Official Title of Study:

A Global Randomized Multicenter Phase 3 Trial of JCAR017 Compared to Standard of Care in Adult Subjects With High-risk, Second-line, Transplant-eligible Relapsed or Refractory Aggressive B-cell Non-Hodgkin Lymphomas (TRANSFORM)

NCT Number: NCT03575351

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A GLOBAL RANDOMIZED MULTICENTER PHASE 3 TRIAL TO COMPARE THE EFFICACY AND SAFETY OF JCAR017 TO STANDARD OF CARE IN ADULT SUBJECTS WITH HIGH-RISK, TRANSPLANT-ELIGIBLE RELAPSED OR REFRACTORY AGGRESSIVE B-CELL NON-HODGKIN LYMPHOMAS (TRANSFORM)

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TRANSFORM

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PROTOCOL SUMMARY

Study Title

A global randomized multicenter Phase 3 trial to compare the efficacy and safety of JCAR017 to standard of care in adult subjects with high-risk, transplant-eligible relapsed or refractory aggressive B-cell non-Hodgkin lymphomas (TRANSFORM).

Indication

Transplant-eligible relapsed or refractory (R/R) aggressive B-cell non-Hodgkin lymphomas (NHL) in subjects ≥ 18 and ≤ 75 years.

Objectives

Primary Objective:

To compare the efficacy in subjects treated with JCAR017 versus subjects treated according to standard of care (SOC) defined as event-free survival (EFS)

Key Secondary Objectives:

To compare additional parameters of efficacy in subjects treated with JCAR017 versus subjects treated according to SOC defined as complete response rate (CRR), progression-free survival (PFS), and overall survival (OS)

Secondary Objectives:

- To compare other parameters of efficacy, defined as duration of response (DoR), overall response rate (ORR), and PFS on next line of treatment (PFS-2)
- To compare efficacy rates (EFS, PFS, OS) at 6, 12, 24 and 36 months after randomization
- To compare safety defined as type and frequency of adverse events (AEs), serious adverse events (SAEs), and laboratory abnormalities
- To compare the safety and efficacy in clinical, histological and molecular subgroups
- To compare 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-Lym)
- To compare hospital resource utilization (HRU)
- To describe the rate of completion of high dose chemotherapy (HDCT) and hematopoietic stem cell transplant (HSCT)
- To assess the response 3 months after HSCT

Study Design

This is a randomized, open-label, parallel-group, multi-center, Phase 3 study to demonstrate the efficacy and safety of JCAR017 (also known as lisocabtagene maraleucel or liso-cel) versus SOC salvage therapies in subjects with aggressive B-cell NHL (defined as diffuse large B-cell lymphoma [DLBCL] not otherwise specified [NOS], de novo or transformed indolent NHL),

high grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements with DLBCL histology (double-hit lymphoma/ triple-hit lymphoma [DHL/THL]), primary mediastinal (thymic) large B-cell lymphoma [PMBCL], T cell/histiocyte-rich large B-cell lymphoma [THRBCL] or follicular lymphoma Grade 3B [FL3B]) who are refractory to front-line immunochemotherapy or have relapsed within 12 months and are eligible for HDCT and HSCT. The time of relapse is calculated from the date of the first disease assessment confirming a complete response (CR) obtained with first-line treatment for disease under study, to the date of first assessment demonstrating a relapse.

During screening, a tumor biopsy will be collected for central confirmation of diagnosis.

During screening, all subjects will undergo an unstimulated leukapheresis to enable JCAR017 product generation.

Subjects will be randomized to receive either:

- Arm A (SOC): three cycles of SOC salvage therapy. Responding subjects are expected to proceed to HDCT and HSCT
- Arm B (JCAR017): lymphodepleting (LD) chemotherapy followed by JCAR017 infusion

Subjects in Arm B may receive bridging therapy with a protocol-defined SOC regimen to stabilize their disease during JCAR017 manufacturing. Investigational therapies are not allowed.

Subjects will be followed for safety and efficacy for up to 3 years under this protocol.

If requested by the investigator, subjects in Arm A may be allowed to receive JCAR017 upon central confirmation of one of the following criteria:

- Failure to achieve CR or PR by 9 weeks post-randomization (after 3 cycles of SOC)
- Progression at any time
- Need to start a new antineoplastic therapy due to efficacy concerns after 18 weeks post-randomization

Subjects who cross over to JCAR017 will be followed in the study for up to 1 year after the JCAR017 infusion. All subjects who received JCAR017 will continue to be monitored for long-term safety and efficacy after exposure to gene-modified T cells under a separate long-term follow-up (LTFU) protocol for up to 15 years after JCAR017 infusion, as per competent authority guidelines.

The conduct of the study will be overseen by a scientific steering committee (SSC).

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

Study Population

Adult subjects with aggressive B-cell NHL (defined as DLBCL NOS [de novo or transformed indolent NHL], high grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements with DLBCL histology (DHL/THL), PMBCL, THRBCL or FL3B according to WHO 2016 classification) who are refractory to front-line immunochemotherapy or have relapsed within 12 months and are eligible for HDCT and HSCT.

Length of Study

The study will last approximately 3 years from the time the last subject is randomized.

The End of Trial is defined as either the date of the last visit of the last subject to complete the post-treatment follow-up, 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 prespecified in the protocol, whichever is the later date.

Study Treatments

1. Arm A: SOC salvage therapy defined as 3 cycles of either:
    - R-DHAP[ab] (Rituximab 375 mg/m² - Day 1, dexamethasone 40 mg – Days 1 to 4, cytarabine 2 x 2000 mg/m² - Day 2, cisplatin 100 mg/m² – Day 1), or
    - R-ICE[ab] (Rituximab 375 mg/m² - Day 1, ifosfamide 5000 mg/m² - Day 2, etoposide 100 mg/m² - Days 1 to 3, carboplatin area under the curve [AUC] 5 [maximum dose 800 mg]) – Day 2, or
    - R-GDP[ab](Rituximab 375 mg/m² - Day 1, dexamethasone 40 mg – Days 1 to 4, gemcitabine 1000 mg/m² - Days 1 and 8, cisplatin 75 mg/m² - Day 1)

    and followed by high-dose chemotherapy and HSCT in responding subjects:
    - BEAM[a] (Carmustine [BCNU] 300 mg/m² - Day 1, etoposide 200 mg/m² - Days 2 to 5, cytarabine 200 mg/m² - Days 2 to 5, melphalan 140 mg/m² - Day 6), and
    - HSCT
2. Arm B: LD chemotherapy with intravenous (IV) fludarabine (30 mg/m^2/day for 3 days) plus cyclophosphamide IV (300 mg/m^2/day for 3 days) (flu/cy) concurrently followed at least 2 days later by JCAR017 infusion (100 x 10^6 chimeric antigen receptor [CAR]+ T cells)

Note: Intrathecal (IT) treatment with methotrexate and/or cytarabine is allowed for prophylaxis and for treatment of subjects with secondary CNS involvement. For subjects randomized in Arm B, a minimum of 7 days wash-out period after IT treatment is required before start of lymphodepleting chemotherapy.

[a] Selection of the protocol defined SOC regimen, schedule of the regimen, dose adjustment for toxicities and premedication as per site standard, local label and investigator's decision. In Japan, due to unavailability of intravenous BCNU, ranimustine (MCNU) will be used at the same dosage and schedule as BCNU.
[b] Allowable bridging therapy during manufacturing of JCAR017, if needed for disease control.

Treatment options upon EFS event:

- Arm A: subjects will be treated according to physician's choice. If requested by the investigator, subjects may be allowed to receive JCAR017 upon central confirmation of one of above mentioned criteria.
- Arm B: subjects will be treated according to physician's choice, which may include HDCT followed by HSCT.

Overview of Key Efficacy Assessments

Efficacy will be assessed according to the Celgene "Guidelines for Efficacy Evaluation in PET-avid Non-Hodgkin Lymphoma" by an independent review committee (IRC) based on

radiographic tumor evaluation by positron emission tomography (PET)/computed tomography (CT) scans. These guidelines are based on "The Lugano Classification" (Cheson, 2014). Disease will be assessed using diagnostic quality CT/ magnetic resonance imaging (MRI) scans (chest, neck, abdomen, and pelvis) and PET scans. Assessment of bone marrow involvement by lymphoma will be done by PET scan only; bone marrow aspirates and biopsies will not be required for assessment of disease response.

The IRC will confirm the response to therapy and the time of progressive disease (PD) for each subject.

Overview of Key Safety Assessments

Safety will be monitored continuously. Adverse events (AEs) / serious adverse events (SAEs) and laboratory abnormalities (type, frequency, and severity) will be collected, graded and reported according to common terminology criteria for adverse events (CTCAE).

Adverse events of special interest (AESI) may include but not limited to:

- Infusion-related reaction
- Cytokine release syndrome (CRS)
- Neurological toxicity (NT)
- Macrophage activation syndrome (MAS)
- Tumor lysis syndrome (TLS)
- Prolonged cytopenias
- Hypogammaglobulinemia
- Infections
- Autoimmune disorders
- Second primary malignancy (SPM)

The study data will be regularly reviewed by an independent data safety monitoring board (DSMB).

Statistical Methods

Subjects will be randomized at 1:1 ratio into one of the two arms: Arm A (SOC) or Arm B (JCAR017). Randomization will be based on a permuted-blocks randomization method, with the following stratification factors:

1. Best overall response to first-line therapy: refractory (defined as stable disease [SD], progressive disease [PD], partial response [PR] or complete response [CR] with relapse before 3 months) versus relapse (CR with relapse on or after 3 months)
2. Secondary age adjusted International Prognostic Index (sAAIPI): 0 or 1 versus 2 or 3

The primary efficacy endpoint is event-free survival (EFS), defined as the time from randomization to death from any cause, progressive disease (PD), failure to achieve complete response (CR) or partial response (PR) by 9 weeks post-randomization, or start of new antineoplastic therapy due to efficacy concerns, whichever occurs first.

The key secondary efficacy endpoints are:

- Complete response rate (CRR), defined as the proportion of subjects achieving a CR from randomization up to 3 years post-randomization. Subjects with unknown or missing response will be counted as non-responders in the analysis. Any responses after a start of a new antineoplastic therapy will not be considered. Responses after cross over will be analyzed descriptively;
- Progression-free survival (PFS), defined as the time from randomization to PD or death from any cause, whichever occurs first;
- Overall survival (OS), defined as the time from randomization to death due to any cause.

A first interim analysis will be conducted when approximately 30 evaluable subjects (~15 subjects per arm and having received their assigned treatment) have their 9 weeks response assessment (after 3 cycles of SOC for Arm A and 5 weeks after the JCAR017 infusion) or have been confirmed with disease progression prior to this timepoint. The purpose of this interim analysis is to stop for futility. The study may be terminated if the CRR in JCAR017 arm is lower than the CRR in the SOC arm. No type I error adjustment is implemented for this futility analysis.

A second interim analysis will be performed at approximately 60% information time (ie, at around 71 EFS events). The purpose of this interim analysis is to demonstrate superiority of JCAR017 versus SOC on EFS. The O'Brien-Fleming method will be used for defining the efficacy boundaries. The study will continue as planned regardless of the results at this interim analysis unless the experimental arm should be inferior to the reference treatment arm.

Subjects treated with SOC have median EFS of 3 months. Subjects receiving experimental treatment JCAR017 are expected to have an increase of ~81% in the median EFS (equivalent to a hazard ratio [HR] of 0.55) compared to subjects treated with SOC, bringing the median EFS in the experimental group to 5.455 months. Given these assumptions, using a log rank test with 2.5% one-sided significance level, 119 EFS events will provide at least 90% power to reject the null hypothesis of HR greater than or equal to 1. Given a peak randomization rate at about 12 subjects per month, a 20% drop out rate before first response assessment and a yearly dropout rate of 10% (30% cumulative), a sample size of 182 subjects is expected to be randomized and 215 subjects to be screened (screen failure rate of 15%).

If the planned subject randomization rate does not appear adequate to accrue the expected number of events within the proposed follow-up period or if lower than expected number of events are observed, the sample size may be increased (see Section 9).

The primary analysis of EFS will be conducted based on the intention-to-treat (ITT) population (defined as all subjects randomized) when 119 EFS events accumulate from both JCAR017 and SOC arms. If null hypothesis on primary endpoint is rejected, hypothesis testing on key secondary endpoints will be performed hierarchically (CRR, PFS and subsequently on OS). For time to event endpoints, Kaplan-Meier (K-M) survival analyses will be performed. Number and percent of subjects experiencing event of interest and censored will be provided. Kaplan-Meier product limit method will be used to estimate the survivorship function. Event rates at specific time points will be estimated from K-M curves. Medians together with 2-sided 95% confidence intervals will be computed using a log-log transformation. Hazard ratio and its confidence

interval will be estimated using a stratified Cox-proportional hazards (Cox-PH) model using the Efron method for handing ties. In case of violation of the proportional hazard assumption, piecewise Cox regression model will be used. For categorical endpoints, the Cochran-Mantel-Haenszel (CMH) test with stratification factors as strata will be used for analysis and calculation of p-values. The final analysis will be performed after the last subject randomized has either reached an event or been followed for 3 years after randomization.

Sample Size calculation was based on EAST 6.3 software (Cytel Inc.).

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1. INTRODUCTION

1.1. Disease Background

Non-Hodgkin lymphomas (NHLs) comprise a heterogeneous group of malignancies. Within Europe, the incidence of NHL is approximately 49,533 new cases annually with 20,347 deaths per year (Ferlay, 2015).

In the United States (US), it is estimated that approximately 72,580 new cases of NHL will be diagnosed and approximately 20,150 subjects will die of their disease per year (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, which can develop de novo or secondary to transformation of an indolent NHL, eg, from follicular lymphoma. In the United States 27,650 estimated new cases were diagnosed in 2016 (Teras, 2016); incidence in Europe 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 United States (US) (National Cancer Institute [NCI]).

