR017 cell product will be identified on the package labeling.

13. REGULATORY CONSIDERATIONS

13.1. Good Clinical Practice

The procedures set out in this study protocol pertaining to the conduct, evaluation, and documentation of this study are designed to ensure that Celgene, its authorized representative, and Investigator abide by Good Clinical Practice (GCP), as described in ICH Guideline E6 and in accordance with the general ethical principles outlined in the Declaration of Helsinki. The study will receive approval from an IRB/EC prior to commencement. The Investigator will conduct all aspects of this study in accordance with applicable national, state, and local regulations of the pertinent regulatory authorities.

13.2. Investigator Responsibilities

Investigator responsibilities are set out in the ICH Guideline for Good Clinical Practice and in the local regulations. Celgene staff or an authorized representative will evaluate and approve all Investigators who in turn will select their staff.

The Investigator should ensure that all persons assisting with the study are adequately informed about the protocol, amendments, study treatments, as well as study-related duties and functions, including obligations of confidentiality of Celgene information. The Investigator should maintain a list of Sub-Investigators and other appropriately qualified persons to whom he or she has delegated significant study-related duties.

The Investigator is responsible for keeping a record of all subjects who sign an informed consent form and are screened for entry into the study. Subjects who fail screening must have the reason(s) recorded in the subject's source documents.

The Investigator, or a designated member of the Investigator's staff, must be available during monitoring visits to review data, resolve queries and allow direct access to subject records (eg, medical records, office charts, hospital charts, and study-related charts) for source data verification. The Investigator must ensure timely and accurate completion of CRFs and queries.

The information contained in the protocol and amendments (with the exception of the information provided by Celgene on public registry websites) is considered Celgene confidential information. Only information that is previously disclosed by Celgene on a public registry website may be freely disclosed by the Investigator or its institution, or as outlined in the Clinical Trial Agreement. Celgene protocol, amendment and IB information is not to be made publicly available (for example on the Investigator's or their institution's website) without express written approval from Celgene. Information proposed for posting on the Investigator's or their institution's website must be submitted to Celgene for review and approval, providing at least 5 business days for review.

At the time results of this study are made available to the public, Celgene will provide Investigators with a summary of the results that is written for the lay person. The Investigator is responsible for sharing these results with the subject and/or their caregiver as agreed by the subject.

13.3. Subject Information and Informed Consent

The Investigator must obtain informed consent of a subject and/or a subject's legal representative prior to any study related procedures.

Documentation that informed consent occurred prior to the study subject's entry into the study and of the informed consent process should be recorded in the study subject's source documents including the date. The original ICF signed and dated by the study subject and by the person consenting the study subject prior to the study subject's entry into the study, must be maintained in the Investigator's study files and a copy given to the study subject. In addition, if a protocol is amended and it impacts on the content of the informed consent, the ICF must be revised. Study subjects participating in the study when the amended protocol is implemented must be re-consented with the revised version of the ICF. The revised ICF signed and dated by the study subject and by the person consenting the study subject must be maintained in the Investigator's study files and a copy given to the study subject.

13.4. Confidentiality

Celgene affirms the subject's right to protection against invasion of privacy and to be in compliance with ICH and other local regulations (whichever is most stringent). Celgene requires the Investigator to permit Celgene's representatives and, when necessary, representatives from regulatory authorities, to review and/or copy any medical records relevant to the study in accordance with local regulations.

Should direct access to medical records require a waiver or authorization separate from the subject's signed ICF, it is the responsibility of the Investigator to obtain such permission in writing from the appropriate individual.

13.5. Protocol Amendments

Any amendment to this protocol must be approved by the Celgene Clinical Research Physician/Medical Monitor. Amendments will be submitted to the IRB/EC for written approval. Written approval must be obtained before implementation of the amended version occurs. The written signed approval from the IRB/EC should specifically reference the Investigator name, protocol number, study title and amendment number(s) that is applicable. Amendments that are administrative in nature do not require IRB/EC approval but will be submitted to the IRB/EC for information purposes.

13.6. Institutional Review Board and Independent Ethics Committee Review and Approval

Before the start of the study, the study protocol, ICF, and any other appropriate documents will be submitted to the IRB/EC with a cover letter or a form listing the documents submitted, their dates of issue, and the site (or region or area of jurisdiction, as applicable) for which approval is sought. If applicable, the documents will also be submitted to the authorities in accordance with local legal requirements.

JCAR017 cell product can only be supplied to an Investigator by Celgene or its authorized representative after documentation on all ethical and legal requirements for starting the study has

been received by Celgene or its authorized representative. This documentation must also include a list of the members of the IRB/EC and their occupation and qualifications. If the IRB/EC will not disclose the names, occupations and qualifications of the committee members, it should be asked to issue a statement confirming that the composition of the committee is in accordance with GCP. For example, the IRB General Assurance Number may be accepted as a substitute for this list. Formal approval by the IRB/EC should mention the protocol title, number, amendment number (if applicable), study site (or region or area of jurisdiction, as applicable), and any other documents reviewed. It must mention the date on which the decision was made and must be officially signed by a committee member. Before the first subject is enrolled in the study, all ethical and legal requirements must be met.

The IRB/EC and, if applicable, the authorities, must be informed of all subsequent protocol amendments in accordance with local legal requirements. Amendments must be evaluated to determine whether formal approval must be sought and whether the ICF should also be revised.

The Investigator must keep a record of all communication with the IRB/EC and, if applicable, between a Coordinating Investigator and the IRB/EC. This statement also applies to any communication between the Investigator (or Coordinating Investigator, if applicable) and regulatory authorities.

Any advertisements used to recruit subjects for the study must be reviewed by Celgene and the IRB/EC prior to use.

13.7. Ongoing Information for Institutional Review Board and Ethics Committee

If required by legislation or the IRB/EC, the Investigator must submit to the IRB/EC:

- Information on serious or unexpected adverse events as soon as possible;
- Periodic reports on the progress of the study;
- Deviations from the protocol or anything that may involve added risk to subjects.

13.8. Termination of the Study

Celgene reserves the right to terminate this study prematurely at any time for reasonable medical or administrative reasons. Any premature discontinuation will be appropriately documented according to local requirements (eg, IRB/EC, regulatory authorities, etc).

In addition, the Investigator or Celgene has the right to discontinue a single site at any time during the study for medical or administrative reasons such as:

- Unsatisfactory enrollment;
- GCP noncompliance;
- Inaccurate or incomplete data collection;
- Falsification of records;
- Failure to adhere to the study protocol.

14. DATA HANDLING AND RECORDKEEPING

14.1. Data and Documents

The Investigator must ensure that the records and documents pertaining to the conduct of the study and the distribution of the JCAR017 cell product are complete, accurate, filed and retained. Examples of source documents include: hospital records; clinic and office charts; laboratory notes; memoranda; evaluation checklists; dispensing records; recorded data from automated instruments; copies or transcriptions certified after verification as being accurate copies; microfiche; x-ray film and reports; and records kept at the pharmacy, and the laboratories, as well as copies of CRFs or CD-ROM.

14.2. Data Management

Data will be collected via CRF and entered into the clinical database per Celgene standard operating procedures (SOPs). This data will be electronically verified through use of programmed edit checks specified by the clinical team. Discrepancies in the data will be brought to the attention of the clinical team, and investigational site personnel, if necessary. Resolutions to these issues will be reflected in the database. An audit trail within the system will track all changes made to the data.

14.3. Record Retention

Essential documents must be retained by the Investigator according to the period of time outlined in the clinical trial agreement. The Investigator must retain these documents for the time period described above or according to local laws or requirements, whichever is longer. Essential documents include, but are not limited to, the following:

- Signed ICFs for all subjects;
- Subject identification code list, screening log (if applicable), and enrollment log;
- Record of all communications between the Investigator and the IRB/EC;
- Composition of the IRB/EC;
- Record of all communications between the Investigator, Celgene, and their authorized representative(s);
- List of Sub-Investigators and other appropriately qualified persons to whom the Investigator has delegated significant study-related duties, together with their roles in the study, curriculum vitae, and their signatures;
- Copies of CRFs (if paper) and of documentation of corrections for all subjects;
- JCAR017 accountability records;
- Record of any body fluids or tissue samples retained;
- All other source documents (subject records, hospital records, laboratory records, etc.);

- All other documents as listed in Section 8 of the ICH consolidated guideline on GCP (Essential Documents for the Conduct of a Clinical Trial).

The Investigator must notify Celgene if he/she wishes to assign the essential documents to someone else, remove them to another location or is unable to retain them for a specified period. The Investigator must obtain approval in writing from Celgene prior to destruction of any records. If the Investigator is unable to meet this obligation, the Investigator must ask Celgene for permission to make alternative arrangements. Details of these arrangements should be documented.

All study documents should be made available if required by relevant health authorities. Investigator or institution should take measures to prevent accidental or premature destruction of these documents.

15. QUALITY CONTROL AND QUALITY ASSURANCE

All aspects of the study will be carefully monitored by Celgene or its authorized representative for compliance with applicable government regulations with respect to current GCP and SOPs.

15.1. Study Monitoring and Source Data Verification

Celgene ensures that appropriate monitoring procedures are performed before, during and after the study. All aspects of the study are reviewed with the Investigator and the staff at a study initiation visit and/or at an Investigators' Meeting. Prior to enrolling subjects into the study, a Celgene representative will review the protocol, CRFs, procedures for obtaining informed consent, record keeping, and reporting of AEs/SAEs with the Investigator.

Monitoring details describing strategy, including definition of study critical data items and processes (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan.

Accuracy will be checked by performing source data verification that is a direct comparison of the entries made onto the CRFs against the appropriate source documentation. Any resulting discrepancies will be reviewed with the Investigator and/or his/her staff. Any necessary corrections will be made directly to the CRFs or via queries by the Investigator and/or his/her staff. Monitoring procedures require that informed consents, adherence to inclusion/exclusion criteria and documentation of SAEs and their proper recording be verified. Additional monitoring activities may be outlined in a study-specific monitoring plan.

15.2. Audits and Inspections

In addition to the routine monitoring procedures, a Good Clinical Practice Quality Assurance unit exists within Celgene. Representatives of this unit will conduct audits of clinical research activities in accordance with Celgene SOPs to evaluate compliance with Good Clinical Practice guidelines and regulations.

The Investigator is required to permit direct access to the facilities where the study took place, source documents, CRFs and applicable supporting records of study subject participation for audits and inspections by IRB/ECs, regulatory authorities (eg, FDA, European Medicines Agency [EMA]) and company authorized representatives. The Investigator should make every effort to be available for the audits and/or inspections. If the Investigator is contacted by any regulatory authority regarding an inspection, he/she should contact Celgene immediately.

16. PUBLICATIONS

As described in Section 13.2, all protocol- and amendment-related information, with the exception of the information provided by Celgene on public registry websites, is considered Celgene confidential information and is not to be used in any publications. Celgene protocol-related information proposed for use in a publication must be submitted to Celgene for review and approval, and should not be utilized in a publication without express written approval from Celgene, or as described in the Clinical Trial Agreement.

Celgene will ensure Celgene-sponsored studies are considered for publication in the scientific literature in a peer-reviewed journal, irrespective of the results. At a minimum, this applies to results from all Phase 3 clinical studies, and any other study results of significant medical importance. This also includes results relating to investigational medicines whose development programs have been discontinued.

Study results may also be presented at one or more medical congresses, and may be used for scientific exchange and teaching purposes. Additionally, this study and its results may be submitted for inclusion in all appropriate health authority study registries, as well as publication on health authority study registry websites, as required by local health authority regulations.

Eligibility for external authorship, as well as selection of first authorship, will be based on several considerations, including, but not limited to, contribution to protocol development, study recruitment, data quality, participation in data analysis, participation in study steering committee (when applicable) and contribution to abstract, presentation and/or publication development.

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APPENDIX A. TABLE OF ABBREVIATIONS

Abbreviation or Specialist Term	Explanation
ABC	Activated B-cell
ADL	Activities of daily life
AE	Adverse event
AESI	Adverse event of special interest
ALL	Acute lymphoblastic leukemia
ALT	Alanine aminotransferase (SGPT)
ANC	Absolute neutrophil count
aPTT	Activated partial thromboplastin time
ASCT	Autologous stem cell transplant
AST	Aspartate aminotransferase (SGOT)
ATA	Anti-therapeutic antibody
AUC	Area under the curve
B-NHL	B-cell non-Hodgkin lymphoma
BCM	B-cell malignancies
β-hCG	Beta human chorionic gonadotropin
BMA	Bone marrow aspirate
BMB	Bone marrow biopsy
BOR	Best overall response
BUN	Blood urea nitrogen
CAR	Chimeric antigen receptor
CBC	Complete blood count
CI	Confidence interval
CLL	Chronic lymphocytic leukemia
C_{max}	Maximum plasma concentration of drug
CNS	Central nervous system
COO	Cell of origin
CR	Complete response
CrCl	Creatinine clearance
CRF	Case report form
CRP	C-reactive protein
CRR	Complete response rate

Abbreviation or Specialist Term	Explanation
CRS	Cytokine release syndrome
CRu	Complete response unconfirmed
CSF	Cerebrospinal fluid
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DHL	Double hit lymphoma
DL	Dose level
DLBCL	Diffuse large B-cell lymphoma
DLCO	Diffusion capacity of carbon monoxide
DLI	Donor lymphocyte infusions
DLT	Dose-limiting toxicity
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic acid
DOR	Duration of response
DSMB	Data Safety Monitoring Board
DSMP	Data Safety and Monitoring Plan
EBV	Epstein-Barr virus
EC	Ethics Committee
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
EEA	European Economic Area
EFS	Event-free survival
eGFR	Estimated glomerular filtration rate
EGFRt	Truncated epidermal growth factor receptor
EMA	European Medicines Agency
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer – Quality of Life C30
EOS	End of study
EQ-5D-5L	European Quality of Life-5 Dimensions health state classifier to 5 Levels
EQ VAS	EQ visual analogue scale
ET	Early termination

Abbreviation or Specialist Term	Explanation
EU	European Union
FACT-LymS	Functional Assessment of Cancer Therapy-Lymphoma "Additional concerns" subscale
FDA	Food and Drug Administration
FEV_1	Forced expiratory volume in one second
FISH	Fluorescence in situ hybridization
FL3B	Follicular lymphoma Grade 3B
Flu/Cy	Fludarabine/cyclophosphamide
GCB	Germinal center B-cell
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GEP	Gene expression profiling
GVHD	Graft-versus-host disease
HBsAb	Hepatitis B surface antibody
HBsAg	Hepatitis B surface antigen
HBcAb	Hepatitis B core antibody
HCT	Hematopoietic cell transplantation
HCT-CI	HCT-specific comorbidity index
HCV	Hepatitis C virus
HDCT	High-dose chemotherapy
HGBL	High-grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements with DLBCL histology
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HLH	Hemophagocytic lymphohistiocytosis
HRQoL	Health-related quality of life
HSCT	Hematopoietic stem cell transplantation
Hyper-CVAD	Fractionated cyclophosphamide, vincristine, doxorubicin and dexamethasone
IB	Investigator's Brochure
ICE	Immune Effector Cell-Associated Encephalopathy
ICF	Informed consent form
ICH	International Council for Harmonisation

Abbreviation or Specialist Term	Explanation
ICU	Intensive care unit
IFN-γ	Interferon gamma
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IHC	Immunohistochemistry
IL	Interleukin
IND	Investigational New Drug
INR	International normalized ratio
IP	Investigational Product
IPI	International Prognostic Index
IRB	Institutional Review Board
IRC	Independent Review Committee
IRT	Interactive Response Technology
IUD	Intrauterine device
IV	Intravenous
IVIG	Intravenous immunoglobulins
IWG	International Working Group
KPS	Karnofsky performance score
L	Line of therapy
LD	Lymphodepleting
LDH	Lactate dehydrogenase
LDi	Longest transverse diameter of a lesion
LTFU	Long-term follow-up
LTLS	Laboratory tumor lysis syndrome
LVEF	Left ventricular ejection fraction
MA	Methotrexate and cytarabine
mAb	Monoclonal antibody
MAS	Macrophage activation syndrome
MATRix regimen	High dose metothrexate, high dose cytarabine, rituximab and thiotepa
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation or Specialist Term	Explanation
MHLW	Ministry of Health, Labour and Welfare
MMSE	Mini Mental State Examination
MRD	Minimal residual disease
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
MUGA	Multigated acquisition
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NHL	Non-Hodgkin lymphoma
NK	Natural killer
NOS	Not otherwise specified
nPR	Nodular partial response
NT	Neurotoxicity
NYHA	New York Heart Association
ORR	Overall response rate
OS	Overall survival
PBMC	Peripheral blood mononuclear cell
PBSC	Peripheral blood stem cell
PCNSL	Primary central nervous system lymphoma
PCP	Pneumocystis pneumonia
PCR	Polymerase chain reaction
PD	Progressive disease
PD-1	Programmed cell death protein 1
PET	Positron emission tomography
PFS	Progression-free survival
PK	Pharmacokinetic, pharmacokinetics
PMBCL	Primary mediastinal large B-cell lymphoma
PO	Per os
PPDP	Protocol Product Deviation Plan
PR	Partial response
PRL	Partial response with lymphocytosis
PRO	Patient-reported outcome

Abbreviation or Specialist Term	Explanation
PS	Performance status
PT	Preferred term
PT	Prothrombin time
Q	Each, every
qPCR	Quantitative polymerase chain reaction
RBC	Red blood cell
R-CHOP	Rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, prednisone
R-EPOCH	Rituximab, etoposide, prednisolone, oncovin, cyclophosphamide, hydroxydaunorubicin
RCL	Replication-competent lentivirus
RCP	Réunion de concertation pluridisciplinaire
RNA	Ribonucleic acid
RNA-Seq	RNA sequencing
r/r	Relapsed/refractory
RSI	Reference Safety Information
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SC	Steering committee
scFv	Single chain variable fragment
sCRS	Severe cytokine release syndrome
SD	Stable disease
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SmPC	Summary of Product Characteristics
SOP	Standard operating procedure
SPD	Sum of the product of the perpendicular diameters for multiple lesions
SUSAR	Suspected unexpected serious adverse reaction
$t_{1/2}$	Half-life
TEAE	Treatment-emergent adverse event
tFL	Transformed follicular lymphoma
TGF-α	Transforming growth factor alpha

Abbreviation or Specialist Term	Explanation
THL	Triple-hit lymphoma
TLS	Tumor lysis syndrome
T_{max}	Time to peak concentration
TNE	Transplant not eligible
TNF	Tumor necrosis factor
TNM	Tumor, nodes, metastasis
ULN	Upper limit of normal
US	United States
USPI	United States Prescribing Information
WBC	White blood cell
WBRT	Whole brain radiation therapy
WHO	World Health Organization

APPENDIX B. PERFORMANCE STATUS BY EASTERN COOPERATIVE ONCOLOGY GROUP SCALE

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

Source:(Oken, 1982).

APPENDIX C. RECOMMENDATIONS FOR INITIAL EVALUATION, STAGING, AND RESPONSE ASSESSMENT OF HODGKIN AND NON-HODGKIN LYMPHOMA: THE LUGANO CLASSIFICATION

The guidelines for Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification are outlined in a report (Cheson, 2014).

Table C1: Criteria for Involvement of Site

Tissue Site	Clinical	FDG Avidity	Test	Positive Finding
Lymph nodes	Palpable	FDG-avid histologies Nonavid disease	PET-CT CT	Increase FDG uptake Unexplained node enlargement
Spleen	Palpable	FDG-avid histologies Nonavid disease	PET-CT CT	Diffuse uptake, solitary mass, military lesions, nodules > 13 cm in vertical length, mass, nodules
Liver	Palpable	FDG-avid histologies Nonavid disease	PET-CT CT	Diffuse uptake, mass Nodules
CNS	Signs, symptoms		CT MRI CSF assessment	Mass lesion(s) Leptomeningeal infiltration, mass lesions Cytology, flow cytometry
Other (eg, skin, lung, GI tract, bone, bone marrow)	Site dependent		PET-CT[a], biopsy	Lymphoma involvement

Abbreviations: CNS = central nervous system; CSF = cerebrospinal fluid; CT = computed tomography; FDG = fluorodeoxyglucose; GI = gastrointestinal; MRI = magnetic resonance imaging; PET = positron emission tomography.

[a] PET-CT is adequate for determination of bone marrow involvement and can be considered highly suggestive for involvement of other extralymphatic sites. Biopsy confirmation of those sites can be considered if necessary.

Table C2: Revised Criteria for Response Assessment

Response and Site	PET-CT Based Response	CT-Based Response
Complete	**Complete metabolic response**	**Complete radiologic response (all of the following)**
Lymph nodes and extralymphatic sites	Score 1, 2, or 3[a] with or without a residual mass on 5PS[b] It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (eg, with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake	Target nodes/nodal masses must regress to ≤ 1.5 cm in the longest transverse diameter of a lesion (LDi) No extralymphatic sites of disease
Nonmeasured lesion	Not applicable	Absent
Organ enlargement	Not applicable	Regress to normal
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, IHC negative
Partial	**Partial metabolic response**	**Partial remission (all of the following)**
Lymph nodes and extralymphatic sites	Score 4 or 5[b] with reduced uptake compared with baseline and residual mass(es) of any size At interim, these findings suggest responding disease At end of treatment, these findings indicate residual disease	≥ 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites When a lesion is too small to measure on CT, assign 5 mm × 5 mm as the default value When no longer visible, 0 × 0 mm For a node > 5 mm × 5 mm, but smaller than normal, use actual measurement for calculation
Nonmeasured lesion	Not applicable	Absent/normal, regressed, but no increase
Organ enlargement	Not applicable	Spleen must have regressed > 50% in length beyond normal
New lesions	None	None

Table C2: Revised Criteria for Response Assessment (Continued)

Response and site	PET-CT based response	CT-based response
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan	Not applicable
No response or stable disease	**No metabolic response**	**Stable disease**
Target nodes/nodal masses, extranodal lesions	Score 4 or 5[b] with no significant change in FDG uptake from baseline at interim or end of treatment	< 50% decrease from baseline in SPD of up to 6 dominant measurable nodes and extranodal sites; no criteria for progressive disease are met
Nonmeasured lesion	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesions	None	None
Bone marrow	No change from baseline	Not applicable
Progressive disease	**Progressive metabolic response**	**Progressive disease requires at least 1 of the following**
Individual target nodes/nodal masses	Score 4 or 5[b] with an increase in intensity of uptake from baseline and/or	PPD progression:
Extranodal lesions	New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	An individual node/lesion must be abnormal with: LDi > 1.5 cm and Increase by ≥ 50% from PPD nadir and An increase in LDi or SDi from nadir 0.5 cm for lesions ≤ 2 cm 1.0 cm for lesions > 2 cm In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (eg, a 15 cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline New or recurrent splenomegaly
Nonmeasured lesions	None	New or clear progression of preexisting nonmeasured lesions

Table C2: Revised Criteria for Response Assessment (Continued)

Response and site	PET-CT based response	CT-based response
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	Regrowth of previously resolved lesions A new node > 1.5 cm in any axis A new extranodal site > 1.0 cm in any axis, if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma
Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

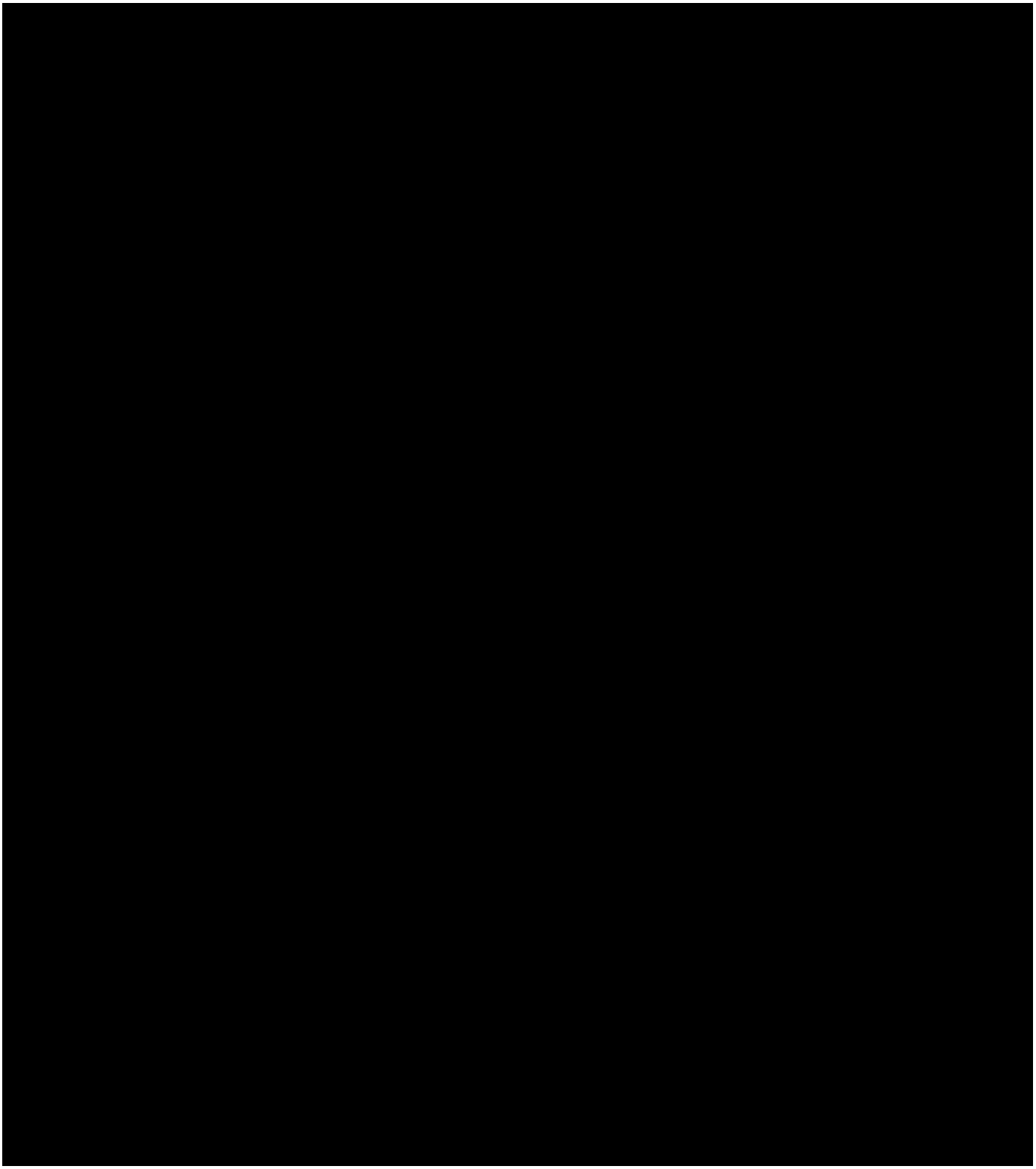
Abbreviations: 5PS = 5-point scale; CT = computed tomography; FDG = fluorodeoxyglucose; GI = gastrointestinal; IHC = immunohistochemistry; LDi = longest transverse diameter of a lesion; MRI = magnetic resonance imaging; PET = positron emission tomography; PPD = cross product of the LDi and perpendicular diameter; SDi = shortest axis perpendicular to the LDi; SPD = sum of the product of the perpendicular diameters for multiple lesions.

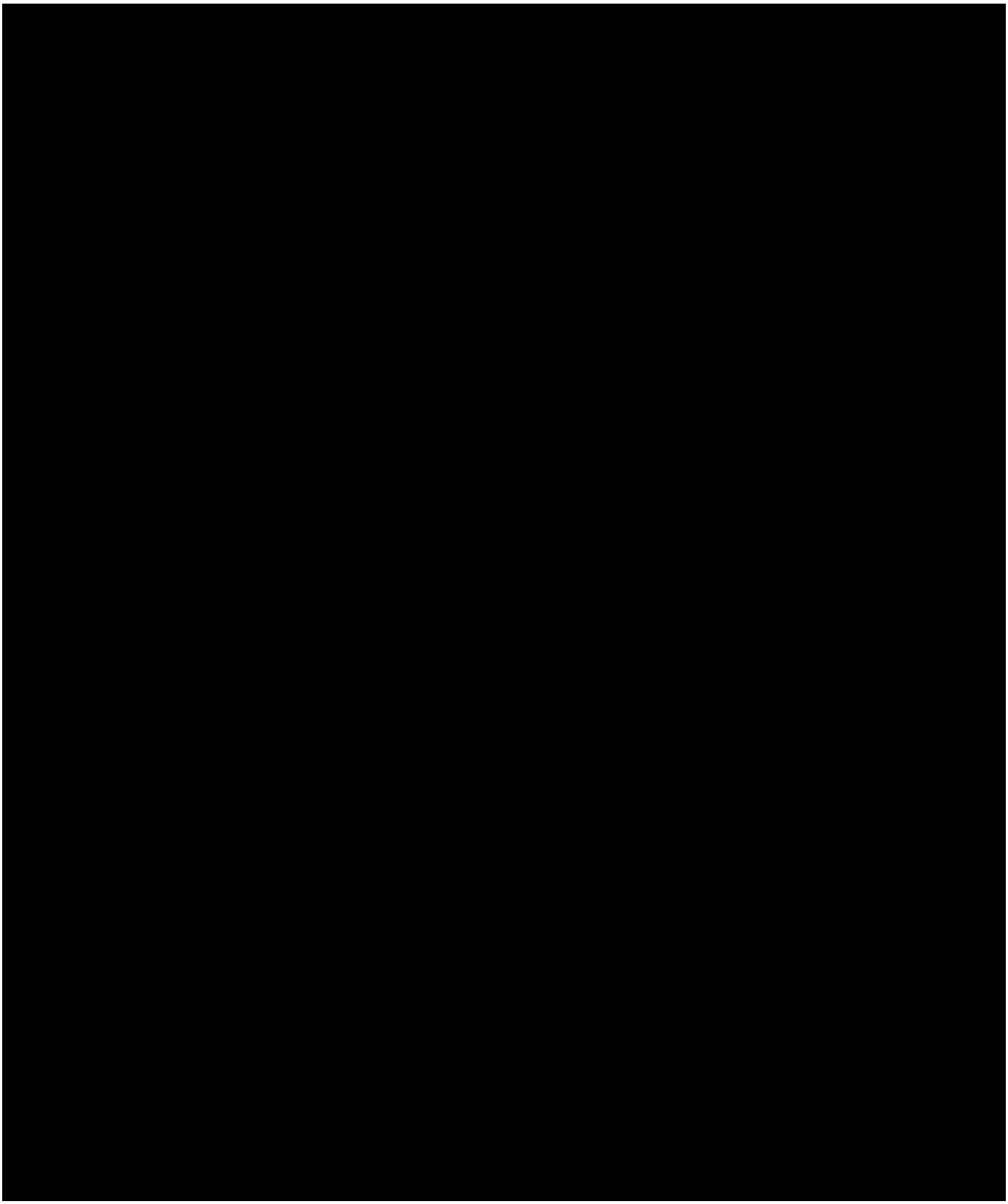
[a] A score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where deescalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid undertreatment).
Measured dominant lesions: Up to 6 of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in two diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (eg, liver, spleen, kidneys, and lungs), GI involvement, cutaneous lesions, or those noted on palpation. Nonmeasured lesions: Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extranodal sites (eg, GI tract, liver, bone marrow), FDG uptake may be greater than in the mediastinum with complete metabolic response, but should be no higher than surrounding normal physiologic uptake (eg, with marrow activation as a result of chemotherapy or myeloid growth factors).

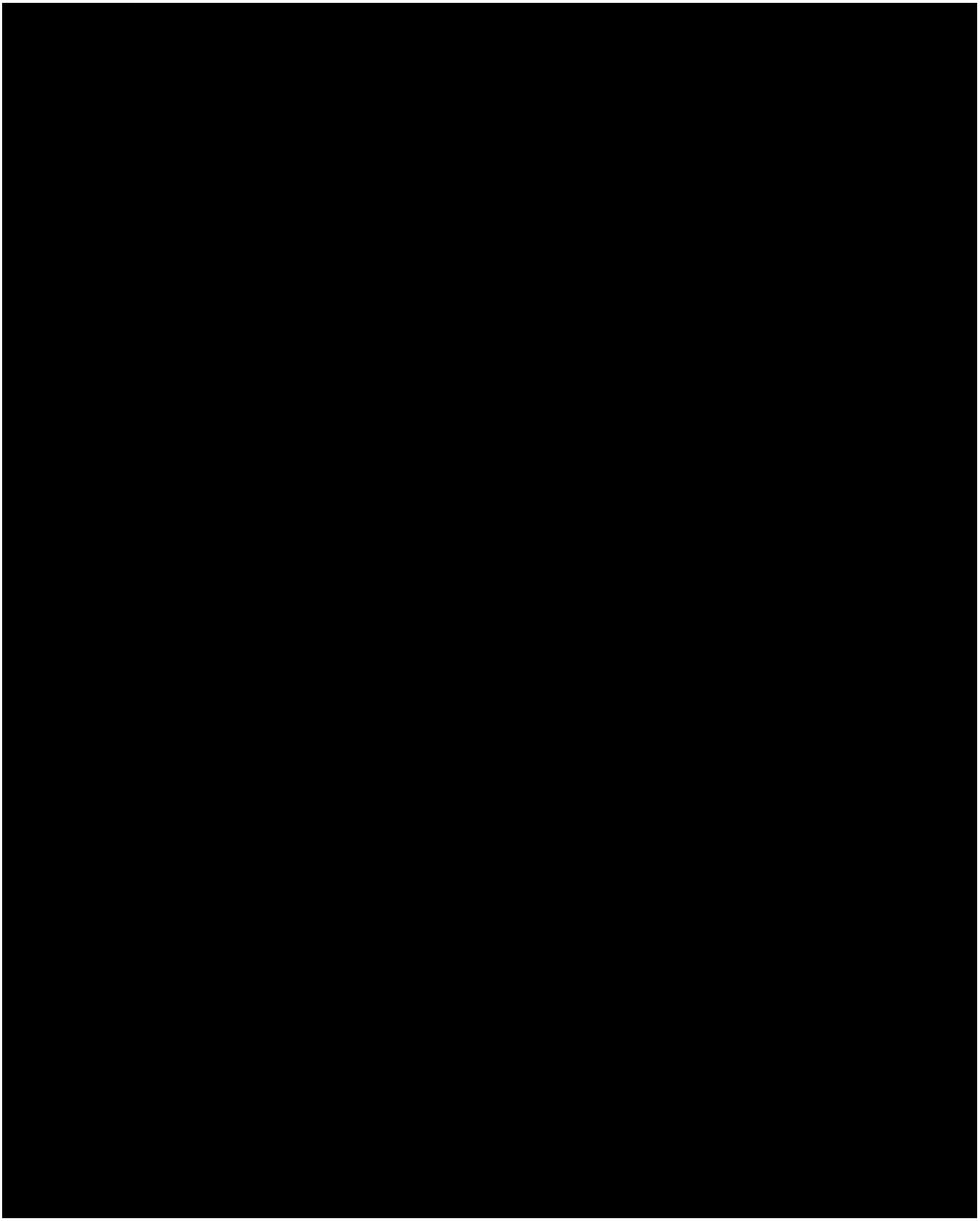
[b] PET 5PS: 1, no uptake above background; 2, uptake ≤ mediastinum; 3, uptake > mediastinum but ≤ liver; 4, uptake moderately > liver; 5, uptake markedly higher than liver and/or new lesions; X, new areas of uptake unlikely to be related to lymphoma.

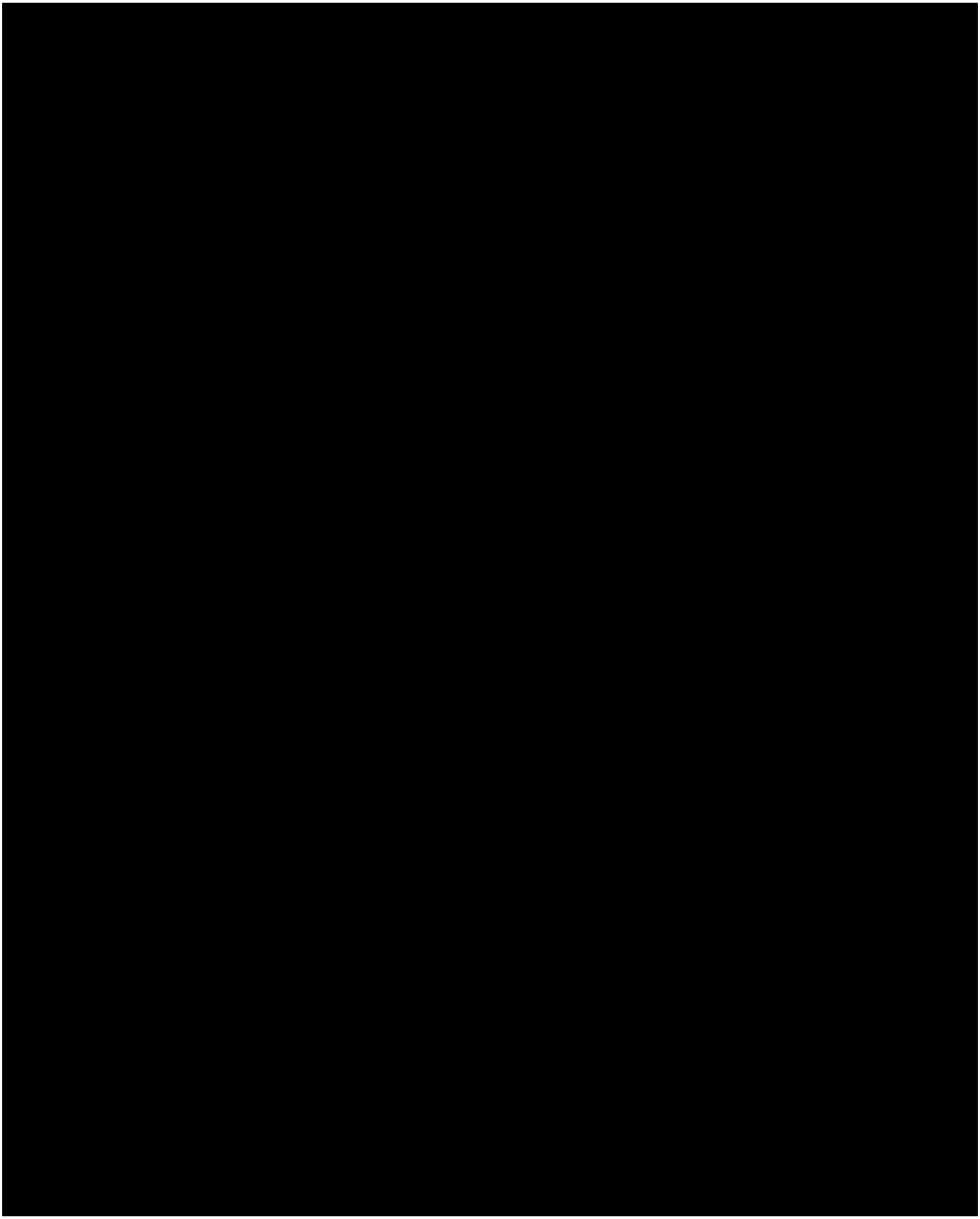
Source: (Cheson, 2014).