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 based on biologic similarity to normal stages of B-cell development (cell of origin [COO]) helped to further divide DLBCL into germinal center like (GCB), activated B-cell-like (ABC) tumors, and primary mediastinal large B-cell lymphoma (PMBCL) (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. Within the GCB group a specific high-risk group is defined by concurrent chromosomal rearrangements of c-MYC and the anti-apoptotic oncogene BCL2, referred to as double-hit lymphomas (DHL). In addition, in some cases there is a concurrent rearrangement of c-MYC and both antiapoptotic oncogenes BCL2 and BCL6, which are referred to as triple-hit lymphoma. Double-hit lymphomas represents approximately 5% of de novo cases of DLBCL with very poor overall survival (OS) of ≤ 12 months when treated with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) (Camicia, 2015). Newer data suggest negative prognostic impact of p53 mutations or deletions in DLBCL (Schiefer, 2015). Primary mediastinal (thymic) large B-cell lymphoma (PMBCL), T cell/histiocyte-rich large B-cell lymphoma (THRBCL) are considered different histological subtypes in World Health Organization 2016 classification (Swerdlow, 2016), but international guidelines recommend to use DLBCL treatment algorithm (National Comprehensive Cancer Network [NCCN]) (NCCN, 2019), especially for refractory and relapsed disease.

Despite follicular lymphoma being an indolent lymphoma type, follicular lymphoma Grade 3B (FL3B) is regarded as an aggressive lymphoma. Clinical behavior is very similar to DLBCL, and

follicular lymphoma (FL) frequently undergoes histological transformation into DLBCL. Consequently, current guidelines recommend treating FL3B according to the DLBCL treatment algorithm (NCCN, 2019; Dreyling 2016; Dreyling, 2017). 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.

Most subjects with localized DLBCL can be cured with conventional combination immuno-chemo- or combined-modality therapy (Tilly, 2015). For subjects with advanced-stage disease, the majority of subjects can be cured with doxorubicin-based combination chemotherapy and rituximab (eg, R-CHOP). Prognosis depends on individual risk factors. The International Prognostic Index (IPI) for aggressive NHL includes five significant risk factors prognostic of OS: Subject age, serum lactate dehydrogenase (LDH) level, Eastern Cooperative Oncology Group (ECOG) performance status, disease stage, and extranodal involvement. Subjects with ≥ 2 risk factors after age-adjustment have a poor prognosis with a 5-year OS-rate of 21% to 46%. Age and stage-adjusted modifications are used for younger subjects with localized disease (Moller, 2003).

Despite overall improvement in outcomes of DLBCL, approximately one-third of subjects do not respond to initial therapy or will relapse (relapsed/refractory [R/R] disease) that remains a major cause of mortality.

The standard of care for patients with R/R DLBCL after initial therapy is salvage therapy with platinum-based chemotherapy regimens (ie, rituximab, dexamethasone, cytarabine and cisplatin [R-DHAP], rituximab, ifosfamide, carboplatin and etoposide [R-ICE], or rituximab, gemcitabine, dexamethasone, and cisplatin [R-GDP]) if they are deemed to be eligible for high dose chemotherapy (HDCT) and autologous hematopoietic stem cell transplantation (autologous HSCT; ASCT) (Tilly, 2015). Patients responding to second line salvage therapy, ie, those with chemo-sensitive disease, might proceed to HDCT and ASCT to consolidate their response. While approximately 50-60% of patients with R/R DLBCL remain sensitive to conventional second line therapy, only roughly 30% will eventually proceed to ASCT (Gisselbrecht, 2010; Crump, 2014; van Imhoff, 2016). Yet, only a modest portion of patients undergoing HSCT are cured, and patients with high-risk DLBCL, ie, relapsing within a year from first-line treatment, obtain a limited survival advantage by undergoing HSCT (Van Den Neste, 2017).

Three large randomized phase 3 trials have compared the efficacy of various immunochemotherapy regimens as second line salvage therapy, namely the CORAL trial (Collaborative trial in relapsed aggressive lymphoma) (Van Den Neste, 2017), the National Cancer Institute of Canada (NCIC) Clinical Trials Group's LY.12 trial (Crump, 2014), and the ORCHARRD (Ofatumumab versus Rituximab Salvage Chemoimmunotherapy) trial (van Imhoff, 2016).

The CORAL trial evaluated the efficacy of standard platinum-based (R-ICE or R-DHAP) second line therapy and subsequent consolidation with high dose therapy with ASCT in 396 patients who failed R-CHOP or R-CHOP-like therapy (Gisselbrecht, 2010; Van Den Neste, 2016; Van Den Neste, 2017). Similar response rates were observed after three cycles of R-ICE (64%) or R-DHAP (63%). After a median follow-up time of 27 months, the 3-year event-free survival (EFS) and progression-free survival (PFS) rates were 31% and 37%, respectively, the R-ICE and R-DHAP arms were not significantly different, and the 3-year OS was 49% with no difference between the R-ICE and R-DHAP arms. For patients who underwent ASCT, 3-year PFS was 53%

and there was no difference between the numbers of patients who achieved CR and PR just before ASCT (Gisselbrecht, 2010). Patients failing salvage therapy or relapsing after ASCT had a particularly poor prognosis, with a median OS of 4.4 months and 1- and 2-year OS rates of 23% and 15.7%, respectively (Van Den Neste, 2016; Van Den Neste, 2017). Median time between ASCT and relapse in the CORAL trial was 7.1 months.

The NCIC-CTG LY.12 trial compared the efficacy of gemcitabine, dexamethasone, and cisplatin (GDP) versus dexamethasone, cytarabine, and cisplatin (DHAP) and subsequent consolidation by HDCT/ ASCT in 619 patients with R/R aggressive NHLs. Results were very similar to what had been observed in the CORAL trial. Overall response rate to GDP was 45% and 44% to DHAP with 52% and 49% continuing to ASCT (Crump, 2014). With a median follow-up duration of 53 months, 4-year event-free survival was 26% and overall survival 39% in the overall patient group with no difference between the two arms.

The more recent ORCHARRD study in 447 patients relapsing after rituximab-containing frontline therapy compared DHAP in combination with either rituximab (R) or the cluster of differentiation (CD)20 antibody ofatumumab (O). In contrast to the CORAL and the LY.12 trials, all patients enrolled in this trial were refractory to, or had relapsed following, first-line treatment with rituximab in combination with an anthracycline-containing chemotherapy regimen. In this study, response rate for ofatumumab, dexamethasone, high dose cytarabine (AraC), and cisplatin (O-DHAP) was 38% (CR 15%) versus 42% (CR 22%) for R-DHAP. Only one third of subjects completed ASCT on protocol; 74 patients (33%) in the O-DHAP arm and 83 patients (37%) in the R-DHAP arm. Progression-free survival (defined as time from random assignment until PD, death from any cause, or SD after 2 cycles), EFS, and OS were not significantly different between O-DHAP versus R-DHAP: PFS at 2 years was 24% versus 26% (hazard ratio [HR], 1.12; 95% confidence interval (CI), 0.89 to 1.42; P 5.33); EFS at 2 years was 16% versus 18% (HR, 1.10; P 5.35); and OS at 2 years was 41% versus 38% (HR, 0.90; P 5.38). This study represents the most relevant benchmark for efficacy of salvage therapy in the rituximab era. Complete metabolic response (CMR) before ASCT was highly predictive for superior outcome (van Imhoff, 2016).

All three trials failed to improve on the standard of care (SOC) and identified early relapse (refractory disease or progression within 12 months) as well as secondary age-adjusted elevated IPI as poor prognostic factors. The CORAL trial, furthermore, identified prior exposure to rituximab as a risk factor. In particular subjects relapsing within 12 months of rituximab-containing frontline therapy had a very poor prognosis even with ASCT (Gisselbrecht, 2010). While prior use of rituximab was not identified as an adverse prognostic factor in the LY.12 and ORCHARRD trials, they confirmed the poor prognosis of patients with refractory DLBCL or patients relapsing within 12 months.

Recently, the SCHOLAR-1 meta-analysis (n=636) has reported on the very poor outcome of patients with DLBCL refractory to anti-CD20 monoclonal antibody- and anthracycline-containing regimens (Crump, 2017). Chemo-refractoriness was defined as: progressive disease (PD) as best response to chemotherapy, or stable disease (SD) as best response to chemotherapy (received at least 4 cycles of first-line or 2 cycles of later-line therapy), or relapse within 12 months from prior autologous HSCT. The median overall response rate (ORR) was 26% (CR 8%, PR 18%) and the median OS was 6.6 months.

In summary, while many patients with DLBCL achieve long-term remission after rituximab and anthracycline containing first-line immunochemotherapy, there is a high unmet medical need for patients with R/R DLBCL. While subjects with chemotherapy sensitive disease (defined as relapsing after 12 months of response to first-line therapy) have a relatively good prognosis, the majority of subjects with chemotherapy refractory disease (defined as best response of PD, SD or relapse within 12 months from response) undergoing second line salvage therapy will not derive long term benefit. Thus, novel therapies are urgently needed for this patient population.

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.

CD19 is an attractive therapeutic target because it is expressed by most B-cell malignancies, including B-cell NHL (Li, 1993). 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 CD19-targeted CARs in autologous T cells typically is achieved by ex vivo transduction 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 R/R B-cell acute lymphoblastic leukemia (ALL) and B-cell NHL (Porter, 2011; Davila, 2014; Maude, 2014; Kochenderfer, 2015; Lee, 2015; Turtle, 2016a; Turtle, 2016b). Promising results have been reported for different CD19-directed CARs in the treatment of adult (Neelapu, 2017; Schuster, 2017; Turtle, 2016b) and pediatric (Park, 2016) CD19-positive lymphoid malignancies.

Two CD19-directed CAR T therapies have recently been approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA):

- Tisagenlecleucel for the treatment of:
  - Patients up to age 25 years with B-cell precursor ALL that is refractory or in second or later relapse.
  - Adult patients with relapsed or refractory (R/R) large B-cell lymphoma after two or more lines of systemic therapy.
- Axicabtagene ciloleucel to treat adult patients with certain types of large B-cell lymphoma who have not responded to or who have relapsed after at least two other kinds of treatment.

1.2.3. JCAR017 Investigational Drug Product

The final JCAR017 investigational drug product (also known as lisocabtagene maraleucel or liso-cel) includes two individually formulated CD4+CAR+ and CD8+ CAR+ frozen T cell suspensions in media containing dimethyl sulfoxide (DMSO) that are thawed and infused separately. JCAR017 is administered by intravenous (IV) infusion.

The CD19-specific CAR and truncated human epidermal growth factor receptor (EGFRt) are introduced into autologous CD8+ and CD4+ T cells ex vivo using a replication-incompetent, self-inactivating lentiviral vector. The CD19-specific CAR includes an scFv binding domain derived from a murine CD19-specific monoclonal antibody (mAb; FMC63) and 4-1BB and CD3ζ chain signaling domains. The EGFRt protein is expressed as a separate cell surface protein for purposes of cell tracking.

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

1.2.4. Clinical Experience with JCAR017

JCAR017 is currently being evaluated in adult subjects with relapsed and refractory B-cell NHL (Study 017001 - TRANSCEND NHL001; ClinicalTrials.gov No. NCT02631044) (Abramson, 2017a). A total of 108 patients had received JCAR017 at the time of data cutoff (October 9, 2017). Preliminary data suggest promising antitumor activity of JCAR017 in these heavily pretreated, poor prognosis R/R patients with aggressive NHL (median of 3 prior lines of therapy). In 65 patients with R/R DLBCL the best ORR reported was 80% and the complete response rate (CRR) at 6 months 47%, and an acceptable safety profile. No dose-limiting toxicity (DLT) was observed at DL2 (JCAR017 infusion of 100 x 10^6 viable CAR+ T cells). Pharmacokinetics (PK) analyses showed that in vivo expansion of JCAR017+ 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], neurotoxicity [NT]) occurring within the first 14 days after infusion.

Out of 91 patients evaluable for safety, major safety findings include CRS, NT, and hematological disorders, including neutropenia, thrombocytopenia, and anemia. The most significant toxicities reported have been severe CRS (sCRS) and NT. Cytokine release syndrome was observed in 32 (35%) patients treated, with only 1 patient developing sCRS (Grade 3-4). NT was observed in 19% of the patients, of which 12% 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 10 days. The median time to resolution to grade 1 or better was 5 days for CRS and 10 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, 2017a, Maloney, 2017). Ability of CAR cells to cross the blood-brain-barrier has been reported (Kochenderfer, 2017) and has been observed in Study 017001 (Abramson, 2019). At time of data analysis, the subjects enrolled and experiencing NT had no evidence of central nervous system (CNS) involvement. This supports the rational to further investigate CAR T cell therapy in patients with primary CNS or secondary CNS involvement. Two patients with secondary CNS involvement by DLBCL were included in Study

017001. Both patients experienced complete resolution of their CNS disease with no neurologic adverse events observed.

Study JCAR017-BCM-001 will explore the efficacy of JCAR017 in various aggressive large cell lymphomas, including primary CNS lymphoma (PCNSL). One additional trial will evaluate JCAR017 in subjects with R/R chronic lymphocytic leukemia (CLL). Another trial, JCAR017-BCM-002 (NCT03310619) will explore safety and efficacy of JCAR017 in combination with other agents.

See the JCAR017 Investigator's Brochure (IB) for further details.

1.3. Rationale

1.3.1. Study Rationale and Purpose

Despite an improvement in long-term remissions after first-line therapy for subjects with DLBCL, outcomes of subjects who have failed front-line therapy are poor, and additional options are needed.