APPENDIX D. MINI MENTAL STATE EXAMINATION









APPENDIX E. CLINICAL LABORATORY EVALUATIONS

Laboratory Panel	Analytes
Chemistry	Glucose, BUN, creatinine, sodium, potassium, chloride, calcium, total protein, albumin, total bilirubin, direct bilirubin, alkaline phosphatase, ALT (SGPT), AST (SGOT), magnesium, phosphate, bicarbonate, LDH, ß2-microglobulin, uric acid, triglycerides
Hematology	CBC with differential
Coagulation	PT, aPTT, INR, fibrinogen, and D-dimer
Urinalysis*	Appearance, pH, specific gravity, protein Glucose, ketones, RBCs, WBCs Casts, crystals, or other components
Pregnancy*	ß-hCG (serum)
Viral serology	HIV HBsAb, HBsAg, HBcAb, HCV antibody
HLA typing*	HLA-A, HLA-B, HLA-C, HLA-DRB1, HLA-DQB1
Inflammatory markers	CRP, ferritin
Donor chimerism*	% stem cell donor
Disease characterization	Histology, cell of origin, immunochemistry, cytogenetics, molecular sub-typing
Cerebrospinal fluid*	RBCs, WBCs with differential, lymphoma cells, glucose, protein
Immunoglobulins	IgG, IgM, IgA

* Local assessment only.

Abbreviations: ALT (SGPT) = alanine aminotransferase (serum glutamic pyruvic transaminase); aPTT = activated partial thromboplastin time; AST (SGOT) = aspartate aminotransferase (serum glutamic oxaloacetic transaminase); ß-hCG = beta human chorionic gonadotropin; BUN = blood urea nitrogen; CBC = complete blood count; CRP = C-reactive protein; HBcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HIV= human immunodeficiency virus; HLA = human leukocyte antigen; IgG = immunoglobulin G; INR = international normalized ratio; LDH = lactate dehydrogenase; PT = prothrombin time; RBC = red blood cell; WBC = white blood cell.

APPENDIX F. COCKCROFT-GAULT EQUATION FOR CALCULATING ESTIMATED CREATININE CLEARANCE

Serum creatinine units	Gender	Estimated Creatinine Clearance (mL/min)
mg/dL	Male	$\frac{(140 - \text{subject age [years]}) \times \text{subject weight (kg)}}{72 \times \text{subject serum creatinine (mg/dL)}}$
	Female	$\frac{(140 - \text{subject age [years]}) \times \text{subject weight (kg)} \times 0.85}{72 \times \text{subject serum creatinine (mg/dL)}}$
µM/dL	Male	$\frac{(140 - \text{subject age [years]}) \times \text{subject weight (kg)} \times 1.23}{\text{Subject serum creatinine (µM/dL)}}$
	Female	$\frac{(140 - \text{subject age [years]}) \times \text{subject weight (kg)} \times 1.04}{\text{Subject serum creatinine (µM/dL)}}$

APPENDIX G. HCT-CI SCORE CALCULATOR

Co-morbidity	Definition	Yes	Score
Arrhythmia	Atrial fibrillation[a]		1
	Atrial flutter[a]		
	Sick sinus syndrome[a]		
	Ventricular arrhythmia[a]		
Cardiovascular	Coronary artery disease[a]		1
	Congestive heart failure[a]		
	Myocardial infarction[a]		
	Ejection fraction ≤ 50%[b]		
Inflammatory bowel disease	Crohn's disease[a]		1
	Ulcerative colitis[a]		
Diabetes	Treated with insulin or oral hypoglycemic drugs[b]		1
Cerebro-vascular	Transient ischemic attacks[a]		1
	Cerebro-vascular ischemic or hemorrhagic stroke[a]		
Depression/ anxiety	Requiring psychological consultation and/or specific treatments[b]		1
Hepatic - mild	Chronic hepatitis[b]		1
	Bilirubin > ULN - 1.5 x ULN[b]		
	AST/ALT > ULN - 2.5 x ULN[b]		
Obesity	Body mass index >35 (adults)[b]		1
	Body mass index-for-age ≥ 95% percentile (children)[b]		
Infection	Requiring anti-microbial treatment before, during, and after the start of conditioning[b]		1
Rheumatologic	Requiring Treatment[a]		2
Peptic ulcer	Confirmed by endoscopy and requiring treatment[a]		2
Renal	Serum creatinine > 2 mg/dl (or > 177µmol/L)[b]		2
	On dialysis[b]		
	Prior renal transplantation[a]		
Pulmonary - Moderate	DLCO adjusted with Dinakara equation (adjusted DLCO = Predicted DLCO / [0.06965 x hemoglobin]) of 66-80% of predicted[b]		2
	FEV1 66-80% of predicted[b]		

Co-morbidity	Definition	Yes	Score
	Dyspnea on slight activity[b]		
Pulmonary - Severe	DLCO adjusted with Dinakara equation (adjusted DLCO = Predicted DLCO / [0.06965 x hemoglobin]) of ≤ 65% of predicted[b]		3
	FEV1 ≤ 65% of predicted[b]		
	Dyspnea at rest or requiring oxygen therapy[b]		
Heart valve disease	Except asymptomatic mitral valve prolapse		3
Prior solid malignancy	Treated with surgery, chemotherapy, and/or radiotherapy, excluding non-melanoma skin cancer[a]		3
Hepatic - moderate/severe	Liver cirrhosis[b]		3
	Bilirubin > 1.5 x ULN[b]		
	AST/ALT > 2.5 x ULN[b]		
Total Score			

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; DLCO = diffusion capacity of carbon monoxide; FEV1 = forced expiratory volume in one second; ULN = upper limit of normal.

[a] Diagnosed at any time in the patient's past history.

[b] Detected at the time of pretransplant assessment.

APPENDIX H. FRAILTY SCALE

Frailty scale, validated by International Myeloma Working Group	
Category	Score
Age	
≤ 75 years	0
76-80 years	1
> 80 years	2
Charlson Comorbidity Index	
≤ 1	0
> 1	1
ECOG Performance Status Scale	
ECOG = 0	0
ECOG = 1	1
ECOG ≥ 2	2
Sum of Scores	
Non-frail	0-1
Frail	≥ 2

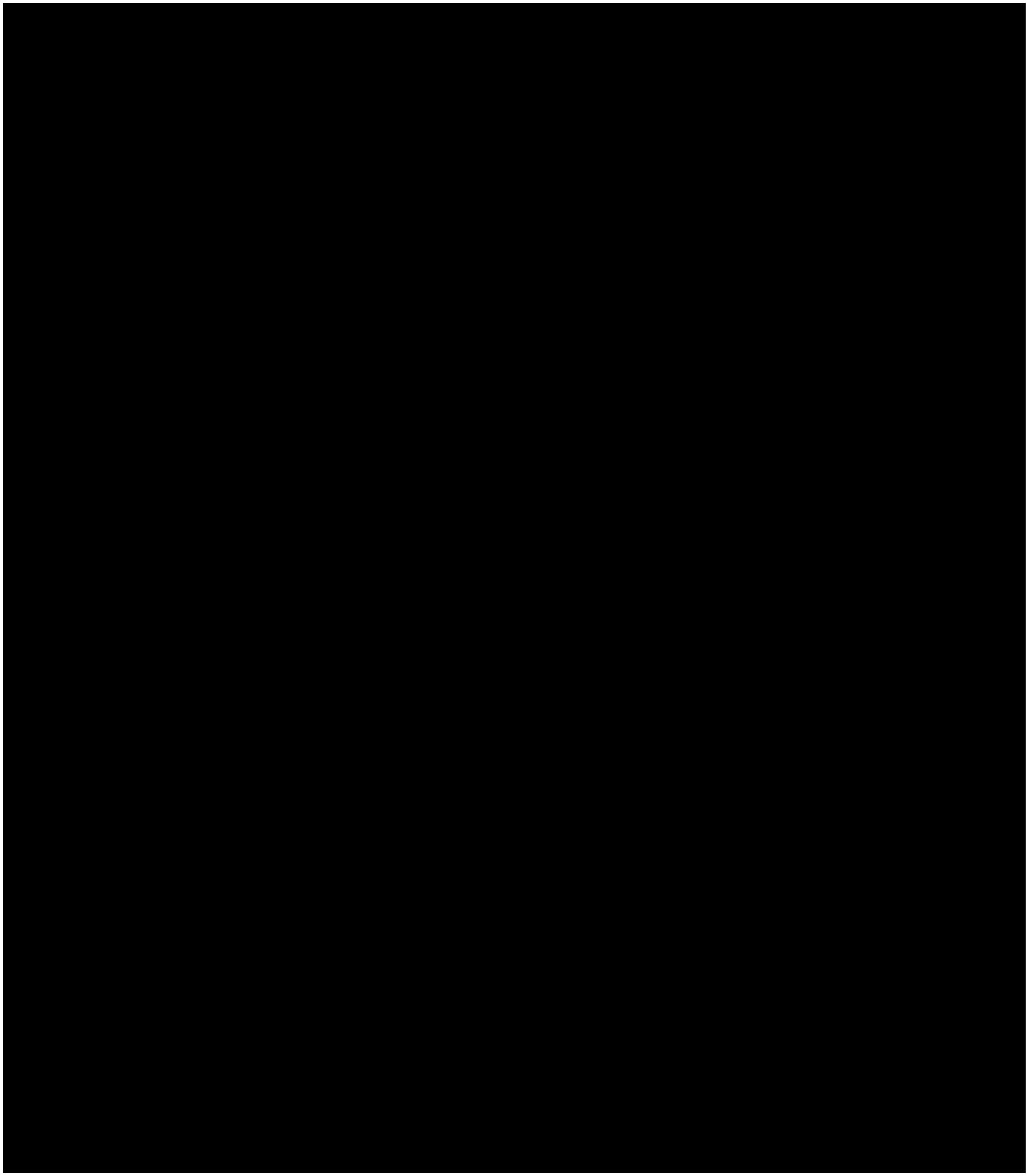
Abbreviations: ECOG = Eastern Cooperative Oncology Group.
Source: (Larocca, 2016).

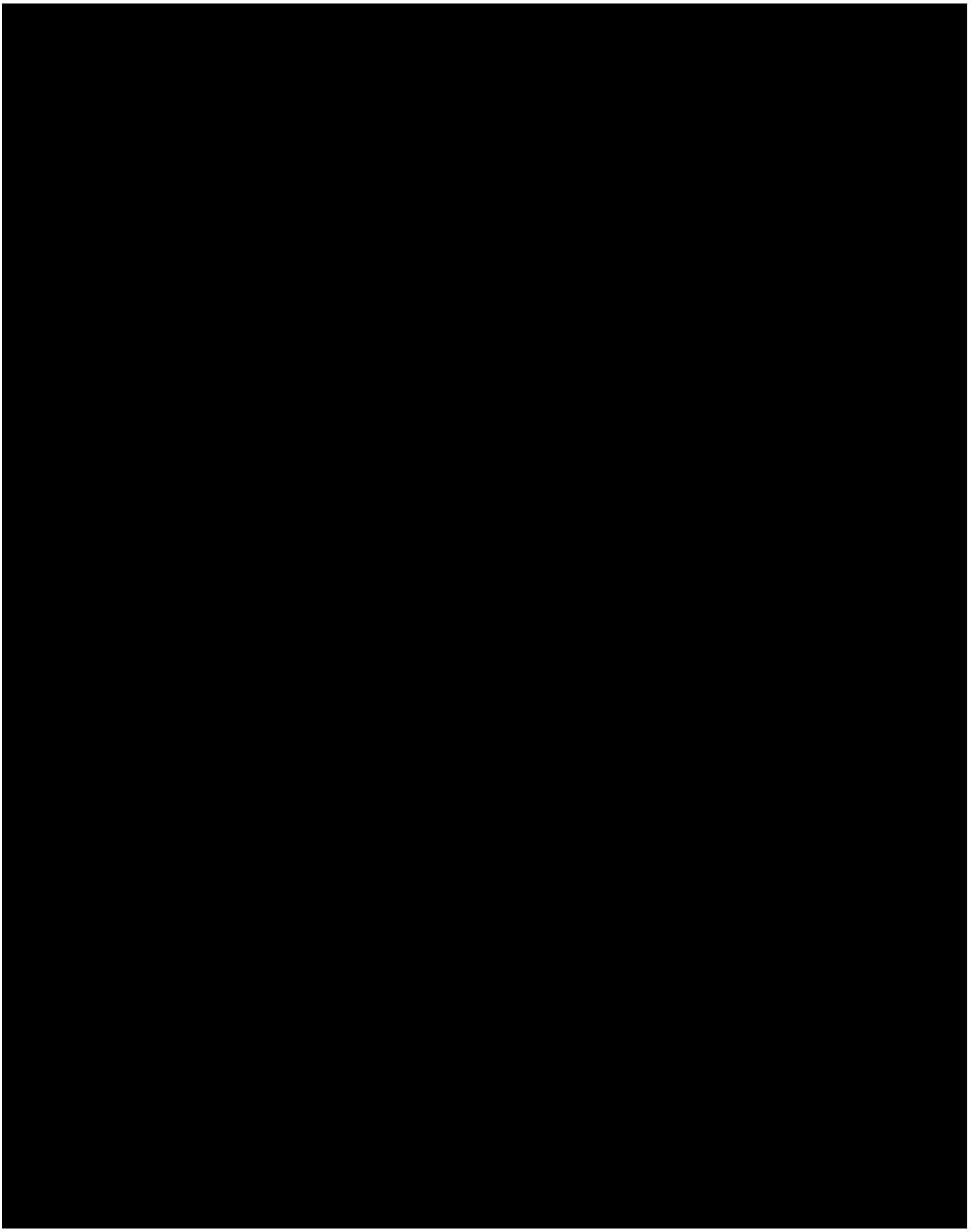
Charlson Comorbidity Index Scoring (Charlson, 1987)

Condition	Points	Notes
Congestive heart failure	1	
Peripheral vascular disease or bypass	1	
Cerebrovascular disease or transient ischemic disease	1	
Hemiplegia	2	If hemiplegia do not count cerebrovascular disease or transient ischemic disease separately
Pulmonary disease / asthma	1	
Diabetes	1	
Diabetes with end organ damage	2	If end organ damage do not count diabetes separately
Renal disease	2	
Mild liver disease	2	
Severe liver disease	3	
Gastric or peptic ulcer	2	
Cancer (lymphoma, leukemia, solid tumor)	2	Nonmetastatic cancer only
Metastatic solid tumor	6	If metastatic do not count cancer separately
Dementia or Alzheimer's disease	1	
Rheumatic or connective tissue disease	1	
HIV or AIDS	6	
Hypertension	1	
Skin ulcers / cellulitis	2	
Depression	1	
Warfarin	1	

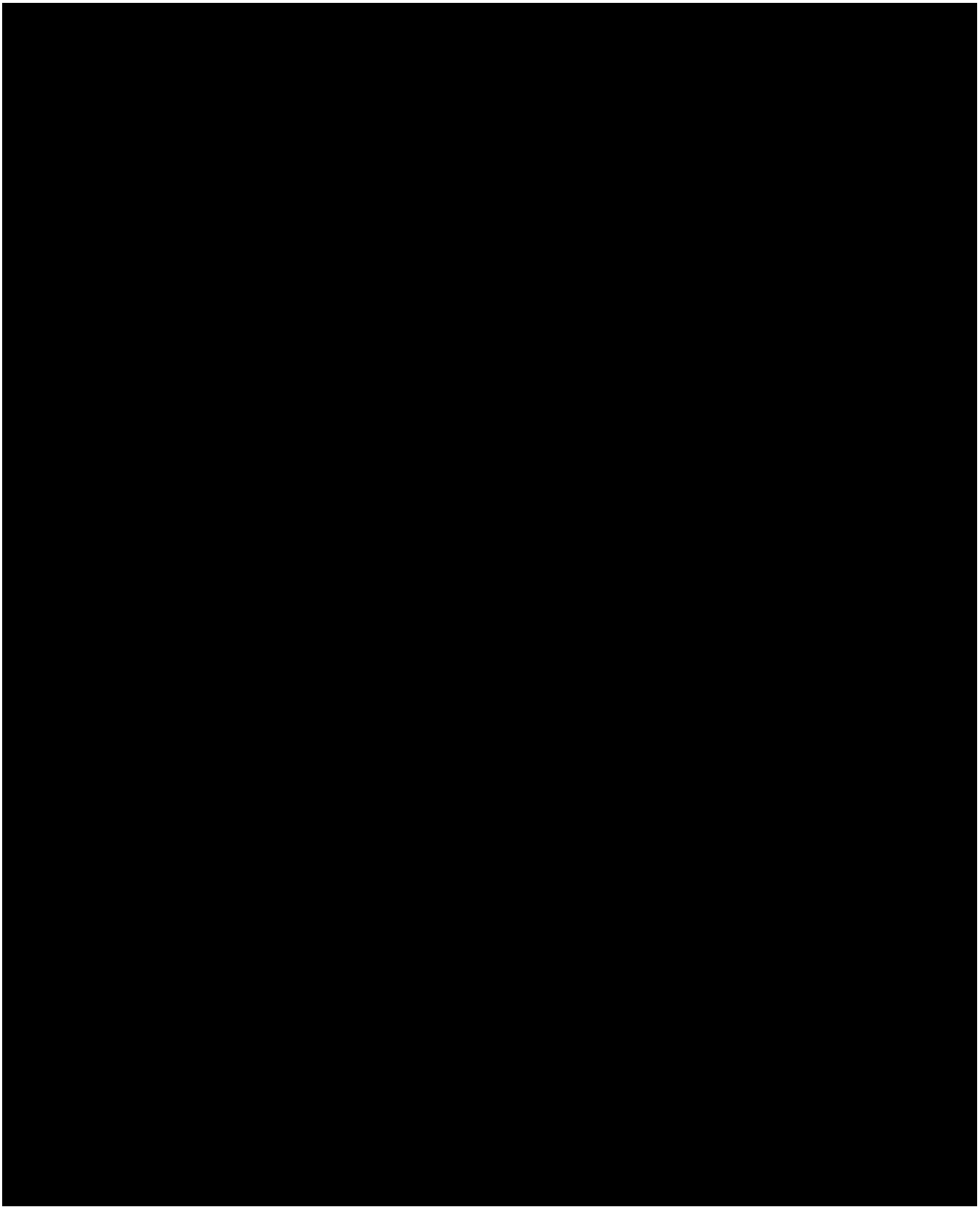
Source: (Charlson, 1987).