Although several second-line salvage therapies, such as R-DHAP, R-ICE, or R-GDP, each followed by HDCT and autologous stem cell transplant (ASCT), have been the standard of care (SOC) for subjects who are refractory to or who relapse following first-line treatment with combination immuno-chemotherapy, the clinical outcome of these subjects is disappointing. Three and 4-year progression free survival (PFS) and overall survival (OS) rates range between 30% to 40% and 40% to 50%, respectively (Crump, 2014; Gisselbrecht, 2010). Especially subjects whose disease is refractory to standard R-CHOP first-line therapy or are relapsing within 12 months after diagnosis have a very poor prognosis, with a 3 year PFS rate of 23% (Gisselbrecht, 2010).

The most recent randomized clinical trial in second-line, transplant-eligible subjects shows an ORR to DHAP-based salvage therapy of 40% with approximately 35% of subjects proceeding to HDCT/ASCT (van Imhoff, 2016). The overall 2-year PFS rate was approximately 25%, and the 2-year OS rate was approximately 40%. In this trial, 71% of the subjects had high-risk poor prognostic disease (refractory or relapsing within 12 months to R-CHOP). In this high-risk population, the ORR and percentage of subjects that completed HDCT/ASCT were 29% and 26% compared with 67% and 59% for the subject subgroup with CR of more than 1 year from R-CHOP, respectively. Median PFS in the high-risk versus standard risk populations was approximately 2 months versus 24 months, and median OS was approximately 10 months versus not reached (van Imhoff, 2016), clearly showing the urgent need for improved therapeutic options in this the high-risk population.

The National Comprehensive Cancer Network (NCCN) guidelines recommend that as a second-line therapy, subjects should receive salvage chemotherapy followed by HDCT with ASCT for subjects in CR. Subjects with SD and PD after salvage chemotherapy should receive next line of therapy. Subjects who only achieve PR after salvage chemotherapy are recommended to receive either CAR T cells, HDCT with ASCT, be enrolled in a clinical trial, or continue to allogeneic HSCT in selected cases (NCCN, 2019). For subjects with PR, relapse or PD after consolidation with HDCT and ASCT, the recommendation is to use CAR T cell therapy (if not previously given), to enroll in a clinical trial, or to use alternative second-line therapy, if available (NCCN,

2019). Data from Study 017001 in subjects with aggressive B-cell NHL who have failed two or more lines of therapy, including subjects who were refractory to first-line and second-line therapies, demonstrate that treatment with JCAR017 results in encouraging efficacy results (ORR of 49% at 6 months, CRR of 46% at 6 months, and median OS in responders has not been reached with a median follow-up of 12 months) and an acceptable safety profile (Abramson, 2018). Based on promising early results in later lines of therapy, JCAR017 has the potential to improve outcomes in this study population. The purpose of this Phase 3 study is to compare the current SOC paradigm for subjects with R/R DLBCL and to demonstrate whether JCAR017, used in an earlier line of therapy will be superior to the current SOC in high-risk, transplant-eligible subjects who have failed one previous line of CD20-directed antibody and anthracycline containing therapy for aggressive B-cell NHL.

1.3.2. Rationale for the Study Design

This is a randomized, open-label, parallel-group, multi-center trial to determine the efficacy and safety of JCAR017 in adult subjects with relapsed or refractory aggressive NHL after failure of anti-CD20 antibody and anthracycline containing first-line immunochemotherapy compared to the SOC strategy. Subjects with R/R aggressive NHL eligible for transplant are usually treated with a salvage immunochemotherapy followed by HDCT and HSCT. This study is designed to compare the current SOC treatment paradigm versus JCAR017 for subjects with high risk DLBCL, DHL/THL, PMBCL, THRBCL and FL3B.

Subjects will be randomized to either receive SOC (Arm A) or to receive JCAR017 (Arm B). Randomization will be stratified by response to first-line therapy (relapsed versus refractory), and secondary age-adjusted International Prognostic Index (sAAIPI) (0 to 1 versus 2 to 3). Both stratification factors have been used previously in large randomized Phase 3 trials and shown to control for imbalances during the randomization (Gisselbrecht, 2010; Crump, 2014; van Imhoff, 2016).

The reference treatment in Arm A corresponds to the SOC in this setting based on the CORAL, the LY.12, and the ORCHARRD trials. These consist of the R-DHAP, R-ICE, or R-GDP regimen followed by HDCT and HSCT (NCCN, 2019; Tilly, 2015). All subjects randomized to Arm A will receive 3 cycles of SOC salvage therapy (R-DHAP, R-ICE or R-GDP) as per physician's choice, during which peripheral blood hematopoietic stem cells for HSCT are harvested. After 3 cycles, response will be evaluated by PET-CT. Subjects responding to SOC (CR and PR) will proceed to HDCT and HSCT.

Subjects randomized to Arm B will receive LD chemotherapy followed by JCAR017 infusion. Subjects may receive one cycle of SOC salvage therapy to bridge the time between randomization and availability of the JCAR017 cell product (manufacturing time). Based on promising preliminary results from Study 017001, which show high response rates even in subjects with refractory DLBCL (Abramson, 2018), it is expected that subjects in high risk second line DLBCL will also derive a meaningful benefit from treatment with JCAR017.

The primary objective of the study is to compare the efficacy of JCAR017 therapy to SOC salvage therapy (immunochemotherapy followed by HDCT and HSCT) with respect to event-free survival (EFS) in adult subjects with relapsed or refractory DLBCL, DHL/THL, PMBCL, THRBCL or FL3B who have received one prior therapy but relapsed within 12 months from response to or are refractory to first-line treatment regimen (Hitz, 2015) including an anti-CD20

antibody and an anthracycline, based on the Lugano criteria (Cheson, 2014) as determined by an independent review committee (IRC). Event-free survival is defined as the time from randomization to death from any cause, progression, failure to achieve CR or PR by 9 weeks post-randomization or start of new antineoplastic therapy due to efficacy concerns, whichever comes first. This definition represents the clinical decision path, where only subjects with CR or PR would continue on the SOC paradigm and receive HDCT and HSCT, and non-responding subjects being subjected to third line rescue therapy. In contrast, the key secondary endpoint, PFS, is defined as the time from randomization to PD or death from any cause, as per IRC review, whichever occurs first.

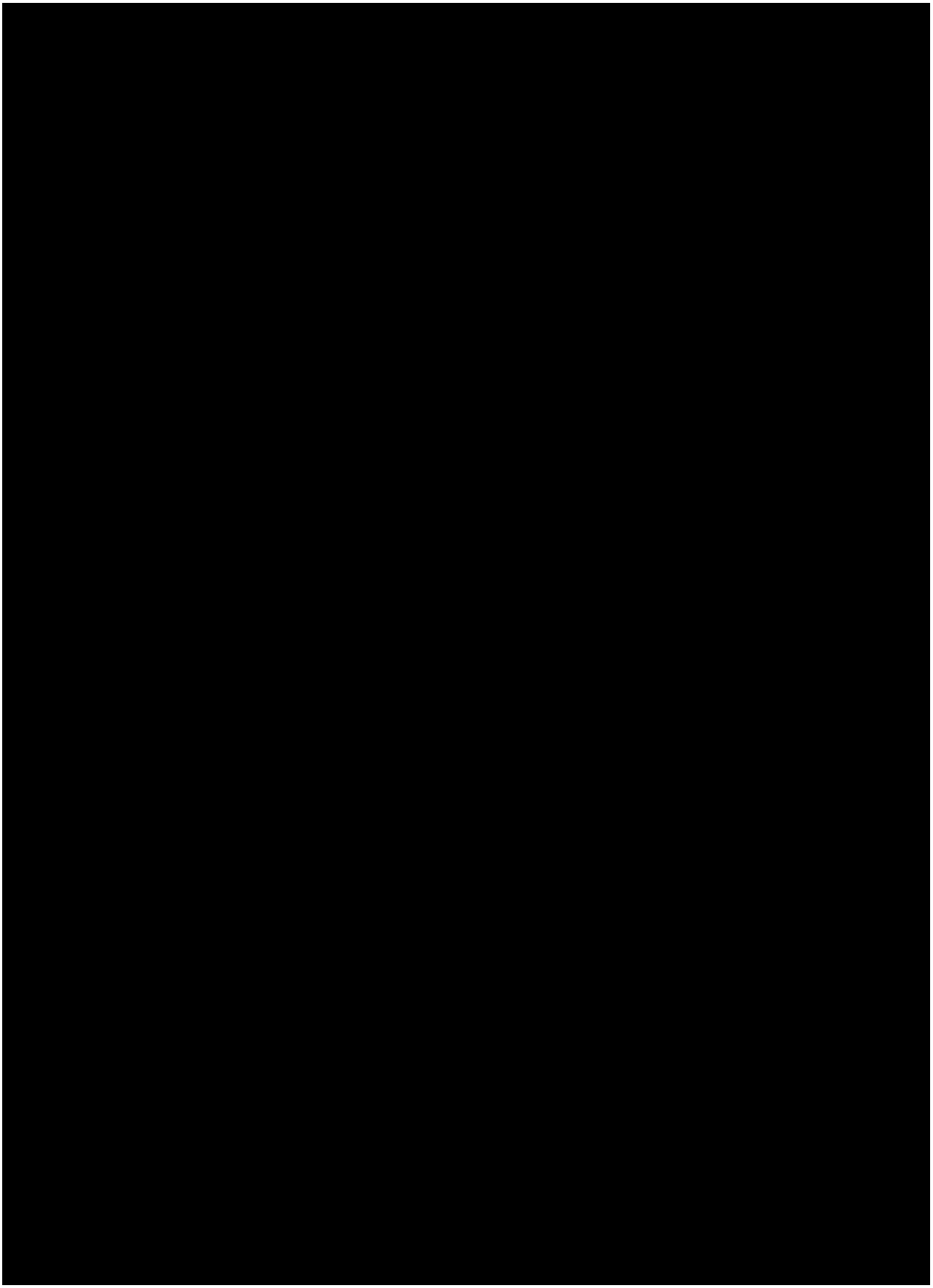
1.3.3. Rationale for Dose, Schedule and Regimen Selection

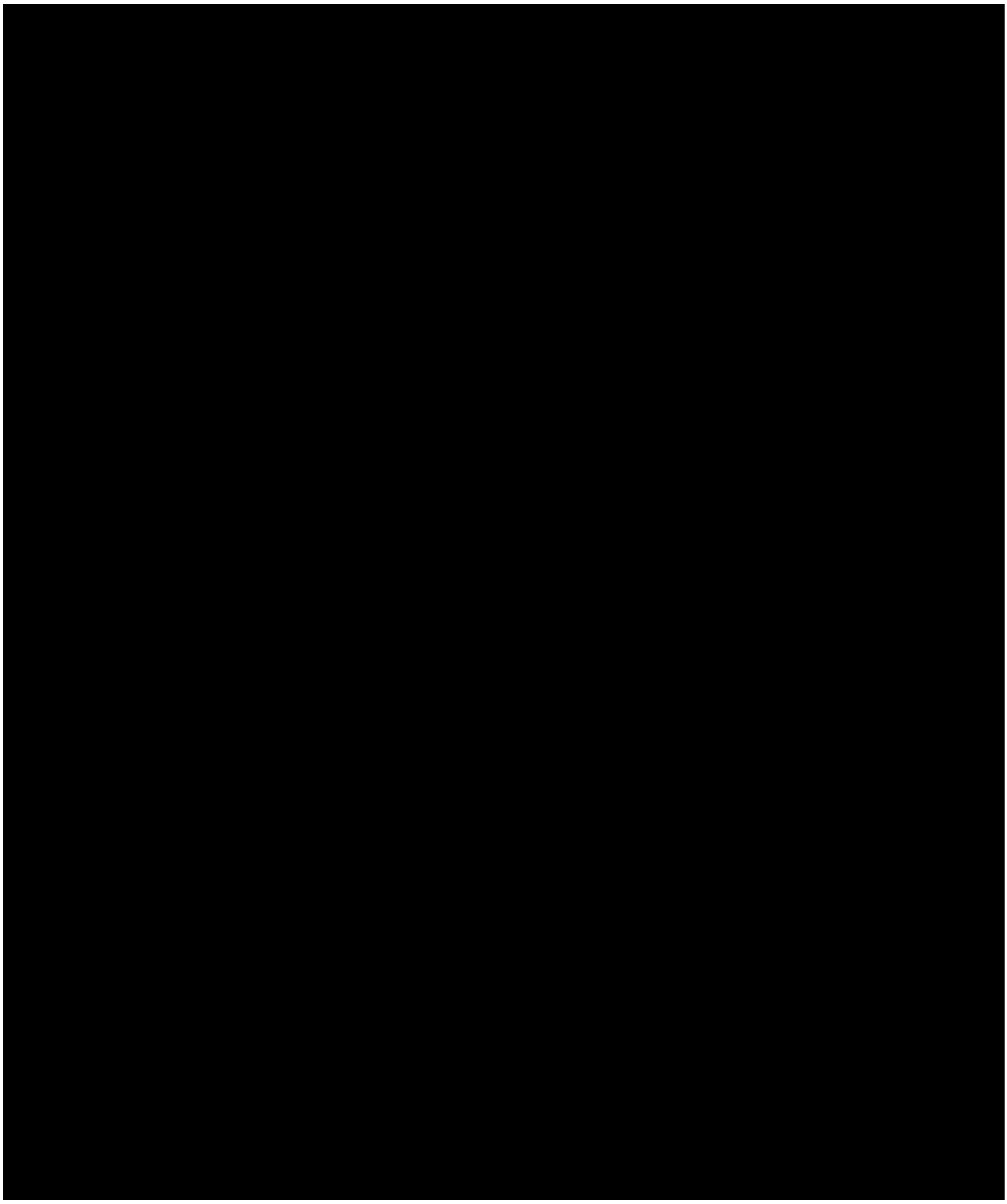
The Phase 1 trial (Study 017001- NCT02631044) is evaluating JCAR017 at several dose levels after LD chemotherapy with cyclophosphamide (300 mg/m^2/day x 3 days) combined with fludarabine (30 mg/m^2/day x 3 days). The initial dose level evaluated (DL1: 50 x 10^6 CAR+ T cells) was found to be tolerable, the dose was escalated and a dose of 100 x 10^6 CAR+ T cells (DL2) and additional dosing schedules are currently being evaluated (Abramson, 2016). Safety and efficacy of 18 subjects treated at DL2 showed good tolerability and efficacy with a single JCAR017 infusion. This dose was selected for the pivotal cohort in the Study 017001 as the recommended Phase 2 dose and therefore was selected for this Phase 3 trial.