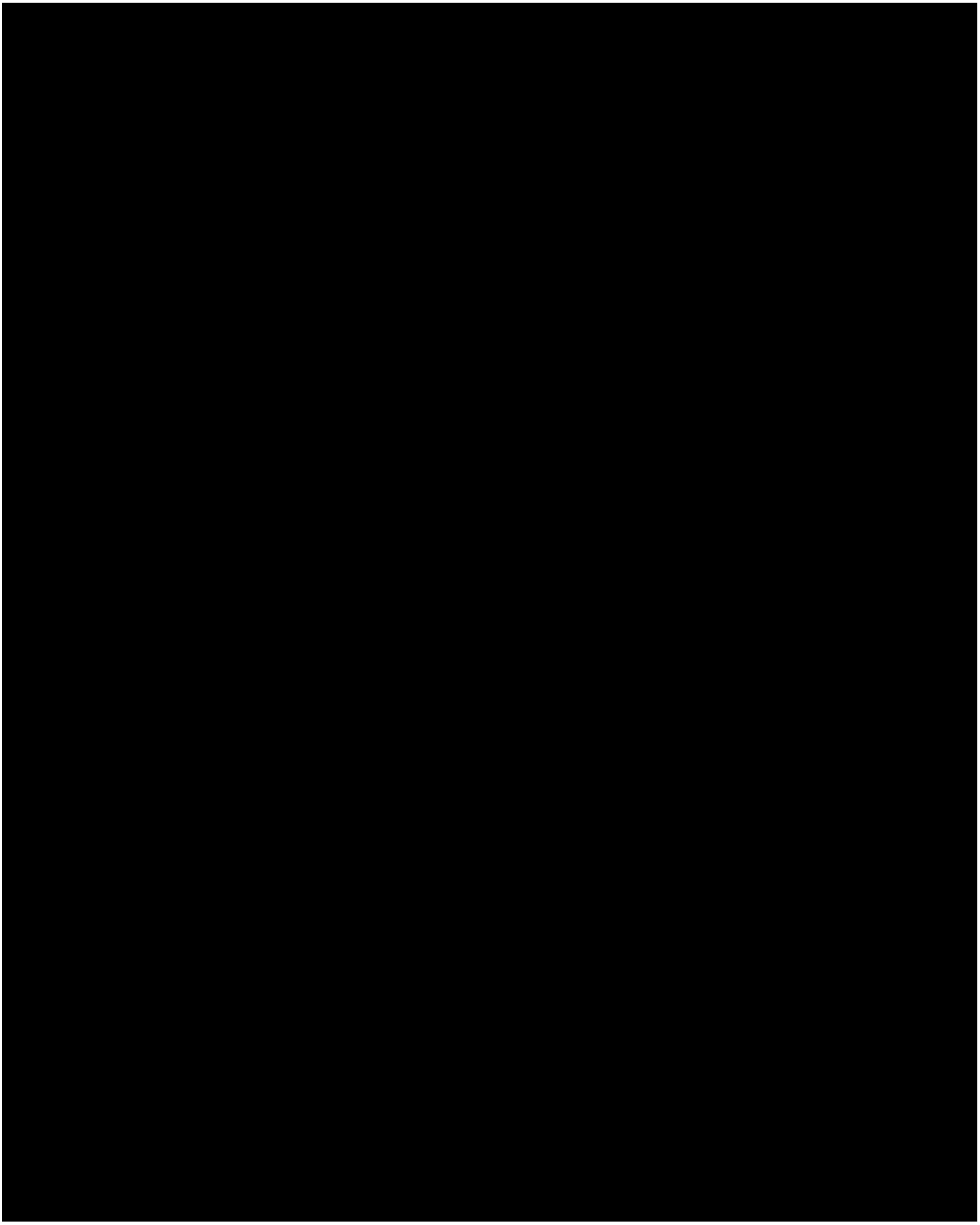
APPENDIX I. PATIENT-REPORTED OUTCOMES: EORTC QLQ C-30



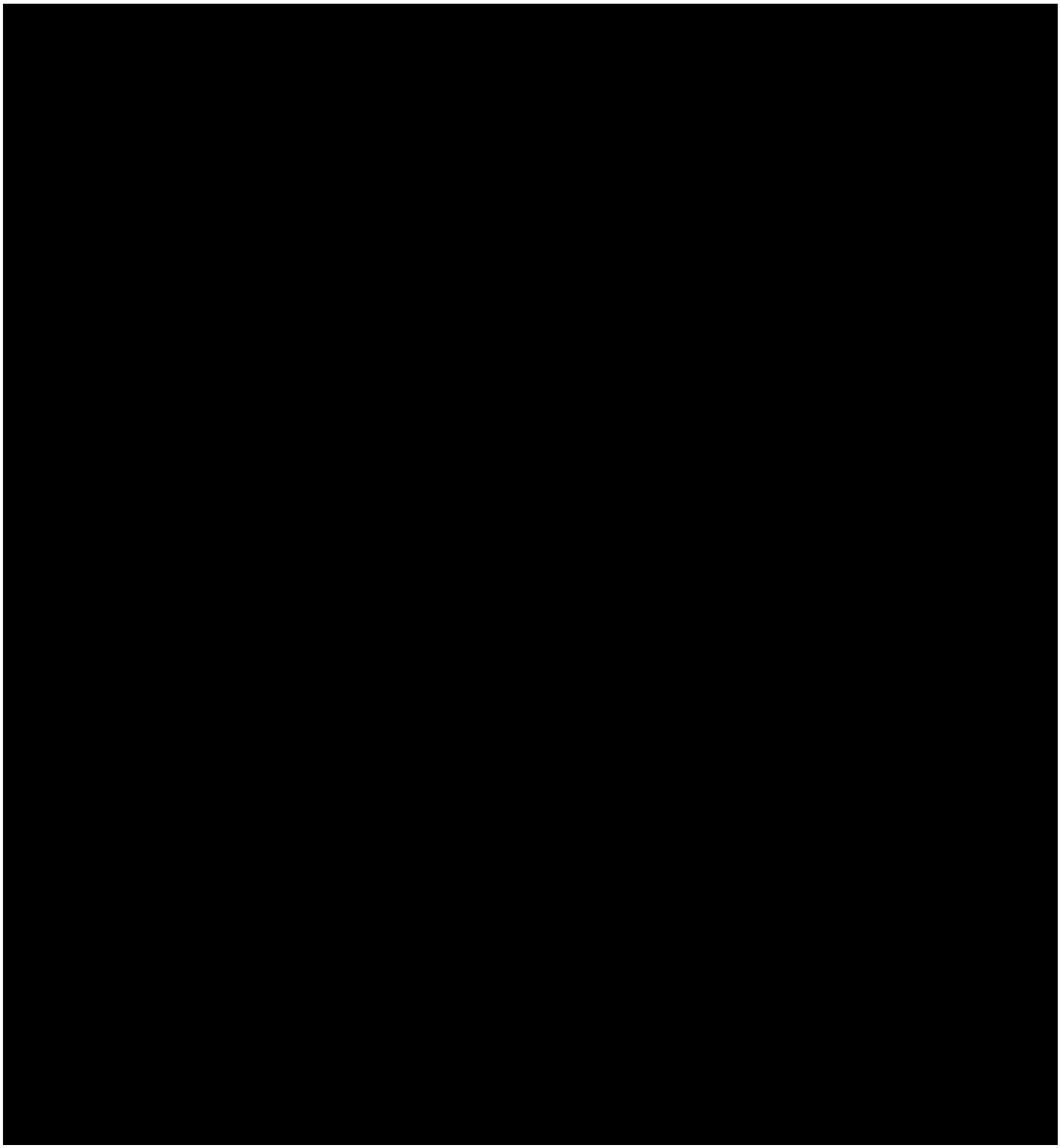


APPENDIX J. PATIENT-REPORTED OUTCOMES: EQ-5D-5L





APPENDIX K. PATIENT-REPORTED OUTCOMES: FACT-LYMS



APPENDIX L. CAIRO-BISHOP DEFINITIONS OF TUMOR LYSIS SYNDROME

Cairo-Bishop Definition of Laboratory Tumor Lysis Syndrome (LTLS)

Laboratory Parameter	Laboratory Result
Uric acid	≥ 476 µmol/L (≥ 8.0 mg/dL) or 25% increase from baseline
Potassium	≥ 6.0 mmol/L (≥ 6.0 mEq/L) or 25% increase from baseline
Phosphorous	≥ 1.45 mmol/L (≥ 4.5 mg/dL) or 25% increase from baseline
Calcium	≤ 1.75 mmol/L (≤ 7.0 mg/dL) or 25% decrease from baseline

Laboratory tumor lysis syndrome (LTLS) is defined as either a 25% change or level above or below normal, as defined above, for any two or more serum values of uric acid, potassium, phosphate, and calcium within 3 days before or 7 days after the initiation of chemotherapy. This assessment assumes that a patient has or will receive adequate hydration (± alkalinization) and a hypouricaemic agent(s).

Cairo-Bishop Definition of Clinical TLS

The presence of laboratory TLS and one or more of the following criteria:
1. Creatinine: ≥ 1.5 ULN (age > 12 years or age adjusted)
2. Cardiac arrhythmia/sudden death[a]
3. Seizure[a]

Abbreviations: TLS = tumor lysis syndrome; ULN = upper limit of normal.
[a] Not directly attributable to a therapeutic agent.

Cairo-Bishop Grading System for TLS

Grade	LTLS	Creatinine	Cardiac Arrhythmia	Seizure
0	-	≤ 1.5 × ULN	None	None
1	+	1.5 × ULN	Intervention not indicated	None
2	+	> 1.5 – 3.0 × ULN	Non-urgent medical intervention indicated	One brief generalized seizure; seizure(s) well controlled or infrequent; focal motor seizures not interfering with activities of daily life (ADL)

Cairo-Bishop Grading System for TLS (Continued)

Grade	LTLS	Creatinine	Cardiac Arrhythmia	Seizure
3	+	> 3.0 – 6.0 × ULN	Symptomatic and incompletely controlled medically or controlled with device	Seizure in which consciousness is altered; poorly controlled seizure disorder; breakthrough generalized seizures despite medical intervention
4	+	> 6.0 × ULN	Life-threatening	Seizures of any kind that are prolonged, repetitive, or difficult to control
5	+	Death[a]	Death[a]	Death[a]

Abbreviations: ADL = activities of daily living; LTLS = laboratory tumor lysis syndrome; TLS = tumor lysis syndrome; ULN = upper limit of normal.
[a] Probably or definitely attributable to clinical TLS.
Source:(Cairo, 2004).

APPENDIX M. JCAR017 MANAGEMENT GUIDELINES FOR CYTOKINE RELEASE SYNDROME AND NEUROLOGIC TOXICITIES (V3.2)

1. MANAGEMENT OF TOXICITIES ASSOCIATED WITH JCAR017

Cytokine release syndrome (CRS) and neurologic toxicities (NT) are associated with chimeric antigen receptor (CAR) T cell therapies. Celgene has developed the toxicity management guidelines (TMG) for CRS and NT associated with Celgene cellular products based on current clinical experience across the clinical development programs. These recommendations are based on the CRS revised grading system (Lee, 2014) and the Common Terminology Criteria for Adverse Events (CTCAE) and need to be used for grading of CRS and NT to guide management in this trial.

If available and adopted as per site standard practice, CRS and NT grading according to the American Society for Transplantation and Cellular Therapy (ASTCT) Consensus Grading System (Lee, 2019) should also be recorded in the electronic case report form (eCRF) to inform future modifications of the management guidelines.

2. CYTOKINE RELEASE SYNDROME

Administration of cellular products such as CAR-expressing T cells can be associated with cytokine-associated toxicity due to systemic production and release of various cytokines into the circulation. Cytokine-associated toxicity, also known as CRS, is a toxicity that occurs as a result of immune activation (Lee, 2014; Gardner 2017).

2.1. Pathophysiology of Cytokine Release Syndrome

The hallmark of CRS is immune activation resulting in elevated inflammatory cytokines. Cytokine release syndrome clinically manifests when large numbers of lymphocytes (B-cells, T-cells, and/or natural killer cells) and/or myeloid cells (macrophages, dendritic cells, and monocytes) become activated and release inflammatory cytokines. Cytokine release syndrome has classically been associated with therapeutic monoclonal antibody (mAb) infusions, most notably anti-CD3 (OKT3), anti-CD52 (alemtuzumab), anti-CD20 (rituximab), and the CD28 super-agonist, TGN1412. Cytokine release syndrome is also frequently observed following administration of bi-specific T cell engaging antibodies for leukemia, and adoptive cellular immunotherapies for cancer, most notably CAR T cells. Incidence, time to onset and severity of CRS due to CAR T cells is at least partially dependent on the infused cell dose and tumor burden/antigen density, presumably due to more rapid and higher levels of CAR T cell activation. Onset of CRS symptoms typically occurs days to occasionally weeks after the CAR T cell infusion, usually preceding maximal in vivo T cell expansion. Cytokine release syndrome is associated with elevated interferon gamma (IFN-γ), interleukin (IL)-6, and tumor necrosis alpha (TNF-α) levels, and increases in IL-2, granulocyte macrophage colony-stimulating factor (GM-CSF), IL-10, IL-8, IL-5, and fractalkine although the pattern of elevated cytokines varies among subjects (Davila, 2014; Hay, 2017). IL-6 has been identified as a central mediator of toxicity in CRS. IL-6 is a pleiotropic cytokine with anti-inflammatory and proinflammatory properties. High levels of IL-6, present in the context of CRS, likely initiates a proinflammatory IL-6-mediated signaling cascade.

2.2. Clinical Presentation of Cytokine Release Syndrome

Cytokine release syndrome is characterized by high fever, fatigue, nausea, headache, dyspnea, tachycardia, rigors, hypotension, hypoxia, myalgia/arthralgia, and anorexia. Clinical symptoms and severity of CRS are highly variable (Lee, 2014), and management can be complicated by concurrent conditions. In non-Hodgkin lymphoma (NHL) subjects treated with JCAR017, CRS usually occurs within two weeks after infusion (Abramson, 2017).

- Fever, especially high fever (≥ 38.5 °C or ≥ 101.3 °F), is a commonly-observed hallmark of CRS, and many features of CRS mimic infection. Hence, infection must be considered in all subjects presenting with CRS symptoms, and appropriate cultures must be obtained and empiric antibiotic therapy initiated per institution standard of care.
- Less common symptoms associated with CRS include cardiac dysfunction, adult respiratory distress syndrome, renal and/or hepatic failure, coagulopathies, disseminated intravascular coagulation, and capillary leak syndrome.
- Neurologic toxicity has been observed concurrently with CRS; refer to Section 4.
- CRS has been reported in some cases to be associated with findings of macrophage activation syndrome (MAS)/hemophagocytic lymphohistiocytosis (HLH), and the physiology of the syndromes may overlap; refer to Section 3.

2.3. Clinical Management of Cytokine Release Syndrome

Across various CD19 CAR T cell products, early manifestations of CRS can predict more severe toxicity for both CRS and NT.

Subjects with B-cell acute lymphoblastic leukemia (ALL) and high burden of disease are at high risk of developing CRS (Frey, 2017). Subjects with NHL who have high baseline tumor burden (measured by the sum of product of the perpendicular diameters [SPD] or high serum lactate dehydrogenase [(LDH); ≥ 500 U/L] prior to the start of lymphodepletion) also have a higher risk for developing CRS and/or neurotoxicity (Siddiqi, 2017).

High baseline levels of other commonly measured inflammatory markers, such as ferritin and C-reactive protein (CRP), were also associated with CRS.

It should be noted that, although useful for identifying subjects at higher risk for developing CRS, CRP, ferritin, and serum cytokine levels should not be used for CRS clinical management/treatment decisions in the absence of other clinical signs and symptoms of CRS; for example, a subject with an elevated CRP but no concomitant symptoms may not require intervention (Park, 2017). Thus, close observation of these subjects is strongly recommended.

A modification of the CTCAE CRS grading scale has been established to better reflect CAR T cell-associated CRS, as detailed in Table 1 (Lee, 2014).

Table 1: Grading Criteria for Cytokine Release Syndrome

	Symptoms/Signs	Cytokine Release Syndrome (CRS) Grade 1 (mild)	CRS Grade 2 (moderate)	CRS Grade 3 (severe)	CRS Grade 4 (life-threatening)
			CRS grade is defined by the most severe symptom (excluding fever)		
Vital Signs	Temperature ≥38.5 °C/101.3 °F	Yes	Any	Any	Any
	Systolic blood pressure (SBP) ≤ 90 mmHg	N/A	Responds to intravenous (IV) fluids or single low-dose vasopressor[a]	Needs high-dose[a] or multiple vasopressors	Life-threatening
	Need for oxygen to reach oxygen saturation (SaO_2) > 90%	N/A	Fraction of inspired oxygen (FiO_2) < 40%	FiO_2 ≥ 40%	Needs ventilator support
Organ Toxicity		N/A	Grade 2	Grade 3 or transaminitis Grade 4	Grade 4 (excluding transaminitis)

[a] Definition of high-dose vasopressors in Table 2.

Table 2: High Dose Vasopressors (all doses required for ≥ 3 hours)

Vasopressor	Dose
Norepinephrine monotherapy	≥ 20 µg/min
Dopamine monotherapy	≥ 10 µg/kg/min
Phenylephrine monotherapy	≥ 200 µg/min
Epinephrine monotherapy	≥ 10 µg/min
If on vasopressin	Vasopressin + norepinephrine equivalent (NE) of ≥ 10 µg/min[a]
If on combination vasopressors (not vasopressin)	Norepinephrine equivalent of ≥20 µg/min[a]

[a] VASST Trial Vasopressor Equivalent Equation: Norepinephrine equivalent dose = [norepinephrine (µg/min)] + [dopamine (µg/kg/min) ÷ 2] + [epinephrine (µg/min)] + [phenylephrine (µg/min) ÷ 10].

Adapted from (Lee, 2014).