1.3.4. Rationale for Choice of Comparator Compounds

The current SOC salvage therapies for R/R DLBCL in second line are defined as R-DHAP, R-ICE or R-GDP.

These regimens are widely used and accepted, backed by large randomized trials and recommended by international treatment guidelines (Tilly, 2015; NCCN, 2019). As described in Section 1.1, it has been demonstrated that the three regimens are comparable in terms of efficacy and safety. The most commonly used high dose chemotherapy in NHL is carmustine (BCNU), etoposide, cytarabine, and melphalan (BEAM) and will be used as standard HDCT for this trial. In Japan, due to unavailability of intravenous BCNU, ranimustine (MCNU) will be used. Ranimustine is in the same class of nitrosourea anticancer agents as BCNU and has shown efficacy equivalent outcomes (Sugimoto, 2016). Standard of care regimen, schedule of the regimen, dose adjustment for toxicities and premedication will be done as per site standard, local label and investigator's decision. Please see Section 7.3 for further details.





2. STUDY OBJECTIVES AND ENDPOINTS

Table 1: Study Objectives

Primary Objective
The primary objective of the study is to compare the efficacy in subjects treated with JCAR017 versus subjects treated according to standard of care (SOC) defined as event-free survival (EFS)
Key Secondary Objectives
The key secondary objectives are to compare the efficacy in subjects treated with JCAR017 versus subjects treated according to SOC defined as complete response rate (CRR), progression-free survival (PFS) and overall survival (OS)
Secondary Objectives
The secondary objectives are: • To compare other parameters of efficacy, defined as duration of response (DoR), overall response rate (ORR), PFS on next line of treatment (PFS-2) • To compare efficacy rates (EFS, PFS, OS) at 6, 12, 24 and 36 months after randomization • To compare the safety defined as type and frequency of adverse events (AEs), serious adverse events (SAEs), and laboratory abnormalities • To compare the safety and efficacy in clinical, histological and molecular subgroups • To compare 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-Lym) • To compare hospital resource utilization (HRU) • To describe the rate of completion of high dose chemotherapy (HDCT) and hematopoietic stem cell transplant (HSCT) • To assess the response 3 months after-HSCT

Table 1: Study Objectives (Continued)

Exploratory Objectives
The exploratory objectives are: • To characterize the pharmacokinetic (PK) profile of JCAR017 • To evaluate pharmacodynamic (PD) markers of JCAR017, including B-cell aplasia [redacted] • To describe the effect of treatments directed at severe cytokine release syndrome (sCRS) and neurotoxicity on duration and severity of these events and whether these safety features are affected by initial SOC treatment for subjects that cross over to JCAR017 • To assess the safety and efficacy for subjects who crossed over to JCAR017 • To describe changes in the other domains of HRQoL using the rest of the subscales in EORTC QLQ-C30 (ie, those not specified in the secondary objectives) [redacted]

Table 2: Study Endpoints

Endpoint	Name	Description	Timeframe
Primary	Event-free survival (EFS)	Time from randomization to death from any cause, progressive disease (PD), failure to achieve complete response (CR) or partial response (PR) by 9 weeks post-randomization, or start of new antineoplastic therapy due to efficacy concerns, whichever occurs first	Up to 3 years post-randomization
Key Secondary	Complete response rate (CRR)	Percentage of subjects achieving a complete response (CR)	Up to 3 years post-randomization
	Progression-free survival (PFS)	Time from randomization to PD, or death from any cause, whichever occurs first	Up to 3 years post-randomization
	Overall survival (OS)	Time from randomization to time of death due to any cause	Up to last subject last visit
Secondary	Overall response rate (ORR)	Percentage of subjects achieving an objective response of partial response (PR) or better	Up to 3 years post-randomization

Table 2: Study Endpoints (Continued)

Endpoint	Name	Description	Timeframe
	Duration of response (DoR)	Time from first response to disease progression, start of new antineoplastic therapy due to efficacy concerns or death from any cause	Up to 3 years post-randomization
	PFS on next line of treatment (PFS-2)	Time from randomization to second objective disease progression or death from any cause, whichever occurs first.	Up to 3 years post-randomization
	EFS rate	Percentage of subjects free of any EFS event at fixed timepoints	At 6, 12, 24 and 36 months post-randomization
	PFS rate	Percentage of subjects free of any PFS event at fixed timepoints	At 6, 12, 24 and 36 months post-randomization
	OS rate	Percentage of subjects alive at fixed timepoints	At 6, 12, 24 and 36 months post-randomization
Secondary	Safety	Type, frequency and severity of adverse events (AEs), serious adverse events (SAEs), and laboratory abnormalities (overall and in clinical, histological and molecular subgroups)	Up to 3 years post-randomization
	Clinical, histological and molecular subgroup analyses	Response rate, EFS, PFS, OS in clinical, histological and molecular subgroups	Up to 3 years post-randomization
	Health-related quality of life (HRQoL) (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-Lym)	Up to 3 years post-randomization
	Hospital resource utilization (HRU)	Frequency of hospitalizations, inpatient days, intensive care unit (ICU) days, outpatient visits and reasons for hospitalization	Up to 3 years post-randomization
	Rate of high dose chemotherapy (HDCT) completion	Percentage of subjects in Arm A completing HDCT	Up to 3 years post-randomization

Table 2: Study Endpoints (Continued)

Endpoint	Name	Description	Timeframe
	Rate of hematopoietic stem cell transplant (HSCT) completion	Percentage of subjects in Arm A completing HSCT	Up to 3 years post-randomization
	Response rate post-HSCT	Percentage of subjects in response after undergoing HSCT	At 3 months post-HSCT
Exploratory	[redacted]		
	Pharmacokinetics	Maximum concentration (Cmax),time to maximum concentration (Tmax), area under the curve (AUC), and other relevant PK parameters of JCAR017 as assessed by droplet digital polymerase chain reaction (ddPCR) [redacted]	Up to 3 years post-randomization
	Blood biomarker	Analyses of pharmacodynamic (PD) biomarkers including but not limited to [redacted] B-cell aplasia; [redacted]	Up to 1 year post-randomization
[redacted]	[redacted]		
	Efficacy analyses for subjects who crossed over to JCAR017	PFS, EFS, DOR, ORR and CRR for subjects from Arm A who crossed over to JCAR017	Up to 1 year post-JCAR017 infusion
	Efficacy analyses for subjects who crossed over to JCAR017	OS for subjects who crossed over to JCAR017	Up to last subject last visit
	HRQoL (other)	Other domains of HRQoL (not specified as secondary endpoints) measured by the rest of subscales of EORTC QLQ-C30	Up to 3 years post-randomization
	[redacted]		

Responses will be assessed according to the Celgene "Guidelines for Efficacy Evaluation in PET-avid Non-Hodgkin Lymphoma" by an independent review committee (IRC). These guidelines are based on "The Lugano Classification" (Cheson, 2014) and will be referred to as the Celgene Lugano Classification guidelines throughout this document.

3. OVERALL STUDY DESIGN

3.1. Study Design

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.

This is a randomized, open-label, parallel-group, multi-center trial in adult subjects with R/R aggressive NHL to compare safety and efficacy between the standard of care (SOC) strategy versus JCAR017. Subjects will be randomized to either receive SOC (Arm A) or to receive JCAR017 (Arm B). See Figure 1.

Randomization will be stratified by response to first-line therapy (SD, PD, PR or CR with relapse before 3 months versus CR with relapse on or after lasting at least 3 months), and sAAIPI (0 to 1 versus 2 to 3).

All subjects randomized to Arm A will receive 3 cycles of SOC salvage therapy (R-DHAP, R-ICE or R-GDP) as per physician's choice, during which peripheral blood hematopoietic stem cells for HSCT are harvested. If peripheral blood hematopoietic stem cells are available from a collection done prior to screening, they may be used and a collection does not need to be repeated during the study. After 3 cycles, response will be evaluated by PET-CT. Subjects responding to SOC (metabolic CR or metabolic PR, see Table 12) are expected to undergo HDCT and HSCT. In case of toxicity or not satisfactory response as per investigator judgment to the selected SOC regimen, a switch within the 3 defined SOC regimen will be allowed and will not be counted as an EFS event.

Subjects randomized to Arm B will receive LD chemotherapy followed by JCAR017 infusion. Subjects may receive one cycle of SOC chemotherapy to bridge the manufacturing time.

A staggered dosing approach will be utilized for all sites without prior experience of administering CAR T cell therapies as follows:

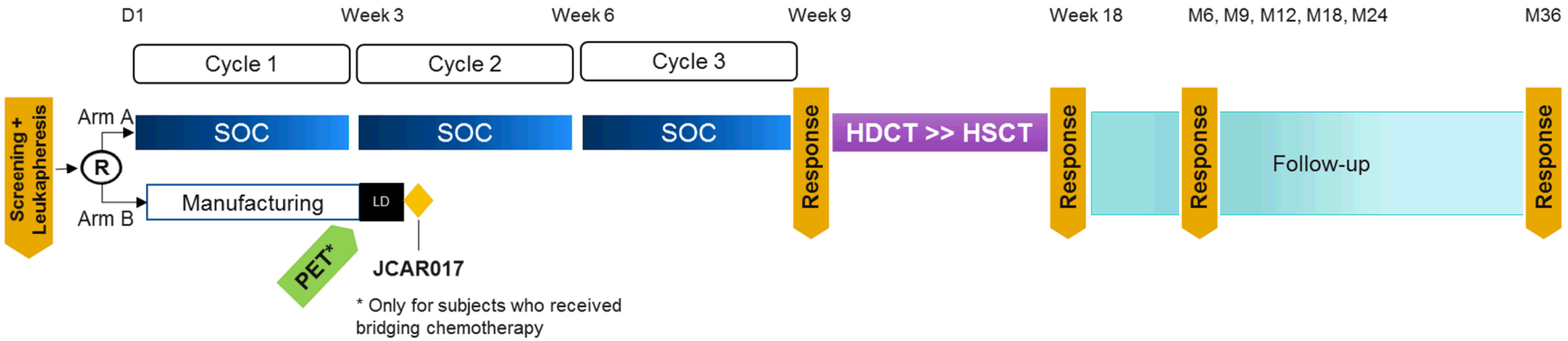
- 1st subject infusion, wait 14 days
- 2nd subject infusion, wait 14 days

Following completion of this site-staggered randomization approach, the site may proceed with subject randomization as communicated by Celgene.

If requested by the investigator, subjects in Arm A may be allowed to receive JCAR017 upon central confirmation of one of the following criteria:

- Failure to achieve CR or PR by 9 weeks post-randomization (after 3 cycles of SOC)
- Progression at any time
- Need to start a new antineoplastic therapy due to efficacy concerns after 18 weeks post-randomization

Figure 1: Overall Study Design



Abbreviations: D = day; HDCT = high dose chemotherapy; HSCT = hematopoietic stem cell transplant; LD = lymphodepleting chemotherapy; M = month; PET = positron emission tomography; R = randomization; SOC = standard of care.

3.2. Study Duration for Subjects

The duration of participation for subjects who complete the study will be approximately 37 months. All subjects who receive JCAR017 will be eligible and asked to enroll into a separate long-term follow-up (LTFU) protocol after completion of this study. Subjects who cross over to JCAR017 will be followed in the study for 12 months after the JCAR017 infusion.

3.3. End of Trial

The End of Trial is defined as either the date of the last visit of the last subject to complete the post-treatment follow-up, 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 prespecified in the protocol, whichever is the later date.

4. STUDY POPULATION

4.1. Number of Subjects

Approximately 182 subjects with R/R aggressive B-cell NHL will be randomized worldwide.

4.2. Inclusion Criteria

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

1. Subject is ≥ 18 years and ≤ 75 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. ECOG performance status ≤ 1.
5. Histologically proven diffuse large B-cell lymphoma (DLBCL) NOS (de novo or transformed indolent NHL), high grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements with DLBCL histology (double/triple-hit lymphoma [DHL/THL]), primary mediastinal (thymic) large B-cell lymphoma (PMBCL), T cell/histiocyte-rich large B-cell lymphoma (THRBCL) or follicular lymphoma grade 3B (FL3B). Enough tumor material must be available for confirmation by central pathology. If archival sample is before most recent relapse or if there is no or insufficient archival sample available, a new tumor biopsy is mandated to confirm diagnosis. If the patient is refractory to first line of treatment, a tumor biopsy sample from disease diagnosis can be used if enough archival material is available.

   Note: Subjects with secondary CNS involvement are eligible. Subject selection must consider clinical risk factors for severe adverse events (AEs) and alternative treatment options. Subjects should only be enrolled if the Investigator assesses that the potential benefit outweighs the risk for the subject.
6. Refractory disease (SD, PD, PR or CR with relapse before 3 months) or relapsed disease (defined as CR with relapse on or after lasting at least 3 months but no more than 12 months), to CD20 antibody and anthracycline containing first-line therapy for disease under study.

   Note: The time of relapse is calculated from the date of the first disease assessment confirming a CR obtained with first-line treatment for disease under study, to the date of first assessment demonstrating a relapse.
7. [18F] fluorodeoxyglucose (FDG) positron emission tomography (PET) positive lesion per Lugano criteria at screening (Deauville score 4 or 5).
8. Adequate organ function, defined as:
   - Adequate bone marrow function defined as: absolute neutrophil count (ANC) ≥ 1.0 x 10^9 cells/L and platelets ≥ 50 x 10^9 cells/L in absence of bone marrow involvement

- Serum creatinine < 1.5 x upper limit of normal (ULN) or creatinine clearance > 45 mL/min (estimated by Cockcroft Gault; see Appendix D for calculation)
- 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 and $FEV_1 \geq 50\%$
- Adequate cardiac function, defined as left ventricular ejection fraction (LVEF) ≥ 40% as assessed by echocardiogram (ECHO) or multi-gated acquisition scan (MUGA) performed within 4 weeks of randomization

9. Adequate vascular access for leukapheresis.
10. Subjects must agree to not donate blood, organs, sperm or semen, and egg cells for usage in other individuals for at least 12 months following lymphodepleting chemotherapy. There is insufficient exposure data to provide any recommendation concerning the duration of refraining from tissue donation following treatment with JCAR017. Therefore, subjects treated with JCAR017 should not donate blood, organs, sperm or semen and egg cells for usage in other individuals for at least 12 months following lymphodepleting chemotherapy.
11. Females of childbearing potential (FCBP*) must:

- Have a negative pregnancy test (2 for Arm B) as verified by the Investigator prior to starting study therapy (one negative serum beta-human chorionic gonadotropin [ß-hCG] pregnancy test result at screening [Arm A and B], and within 7 days prior to the first dose of lymphodepleting chemotherapy [Arm B and cross over]). She must agree to ongoing pregnancy testing during the course of the study, and after end of study treatment. This applies even if the subject practices true abstinence** from heterosexual contact.
- 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 method of contraception from screening until at least 12 months after receiving lymphodepleting chemotherapy or until 12 months after the last chemotherapy, whichever is later.
- Agree to abstain from breastfeeding during study participation and for at least 1 year after lymphodepleting chemotherapy.
- 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.

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 highly effective methods of contraception:

- Intrauterine device (IUD)
- Hormonal (birth control pill, injections, implants)
- Tubal ligation
- Partner's vasectomy

12. Male subjects must:
    - Practice true abstinence** (which must be reviewed on a monthly basis) or agree to use a condom during sexual contact with a pregnant female or a female of childbearing potential while participating in the study, during dose interruptions and for 12 months after lymphodepleting chemotherapy and for 12 months after the last chemotherapy, whichever is later even if he has undergone a successful vasectomy. 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.

* A female subject of childbearing potential (FCBP) is a female who: 1) has achieved menarche at some point, 2) has not undergone a hysterectomy or bilateral oophorectomy or 3) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 12 consecutive months (ie, has had menses at any time in the preceding 12 consecutive months).
**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 randomization:

1. Subject has any significant medical condition, laboratory abnormality, or psychiatric illness that would prevent the subject from participating in the study based on investigator´s judgment.
2. Subject has any condition including the presence of laboratory abnormalities, which places the subject at unacceptable risk if he/she were to participate in the study based on investigator´s judgment.
3. Subject has any condition that confounds the ability to interpret data from the study based on investigator´s judgment.
4. Subjects not eligible for hematopoietic stem cell transplantation (HSCT).
5. Subjects planned to undergo allogeneic stem cell transplantation.
6. Subjects with primary cutaneous large B-cell lymphoma, EBV (Epstein-Barr virus) positive DLBCL, Burkitt lymphoma or transformation from chronic lymphocytic leukemia/small lymphocytic lymphoma (Richter transformation).

7. Subjects with prior history of malignancies, other than aggressive R/R NHL, unless the subject has been free of the disease 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
8. Treatment with any prior gene therapy product.
9. Subjects who have received previous CD19-targeted therapy.
10. Subjects with active hepatitis B, or active hepatitis C are excluded. Subjects with 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. Subjects with a history of or active human immunodeficiency virus (HIV) are excluded.
11. Subjects with uncontrolled systemic fungal, bacterial, viral or other infection (including tuberculosis) despite appropriate antibiotics or other treatment.
12. Active autoimmune disease requiring immunosuppressive therapy.
13. History of any one of the following cardiovascular conditions within the past 6 months prior to signing the ICF: Class III or IV heart failure as defined by the New York Heart Association (NYHA), cardiac angioplasty or stenting, myocardial infarction, unstable angina, or other clinically significant cardiac disease.
14. History or presence of clinically relevant central nervous system (CNS) pathology such as epilepsy, seizure, aphasia, stroke, cerebral edema, severe brain injuries, dementia, Parkinson's disease, cerebellar disease, organic brain syndrome, or psychosis.
15. Progressive vascular tumor invasion, thrombosis, or embolism.
16. Venous thrombosis or embolism not managed on a stable regimen of anticoagulation.
17. Pregnant or nursing (lactating) women.
18. 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 unstimulated leukapheresis. Physiologic replacement, topical, and inhaled steroids are permitted.

- Cytotoxic chemotherapeutic agents that are not considered lymphotoxic (see below) and intrathecal (IT) chemotherapy must be stopped ≥ 7 days prior to unstimulated leukapheresis.
- Lymphotoxic chemotherapeutic agents (eg, cyclophosphamide, ifosfamide, bendamustine) 2 weeks prior to unstimulated leukapheresis.
- Experimental agents within 4 weeks prior to signing the ICF unless no response or progressive disease (PD) is documented on the experimental therapy and at least 3 half-lives have elapsed prior to unstimulated leukapheresis.
- Immunosuppressive therapies within 4 weeks prior to unstimulated leukapheresis (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).
- Radiation within 4 weeks prior to signing the ICF. 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 unstimulated leukapheresis.
- 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.

19. Known allergy to DMSO or Dextran.

5. TABLES OF EVENTS

Table 3: Table of Events

Note: If study treatment needs to be postponed (eg, due to adverse event), the visit should be documented as an unscheduled visit. Before the actual study treatment, the initially planned study visit needs to be repeated and documented as such (eg, if a subject in Arm A cannot start their 2nd cycle of SOC on Day 22, but there were assessments performed on the scheduled visit day, these will be documented as unscheduled. Once the subject can receive their treatment, all assessments from Day 22 should be performed and next visits scheduled as per the below table. Same example would apply to Arm B JCAR017 infusion at Day 29 and following visits). Please refer to the specified protocol section for further details on each procedure.

		Treatment Period																	**Post-Treatment Period**		**Survival Follow-up**
	Screening	**Random-ization**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**Follow-up Period**		
Study Month	**-**	**-**	**-**	**-**	**-**	**1**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**3**	**-**	**-**	**-**	**6**	**9, 12, 18, 24 and 36 (EOS or ET)**	**-**
Study Week	**-**	**-**	**-**	**-**	**3**	**-**	**-**	**-**	**-**	**-**	**6**	**-**	**9**	**-**	**-**	**-**	**-**	**18**	**-**	**-**	**-**
Study Day	**-28 to -1**	**1**	**8**	**15**	**22**	**29**	**31[b]**	**32[b]**	**36**	**39[b]**	**43**	**50**	**64**	**71**	**85**	**99**	**106[a]**	**126**	**-**	**-**	**q3m**
Visit Window (days)	**-**	**+3**	**± 2**	**± 2**	**± 7**	**± 7**	**± 1**	**±1**	**±1**	**±1**	**±6**	**±2**	**± 6**	**± 6**	**± 6**	**± 7**	**± 7**	**± 7**	**± 10**	**± 14**	**± 30**
Obtain consent	x[c]	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Eligibility criteria	x	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
IRT registration	x	x[j]	-	-	x	x[b]	-	-	-	-	x[a]	-	-	x[a]	-	-	-	-	-	x M36	-
Medical history	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Demographics	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
sAAIPI	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
ECOG	x[e]	x	-	-	x[b,h]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	-
HCT-CI	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Table 3: Table of Events (Continued)

		Treatment Period																	Post-Treatment Period		Survival Follow-up
	Screening	Random-ization	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	Follow-up Period		
Study Month	-	-	-	-	-	1	-	-	-	-	-	-	-	-	3	-	-	-	6	9, 12, 18, 24 and 36 (EOS or ET)	-
Study Week	-	-	-	-	3	-	-	-	-	-	6	-	9	-	-	-	-	18	-	-	-
Study Day	-28 to -1	1	8	15	22	29	31[b]	32[b]	36	39[b]	43	50	64	71	85	99	106[a]	126	-	-	q3m
Visit Window (days)	-	+3	± 2	± 2	± 7	± 7	± 1	±1	±1	±1	±6	±2	± 6	± 6	± 6	± 7	± 7	± 7	± 10	± 14	± 30
Pulmonary function test (FEV_1)	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Height	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Weight	x	x	-	-	x	-	-	-	-	-	x[a]	-	-	x[a]	-	-	-	-	-	-	-
Body surface calculation	-	x	-	-	x	-	-	-	-	-	x[a]	-	-	x[a]	-	-	-	-	-	-	-
Physical examination	x	x	-	-	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	-
Routine neurologic examination	x	x	-	-	-	x	x	x	x	x	-	x	x	-	x	x	-	-	-	-	-
MMSE[z]	-	x	-	-	-	x	x	x	x	x	-	x	x	-	x	x	-	-	-	-	-
Vital signs[d]	x[e]	x	-	-	x	x[f]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	-
Pulse oximetry	x	x	-	-	x	x[f]	x	x	x	x	x	x	x	-	-	-	-	-	-	-	-
12-lead ECG	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
MUGA/ECHO	x[y]	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Viral serology	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Table 3: Table of Events (Continued)

		Treatment Period																	Post-Treatment Period		Survival Follow-up
	Screening	Random-ization	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	Follow-up Period		
Study Month	-	-	-	-	-	1	-	-	-	-	-	-	-	-	3	-	-	-	6	9, 12, 18, 24 and 36 (EOS or ET)	-
Study Week	-	-	-	-	3	-	-	-	-	-	6	-	9	-	-	-	-	18	-	-	-
Study Day	-28 to -1	1	8	15	22	29	31[b]	32[b]	36	39[b]	43	50	64	71	85	99	106[a]	126	-	-	q3m
Visit Window (days)	-	+3	± 2	± 2	± 7	± 7	± 1	±1	±1	±1	±6	±2	± 6	± 6	± 6	± 7	± 7	± 7	± 10	± 14	± 30
Serum pregnancy[g]	x	-	-	-	x[b,h]	-	-	-	-	-	-	-	-	-	-	-	-	x[b]	x	x M9[b], 12[b] & EOS	-
Urinalysis	x	-	-	-	-	x	-	-	-	-	-	-	-	x[a]	-	-	-	-	-	-	-
CSF assessment[i]	x	As clinically indicated																			-
Hematology	x[e]	x	x	x	x[h]	x	x	x	x	x	x	x	x	x[a]	x	x	x	x	x	x	-
Coagulation	x	x	-	-	x[h]	x	x	x	x	x	x	x	x	x[a]	-	-	-	-	-	-	-
Chemistry	x[e]	x	x	x	x[h]	x	x	x	x	x	x	x	x	x[a]	x	x	x	x	x	x	-
Creatinine clearance	x	-	-	-	x[b,h]	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Inflammatory markers	x	x	x	x	x[h]	x	x	x	x	x	x	x	x	x[a]	x	-	-	x	-	-	-
Immunoglobulins	x	-	-	-	-	x	-	-	-	-	-	-	x	-	x	-	-	x	x	x	-
Unstimulated leukapheresis	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Table 3: Table of Events (Continued)

		Treatment Period																	Post-Treatment Period		Survival Follow-up
	Screening	Random-ization	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	Follow-up Period		
Study Month	-	-	-	-	-	1	-	-	-	-	-	-	-	-	3	-	-	-	6	9, 12, 18, 24 and 36 (EOS or ET)	-
Study Week	-	-	-	-	3	-	-	-	-	-	6	-	9	-	-	-	-	18	-	-	-
Study Day	-28 to -1	1	8	15	22	29	31[b]	32[b]	36	39[b]	43	50	64	71	85	99	106[a]	126	-	-	q3m
Visit Window (days)	-	+3	± 2	± 2	± 7	± 7	± 1	±1	±1	±1	±6	±2	± 6	± 6	± 6	± 7	± 7	± 7	± 10	± 14	± 30
Arm A treatment																					
SOC chemotherapy	-	x	-	-	x	-	-	-	-	-	x	-	-	-	-	-	-	-	-	-	-
Stem cell collection	-	-	x[k]											-	-	-	-	-	-	-	-
HDCT/HSCT	-	-	-	-	-	-	-	-	-	-	-	-	-	x[l]	-	-	-	-	-	-	-
Arm B treatment																					
Bridging chemotherapy[m]	-	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Pre-lymphodepletion evaluation	-	-	-	-	x[b]	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
LD chemotherapy (3 days)	-	-	-	-	x[b,n]	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Pre-JCAR017 infusion evaluation	-	-	-	-	-	x[b]	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
JCAR017 administration	-	-	-	-	-	x[b,o]	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Table 3: Table of Events (Continued)