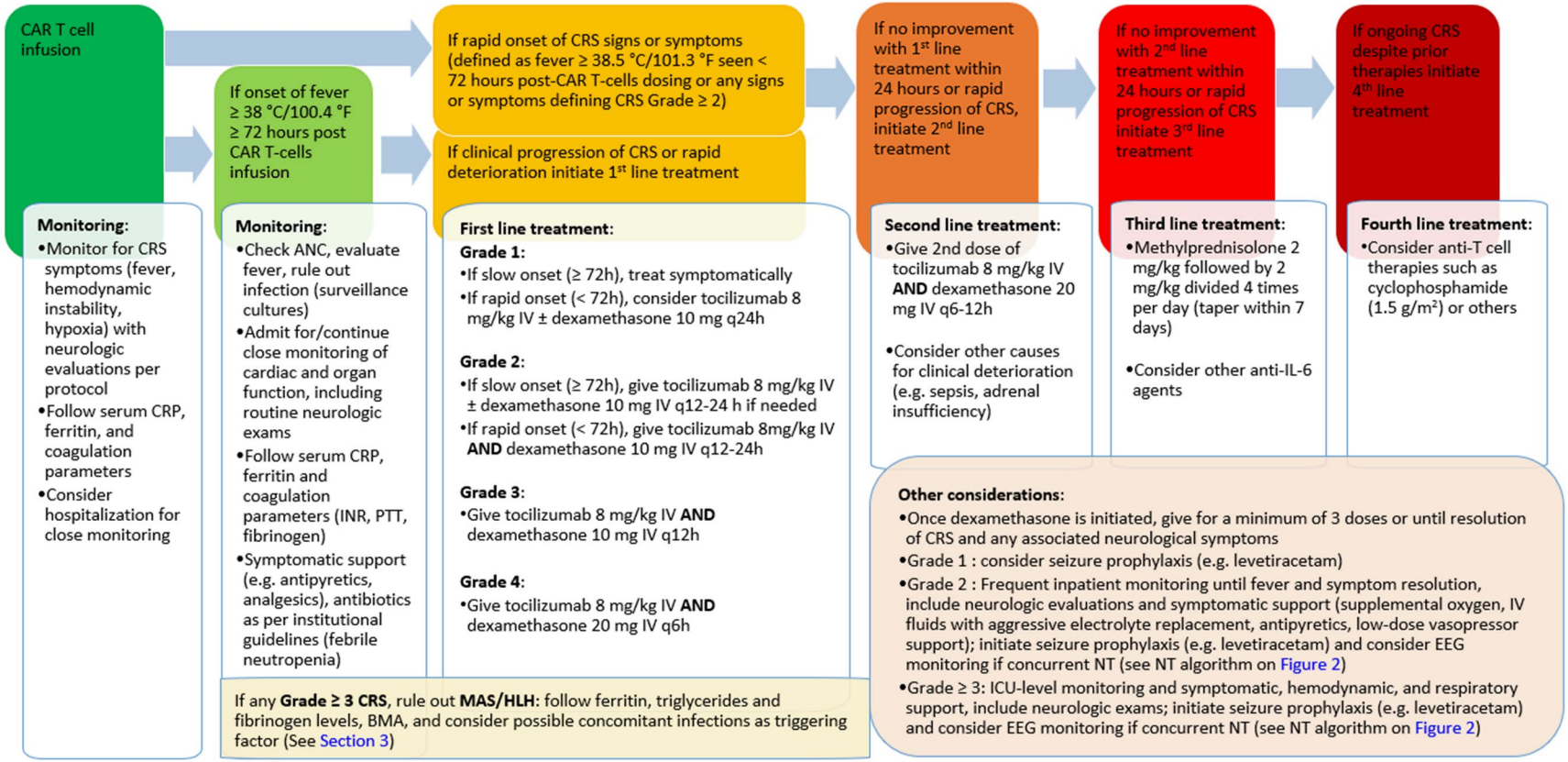
Detailed CRS management guidelines are shown in Figure 1. Treatment should be individualized for each subject's clinical needs. This guidance emphasizes the importance of early intervention for Grade 2 CRS, or in the setting of a rapid onset or rapid progression of CRS symptoms, to prevent the development of severe (Grade 3 or greater) CRS and NT.

In some cases, tocilizumab, an anti-IL-6R-antibody, may be required to treat toxicities such as severe CRS. Please refer to the currently approved Actemra® prescribing information (US) or RoActemra SmPC (EU). Actemra® has been approved by the Food and Drug Administration (FDA) for the treatment of CAR T cell-induced severe or life-threatening CRS in adults. RoAcetmra® has been approved by the European Medicines Agency (EMA) for the treatment of CAR T cell-induced severe or life-threatening CRS in adults. The preferred dose to intervene in adult subjects with CRS is 8 mg/kg (maximum 800 mg) IV. If no clinical improvement in the signs and symptoms of CRS occurs after the first dose, additional doses of tocilizumab may be administered (please see Figure 1, Actemra® prescribing information [US] and RoAcetmra® SmPC [EU]).

Other anti-IL-6 agents, if available in the country, should be considered in the event of severe CRS not responding to tocilizumab and corticosteroids. Dosing of any other anti-IL-6 agent should be per prescribing information.

In the most unresponsive severe cases additional treatments with T cell depleting therapies such as cyclophosphamide should be considered (Brudno, 2016).

Figure 1: JCAR017 Cytokine Release Syndrome Treatment Algorithm



Abbreviations: ANC = absolute neutrophil count; BMA = bone marrow aspirate; CAR = chimeric antigen receptor; CRP = C-reactive protein; CRS = cytokine release syndrome; EEG = electroencephalogram; HLH = hemophagocytic lympho-histiocytosis; ICU = intensive care unit; IL-6 = interleukin 6; INR = international normalized ratio; IV = intravenous; MAS = macrophage activation syndrome; NT = neurotoxicity; PTT = partial thromboplastin time; q = every.

3. MACROPHAGE ACTIVATION SYNDROME /HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS

Macrophage activation syndrome (MAS) or HLH is a rare, potentially fatal immune-mediated disease, which is caused by impaired natural killer and cytotoxic T-cell function. This syndrome has a wide range of causes, symptoms, and outcomes, but all lead to a hyperinflammatory response (with some characteristics that overlap with CRS and organ damage (Ramos-Casals, 2014). Cases of MAS/HLH have been described in patients treated with CAR T-cell therapies (Neelapu, 2017).

3.1. Pathophysiology of Macrophage Activation Syndrome/Hemophagocytic Lymphohistiocytosis

Macrophage activation syndrome/hemophagocytic lymphohistiocytosis is divided into primary (genetic) and secondary (reactive) forms. Secondary MAS/HLH is subclassified as viral, autoimmune, or tumor related. MAS/HLH has both infectious and non-infectious triggers (Ramos-Casals, 2014). Viral infection is the most frequent trigger, either due to primary infection or after reactivation in immunosuppressed patients. Bacterial and fungal infections can also trigger MAS/HLH. Macrophage activation like syndrome (MALS) is a distinct entity that leads to early death in septic patients and must be carefully ruled out in patients who are prone to develop severe infections, including patients following CAR T-cell therapy (Karakike, 2019). Patients with hematological malignancies, in particular lymphoma, have a higher risk of developing MAS/HLH.

3.2. Clinical Presentation and Diagnosis of Macrophage Activation Syndrome/Hemophagocytic Lymphohistiocytosis

The presentation of secondary MAS/HLH is heterogeneous and characterized by a panoply of clinical signs and symptoms. The clinical syndrome can be acute or subacute with non-specific symptoms appearing over few days to 4 week(s) (Ramos-Casals, 2014). The cardinal features are continuous high fever (≥ 38.5 °C) and enlarged lymphohematopoietic organs (spleno/hepatomegaly, occasionally accompanied by adenopathy). Pulmonary, neurologic, cutaneous and gastrointestinal involvement may also be present.

Laboratory markers associated with MAS/HLH include pancytopenia, hyperferritinemia, hypofibrinogenemia and raised D-dimer levels, hypertriglyceridemia, and abnormalities in liver function.

Detection of any ongoing infection acting as a trigger for MAS/HLH is critical (Figure 1). Standard tests should be used to screen for infections caused by the most common viruses such as herpes, cytomegalovirus (CMV) and Epstein-Barr virus (EBV). Other infectious agents (eg, mycobacteria, parasites, and fungi, particularly Candida and Mucor) should be ruled out according to specific clinical or epidemiological features (Ramos-Casals, 2014; Lehmberg, 2015).

Bone marrow is the preferred anatomical site for investigation of suspected MAS/HLH. Bone marrow aspirate can be negative at the initial stage of MAS/HLH and should be repeated during the clinical course if there is a high suspicion of MAS/HLH.

The diagnosis of MAS/HLH (according to HLH-2004 consensus criteria, further revised in 2014 for HLH associated with malignancies) (Lehmberg, 2015) can be established if either of the two criteria below is fulfilled:

1. A molecular diagnosis consistent with MAS/HLH
2. Diagnostic criteria for MAS/HLH fulfilled (five out of the eight criteria below):
   - High persistent fever (≥ 38.5 °C)
   - Splenomegaly
   - Cytopenias (affecting 2 of 3 lineages in the peripheral blood): Hemoglobin < 90 g/L, platelets < 100 x 10^9/L, neutrophils < 1.0 x 10^9/L
   - Triglycerides ≥ 3.0 mmol/L (ie, 265 mg/dL) or fibrinogen ≤ 1.5 g/L
   - Hemophagocytosis in bone marrow, spleen and/or lymph nodes
   - Low or absent NK-cell activity (according to local laboratory reference)
   - Ferritin ≥ 500 ng/mL
   - Soluble CD25 (ie, soluble IL-2 receptor) ≥ 2,400 U/mL

3.3. Clinical Management of Macrophage Activation Syndrome/Hemophagocytic Lymphohistiocytosis

Effective treatment of MAS/HLH requires multiple simultaneous approaches (Ramos-Casals, 2014, Lehmberg, 2015).

1. Supportive care is essential because of frequent life-threatening severe manifestations at presentation.
2. The elimination of triggers (particularly infection) is crucial to remove the stimuli that initiate the abnormal immune system activation. Appropriate broad-spectrum antiviral, antibacterial, antifungal prophylaxis and treatment must be initiated.
3. Suppression of the inflammatory response and cell proliferation by immunosuppressive and cytotoxic drugs, respectively, is necessary. First line treatment includes IL-6-blockade with tocilizumab. Glucocorticoids are also indicated for the initial treatment of MAS/HLH, irrespective of the cause (CRS Grade 4 treatment recommendations should be followed). IL-1 blockade with anakinra is suggested as second line treatment or in case of rapidly progressing clinical course. Anti-IL-6 antibody siltuximab might be considered as well as second line therapy. The use of cyclosporin, cyclophosphamide, etoposide and/or intrathecal methotrexate is not generally indicated in patients who develop MAS/HLH after CAR T-cell therapy, but may have to be employed in refractory cases.

Newer emerging treatments include emapalumab (anti IFN-gamma antibody), which has been approved by FDA for the treatment of primary refractory or recurrent MAS/HLH (Benedetti, 2019).

4. NEUROLOGIC TOXICITIES

CAR T cell therapy is associated with unique neurologic toxicities. Neurologic symptoms may include altered mental status, aphasia, altered level of consciousness, and seizures or seizure-like activity. With JCAR017, to date, the start of neurologic symptoms has been noted between 3 to 23 days (median 10 days) (Abramson, 2017) after CAR T cell infusion and in severe cases may require admission to the intensive care unit (ICU) for frequent monitoring, respiratory support, or intubation for airway protection. The symptoms are variable and generally occur as CRS is resolving or after CRS resolution.

4.1. Pathophysiology of Neurologic Toxicities

The pathogenesis of neurotoxicity is poorly defined. Analysis of a subset of subjects treated with JCAR017 (study 017001 – TRANSCEND NHL001) with NHL who have high baseline tumor burden (measured by the sum of product of the perpendicular diameters or high serum LDH (≥ 500 U/L) prior to the start of lymphodepletion) also have a higher risk for developing neurotoxicity (Siddiqi, 2017). In addition, severe neurotoxicity has also been reported in subjects with B-cell ALL and higher disease burden at the time of CD19 directed CAR T cell infusion (Park, 2017; Gust, 2017).

Peak levels of IL-6, IFN-γ, ferritin, and CRP are significantly higher in subjects who develop any Grade or Grade 3 or higher neurotoxicity (Turtle, 2016; Heipel, 2017). Protein levels in the cerebrospinal fluid (CSF) are usually elevated in patients with neurotoxicity, compared with baseline measurements, suggesting disruption of the blood-brain barrier. Other organ dysfunction (hepatic and renal), as well as hypoxemia, and infection, might also contribute to the encephalopathy (Neelapu, 2018). In another study, it has been reported that evidence for cytokine-mediated endothelial activation causes coagulopathy, capillary leak, and blood-brain barrier disruption allowing transit of high concentrations of systemic cytokines into the CSF (Gust, 2017).

4.2. Clinical Management of Neurologic Toxicities

The optimal management of CAR T cell-induced neurotoxicity is unknown at this time. These management guidelines represent the current state of knowledge and additional information will be provided to Investigators as it becomes available. Management should also be guided as per institutional or standard clinical practice, and as determined by the Investigator or treating physician and/or consulting neurologist. A thorough neurologic evaluation, including electroencephalogram (EEG), magnetic resonance imaging (MRI) or computer tomography (CT) scan of the brain and diagnostic lumbar puncture and frequent monitoring of cognitive function (eg, mini mental status exams or handwriting tests) should be considered.

Treatable causes of neurologic dysfunction, such as infection or hemorrhage should be ruled out. Common manifestations of neurotoxicity (eg, confusion, seizure, aphasia), can also be seen with infection, electrolyte imbalances, metabolic acidosis, uremia, concomitant medication use (eg, narcotics), and other medical conditions. Other causes for such symptoms should be considered.

Magnetic resonance imaging and CT scans of the brain are usually negative for any anatomical pathology that would account for the neurotoxicity symptoms observed in subjects treated with CAR T cell therapy, although rare cases of reversible T2/fluid attenuated inversion recovery

(FLAIR) MRI hyperintensity involving the thalami, dorsal pons, and medulla, and cerebral edema have been reported (Neelapu, 2018).

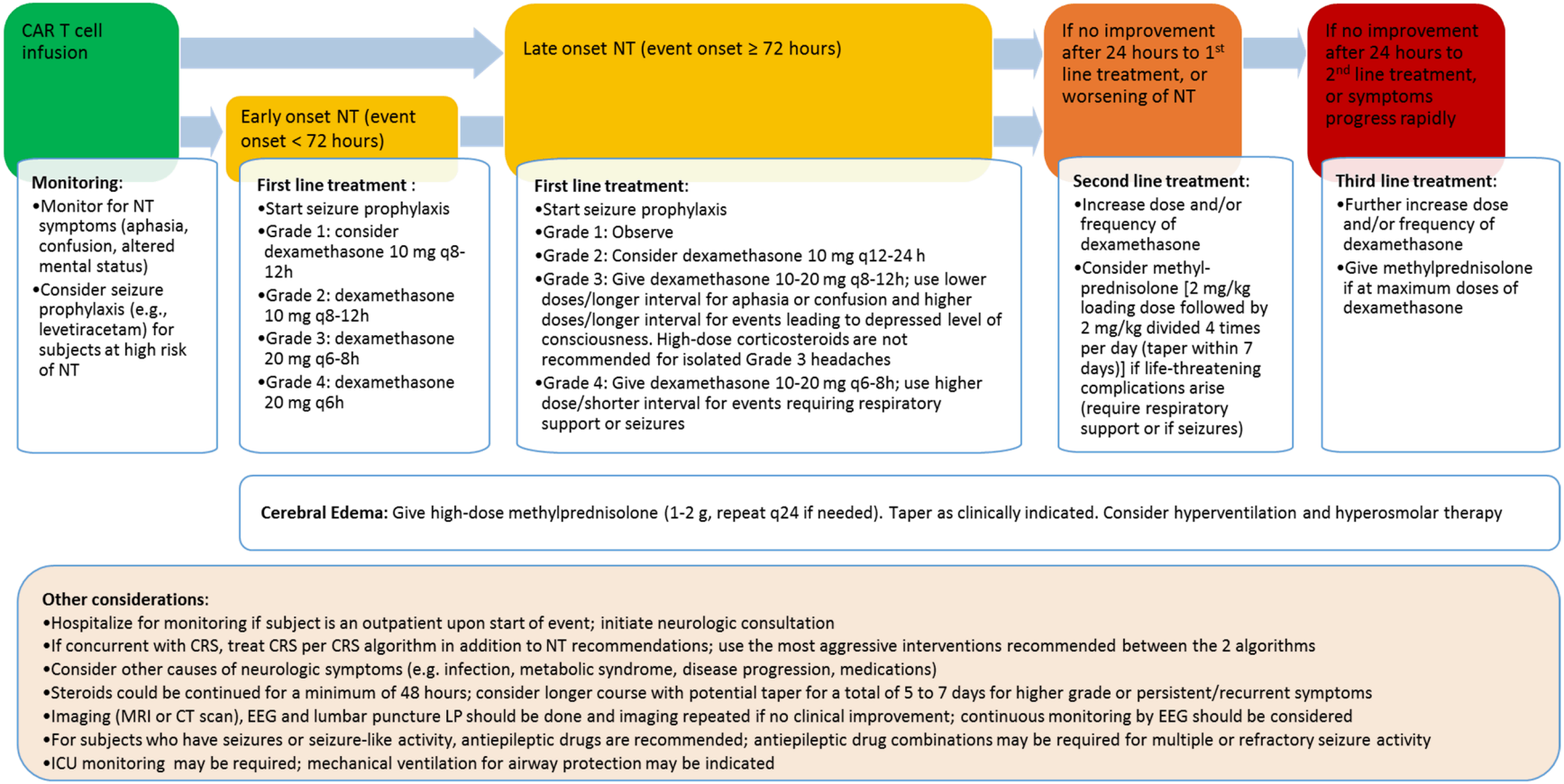
For subjects who have neurologic toxicity in the presence of CRS, the CRS should be managed following the guidelines provided in Figure 1.

Neurotoxicity should be evaluated following the guidelines provided in Figure 2. For concurrent CRS and neurotoxicity, the most aggressive intervention recommended by either guideline should be employed (if the recommendations for steroid doses differ, use the highest dose and/or frequency). For subjects with Grade 4 neurotoxicity with cerebral edema, high-dose corticosteroids, hyperventilation and hyperosmolar therapy has been recommended (Neelapu, 2018).

Note: Tocilizumab is not recommended for the treatment of neurotoxicity related to CAR T cell therapy, unless CRS or MAS/HLH is also present. Results from 2 studies, one of preemptive use of tocilizumab shortly after anti-CD19 CAR T cell therapy in relapsed/refractory NHL subjects (Locke, 2017), and the other mandatory use of tocilizumab at first fever (> 38.5 °C) in pediatric ALL patients treated with anti-CD19 CAR T cells (Gardner, 2017), demonstrated that early tocilizumab use either increased overall neurotoxicity and Grade ≥ 3 neurotoxicity rates (85% vs 62% overall; 35% vs 26% Grade ≥ 3) or provided no improvement in neurotoxicity rates, respectively. These findings support the hypothesis that tocilizumab does not improve and may worsen isolated neurotoxicity (Locke, 2017).

Neurotoxicity management guidelines are provided in Figure 2.

Figure 2: Neurotoxicity Treatment Algorithm



Abbreviations: CAR = chimeric antigen receptor; CRS = cytokine release syndrome; CT = computed tomography; EEG = electroencephalogram; ICU = intensive care unit; LP = lumbar puncture; MRI = magnetic resonance imaging; NT = neurotoxicity; q = every.

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[redacted]

Date: Friday, 13 August 2021, 09:26 AM Eastern Daylight Time
Meaning: Approved, no changes necessary.
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– SUMMARY OF CHANGES –

AMENDMENT NO. 5

A PHASE 2, SINGLE-ARM, MULTI-COHORT, MULTI-CENTER TRIAL TO DETERMINE THE EFFICACY AND SAFETY OF JCAR017 IN ADULT SUBJECTS WITH AGGRESSIVE B-CELL NON-HODGKIN LYMPHOMA

(TRANSCEND WORLD)

INVESTIGATIONAL PRODUCT (IP):	**JCAR017**
PROTOCOL NUMBER:	**JCAR017-BCM-001**
ORIGINAL DATE:	**24 Apr 2017**
AMENDMENT No. 1 DATE:	**08 Jan 2018**
AMENDMENT No. 2 DATE:	**28 Dec 2018**
AMENDMENT No. 3 DATE:	**21 Nov 2019**
AMENDMENT No. 4 DATE:	**16 Nov 2020**
AMENDMENT No. 5 DATE:	**12 Aug 2021**
EudraCT NUMBER:	**2017-000106-38**
IND NUMBER:	**Not applicable**

Contact Information:

Name: [redacted]

Title: [redacted]

Address: Route de Perreux 1, 2017 Boudry, Switzerland

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E-mail: [redacted]

CELGENE THERAPEUTIC AREA HEAD SIGNATURE PAGE

{See appended electronic signature page}
Signature of Celgene Therapeutic Area Head **dd mmm yyyy**
[redacted]
Printed Name of Celgene Therapeutic Area Head and Title
By my signature, I indicate I have reviewed this summary of changes and find its content to be acceptable.

1. JUSTIFICATION FOR AMENDMENT

Significant changes included in this amendment are summarized below:

- **Cohort 2 sample size was modified from a maximum of 28 to approximately 28 subjects**

The change made to the Cohort 2 sample size allows for additional flexibility in the number of subjects included in the study to account for potential dropout of subjects during the pre-treatment phase.

Revised sections: Figure 1, Overall Study Design, Section 9.3.2, Cohort 2

- **Specified that Cohort 2 will have formal hypothesis testing at the time of the primary analysis**

[redacted] a formal hypothesis testing will be performed on Cohort 2 instead of on the pooled analysis from JCAR017-BCM-001 Cohort 2 and Study 017006 [PILOT] combined.

Revised sections: Section 9.1, Overview, Section 9.3.2, Cohort 2

- **Cohort 2 primary analysis will be triggered when approximately 28 subjects treated with JCAR017 have been followed for at least 6 months**

[redacted] the timing of the primary efficacy analysis was amended to occur after approximately 28 treated subjects have been followed for at least 6 months after first response.

Revised section: Section 9.3.2, Cohort 2

- **Reference rate for null hypothesis testing for Cohort 2 will be estimated from a Real-World Study**

The reference rate to be used for the null hypothesis testing for Cohort 2 will be generated from a retrospective patient-level Real-World data synthetic cohort better matching the population to be enrolled in the current study when compared to estimate from literature.

Revised section: Section 9.3.2, Cohort 2

- **Cohort 5 inclusion criteria were amended to allow for enrollment of subjects who failed to proceed to HDCT and ASCT following induction therapy**

Study population in Cohort 5 was expanded to include subjects intended for transplant but who failed to proceed due to insufficient response at time of induction completion or due to failure of PBSC mobilization, given the poor prognosis and unmet medical need in these patients.

Revised sections: Protocol Summary, Section 3.1, Study Design, Section 4.2, Inclusion Criteria

- **Timing of cohort 7 analysis was added**

Cohort 7 analysis will be performed after all subjects have been followed for at least 6 months.

Revised section: Section 9.3.4, Cohort 7

- **Requirement that no more than 1 subject per week treated at a given site was removed**

Gating was removed given all participating sites have now gained sufficient experience with CAR-T products and CAR-T administration is becoming routine procedure at participating BCM-001 study sites.

Revised sections: Protocol Summary, Section 3.1, Study Design

- **Updated SAE reporting requirement for clonal outgrowth or monoclonality from vector site insertion**

Requirement to report clonal outgrowth or monoclonality from vector site insertion as an SAE was removed because the occurrence of clonal outgrowth will not result in a malignancy. All subjects will be closely monitored for signs of malignancy [redacted]. In the event of an SPM, a sample of the neoplastic tissue will be requested for causality analysis related to use of integrating vector to determine if insertional oncogenesis is suspected.

Revised sections: Section 6.4.10, Persistent Vector Sequence Monitoring, Section 10.2.1, Seriousness, 10.8.1.14, New Malignancies

The amendment also includes other minor clarifications and corrections:

- Added wording on approved CD19-directed CAR T therapies

  Revised Section: Section 1.2.2, CD19-targeted Chimeric Antigen Receptors

- Updated Table 4, Table of Events
  - Footnote [ll] was added to clarify timing of brain magnetic resonance imaging (MRI)

  Revised section: Table 4, Table of Events

- Clarified timing of CSF assessment for subjects enrolled in Cohort 5

  Revised sections: Protocol Summary, Table 4, Table of Events, Section 6.1.4, Pretreatment Evaluation, Section 6.2.7, Days 15, 22, and 29 (±2 days), Section 6.4.5, Cerebrospinal Fluid Assessment and Central Nervous System Symptom Assessment, Section 6.5, Efficacy Assessment

- Timing of interactions between the sponsor and the sites was updated from weekly to at least monthly

  Revised Section: 3.1, Study Design

- Added wording regarding alternate administration methods of MMSE in case of exceptional circumstances

  Revised sections: Table 4, Table of Events, Section 6.4.4, Routine Neurologic and Mini Mental State Examinations

  - Clarified that an autopsy tissue sample will be collected when there is a safety concern

  Revised section: Section 6.3.4, Assessments at Time of Death

- Added wording regarding the statistical test to be used for hypothesis testing of the primary endpoint

  Revised Section: Section 9.6.2, Primary Endpoint

- Updated Study Monitoring and Source Data Verification guidelines

  Revised Section: Section 15.1, Study Monitoring and Source Data Verification

- Updated references

  Revised Section: Section 17, References

- Update of abbreviations

  Revised Section: Appendix A, Table of Abbreviations

Additional spelling, style, formatting corrections and minor editorial revisions were made throughout the document.

– SUMMARY OF CHANGES –

AMENDMENT NO. 4

A PHASE 2, SINGLE-ARM, MULTI-COHORT, MULTI-CENTER TRIAL TO DETERMINE THE EFFICACY AND SAFETY OF JCAR017 IN ADULT SUBJECTS WITH AGGRESSIVE B-CELL NON-HODGKIN LYMPHOMA

(TRANSCEND WORLD)

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IND NUMBER:	**Not applicable**

Contact Information:

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CELGENE THERAPEUTIC AREA HEAD SIGNATURE PAGE

{See appended electronic signature page}
Signature of Celgene Therapeutic Area Head **dd mmm yyyy**
[redacted]
Printed Name of Celgene Therapeutic Area Head and Title
By my signature, I indicate I have reviewed this summary of changes and find its content to be acceptable.

1. JUSTIFICATION FOR AMENDMENT

Significant changes included in this amendment are summarized below:

- **Cohort 2 sample size was modified from N=28 to a maximum of 28 subjects to be treated with JCAR017**

The hypothesis-testing primary analysis will be based on a sample size of 80 subjects pooled from Cohort 2 of this study and Study 017006 (PILOT) enrolling a population in the United States (US) that mirrors the population treated in Cohort 2. The change made to the Cohort 2 sample size allows for flexibility in the number of subjects included from each study.

Revised sections: Figure 1, Overall Study Design, Section 9.3.2, Cohort 2

- **Specified that the primary analysis for Cohort 2 will be descriptive without formal hypothesis testing**

Cohort 2 primary analysis (N= max 28) will be descriptive only. A formal hypothesis testing will be performed on the pooled analysis set (JCAR017-BCM-001 Cohort 2 and Study 017006 [PILOT]) which comprises 80 evaluable subjects across both studies.

Revised section: Section 9.3.2, Cohort 2

- **Clarified that the pooled analysis from Cohort 2 and Study 017006 (PILOT) will be reported outside of the JCAR017-BCM-001 Clinical Study Report (CSR)**

Since data from JCAR017-BCM-001 Cohort 2 will be pooled with data from Study 017006 (PILOT), the details of the pooled analysis will be presented in a separate statistical analysis plan (SAP) and the results of this analysis reported outside of the JCAR017-BCM-001 CSR.

Revised section: Section 9.3.2, Cohort 2

- **Cohort 2 descriptive analysis will be triggered when the last subject treated with JCAR017 has been followed for at least one post-baseline efficacy assessment instead of 6 months**

The Cohort 2 descriptive analysis will be performed when a total of 80 evaluable subjects across Cohort 2 and Study 017006 (PILOT) have been followed for at least one post-baseline efficacy assessment. This allows to reliably assess the primary endpoint of overall response rate (ORR). Duration of response will be evaluated and updated at a later time point.

Revised section: Section 9.3.2, Cohort 2

- **Updates on required screening, baseline and post-baseline evaluations for primary central nervous system lymphoma(PCNSL) (Cohort 5) subjects were provided to align with standardized baseline evaluations according to Abrey, 2005** It was clarified that an ophthalmologic evaluation is required at screening for subjects with PCNSL (Cohort 5) to exclude ocular lymphoma infiltration and does not need to be repeated thereafter unless symptoms occur. Cerebrospinal fluid does not need to be repeated if negative at screening, unless to confirm disease progression.

Revised sections: Protocol Summary, Table 4, Table of Events, Section 4.2, Inclusion Criteria, Section 6.1.1, Screening , Section 6.1.4 Pretreatment Evaluation (following enrollment and

within 7 days prior to lymphodepleting chemotherapy), Section 6.2.7, Days 15, 22, and 29 (±2 days), 6.3, Post-Treatment Period (Follow-up), Section 6.3.1, Unscheduled Evaluations, Section 6.5, Efficacy Assessment

- **Inclusion criterion #8 was added back for subjects with non-Hodgkin lymphoma (NHL)**

"For subjects with NHL (except Cohort 5): *Subjects must have positron emission tomography (PET)-positive disease as per Lugano Classification (Cheson, 2014)"*This inclusion criterion was added back, correcting an error at time of last amendment. Instead of only removing the reference to subjects with Richter's transformation, the whole inclusion criterion had been deleted. In the previous protocol amendment, inclusion criterion #8 had been entirely removed, including for subjects with NHL while all subjects enrolled - except Cohort 5 (PCNSL) - must have positron emission tomography (PET)-positive disease as per Lugano Classification (Cheson, 2014).

Revised section: Section 4.2, Inclusion criteria

The amendment also includes other minor clarifications and corrections:

- [redacted]

  Revised section: MEDICAL MONITOR AND EMERGENCY CONTACT INFORMATION

- The length of enrollment period has been extended from 24 to 40 monthsRevised sections: Protocol Summary, Section 3.3, Study Duration for SubjectsUpdated Figure 1, Overall Study Design

  Revised section: Figure 1, Overall Study Design

- Inclusion criterion #9 has been updated to clarify required evaluations for PCNSL subjects

  Revised section: Section 4.2, Inclusion Criteria

- Clarification that restaging for Cohort 4 subjects is mandatory after 2 cycles of induction to check for a complete metabolic responseRevised section: Table 4, Table of Events (footnote [k]), Section 6.1.4, PretreatmentUpdated Table 4, Table of Events
  - peripheral blood sample (hematology) collection at D60 was added
  - Collection timepoints for peripheral blood samples for biomarkers (peripheral blood mononuclear cell (PBMC) and immunophenotyping) were split into 2 separate lines.
  - Footnote [k] and [hh] were updated
  - Footnote jj was added for computed tomography (CT)/magnetic resonance imaging (MRI) at Day 90/120
  - Footnote [kk] was added

  Revised section: Table 4, Table of Events

- Updated Table 5 to clarify that bridging radiation therapy is not allowed for Cohort 5 subjects

  Revised section: Table 5, Washout Periods Prior to Leukapheresis and Prior to Lymphodepleting Chemotherapy

- Updated wording on required biomarkers assessments at different study visits for clarity.

  Revised sections: Section 6.1.2, Leukapheresis, Section 6.1.4, Pretreatment evaluation, Section 6.2.2, JCAR017 Administration: Day 1, Section 6.2.4, Day 4 (+1 day), Section 6.2.5, Day 8 (±1 day), Section 6.2.6, day 11 (±1 day), Section 6.2.7, Days 15, 22, and 29 (±2 days), Section 6.3, Post-Treatment Period (Follow-up)

- Added peripheral blood sample (hematology) required on Month 2

  Revised sections: Section 6.3, Post-Treatment Period (Follow-up), Table 4, Table of Events

- Added ophthalmologic examination among the list of unscheduled evaluations

  Revised section: Section 6.3.1, Unscheduled Evaluations

- Clarified language regarding performing and capturing immune effector cell-associated encephalopathy (ICE) scores coupled with other neurological assessments

  Revised sections: Table 4, Table of Events, Section 6.1.4, Pretreatment Evaluation, Section 6.2.2, JCAR017 Administration: Day 1, Section 6.2.4, Day 4 (+1 day), Section 6.2.5, Day 8 (±1 day), Section 6.2.7, Days 15, 22, and 29 (±2 days), Section 6.3, Post-Treatment Period (Follow-up), Section 6.3.1, Unscheduled Evaluations, Section 6.4.4, Routine Neurologic and Mini Mental State Examinations, Section 9.7, Safety AnalysisProvided clarification on the method of calculation of the viral copy number (VCN) per cell

  Revised section: Section 6.4.10, Viral Vector Sequence Pharmacokinetic Testing

- Clarified that the Enrolled-set will include all subjects that pass eligibility criteria at screening

  Revised Section: Section 9.2.2, Enrolled Set

- Definition of outpatient subjects was added

  Revised section: Section 9.3.4, Cohort 7

- Clarified that the primary efficacy endpoint for Cohort 4, and 5 will be ORR as determined by Investigator assessment

  Revised section: Section 9.6.2, Primary Endpoint

- Changes to subgroup analyses:
  - Added additional subgroup analysis of prior response status: refractory or relapsed within 12 months to last therapy versus relapsed ≥12 months to last prior therapy

  - Clarified that additional age categories per cohorts are defined in the study SAP
  - Clarified that for all subgroup analyses age and Central Nervous System (CNS) disease status at screening will be considered

  Revised section: Section 9.6.4, Subgroup Analyses

- Update of abbreviations

  Revised Section: Appendix A, Table of Abbreviations

Additional spelling, style, formatting corrections and minor editorial revisions were made throughout the document.

– SUMMARY OF CHANGES –

AMENDMENT NO. 3

A PHASE 2, SINGLE-ARM, MULTI-COHORT, MULTI-CENTER TRIAL TO DETERMINE THE EFFICACY AND SAFETY OF JCAR017 IN ADULT SUBJECTS WITH AGGRESSIVE B-CELL NON-HODGKIN LYMPHOMA

(TRANSCEND WORLD)

INVESTIGATIONAL PRODUCT (IP):	**JCAR017**
PROTOCOL NUMBER:	**JCAR017-BCM-001**
ORIGINAL DATE:	**24 Apr 2017**
AMENDMENT No. 1 DATE:	**08 Jan 2018**
AMENDMENT No. 2 DATE:	**28 Dec 2018**
AMENDMENT No. 3 DATE:	**21 Nov 2019**
EudraCT NUMBER:	**2017-000106-38**
IND NUMBER:	**Not applicable**

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CELGENE THERAPEUTIC AREA HEAD SIGNATURE PAGE

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1. JUSTIFICATION FOR AMENDMENT

Significant changes included in this amendment are summarized below:

- **Cohort 4 (High-grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements with diffuse large B-cell lymphoma [DLBCL] histology) clarified to allow consolidation after first line therapy**

The protocol was updated to clarify that enrolled subjects in Cohort 4 will proceed with JCAR017 infusion after first line therapy including anthracycline and rituximab (or other CD20-targeted agent) containing regimen. First line therapy is considered as induction prior to JCAR017 consolidation. Subjects with complete metabolic response after 2 cycles of induction will proceed with JCAR017 infusion only at time of relapse, if applicable.

The rationale for this change is to explore JCAR017 in this high-risk patient population to better address this high unmet medical need.

To align with new 2016 World Health Organization (WHO) classification, the double hit lymphoma (DHL)/triple hit lymphoma (THL) terminology was changed to WHO nomenclature for this population: High-grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements with DLBCL histology (HGBL).

Revised Sections: Protocol Summary; Section 1.1, Disease Background; Section 3.1, Study Design; Figure 1, Overall Study Design; Section 4.2, Inclusion Criteria #6; Section 9.3.5, Gated Cohorts

- **Cohort 5 (Primary Central Nervous System Lymphoma) modified to second line population**

With the recent change in the treatment paradigm with high dose chemotherapy and autologous stem cell transplant (ASCT) as the new standard of care in first line, the second line patient population has become the true unmet medical need.

The protocol was updated to restrict the enrollment to the second line population after failure of first line therapy with high-dose chemotherapy and ASCT.

To allow for closer disease monitoring, the efficacy response assessment schedule was updated to bimonthly response assessments for the first 6 months.

It was specified that prior whole brain radiotherapy clarification is not allowed for subjects enrolled in Cohort 5.

Revised Sections: Protocol Summary; Section 3.1, Study Design; Figure 1, Overall Study Design; Section 4.2, Inclusion Criteria #6; Section 4.3, Exclusion Criteria #16; Table 4, Table of Events; Section 6.3, Post-Treatment Period (Follow-up)

- **Cohort 6 (Richter's transformation) removed**

Preliminary data from ongoing trials suggests that subjects with Richter's transformation may not optimally benefit from chimeric antigen receptor (CAR) T therapy alone and may benefit from novel combinations. Therefore, Cohort 6 has been removed from the protocol.