		Treatment Period																	Post-Treatment Period		Survival Follow-up
	Screening	Random-ization	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	Follow-up Period		
Study Month	-	-	-	-	-	1	-	-	-	-	-	-	-	-	3	-	-	-	6	9, 12, 18, 24 and 36 (EOS or ET)	-
Study Week	-	-	-	-	3	-	-	-	-	-	6	-	9	-	-	-	-	18	-	-	-
Study Day	-28 to -1	1	8	15	22	29	31[b]	32[b]	36	39[b]	43	50	64	71	85	99	106[a]	126	-	-	q3m
Visit Window (days)	-	+3	± 2	± 2	± 7	± 7	± 1	±1	±1	±1	±6	±2	± 6	± 6	± 6	± 7	± 7	± 7	± 10	± 14	± 30
All arms																					
PET	x[p]	-	-	-	x[w]	-	-	-	-	-	-	-	x	-	-	-	-	x	x	x	-
CT/ MRI	x[p]	-	-	-	-	-	-	-	-	-	-	-	x	-	-	-	-	x	x	x	-
Brain MRI[i]	x	As clinically indicated																			-
Tumor biopsy[q]	x	-	-	-	-	-	At progression[r]														-
AEs/ Con meds/ Con procedures (including transfusions)	AEs, con meds and con procedures related to protocol mandated procedure[s]	All AEs, con meds and con procedures until 90 days after last dose of chemotherapy (Arm A) or 90 days after JCAR017 infusion (Arm B)[t, u]																		AEs, con meds and con procedures related to study treatment	-
EORTC QLQ-C30	-	x	-	-	-	x	-	-	-	-	-	-	x	-	-	-	-	x	x	x	-
[redacted]																					
FACT-Lym "Additional concerns" subscale	-	x	-	-	-	x	-	-	-	-	-	-	x	-	-	-	-	x	x	x	-

Table 3: Table of Events (Continued)

		Treatment Period																	Post-Treatment Period		Survival Follow-up
	Screening	Random-ization	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	Follow-up Period		
Study Month	-	-	-	-	-	1	-	-	-	-	-	-	-	-	3	-	-	-	6	9, 12, 18, 24 and 36 (EOS or ET)	-
Study Week	-	-	-	-	3	-	-	-	-	-	6	-	9	-	-	-	-	18	-	-	-
Study Day	-28 to -1	1	8	15	22	29	31[b]	32[b]	36	39[b]	43	50	64	71	85	99	106[a]	126	-	-	q3m
Visit Window (days)	-	+3	± 2	± 2	± 7	± 7	± 1	±1	±1	±1	±6	±2	± 6	± 6	± 6	± 7	± 7	± 7	± 10	± 14	± 30
Hospital resource utilization	-	Ongoing																			-
Disease therapy since study treatment discontinuation	-	x																			-
Survival status	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	x
Peripheral blood sample for RCL testing	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	x[b]	x[b]	x[b] M12, M18, M24, M36	-
[redacted]																					

Table 3: Table of Events (Continued)

		Treatment Period																	Post-Treatment Period		Survival Follow-up
	Screening	Random-ization	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	Follow-up Period		
Study Month	-	-	-	-	-	1	-	-	-	-	-	-	-	-	3	-	-	-	6	9, 12, 18, 24 and 36 (EOS or ET)	-
Study Week	-	-	-	-	3	-	-	-	-	-	6	-	9	-	-	-	-	18	-	-	-
Study Day	-28 to -1	1	8	15	22	29	31[b]	32[b]	36	39[b]	43	50	64	71	85	99	106[a]	126	-	-	q3m
Visit Window (days)	-	+3	± 2	± 2	± 7	± 7	± 1	±1	±1	±1	±6	±2	± 6	± 6	± 6	± 7	± 7	± 7	± 10	± 14	± 30
[redacted]																					
Peripheral blood sample for viral vector sequence PK by ddPCR	x	-	-	-	-	x[b,v]	-	x	x[b]	x	x[b]	x[b]	x[b]	x[b]	x[b]	-	-	x[b]	x[b]	x[b]	-
Peripheral Blood Sample for Flow Cytometry (B-cell aplasia)	x	-	-	-	-	x[b] pre-infusion	-	-	x[b]	-	x[b]	x[b]	x[b]	-	x[b]	-	-	x[b]	x[b]	x[b] M12, M18, M24, M36	-
Plasma samples	x	-	-	-	x[a]	x[b,v]	-	x	x	x	x	-	x	-	[redacted]	-	-	x	[redacted]	x	-
[redacted]																					

Abbreviations: AE = adverse event; CNS = central nervous system; Con = concomitant; Con meds = concomitant medications; CSF = cerebrospinal fluid; CT = computed tomography; ddPCR = droplet digital polymerase chain reaction; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; EFS = Event-free survival; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer – Quality of Life C30 Questionnaire; EOS = end of study; ET = early termination; [redacted] FACT-Lym = Functional Assessment of Cancer Therapy-Lymphoma; FEV1 = forced expiratory volume in one second; HCT-CI = hematopoietic cell transplantation-specific comorbidity index; HDCT = high dose chemotherapy; HSCT = hematopoietic stem cell transplant; IP = investigational product; IRT = interactive response technology; IV = intravenous; LD = lymphodepleting; M = month; MMSE = Mini Mental State Examination; MRI= magnetic resonance imaging; MUGA = multi-gated acquisition scan; [redacted] PET = positron emission tomography; PK = pharmacokinetic; q3m= every 3 months; RCL = replication-competent lentivirus; sAAIPI = secondary age-adjusted international prognostic index; SOC = standard of care.

[a] Only for subject randomized to Arm A.
[b] Only for subject randomized to Arm B. Day 39 visit is mandatory and cannot be combined with Day 43 visit.
[c] To be obtained any time before any study related procedure.
[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] To be performed at screening visit and at pre leukapheresis. Vital signs need to be done pre and post leukapheresis.
[f] For Arm B: Measured approximately every 15 minutes starting from 15 minutes prior to the first IV administration until one hour after the last IV administration, and hourly for the next 2 hours. If the subject's vital signs are not stable 4 hours following the final administration, vital signs should be monitored as clinically indicated until stable.
[g] Serum pregnancy test is to be performed 90 days after the last dose of chemotherapy or JCAR017 infusion.
[h] For Arm B: To be performed once within 24 hours of the start of lymphodepleting chemotherapy.
[i] If CNS involvement is suspected.
[j] Allowed time window of +2 days do not apply to IRT registration.
[k] Peripheral blood hematopoietic stem cells for HSCT are to be harvested during the 3 cycles of SOC. If peripheral blood hematopoietic stem cells are available from a collection done prior to screening, collection does not need to be repeated.
[l] HDCT to be followed by HSCT as per site procedures.
[m] Only if needed for disease control (reason to be recorded in the CRF).
[n] LD chemotherapy (as described in Section 7.2) should start 5 to 7 days before infusion in order to be completed at least 2 days prior to JCAR017 infusion.
[o] JCAR017 infusion should be started at least 2 days after the end of the LD chemotherapy.
[p] Not to be repeated if a positive PET-CT/MRI was performed within 4 weeks from randomization and confirmed available for central reading by the IRC.
[q] Tissue from latest archived tumor biopsy (block or slides) can be used for tumor evaluation. If archival sample is before most recent relapse or if there is no or insufficient archival sample available, a new tumor biopsy is mandated to confirm diagnosis.
[r] To be performed when feasible.
[s] To be collected if occurred within 28 days of screening.
[t] For subjects starting a new antineoplastic therapy, all AEs and associated concomitant medications will be collected through 90 days after the JCAR017 infusion or 90 days after last dose of chemotherapy, whichever occurs last.
[u] 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.
[v] To be performed pre-infusion.
[w] Only for patients randomized in Arm B receiving bridging chemotherapy to be completed before start of lymphodepleting chemotherapy.
[x] [redacted]
[y] Not to be repeated if one was performed within 4 weeks of randomization.
[z] If subjects in Arm B develop neurologic symptoms suspicious of and/or diagnosed as neurologic toxicity, subjects will have daily MMSE exams (see Appendix F) until resolution of symptoms, unless the subject is medically incapacitated and/or medically unable to complete the MMSE.

Table 4: Table of Events for Subjects from Arm A Who Cross Over to JCAR017

		Treatment Period										Post-Treatment Period					Survival Follow-up
	Pre-Treatment Evaluation	LD Chemotherapy	JCAR017 Infusion									Follow-up					
Study Month	-	-	-	-	-	-	-	-	-	-	1	2	3	6	9	12	
Study Day	Within 7 Days Before LD Chemo-Therapy	Start 5 to 10 Days Before Day 1	1	2	3	4	8	11	15	22	29	-	-	-	-	(EOS or ET)	q3m
Visit Window (Days)	-	-	-	-	-	+1	±1	±1	±2	±2	±2	±14	±14	±14	±14	±30	±30
IRT registration	-	x	x	-	-	-	-	-	-	-	-	-	-	-	-	x	-
ECOG	x	x	x	-	-	-	x	-	x	x	x	-	x	x	x	x	-
Weight	x	-	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Physical examination	x	-	x	x	x	x	x	x	x	x	x	x[a]	x[a]	x[a]	x[a]	x	-
Routine neurologic examination	x	-	x	x	x	x	x	x	x	x	x	-	x	x[a]	x[a]	x[a]	-
MMSE[m]	x	-	x	-	-	x	x	-	x	-	x	-	x	-	-	-	-
Vital signs[b]	x	x	x[c]	x	x	x	x	x	x	x	x	-	-	-	-	-	-
12-lead ECG	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
MUGA scan/ECHO	x[k]	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Viral serology	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Serum pregnancy	x	-	-	-	-	-	-	-	-	-	-	-	x	x	x	x EOS	-
Urinalysis	-	-	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-
LD chemotherapy	-	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
JCAR017 infusion	-	-	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Table 4: Table of Events for Subjects from Arm A Who Cross Over to JCAR017 (Continued)

		Treatment Period										Post-Treatment Period					Survival Follow-up
	Pre-Treatment Evaluation	LD Chemotherapy	JCAR017 Infusion									Follow-up					
Study Month	-	-	-	-	-	-	-	-	-	-	1	2	3	6	9	12	
Study Day	Within 7 Days Before LD Chemo-Therapy	Start 5 to 10 Days Before Day 1	1	2	3	4	8	11	15	22	29	-	-	-	-	(EOS or ET)	q3m
Visit Window (Days)	-	-	-	-	-	+1	±1	±1	±2	±2	±2	±14	±14	±14	±14	±30	±30
Adverse events, concomitant medications and con procedures (including transfusions)	All AEs, associated concomitant medications and con procedures[d, e]													AEs related to JCAR017 and/or LD chemotherapy and associated con meds and con procedures			-
Disease therapy since study treatment discontinuation	-	x															-
PET-CT/MRI	x[f]	-	-	-	-	-	-	-	-	-	-	-	x	x	-	-	-
Brain MRI/ CSF assessment	x[g]	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Hematology	x	x[l]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	-
Coagulation	x	-	x	x	x	x	x	x	x	x	x	x	-	-	-	-	-
Chemistry	x	x[l]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	-
Creatinine clearance	-	x[l]	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Inflammatory markers	x	-	x	x	x	x	x	x	x	x[h]	x[h]	-	-	-	-	-	-
Immunoglobulins	x	-	-	-	-	-	-	-	x	x	x	-	x[i]	x[i]	x[i]	x[i]	-
Peripheral blood sample for RCL testing	x	-	-	-	-	-	-	-	-	-	-	-	x	x	x	x	-

Table 4: Table of Events for Subjects from Arm A Who Cross Over to JCAR017 (Continued)

		Treatment Period										Post-Treatment Period					Survival Follow-up
	Pre-Treatment Evaluation	LD Chemotherapy	JCAR017 Infusion									Follow-up					
Study Month	-	-	-	-	-	-	-	-	-	-	1	2	3	6	9	12	
Study Day	Within 7 Days Before LD Chemo-Therapy	Start 5 to 10 Days Before Day 1	1	2	3	4	8	11	15	22	29	-	-	-	-	(EOS or ET)	q3m
Visit Window (Days)	-	-	-	-	-	+1	±1	±1	±2	±2	±2	±14	±14	±14	±14	±30	±30
[redacted]																	
Peripheral blood sample for viral vector sequence PK by ddPCR	x	-	x (pre-infusion)		x	x	x	x	x	x	x	x	x	x	x	x	-
Peripheral blood sample for flow cytometry (B-cell aplasia)	x	-	x (pre-infusion)	-	-	-	x	-	x	x	x	x	x	x	x	x	-
Plasma samples	x	-	x (pre-infusion)	-	-	x	x	x	x	x	x	-	x	-	-	x	-
[redacted]																	
Survival status	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	x

Abbreviations: AE = adverse event; CNS = central nervous system; Con = concomitant; Con meds = concomitant medications; CSF = cerebrospinal fluid; CT = computed tomography; ddPCR = droplet digital polymerase chain reaction; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; EFS =

event-free survival; EOS = end of study; ET = early termination; IRT = interactive response technology; IV = intravenous; LD = lymphodepleting; MMSE = Mini Mental State Examination; MRI= magnetic resonance imaging; MUGA = multi-gated acquisition scan; [redacted] PET = positron emission tomography; q3m= every 3 months; RCL = replication-competent lentivirus.

[a] Not required after progressive disease (PD)/relapse or subsequent antineoplastic treatment.
[b] 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.
[c] Measured approximately every 15 minutes starting from 15 minutes prior to the first IV administration until one hour after the last IV administration, 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.
[d] For subjects starting a new antineoplastic therapy after JCAR017 infusion, all AEs and associated concomitant medications will be collected through 90 days after the JCAR017 infusion or 30 days after the start of the new antineoplastic therapy, whichever occurs last.
[e] 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.
[f] PET-CT/MRI to be performed if EFS cross over event not confirmed on PET-CT/MRI scans prior to the start of the LD chemotherapy.
[g] If CNS involvement suspected.
[h] If clinically indicated.
[i] Not required for subjects with documented B-cell recovery without recent use of intravenous immunoglobulin (IVIG).
[redacted]
[k] Not to be repeated if done within 4 weeks of LD chemo and no chemotherapy received between this assessment and the LD chemo.
[l] To be performed once within 24 hours of the start of lymphodepleting chemotherapy.
[m] If subjects develop neurologic symptoms suspicious of and/or diagnosed as neurologic toxicity, subjects will have daily MMSE exams (see Appendix F) until resolution of symptoms, unless the subject is medically incapacitated and/or medically unable to complete the MMSE.

6. PROCEDURES

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

6.1. Pre-Treatment Period

6.1.1. Screening

Screening evaluations will be performed for all subjects to determine study eligibility. These evaluations should be completed within 4 weeks prior to randomization unless noted otherwise below.

Waivers to the protocol will not be granted during the conduct of this trial, under any circumstances.

Screening laboratory values must demonstrate subject eligibility, but may be repeated within the screening window, if necessary.

The following assessments are to be performed at screening as specified in the Table of Events (see Table 3), after informed consent has been obtained:

- Subject should be registered in the interactive response technology (IRT) system
- Assess eligibility per inclusion/exclusion criteria. All eligibility criteria must be met in order for subjects to be randomized in the study
- Obtain medical history, including: disease diagnosis and history, chemotherapy, radiation and surgical history, and history of prior gene therapy. May include history of toxicities related to prior treatments and allergies
- Demographics
- sAAIPI status (see Appendix M)
- ECOG performance status assessment
- HCT-CI (hematopoietic cell transplantation – specific comorbidity index) (Sorror, 2005; see Appendix K)
- FEV_1 (forced expiratory volume in one second)
- Physical examination, including height, weight, vital signs (see Section 6.4.2), oxygen saturation via pulse oximetry
- Prior and concomitant procedures and medications within 1 month before signing the ICF, except for those related to the disease
- Routine neurologic examination
- 12-lead electrocardiogram (ECG)
- MUGA scan or cardiac ECHO (not to be repeated if one performed within 4 weeks of randomization) for LVEF

- Collection of peripheral blood samples for clinical laboratory evaluations as described in Table 18:
  - Hematology panel
  - Chemistry panel
  - Coagulation tests
  - Inflammatory markers
  - Immunoglobulins
  - Viral serology
  - Creatinine clearance (by Cockcroft-Gault) – see Appendix D
  - Serum ß-hCG pregnancy test on women of child-bearing potential
  - Replication-competent lentivirus (RCL) testing
  - [redacted]
  - Pharmacokinetics (PK) by ddPCR [redacted]
- Urinalysis
- Research samples (see the JCAR017-BCM-003 laboratory manual for details):
  - Plasma samples
  - [redacted]
  - Peripheral blood for the detection of B-cell aplasia by flow cytometry
- Lumbar puncture or Ommaya reservoir tap for CSF assessment if CNS involvement suspected
- Brain magnetic resonance imaging (MRI) if CNS involvement suspected
- Positron emission tomography (PET) and computed tomography (CT) /MRI scan to confirm the presence of PET-positive lymphoma. Not to be repeated if a positive PET and CT/MRI was performed within 4 weeks before randomization and confirmed available and fulfill prerequisite for central reading by the IRC.
- Tumor biopsy will be collected for central confirmation of diagnosis. Tissue from latest archived tumor biopsy (block or slides) can be used for tumor evaluation. If archival sample is before most recent relapse or if there is no or insufficient archival sample available, a new tumor biopsy is mandated to confirm diagnosis. If the patient is refractory to first line of treatment, a tumor biopsy sample from disease diagnosis can be used if enough archival material is available.
- Record all AEs, concomitant medications and concomitant procedures related to protocol mandated procedures

- Record the intention to perform consolidation with radiation therapy after completion of the per-protocol treatment.
- An unstimulated leukapheresis collection will be performed on each subject to obtain a sufficient quantity of [redacted] for the production of the JCAR017 investigational product irrespective of the arm assigned. Please refer to the [redacted] collection laboratory manual for further details.

Should a technical issue arise during the procedure or in the processing of the product such that it cannot be used for JCAR017 administration, the subject may have a second collection procedure performed. Subjects must continue to meet eligibility requirements for repeat leukapheresis.

The following assessments are to be performed on the day of but before the unstimulated leukapheresis:

- Eligibility check: subjects must be evaluated for evidence of active infections prior to the leukapheresis being started. In case of suspected infection, subject should be treated and leukapheresis postponed until the active infection has resolved.
- ECOG performance status assessment
- Vital signs (pre and post leukapheresis)
- Collection of peripheral blood samples for clinical laboratory evaluations as described in Table 18 and leukapheresis preparation:
  - Hematology panel
  - Chemistry panel
- Record AEs, concomitant medications and concomitant procedures related to protocol mandated procedures

6.2. Treatment Period

6.2.1. Day 1 - Randomization (+ 3 days)

Subjects will be randomized to either Arm A or Arm B per the IRT system.

The following assessments are to be performed once the subject is randomized and prior to receiving study treatment:

- Eligibility must have been confirmed
- ECOG performance status assessment
- Physical examination, including weight
- Body surface calculation
- Vital signs (see Section 6.4.2), oxygen saturation via pulse oximetry
- Routine neurologic examination
- Mini Mental State Examination (MMSE) (see Appendix F)

- Collection of peripheral blood samples for clinical laboratory evaluations as described in Table 18:
  - Hematology panel
  - Chemistry panel
  - Coagulation tests
  - Inflammatory markers
- Record all AEs, concomitant medications and concomitant procedures
- Quality of life questionnaires: EORTC QLQ-C30, [redacted] and FACT-Lym "Additional concerns" subscale
- Hospital resource utilization assessment

6.2.1.1. Arm A

Subjects will receive their 1st cycle of SOC salvage therapy according to local practice.

6.2.1.2. Arm B

Subjects may start bridging therapy (reason to be recorded in the CRF) while JCAR017 is manufactured, if needed for disease control.

6.2.2. Days 8 and 15 (± 2 days)

The following assessments are to be performed:

- Collection of peripheral blood samples for clinical laboratory evaluations as described in Table 18:
  - Hematology panel
  - Chemistry panel
  - Inflammatory markers
- Record all AEs, concomitant medications and concomitant procedures
- Stem cell collection to be performed before Day 71. If peripheral blood hematopoietic stem cells are available from a collection done prior to screening, collection does not need to be repeated.
- Hospital resource utilization assessment

Subjects in Arm A who discontinue treatment should be scheduled as soon as possible for early termination (ET) visit and subsequently followed as per Table 3 on Days 29, 36, 50, 64, 71, 85, 99 and 126. In case subjects received subsequent antineoplastic therapies, new disease therapies since study treatment discontinuation should be collected and only the assessments described in Section 6.3.1.2 applicable for each visit should be performed.

6.2.3. Day 22 (± 7 days)

6.2.3.1. Arm A

The following assessments are to be performed prior to receiving study treatment:

- Collection of peripheral blood samples for clinical laboratory evaluations as described in Table 18:
  - Hematology panel
  - Chemistry panel
  - Coagulation tests
  - Inflammatory markers
- Research samples:
  - Plasma samples
  - [redacted]
- Physical examination, including weight
- Body surface calculation
- Vital signs and pulse oximetry
- Record all AEs, concomitant medications and concomitant procedures
- Stem cell collection to be performed before Day 71
- Hospital resource utilization assessment

Subjects will receive their 2nd cycle of SOC. This treatment administration will be registered in IRT system.

Subjects who discontinue treatment should be scheduled as soon as possible for early termination (ET) visit and subsequently followed as per Table 3 on Days 29, 36, 50, 64, 71, 85, 99 and 126. In case subjects received subsequent antineoplastic therapies, new disease therapies since study treatment discontinuation should be collected and only the assessments described in Section 6.3.1.2 applicable for this visit should be performed.

6.2.3.2. Arm B

Upon notification from the Sponsor that JCAR017 will be available, LD chemotherapy should be initiated so as to be completed 2 to 7 days prior to JCAR017 infusion. This treatment administration will be registered in IRT system. For details on LD chemotherapy refer to Section 7.4.2.

Subjects receiving bridging chemotherapy should have a PET prior to the start of LD chemotherapy. Brain MRI and CFS assessment should also be performed if there is secondary CNS involvement. Subjects with secondary CNS involvement who received IT treatment with methotrexate and/or cytarabine should have a minimum of 7 days wash-out period prior to the start of LD chemotherapy.

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 6.2.4.2).

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

- Subjects must be evaluated prior to start of lymphodepletion (pre-lymphodepletion evaluation): adequate organ function and no evidence of active infections prior to the LD chemotherapy are required. In case of suspected infection, subject should be treated accordingly and LD chemotherapy postponed until the active infection has resolved. Subjects with rapid deterioration or rapid disease progression should not start LD chemotherapy. In the event that a subject experiences any of the above, the Sponsor must be contacted and discussion regarding delay of treatment must occur.
- Vital signs and pulse oximetry
- Physical examination, including weight
- Body surface calculation
- ECOG performance status assessment (only once within 24 hours prior to start of LD chemotherapy)
- Collection of peripheral blood samples for clinical laboratory evaluations (only once within 24 hours prior to start of LD chemotherapy) as described in Table 18:
  - Hematology panel
  - Chemistry panel
  - Coagulation tests
  - Inflammatory markers
  - Creatinine clearance (by Cockcroft-Gault – see Appendix D)
  - Serum ß-hCG pregnancy test on women of child-bearing potential
- PET (only for subjects receiving bridging chemotherapy - once prior to start of LD chemotherapy)
- Record all AEs, concomitant medications and concomitant procedures
- Hospital resource utilization assessment
- Collect new disease therapies since study treatment discontinuation (if applicable)

6.2.4. Day 29 (± 7 days)

6.2.4.1. Arm A

The following assessments are to be performed:

- ECOG performance status assessment

- Physical examination
- Routine neurologic examination
- MMSE (see Appendix F)
- Vital signs and pulse oximetry
- Urinalysis
- Collection of peripheral blood samples for clinical laboratory evaluations as described in Table 18:
  - Hematology panel
  - Chemistry panel
  - Coagulation tests
  - Inflammatory markers
  - Immunoglobulins
- Record all AEs, concomitant medications and concomitant procedures
- Stem cell collection to be performed before Day 71 (if applicable)
- Quality of life questionnaires: EORTC QLQ-C30, [redacted] and FACT-Lym "Additional concerns" subscale
- Hospital resource utilization assessment

Subjects who discontinue treatment should be scheduled as soon as possible for early termination (ET) visit and subsequently followed as per Table 3 on Days 36, 50, 64, 71, 85, 99 and 126. In case subjects received subsequent antineoplastic therapies, new disease therapies since study treatment discontinuation should be collected and only the assessments described in Section 6.3.1.2 applicable for this visit should be performed.

6.2.4.2. Arm B

Subjects who do not have adequate social support (a full-time caregiver) outside of the hospital or do not have reliable transportation to the clinic for daily evaluations or emergencies post-therapy should be considered for hospitalization for the first 14 days after JCAR017 infusion.

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

- Subjects must be evaluated for pre-JCAR017 infusion:

  Subjects should not experience a significant worsening in clinical status compared to initial eligibility criteria and/or rapid disease progression 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 6.2.3.2).

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

- ECOG performance status assessment
- Physical examination
- Routine neurologic examination
- MMSE (see Appendix F). If subjects in Arm B develop neurologic symptoms suspicious of and/or diagnosed as neurologic toxicity, subjects will have daily MMSE exams until resolution of symptoms, unless the subject is medically incapacitated and/or medically unable to complete the MMSE (see Section 6.4.5).
- Vital signs (temperature, respiratory rate, heart rate, blood pressure, and SaO_2 by pulse oximetry) will be measured approximately every 15 minutes, starting from 15 minutes prior to the first IV administration until one hour after the last IV administration, and hourly for the next 2 hours (see Section 7.4.5). If the subject's vital signs are not stable 4 hours following the final administration, vital signs should be monitored as clinically indicated until stable.
- Urinalysis
- Collection of peripheral blood samples for clinical laboratory evaluations as described in Table 18:
  - Hematology panel
  - Chemistry panel
  - Coagulation tests

  - Inflammatory markers
  - Immunoglobulins
  - PK by ddPCR [redacted]

- Research samples:
  - Plasma samples
  - [redacted]
  - Peripheral blood for detection of B-cell aplasia by flow cytometry
- Record all AEs, concomitant medications and concomitant procedures
- Quality of life questionnaires: EORTC QLQ-C30, [redacted] and FACT-Lym "Additional concerns" subscale
- Hospital resource utilization assessment
- Collect new disease therapies since study treatment discontinuation (if applicable)

Subjects will receive their JCAR017 infusion. This treatment administration will be registered in IRT system.

6.2.5. Day 31 (±1 day), Day 32 (± 1 day), Day 39 (± 1 day) (Arm B)

These visits and subsequent visits for Arm B subjects should be scheduled based on the actual Day 29 visit (JCAR017 infusion) (eg, Day 31, 2 days after the infusion; Day 32, 3 days after the infusion).

The following assessments are to be performed:

- ECOG performance status assessment
- Physical examination
- Routine neurologic examination
- MMSE (see Appendix F and Section 6.4.5)
- Vital signs and pulse oximetry
- Collection of peripheral blood samples for clinical laboratory evaluations as described in Table 18:
  - Hematology panel
  - Chemistry panel
  - Coagulation tests
  - Inflammatory markers
  - PK on Day 32 by ddPCR [redacted] On Day 39 ddPCR [redacted]

- Research samples:
  - Plasma samples (Days 32, 39)
- Record all AEs, concomitant medications and concomitant procedures
- Hospital resource utilization assessment
- Collect new disease therapies since study treatment discontinuation (if applicable)

6.2.6. Day 36 (± 1 day)

The following assessments are to be performed:

- ECOG performance status assessment
- Physical examination
- Routine neurologic examination
- MMSE (see Appendix F and Section 6.4.5)
- Vital signs and pulse oximetry
- Collection of peripheral blood samples for clinical laboratory evaluations as described in Table 18:
  - Hematology panel
  - Chemistry panel
  - Coagulation tests
  - Inflammatory markers
  - PK (Arm B) by ddPCR [redacted]
- Research samples:
  - Plasma samples
  - Peripheral blood for detection of B-cell aplasia by flow cytometry (Arm B)
- Record all AEs, concomitant medications and concomitant procedures
- Stem cell collection to be performed before Day 71 (if applicable) (Arm A)
- Hospital resource utilization assessment

Subjects in Arm A who discontinue treatment should be scheduled as soon as possible for early termination (ET) visit and subsequently followed as per Table 3 on Days 50, 64, 71, 85, 99 and 126.