Revised Sections: Protocol Summary; Table 1, Study Objectives; Table 2, Study Endpoints; Section 3.1, Study Design; Figure 1, Overall Study Design; Section 4.2, Inclusion Criteria #6

and #8; Table 4, Table of Events; Section 6.1, Pretreatment Period; Section 6.2, Treatment Period; Section 6.3, Post-Treatment Period (Follow-up); Table 6, Exploratory Biomarkers Sampling; Section 9.3.5, Gated Cohorts; Section 9.6.3, Secondary Efficacy Endpoints; Section 9.9.3, Exploratory Analysis

- **Addition of Cohort 7 (Outpatient)**

A favorable benefit/risk profile of JCAR017 and preliminary outpatient data in ongoing JCAR017 clinical trials in the United States (US) has shown outpatient administration to not compromise safety in carefully selected subjects. Cohort 7 was added to explore the benefit/risk profile of JCAR017 outpatient treatment in Europe.

Subjects meeting eligibility criteria for Cohort 1 and suitable for monitoring as outpatients will be enrolled in Cohort 7. These subjects must meet the conditions outlined in the Outpatient Administration and Monitoring Guidance for Lisocabtagene Maraleucel.

The primary objective of Cohort 7 is to evaluate the safety of JCAR017 treatment in subjects intended to be treated as outpatients. Safety monitoring boundaries based on Bayesian framework have been added to the stopping rules for Cohort 7 (Table 3). The secondary objective of Cohort 7 is to determine the efficacy, defined as overall response rate (ORR) of JCAR017 in subjects intended to be treated as outpatients. The primary and secondary objectives of the study have been updated accordingly.

Revised Sections: Protocol Summary; Table 1, Study Objectives; Table 2, Study Endpoints; Section 3.1, Study Design; Figure 1, Overall Study Design; Section 3.2.2, Criteria for Pausing or Stopping Cohort 7; Table 3, Safety Monitoring Boundaries Based on Thall and Simon; Section 4.2, Inclusion Criteria #6; Section 9.3.4, Cohort 7; Table 8, Example Rates (± 95% Confidence Intervals); Section 9.6.2, Primary Endpoint; Section 9.6.3, Secondary Efficacy Endpoints

- **Criteria for Pausing or Stopping the Study**

The criteria for automatically pausing the study were removed from Section 3.2.1 of the protocol since existing data from over 300 subjects (including 33 adult subjects treated in Europe) have shown a tolerable and manageable safety profile, and the Data Safety Monitoring Board (DSMB) review data across all JCAR017 studies on an ongoing basis. Should a significant safety or efficacy issue be identified, all Investigators will be notified immediately and the DSMB will be convened in an expedited fashion to make a recommendation as to the future conduct of the study.

Revised Section: Section 3.2.1 Criteria for Pausing or Stopping the Study

- **Patient interviews**

- For subjects enrolled under Protocol Amendment 3, patient interviews will be reduced to Pretreatment Evaluation, Day 90, and Day 270

Already collected interviews allow valuable conclusions on the short-term impact of treatment. Additional data to assess long-term and longitudinal impact is still needed. To reduce burden on subjects, 8 timepoints were removed for subjects enrolled under Protocol Amendment 3 (ie, Pretreatment evaluation, D1, D29, D60, D180, D365, D545, and D730).

Revised Section: Table 7, Table of Events, Patient Interviews

- **Inclusion criteria and Pregnancy risk updated with information on blood and organ donation, contraception and breastfeeding following exposure to lymphodepletion, combination agent and/or JCAR017**

There are no exposure data to provide a recommendation concerning duration of contraception following treatment with JCAR017. The JCAR017 program excludes pregnant subjects from participation and mandates that subjects use highly effective contraception. So far, no pregnancy has occurred in the JCAR017 clinical development program. No animal studies have been conducted with JCAR017 to assess whether it could cause fetal harm when administered to a pregnant woman. It is not known whether JCAR017 has the potential to be transferred to the fetus via the placenta and cause fetal toxicity, including B-cell lymphocytopenia. As the risk for the mother and fetus or newborn is unknown at this time, and negative CAR T quantitative polymerase chain reaction (qPCR) tests do not reliably predict complete disappearance of CAR T cells from the body, this test cannot be used to guide duration of contraception. Therefore, the indication that contraception may be changed or breastfeeding may be resumed following two subsequent negative CAR T qPCR tests was removed from the inclusion criteria.

Revised Sections: Section 4.2, Inclusion Criteria #12, #13, and #14; Section 10.4, Pregnancy

- **Removal of the deep venous thrombosis (DVT) / pulmonary embolism (PE) / anticoagulation and vascular tumor invasion exclusion criteria as well as statements regarding stable disease/anticoagulation to be added to the Lymphodepleting Chemotherapy and Criteria for JCAR017 Treatment sections of the protocol.**

The following exclusion criteria have been revised to read as follows:

- ~~Tumor invasion of venous or arterial vessels~~Progressive vascular tumor invasion, thrombosis, or embolism
- ~~Deep venous thrombosis (DVT) or pulmonary embolism (PE) within 3 months of leukapheresis and/or DVT or PE that requires ongoing therapeutic levels of anticoagulation~~Venous thrombosis or embolism not managed on a stable regimen of anticoagulation

exclude patients with venous thrombosis or embolism not managed on a stable regimen of anticoagulation or patients with progressive vascular tumor invasion, thrombosis, or embolism.

Revised Sections: Section 4.3, Exclusion Criteria #17 and #18; Section 6.2.2, JCAR017 Administration: Day 1

- **Addition of 2 exclusion criteria** [redacted]
- Known severe hypersensitivity to dimethyl sulfoxide (DMSO) or Dextran
- Systemic immunostimulatory agents (including but not limited to interferon and interleukin [IL]-2) within 6 weeks or 5 half-lives of the drug, whichever is shorter, prior to JCAR017 infusion.

Revised Section: Section 4.3, Exclusion Criteria #16 and #18

- **Update of study number of subjects**

As a result of Cohort 6 removal and Cohort 7 addition, the study number of subjects was updated.

Revised Sections: Protocol Summary; Section 3.1, Study Design; Figure 1, Overall Study Design; Section 4.1, Number of Subjects

- **New conditions to be reported as serious adverse events (SAEs)**

New incidence or exacerbation of a pre-existing neurologic disorder, a prior rheumatologic or other autoimmune disorder and new incidence of a hematologic disorder, will be reported irrespective of causality as SAEs.

Revised Section: Table 9, Recording Periods for Adverse Events

The amendment also includes several other minor clarifications and corrections:

- **Update of protocol product deviation plan language**

Revised Sections: Section 7.3.5, Protocol Product Deviation Plan; Section 7.3.6, Exception Use of Non-conforming Product

- **Addition of Mini Mental State Examination (MMSE) performed on a daily basis in case of Neurotoxicity**

Revised Sections: Table 4, Table of Events, footnote [hh]; Section 6.2.2, Treatment Period; Section 6.3, Post-Treatment Period (Follow-up); Section 6.4.4, Routine Neurologic and Mini Mental State Examinations

- **Modifications of washout periods prior to lymphodepleting chemotherapy**

Revised Section: Table 5, Washout Periods Prior to Leukapheresis (and Prior to Lymphodepleting Chemotherapy)

- **Pharmacokinetic (PK) analysis population split by qPCR and by flow cytometry (previously combined)**

Revised Sections: Table 1, Study Objectives; Table 2, Study Endpoints; Section 9.2.6, qPCR Pharmacokinetic Analysis Set; Section 9.2.7, Flow Cytometry Pharmacokinetic Analysis Set; 9.6.3, Secondary Efficacy Endpoints; Section 9.9.3, Exploratory Analysis

- **Updated wording in Section 9.3.3 Cohort 3 (Japan only)**

In Japan, the analysis will be conducted by combining Cohorts 1, 2 and 3. The primary efficacy analysis will be performed after at least 10 Japanese subjects in Cohort 3 have been treated with JCAR017 conforming product and have been followed for at least 3 months or until death, progressive disease, or withdrawal from study, and at the time when the number of the subjects who are eligible for the Efficacy Evaluable Set has reached at least 34 subjects in total of Cohorts 1, 2 and 3. The primary efficacy analysis and safety analysis will be based on JCAR017-Treated Set (all subjects who have received JCAR017 conforming product).

Revised Sections: Section 9.3.3 Cohort 3 (Japan only)

- **European Organisation for Research and Treatment of Cancer – Quality of Life C30 (EORTC QLQ-C30) subscales split between secondary objectives/endpoints and exploratory objectives/endpoints**

Revised Sections: Protocol Summary; Table 1, Study Objectives; Table 2, Study Endpoints

- **European Quality of Life – 5 Dimensions Health State Classifier to 5 Levels (EQ-5D-5L) moved from secondary objectives/endpoints to exploratory objectives/endpoints**

Revised Sections: Protocol Summary; Table 1, Study Objectives; Table 2, Study Endpoints

- **Functional Assessment of Cancer Therapy – Lymphoma "Additional concerns" subscale (FACT-LymS) specified throughout the Amendment**

Revised Sections: Protocol Summary; Table 1, Study Objectives; Table 2, Study Endpoints; Section 6.8.3, FACT-LymS

- **Removal of saliva sample collection as biomarker for pharmacogenomics**

Revised Sections: Section 6.1, Pretreatment Period; Table 6, Exploratory Biomarkers Sampling

- **Clarification of health-related quality of life sections**

Revised Sections: Table 1, Study Objectives; Table 2, Study Endpoints

- **Clarification of biomarker sections**

Revised Sections: Table 1, Study Objectives; Table 2, Study Endpoints; Section 9.9.3, Exploratory Analysis

- **Reordering of the pregnancy wording applicable for female and male**

Revised Section: Section 10.4, Pregnancy

- **Diffusion capacity of carbon monoxide (DLCO) adjusted with Dinakara equation**

Revised Sections: Protocol Summary; Section 3.1, Study Design; Section 4.2, Inclusion Criteria #6; Section 6.1.1, Screening; Appendix G, hematopoietic cell transplantation (HCT)-specific comorbidity index (HCT-CI) Score Calculator.

- **Clarification of hepatitis exclusion criteria**

Revised Section: Section 4.3, Exclusion Criteria #8

- **Hospital resource utilization listed in exploratory endpoints and added to the table of events**

Revised Sections: Table 2, Study Endpoints; Table 4, Table of Events

- **Removal of the detection of replication-competent lentivirus from exploratory endpoint since already included in safety endpoint**

Revised Section: Table 2, Study Endpoints

- **Clarification of prohibited concomitant medications**

Revised Section: 8.2, Prohibited Concomitant Medications and Procedures

- **Clarification of viral vector sequence pharmacokinetic testing**

Revised Sections: Section 6.4.10, Viral Vector Sequence Pharmacokinetic Testing

- **Clarification of management of toxicities associated with JCAR017**

Revised Sections: Section 10.8, Potential Risks and Management of Treatment Toxicities; Appendix M, JCAR017 Management guidelines for cytokine release syndrome and neurologic toxicities (V3.01)

- **Clarification regarding clinical stability before LDC and JCAR017**

Revised Section: Section 6.2, Treatment Period; 6.2.1, Lymphodepleting Chemotherapy (start 5 to 10 days prior to JCAR017 infusion)

- **The study product doses are written at ten to the power of six (instead of eight)**

Revised Sections: Protocol Summary; Section 1.2.4., Clinical Experience with JCAR017 and Related CAR T Cell Products; Section 1.3.1, Study Rationale and Purpose; Section 1.3.2, Lymphodepleting Chemotherapy Rationale; Section 1.3.3, Rationale for JCAR017 Dose Selection; Section 3.1, Study Design; Figure 1, Overall Study Design; Section 7.3.4, JCAR017 Administration

- **Update of references**

Revised Section: Section 17, References

- **Update of Appendix M**

Revised Section: Appendix M, JCAR017 management guidelines for cytokine release syndrome and neurologic toxicities

- **Update of abbreviations**

Revised Section: Appendix A, Table of abbreviations

– SUMMARY OF CHANGES –

AMENDMENT NO. 2

A PHASE 2, SINGLE-ARM, MULTI-COHORT, MULTI-CENTER TRIAL TO DETERMINE THE EFFICACY AND SAFETY OF JCAR017 IN ADULT SUBJECTS WITH AGGRESSIVE B-CELL NON-HODGKIN LYMPHOMA

INVESTIGATIONAL PRODUCT (IP):	**JCAR017**
PROTOCOL NUMBER:	**JCAR017-BCM-001**
ORIGINAL DATE:	**24 Apr 2017**
AMENDMENT No. 1 DATE:	**8 Jan 2018**
AMENDMENT No. 2 DATE:	**28 Dec 2018**
EudraCT NUMBER:	**2017-000106-38**
IND NUMBER:	**Not applicable**

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CELGENE THERAPEUTIC AREA HEAD SIGNATURE PAGE

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[redacted]
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By my signature, I indicate I have reviewed this summary of changes and find its content to be acceptable.

1. JUSTIFICATION FOR AMENDMENT

Significant changes included in this amendment are summarized below:

- **Safety: Inclusion of subjects with Eastern Cooperative Oncology Group (ECOG) performance status was restricted to ECOG 0-1, unless otherwise specified (Section 4.2)**

[redacted]

"Inclusion criterion 5. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (Cohort 1, 4, 5 or 6). Subjects not eligible for transplants (TNE) with ECOG performance status 0, 1 or 2 may be enrolled in Cohort 2 or 3 only, if they meet all other inclusion/exclusion criteria."

- **Safety: Subjects with vascular tumor invasion will not be eligible**

[redacted]

"Exclusion criterion 17. Tumor invasion of venous or arterial vessels"

Revised Section: Section 4.3.

- **Safety: Subjects with deep venous thrombosis (DVT) and/or pulmonary embolism (PE) will not be eligible**

As additional measure, subjects with deep venous thrombosis (DVT) and/or pulmonary embolism (PE) will not be eligible.

"Exclusion criterion 18. Deep venous thrombosis (DVT)/pulmonary embolism (PE) within 3 months of ICF signature and/or DVT/PE that requires ongoing therapeutic levels of anti-coagulation."

Revised Section: Section 4.3.

- **A note was added for selection of subjects with central nervous system (CNS) involvement**

Clarification on the selection of subjects with primary or secondary CNS involvement must consider risk factors for severe adverse events and alternative treatment options. Subjects should only be enrolled if the potential benefit outweighs the risk for the subject, as considered by the Investigator

"Note: Subjects with secondary central nervous system (CNS) lymphoma involvement may enroll in Cohorts 1 to 4 and 6; subjects with primary central nervous system lymphoma (PCNSL) are eligible for Cohort 5. Subject selection must consider clinical risk factors for severe adverse events (AEs) and alternative treatment options. Subjects should only be enrolled if the Investigator considers the potential benefit outweighs the risk for the subject."

Revised Sections: Protocol Summary, Section 3.1, and Section 4.2.

- **Safety: Subjects must be clinically stable prior to receiving JCAR017 infusion**

Treating physicians must evaluate a subject's medical condition to assess recovery from prior toxicities and exclude significant worsening in clinical status when compared to initial eligibility criteria at time of LD chemotherapy and of JCAR017 infusion.

"Subjects must be clinically stable and must have recovered from prior toxicities, to receive LD chemotherapy and proceed to JCAR017 infusion. Neither LD chemotherapy nor JCAR017 treatment should be administered if there is a worsening of performance status to ECOG 2, rapid clinical deterioration, or evidence of rapidly progressive disease. Note: subjects who are transplant not eligible may have ECOG 2 however must be clinically stable, recover from prior toxicities, and not have evidence of rapidly progressive disease or rapid clinical deterioration prior to receiving LD chemotherapy or JCAR017 infusion."

Revised Section: Protocol Summary.

- **Safety: Pre-infusion criteria evaluation of subject's clinical status was added prior to receiving JCAR017 infusion as an additional safety measure.**

An added safety evaluation of subject's clinical status (e.g. ECOG status, rapid deterioration and rapid progression) must be performed prior to JCAR017 infusion. A pre-infusion criteria check was added for treating physicians to determine that subjects are not experiencing any significant worsening of their clinical status as compared to initial eligibility criteria.

"Subjects should not experience a significant worsening in clinical status compared to initial eligibility criteria that would, in the opinion of the treating physician, increase the risk of adverse events associated with JCAR017 infusion. Subjects who meet at least one of the following criteria on the day of scheduled JCAR017 infusion should have JCAR017 administration delayed:

- Suspected or active systemic infection
- Onset of fever ≥ 38°C/100.4°F, not related to underlying disease
- Presence of progressive radiographic abnormalities on chest x-ray, or requirement for supplemental oxygen to keep saturation greater than 91%
- Cardiac arrhythmia not controlled with medical management
- Hypotension requiring vasopressor support
- New-onset or worsening of other non-hematologic organ dysfunction ≥ Grade 3
- Taking any of the prohibited medications as described in Section 8.2

Subjects with active infection must have JCAR017 infusion postponed until the active infection has resolved (subjects with suspected/ active infection must have negative culture for at least 24 hours on appropriate antibiotics or negative rapid viral panel). Subjects with organ toxicities may not receive JCAR017 until the organ toxicities have recovered to ≤ Grade 2. In case of delayed infusion, lymphodepleting chemotherapy may need to be repeated after discussion with the Sponsor (see Section 6.2.1).

In the event that a subject experiences any of the above, the Sponsor must be contacted and discussion regarding delay of treatment must occur."

Revised Sections: Section 6.2.2.

The amendment also includes several other minor clarifications and corrections:

- Editorial changes. – Protocol Summary, Section 1.3.1.
- Clarification for subjects with transformed disease to have at least 2 lines of systemic therapy for his/her transformed disease (i.e. DLBCL) for Cohort 1 and 1 line for Cohort 2 to be eligible. – Protocol Summary, Section 3.1, Section 4.2.
- Clarification to continue enrollment in Cohort 1 without gating after safety and feasibility are met per safety evaluation of the first three subjects. – Protocol Summary and Section 3.1.
- The formal interim analysis has been removed from Cohort 2 as data from the 017006 Pilot study will become available sooner and results will be pooled across both trials – Protocol Summary, Section 9.3.2, and Figure 1.
- Instead of the formal interim analysis, added an early safety assessment performed 28 days after JCAR017 is administered to the 10^{th} subject treated in Cohort 2. This was introduced to ensure subject safety as subject with ECOG2 remain eligible in this Cohort. – Protocol Summary, Section 3.1, and Figure 1.
- Specified measurement of pharmacokinetic (PK) profiles of JCAR017 in peripheral blood by qPCR detection for JCAR017 vector sequence (secondary objective) and by flow cytometry (exploratory objective). – Section 2, Table 2, Table 3, and Table 5.
- Added evaluation of MRD of underlying CLL in subjects with Richter's transformation (Cohort 6). – Section 2, Table 2, Table 3, Section 6.3.1, Section 6.7.2, Table 5, and Section 9.9.3.
- Revised timeframe for overall survival (OS) to be assessed up to last subject last visit instead of up to 2 years after JCAR017 infusion. – Table 2.
- Additional language to specify as consistent with Reference Safety Information (RSI) in the Investigator Brochure (IB), all life-threatening or fatal events will be considered unexpected for purpose of reporting SUSARs to regulatory authorities and will be reported in expedited fashion if considered related to JCAR017. – Section 3.2.1.
- Added evaluation of MRD of underlying CLL in subjects with Richter's transformation (Cohort 6). – Section 2, Table 3, Section 6.3.1, Section 6.7.2, Table 5, and Section 9.9.3.
- Clarification on histological confirmation of diagnosis at last relapse if subject did not experience complete response (CR), then the most recent tumor biopsy will be considered adequate. For subjects with PCNSL, corresponding pathology report is required if archival tumor material is not available and repeated biopsy is not feasible. – Section 4.2, and Table 3.
- Erroneous superscript '*' removed. – Section 4.2.
- Superscript '**' updated to superscript '*'. – Section 4.2.

- Specified additional types of non-invasive malignancies listed in Exclusion criterion 5. – Section 4.3.
- Exclusion criterion 13 revised to include cerebral edema and remove paresis – Section 4.3.
- Exclusion criterion 16 added dose for lymphotoxic chemotherapeutic agent, cyclophosphamide > 300 mg/m2. – Section 4.3.
- Revisions to the visit windows at Screening and Follow-up visits (Days 60, 90, 180, 270, 365, 545, and 730 and Survival). Frequency of Survival Follow-up was also updated to every 3 months. – Table 3 and Section 6.3.
- Addition and clarification of brain magnetic resonance imaging (MRI) and cerebral spinal fluid (CSF) assessment at screening are for subjects with suspected or confirmed CNS involvement; and subsequent assessments are only for subjects with confirmed CNS involvement. – Table 3, Section 6.1.1, Section 6.1.4, Section 6.2.7, Section 6.3, Section 6.4.5, Section 6.5.
- Specified to repeat CSF until subject reaches complete response, then obtain subsequent CSF assessment only if suspected of CNS relapse. – Table 3, Section 6.3, and Section 6.4.5.
- Removal of an exploratory optional assessment (tumor biopsy) for restaging if subject received anticancer therapy at pre-treatment evaluation. –Table 3, Section 6.1.4, Table 5.
- Updated the washout periods prior to leukapheresis and prior to lymphodepleting (LD) chemotherapy. – Table 4.
- Specified criteria to assess the subject prior to receiving LD chemotherapy. – Section 6.1.4.
- Revised the recommended administration of LD chemotherapy (fludarabine IV dose reduction percentage (%) is based on updated creatinine clearance [CrCl] ranges). – Section 7.3.1.
- Added language that it is acceptable to use another H1 antihistamine as a JCAR017 premedication, in case diphenhydramine hydrochloride is not available. – Section 7.3.2.
- Clarification on the monitoring of vital signs. – Table 3, Section 6.2.2, and Section 7.3.4.
- Updated list of medications that should be reported during inpatient and Intensive Care Unit (ICU) stays, and list of prohibited medications during treatment and follow-up periods. – Section 8.1.
- Language was added for sites to have tocilizumab readily available prior to JCAR017 administration as required for treatment and management of Cytokine Release Syndrome (CRS). – Section 8.3.

- Additional information provided on specific statistical analyses to be performed for Cohort 3 (Japan only). – Section 9.3.3.
- Removed censoring wording for subjects receiving new anticancer therapy without progressive disease. – Section 9.6.3
- Adverse reporting period was reformatted for clarity. – Section 10.
- Added potential risks associated with cytopenias and infections. – Section 10.8.1.
- Updated CRS and Neurotoxicities (NT) guidelines. – Appendix N
- Misspellings, style and formatting.

– SUMMARY OF CHANGES –

AMENDMENT NO. 1

A PHASE 2, SINGLE-ARM, MULTI-COHORT, MULTI-CENTER TRIAL TO DETERMINE THE EFFICACY AND SAFETY OF JCAR017 IN ADULT SUBJECTS WITH AGGRESSIVE B-CELL NON-HODGKIN LYMPHOMA

INVESTIGATIONAL PRODUCT (IP):	**JCAR017**
PROTOCOL NUMBER:	**JCAR017-BCM-001**
ORIGINAL DATE:	**24 Apr 2017**
AMENDMENT No. 1 DATE:	**8 Jan 2018**
EudraCT NUMBER:	**2017-000106-38**
IND NUMBER:	**Not applicable**

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Approved v2.0
EDMS Doc. Number: 22388982 - 22388469

CELGENE THERAPEUTIC AREA HEAD SIGNATURE PAGE

{See appended electronic signature page}
Signature of Celgene Therapeutic Area Head **dd mmm yyyy**
[redacted]
Printed Name of Celgene Therapeutic Area Head and Title
By my signature, I indicate I have reviewed this summary of changes and find its content to be acceptable.

1. JUSTIFICATION FOR AMENDMENT

Significant changes included in this amendment are summarized below:

- **Transformed indolent B-cell non-Hodgkin lymphoma (B-NHL) was restricted to transformed follicular lymphoma (tFL)**

Transformed indolent B-NHL was restricted to tFL in subjects with diffuse large B-cell lymphoma (DLBCL) not otherwise specified (NOS) to align the sudy population of cohort 1 with that TRANSCEND NHL 001 . [redacted]

Revised Sections: Protocol Summary, Section 3.1., Section 4.2.

- **Definition of transplant not eligible (TNE) subjects was revised**

[redacted], the definition of TNE subjects was revised and better defined to include those who are deemed ineligible for high-dose chemotherapy and HSCT due to age, performance status or comorbidity. At the very least, subjects have to meet one of the following criteria to be considered TNE: age ≥ 70 years, ECOG performance status ≥ 2, impaired pulmonary function (DLCO ≤ 60%), impaired cardiac function (LVEF < 50%), impaired renal function (CrCl < 60 mL/min/1.73m^2) or impaired hepatic function (AST/ALT > 2x ULN, bilirubin > 2 mg/dL or cirrhosis Child-Pugh B or C. However, subjects must meet all protocol specified eligibility criteria to be deemed eligible for JCAR017 therapy.

Subjects with prior hematopoietic stem cell transplant are not eligible for this cohort.

The Frailty Score (Larocca, 2016) was added as a baseline assessment in this patient population.

Revised Sections: Protocol Summary, Section 3.1., Section 4.2.

- **Eligibility criteria for Cohort 3 (Japan only) were revised**

Subjects for Cohort 3 (Japan only) must meet eligibility criteria for either Cohort 1 or 2. This change will allow for TNE subjects to be included in the Japan specific cohort.

Revised Sections: Protocol Summary, Section 3.1., Section 4.2.

- **Eligibility criteria for Cohort 5 were revised**

Cohort 5 will include only subjects with primary central nervous system lymphoma (PCNSL) after ≥ 1 line of therapy instead of ≥ 2 lines of therapy. The prior line of therapy must have included high-dose methotrexate.

In absence of effective treatment option and established standard of care (SOC) at time of first relapse, the protocol was updated to allow those subjects who have failed ≥ 1 line of therapy to be included.

Revised Sections: Protocol Summary, Table 2, Section 3.1., Section 4.2., Table 3

- **Eligibility criteria for Cohort 6 were revised**

Cohort 6 includes subjects after ≥ 1 line of therapy instead of ≥ 2 lines of therapy for Richter's transformation.

In absence of effective treatment option and established SOC at time of first relapse, the protocol was updated to allow those subjects who have failed ≥ 1 line of therapy to be included.

Revised sections: Protocol Summary, Section 3.1., Section 4.2.

- **Safety run-in for Cohort 3 (Japan only) was added**

A similar safety run-in as for subjects treated in Europe (first three subjects treated with a minimum interval between JCAR017 infusions of 14 days and need for hospitalization of the first 10 subjects after JCAR017 infusion) was added for subjects treated in Japan. Cohort 3 was changed to enroll independently from the European cohorts.

Revised Sections: Protocol Summary, Section 3.1. Section 6.2.2.

- **Inclusion criterion for subjects with secondary DLBCL CNS involvement was revised**

Based on preliminary results from the TRANSCEND NHL 001 study showing disease clearing in two subjects with secondary CNS infiltration without the occurrence of CNS toxicity, subjects with secondary DLBCL CNS involvement will be allowed in all but Cohort 5, which will focus on subjects with PCNSL only.

Revised Sections: Protocol Summary, Section 4.2.

The amendment also includes several other minor clarifications and corrections:

- Added clarification to the secondary objectives to evaluate other measures of efficacy of JCAR017 . – Table 1, Protocol Summary.
- Clarified that CAR+ T cell suspension will be provided as 2 individually formulated CD8+CAR+ and CD4+CAR + frozen T cell suspensions. – Protocol Summary, Section 1.2.3, Section 1.3.1.
- Language for clinical experience from PLAT-02 study updated. – Section 1.2.4.
- Latest clinical experience from TRANSCEND NHL 001 study as reported in the literature was added. – Section 1.2.4.
- Latest data on JCAR017 dosing from TRANSCEND NHL 001 as reported in the literature was added.– Section 1.3.1.
- Editorial changes. – Section 1.3.4.
- Added secondary objective corresponding to secondary endpoint ORR in underlying chronic lymphocytic leukemia (CLL) in subjects with Richter's transformation (Cohort 6) as per Table 2. – Protocol Summary, Table 1.
- Addition of FACT-Lym "Additional concerns" subscale, Table 1, Table 2, Table 3, Section 6.1.1, Section 6.1.4, Section 6.2.2, Section 6.2.7., Section 6.3, Section 6.8, Section 6.8.3, Section 9.6.3, Appendix A. and Appendix L.

- Pharmacokinetic (PK) profile of JCAR017 in bone marrow changed from mandatory to when sample available. –Table 1, Table 2, Table 3, Section 6.1.4, Section 6.2.7, Section 6.3.2, Section 6.6, Table 4.
- PK profile of JCAR017 in bone marrow moved from secondary to exploratory objectives. – Protocol Summary, Table 1, Table 2.
- Evaluation of immune and tumor cells in bone marrow biopsy changed from mandatory to when sample available and language related to collection of samples was amended. – Table 1, Table 3, Section 6.1.4, Section 6.2.7, Section 6.3.2, Table 4.
- The exploratory safety endpoint, response and time to resolution for severe cytokine release syndrome (sCRS) and/or neurotoxicity interventions, was amended. – Table 2.
- Language describing Cohort 4 was clarified in the following sections – Protocol Summary, Section 3.1, Section 4.2, and deleted from Section 6.1.2.
- The option of retreatment with JCAR017 was removed. – Section 3.1, Section 6.3.3, Section 9.2.3.
- Language describing the Long-term Follow-up (LTFU) study was amended. – Protocol Summary, Section 3.1, Section 6.3.7.
- Clarification that the study enrollment will be paused if the safety and/or futility boundaries are crossed pending DSMB recommendations. – Section 3.2.1.
- Figure 1 was updated with a new figure. – Figure 1.
- Figure 2 was revised to reflect changes made in this amendment. – Figure 2.
- Exclusion criterion 7 was added (subjects who have received previous CD19-targeted therapy). – Section 4.3.
- Exclusion criterion 15 was revised (lenalidomide and ibrutinib are allowed if at least 3 half-lives have elapsed prior to leukapheresis; graft-versus-host disease (GVHD) therapies was replaced by immunosuppressive therapies). Section 4.3.
- Column for Survival Follow-Up was added. – Table 3.
- Amendments were made to align the table and footnotes with changes in the body text. – Table 3.
- Language was added to involve institutional decision boards in subject selections, where applicable. – Section 6.1.1.
- Assessments applicable to TNE subjects in Cohorts 2 and 3 were clarified. – Table 3 footnote x, Section 6.1.1.
- Formal Neuropsychological Evaluation was removed and Table 3, Section 6.1.1., Section 6.1.4, Section 6.2.7, Section 6.3.6 and Section 10.7.3 edited accordingly.
- Language for PET scan to confirm disease was clarified. – Table 3 footnotes m, n, and p, Section 6.1.1.

- The requirement to complete patient diaries was removed. – Summary, Table 3, Section 6, Section 9.9.2, Section 14.1.
- Patient interviews were removed from Table 3 and are detailed in a new schedule of patient interviews. – Table 3, Table 5, Section 6.8.3.
- Patient interview on Day 29 added. – Section 6.2.7, Table 5.
- Patient interview at leukapheresis added. – Section 6.1.2, Table 5.
- Replication-competent lentivirus (RCL) testing at screening removed. – Table 3, Section 6.1.1.
- Specified that PK by flow cytometry is not required at Japanese sites. Table 3 footnote bb, Section 6.1.1, Section 6.2.2, Section 6.2.4, Section 6.2.5, Section 6.2.6, Section 6.2.7, Section 6.3, Section 6.3.1, Section 6.3.2, Section 6.6.
- Anticancer treatments allowed between leukapheresis and lymphodepleting (LD) chemotherapy specified. – Section 6.1.3.
- Clarified that subjects must meet pre-treatment eligibility criteria before initiation of LD chemotherapy. – Table 3 footnote y, Section 6.1.3, Section 6.1.4.
- Specified that subjects with PCNSL must continue to have measurable disease per MRI after anticancer treatments between leukapheresis and LD chemotherapy. – Summary, Section 6.1.3.
- Measurement of height at pre-treatment evaluation removed. – Table 3, Section 6.1.4.
- Bone marrow aspirate and biopsy at pre-treatment evaluation, Day 15 and upon PD removed. – Table 3, Section 6.1.4, Section 6.2.7, Section 6.6, Section 6.3.2, Table 4.
- Requirement to perform bone marrow aspirate and biopsy for subjects with previous bone marrow involvement upon achieving of a complete response added. – Table 3, Section 6.3.3.
- Language regarding ongoing infections prior to LD chemotherapy removed because this is stated in Section 6.2.1. – Section 6.2.2.
- All assessments performed on Days 2 and 3, except for vital signs, physical examination, and recording of AEs and concomitant medications, were removed. – Table 3, Section 6.2.3, Table 4 (soluble factors).
- Language for assessments/procedures that are required after progressive disease (PD)/relapse and/or after subsequent anticancer treatment clarified. – Table 3 footnote b, Section 6.3.
- Language for RCL sample collection and testing specified. – Table 3 footnote cc, Section 6 , Section 6.4.10.
- Language for viral vector sequence PK by quantitative polymerase chain reaction (qPCR) sample collection and testing specified. – Table 3 footnotes w and cc, Section 6.3, Section 6.4.11.

- Reporting of adverse events (AE) and associated concomitant medications for subjects starting a new anticancer therapy after JCAR017 revised. – Table 3 footnotes b and dd, Section 6.3, Section 8.1, Section 10.1.
- Requirement to collect blood and tissue sample collection in case an autopsy is performed and if feasible added. – Section 6.3.4.
- Requirement to report any confirmed positive result from RCL testing as an SAE within 24 hours and to notify the relevant health authorities added and requirement to report any observations of clonal outgrowth or monoclonality as an SAE within 24 hours.. – Section 6.4.10, Section 6.4.11, and Section 10.2.1.
- Language regarding request for neoplastic tissue samples for RCL assessment at time of disease recurrence and new malignancy was clarified. – Section 6.4.10.
- Specified that clinical management of study subjects will be based on local assessments. – Section 6.4.12.
- Specified that MRD in subjects with Richter's transformation will be assessed on peripheral blood until MRD negative result obtained which should be confirmed on bone marrow aspirate. – Protocol Summary, Section 6.5.
- Definition of pseudoprogression was added. – Section 6.5.1
- Language on biomarker assessments amended. – Section 6.7.2, Table 2, Table 4, Section 9.9.2.
- Detailed description of European Organisation for Research and Treatment of Cancer – Quality of Life C30 (EORTC QLQ-C30) added and questionnaire appended. – Section 6.8.1, Appendix J.
- Detailed description of European Quality of Life-5 Dimensions health state classifier to 5 Levels (EQ-5D-5L) added and questionnaire appended to protocol. – Section 6.8.2. Appendix K.
- Detailed description and schedule of patient interviews added. – Section 6.8.3, Table 5.
- Dosing of JCAR017 premedication specified. – Section 7.3.2, Section 8.3, Section 10.7.5.
- Reporting of AEs and associated concomitant medications for subjects receiving LD chemotherapy but no JCAR017 specified. – Table 3 footnote ee, Section 8.1, Section 10.1.
- Reporting of concomitant medications administered during hospitalizations specified. – Section 8.1.
- sCRS removed as an indication for treatment with cetuximab. – Section 8.2.
- Recommendation for prophylactic treatment for subjects at risk for tumor lysis syndrome added. – Section 8.3.
- Details added on permitted concomitant medications. – Section 8.3.

- Definition of Efficacy Evaluable set added. – Section 9.2.4, Section 9.2.7, Section 9.3.1, Section 9.3.2, Section 9.3.3, Section 9.3.4, Section 9.6.1.
- Clarified that primary efficacy analysis will be based on the JCAR017-treated set and that the Enrolled set and Efficacy Evaluable set will be used for supportive analyses. – Section 9.2.7, Section 9.6.1.
- Significance level for interim and primary analyses in Cohorts 1 and 2 specified. – Section 9.3.1, Section 9.3.2.
- Cohorts 2 and 3 will not be gated. – Section 9.3.4 (formerly Section 9.3.2).
- Aligned definition of overall response rate (ORR) and complete response (CR) rate with TRANSCEND NHL 001 study. – Section 9.6.2.
- Clarified that subjects with unknown/missing response will be included in the analysis counted as non-responders applies to JCAR017-treated set and Enrolled set. – Section 9.6.2, Section 9.6.3.
- Definition of duration of response clarified. – Section 9.6.3.
- Language for exploratory biomarker analysis clarified. – Section 9.9.2.
- AE reporting of manifestations of neurologic toxicities in the presence of cytokine release syndrome or alone specified. – Section 10.1.
- Description of neurologic toxicities revised and toxicity management guidelines appended to protocol. – Section 10.7.3, Appendix N.
- Link to Common Terminology Criteria for Adverse Events CTCAE removed. – Section 10.2.2.
- Reporting of AE outcome revised. – Section 10.2.6.
- Reporting of abnormal laboratory values clarified. – Section 10.3.
- Reporting of progressive disease specified. – Section 10.5.
- Reporting of death due to progressive disease revised. – Section 10.5.2.
- Requirement to upload autopsy reports to the electronic data capture system removed. – Section 10.5.2.
- Description of cytokine release syndrome was revised. Table 5 “Grading Criteria for CRS” and Table 6 “Cytokine Release Syndrome Treatment Algorithm” were removed and toxicity management guidelines appended to protocol. – Section 10.7.1, Appendix N.
- Cairo-Bishop definition of laboratory tumor lysis syndrome added. – Section 10.7.6, Appendix M.
- Manufacturing failure added as reason for treatment discontinuation. – Section 11.1.
- Study termination by Sponsor added as reason for study discontinuation. – Section 11.2.

- Clarified which clinical laboratory evaluations are to be performed locally and/or centrally. – Appendix F.
- Alkaline phosphatase and ß2-microglobulin added to chemistry panel. – Appendix F.
- Pregnancy (serum beta human chorionic gonadotropin [β-hCG]) moved from urinalysis to separate panel. – Appendix F.
- Disease characterization was specified to histology, cell of origin, immunochemistry, cytogenetics, molecular sub-typing. – Appendix F.
- Style and formatting
- Based on revisions, references were added or deleted from Section 17 References Information.