In case subjects received subsequent antineoplastic therapies, new disease therapies since study treatment discontinuation should be collected and only the assessments described in Section 6.3.1.2 applicable for this visit should be performed.

6.2.7. Day 43 (± 6 days)

The following assessments are to be performed (for subjects in Arm A only, the assessments need to be performed prior to the start of the 3rd cycle of SOC):

- ECOG performance status assessment
- Physical examination
- Weight (Arm A)
- Body surface calculation (Arm A)
- Vital signs and pulse oximetry
- Collection of peripheral blood samples for clinical laboratory evaluations as described in Table 18:
  - Hematology panel
  - Chemistry panel
  - Coagulation tests
  - Inflammatory markers
  - [redacted]
  - PK (Arm B) by ddPCR [redacted]
- Research samples:
  - Plasma samples
  - [redacted]
  - Peripheral blood for detection of B-cell aplasia by flow cytometry (Arm B)
- Record all AEs, concomitant medications and concomitant procedures
- Stem cell collection to be performed before Day 71 (if applicable) (Arm A)
- Hospital resource utilization assessment

In case subjects received subsequent antineoplastic therapies, new disease therapies since study treatment discontinuation should be collected and only the assessments described in Section 6.3.1.2 applicable for this visit should be performed.

6.2.7.1. Arm A

Subjects will receive their 3rd cycle of SOC. This treatment administration will be registered in IRT system.

Subjects who discontinue treatment should be scheduled as soon as possible for early termination (ET) visit and subsequently followed as per Table 3 on Days 50, 64, 71, 85, 99 and 126.

6.2.8. Day 50 (± 2 days)

The following assessments are to be performed:

- ECOG performance status assessment
- Physical examination
- Routine neurologic examination
- MMSE (see Appendix F and Section 6.4.5)
- Vital signs and pulse oximetry
- Collection of peripheral blood samples for clinical laboratory evaluations as described in Table 18:
  - Hematology panel
  - Coagulation tests
  - Chemistry panel
  - Inflammatory markers
  - PK (Arm B) by ddPCR [redacted]
- Research samples:
  - Peripheral blood for detection of B-cell aplasia by flow cytometry (Arm B)
- Record all AEs, concomitant medications and concomitant procedures
- Stem cell collection to be performed before Day 71 (if applicable) (Arm A)
- Hospital resource utilization assessment

Subjects in Arm A who discontinue treatment should be scheduled as soon as possible for early termination (ET) visit and subsequently followed as per Table 3 on Days 64, 71, 85, 99 and 126.

In case subjects received subsequent antineoplastic therapies, new disease therapies since study treatment discontinuation should be collected and only the assessments described in Section 6.3.1.2 applicable for this visit should be performed.

6.2.9. Day 64 (± 6 days)

The following assessments are to be performed:

- ECOG performance status assessment
- Physical examination
- Routine neurologic examination
- MMSE (see Appendix F and Section 6.4.5)
- Vital signs and pulse oximetry

- Collection of peripheral blood samples for clinical laboratory evaluations as described in Table 18:
  - Hematology panel
  - Coagulation tests
  - Chemistry panel
  - Inflammatory markers
  - Immunoglobulins
  - PK (Arm B) by ddPCR [redacted]
- Response assessments: PET and CT/MRI
- Research samples:
  - Plasma samples
  - Peripheral blood for detection of B-cell aplasia by flow cytometry (Arm B)
- Record all AEs, concomitant medications and concomitant procedures
- Stem cell collection to be performed before Day 71 (if applicable) (Arm A)
- Quality of life questionnaires: EORTC QLQ-C30, [redacted] and FACT-Lym "Additional concerns" subscale
- Hospital resource utilization assessment

Subjects in Arm A who discontinue treatment should be scheduled as soon as possible for early termination (ET) visit and subsequently followed as per Table 3 on Days 71, 85, 99 and 126.

In case subjects received subsequent antineoplastic therapies, new disease therapies since study treatment discontinuation should be collected and only the assessments described in Section 6.3.1.2 applicable for this visit should be performed.

6.2.10. Day 71 (± 6 days)

The following assessments are to be performed (prior to receiving HDCT for Arm A):

- ECOG performance status assessment
- Weight (Arm A)
- Body surface calculation (Arm A)
- Physical examination
- Vital signs
- Urinalysis (Arm A)

- Collection of peripheral blood samples for clinical laboratory evaluations as described in Table 18:

Arm A:

  - Hematology panel
  - Coagulation tests
  - Chemistry panel
  - Inflammatory markers

Arm B:

  - PK by ddPCR

- Record all AEs, concomitant medications and concomitant procedures
- Hospital resource utilization assessment

In case subjects received subsequent antineoplastic therapies, new disease therapies since study treatment discontinuation should be collected and only the assessments described in Section 6.3.1.2 applicable for this visit should be performed.

6.2.10.1. Arm A

Subjects will undergo HDCT prior to receiving the HSCT. This treatment administration will be registered in IRT system.

Record the intention to perform consolidation with radiation therapy after completion of the per-protocol treatment. Eligibility of subjects to undergo HDCT and HSCT must be evaluated:

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 HDCT and HSCT. Subjects who meet at least one of the following criteria on the day of scheduled HDCT and HSCT should have HDCT and HSCT 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 HDCT and HSCT 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 HDCT and HSCT until the organ toxicities have recovered to ≤ Grade 2. In the event

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

Subjects who discontinue treatment should be scheduled as soon as possible for early termination (ET) visit and subsequently followed as per Table 3 on Day 85, 99 and 126.

6.2.11. Day 85 (± 6 days)

The following assessments are to be performed:

- ECOG performance status assessment
- Physical examination
- Routine neurologic examination
- MMSE (see Appendix F and Section 6.4.5)
- Vital signs
- Collection of peripheral blood samples for clinical laboratory evaluations as described in Table 18:
  - Hematology panel
  - Chemistry panel
  - Inflammatory markers
  - Immunoglobulins
  - [redacted]
  - PK (Arm B) by ddPCR [redacted]
- Research samples:
  - [redacted]
  - [redacted]
  - Peripheral blood for detection of B-cell aplasia by flow cytometry (Arm B)
- Record all AEs, concomitant medications and concomitant procedures
- Hospital resource utilization assessment

Subjects in Arm A who discontinue treatment should be scheduled as soon as possible for early termination (ET) visit and subsequently followed as per Table 3 on Day 99 and 126.

In case subjects received subsequent antineoplastic therapies, new disease therapies since study treatment discontinuation should be collected and only the assessments described in Section 6.3.1.2 applicable for this visit should be performed.

6.2.12. Day 99 (± 7 days)

The following assessments are to be performed

- ECOG performance status assessment
- Physical examination
- Routine neurologic examination
- MMSE (see Appendix F and Section 6.4.5)
- Vital signs
- Collection of peripheral blood samples for clinical laboratory evaluations as described in Table 18:
  - Hematology panel
  - Chemistry panel
- Record all AEs, concomitant medications and concomitant procedures
- Hospital resource utilization assessment

Subjects in Arm A who discontinue treatment should be scheduled as soon as possible for early termination (ET) visit and subsequently followed as per Table 3 on Day 126.

In case subjects received subsequent antineoplastic therapies, new disease therapies since study treatment discontinuation should be collected and only the assessments described in Section 6.3.1.2 applicable for this visit should be performed.

6.2.13. Day 106 (± 7 days) (Arm A)

The following assessments are to be performed:

- ECOG performance status assessment
- Physical examination
- Vital signs
- Collection of peripheral blood samples for clinical laboratory evaluations as described in Table 18:
  - Hematology panel
  - Chemistry panel
- Record all AEs, concomitant medications and concomitant procedures
- Hospital resource utilization assessment
- Collect new disease therapies since study treatment discontinuation (if applicable)

6.2.14. Day 126 (± 7 days)

For Arm A subjects, this visit should be scheduled based on date of the HDCT (Day 71) (ie, 2 months after).

The following assessments are to be performed:

- ECOG performance status assessment
- Physical examination
- Vital signs
- Collection of peripheral blood samples for clinical laboratory evaluations as described in Table 18:
  - Hematology panel
  - Chemistry panel
  - Inflammatory markers
  - Immunoglobulins
  - [redacted]
  - Serum ß-hCG pregnancy test on women of child-bearing potential 3 months after the JCAR017 infusion (Arm B)
  - RCL testing (Arm B)
  - PK (Arm B) by ddPCR
- Research samples:
  - Plasma samples
  - [redacted]
  - Peripheral blood for detection of B-cell aplasia by flow cytometry (Arm B)
- Response assessments: PET and CT/MRI (Week 18)
- Record all AEs, concomitant medications and concomitant procedures
- Quality of life questionnaires: EORTC QLQ-C30, [redacted] and FACT-Lym "Additional concerns" subscale
- Hospital resource utilization assessment

In case subjects received subsequent antineoplastic therapies, new disease therapies since study treatment discontinuation should be collected and only the assessments described in Section 6.3.1.2 applicable for this visit should be performed.

6.3. Post-Treatment Period

6.3.1. Follow-up

All randomized subjects who received study treatment, including subjects who withdraw from treatment period early (early termination [ET]) and those with progressive disease, should complete the post-treatment follow-up visits at approximately Months 6 (± 10 days), 9, 12, 18, 24 and 36 (or end of study [EOS]) ± 14 days after randomization for disease status and survival.

6.3.1.1. Subjects who Have not Received Subsequent Antineoplastic Treatment

6.3.1.1.1. Month 6 (± 10 days)

The following assessments are to be performed:

- ECOG performance status assessment
- Physical examination
- Vital signs
- Collection of peripheral blood samples for clinical laboratory evaluations as described in Table 18:
  - Serum ß-hCG pregnancy test on women of child-bearing potential
  - Hematology panel
  - Chemistry panel
  - Immunoglobulins
  - RCL testing (Arm B)
  - PK (Arm B) by ddPCR
- Research samples:
  - [redacted]
  - [redacted]
  - Peripheral blood for detection of B-cell aplasia by flow cytometry (Arm B)
- Response assessments: PET and CT/MRI
- Record all AEs, concomitant medications and concomitant procedures
- Quality of life questionnaires: EORTC QLQ-C30, [redacted] and FACT-Lym "Additional concerns" subscale
- Hospital resource utilization assessment
- Collect new disease therapies since study treatment discontinuation (if applicable)

6.3.1.1.2. Months 9, 12, 18, 24, and 36 (± 14 days)

The following assessments are to be performed:

- ECOG performance status assessment
- Physical examination
- Vital signs
- Serum ß-hCG pregnancy test on women of child-bearing potential (Month 9, 12 [Arm B] and Month 36 [Arm A and B])
- Collection of peripheral blood samples for clinical laboratory evaluations as described in Table 18:
  - Hematology panel
  - Chemistry panel
  - Immunoglobulins
  - RCL testing (Months 12, 18, 24, 36) (Arm B)
  - [redacted]
  - PK (Arm B) by ddPCR
- Research samples:
  - Plasma samples
  - [redacted]
  - Peripheral blood for detection of B-cell aplasia by flow cytometry (Months 12, 18, 24, 36) (Arm B)
- Response assessments: PET and CT/MRI
- Record only AEs, concomitant medications and concomitant procedures related to study treatment
- Quality of life questionnaires: EORTC QLQ-C30, [redacted] and FACT-Lym "Additional concerns" subscale
- Hospital resource utilization assessment
- Collect new disease therapies since study treatment discontinuation (if applicable)
- The EOS visit will be registered in IRT system (Month 36)

6.3.1.2. Subjects who Have Received Subsequent Antineoplastic Treatment

The following assessments are to be performed:

- Physical examination required on Months 12, 24 and 36
- Immunoglobulins required on Months 6, 9, 12, 18, 24 and 36
- RCL sample collection required on Months 6, 12, 24 and 36 only for subjects who received JCAR017

- Viral vector sequence PK by ddPCR sample collection only for subjects who received JCAR017
- Record AEs, associated concomitant medications and concomitant procedures according to Section 10.1
- Collect information regarding new disease therapies (eg, start and end date, best response) since study treatment discontinuation
- The EOS visit will be registered in IRT system (Month 36)
- Serum ß-hCG pregnancy test on women of child-bearing potential (Month 36)

6.3.2. Assessments for Subjects Crossing Over to JCAR017

If requested by the investigator, subjects in Arm A may be allowed to receive JCAR017 upon central confirmation of one of the following criteria:

- Failure to achieve CR or PR by 9 weeks post-randomization
- Progression at any time
- Need to start a new antineoplastic therapy due to efficacy concerns after 18 weeks post-randomization

Reasons for cross over of a subject will be recorded in the CRF. JCAR017 delivery and administration will be coordinated with the Sponsor once the Investigator confirms the request for a cross over and the sponsor approves and documents the request based on the IRC confirmation. In case the cross over at time of EFS event is not requested by the Investigator, the unstimulated leukapheresis collected at screening and stored at the manufacturing site will be destroyed. Subjects must meet the criteria for LD chemotherapy as well as for starting JCAR017 in addition to the confirmation of an EFS event. Please refer to Table 4 for the schedule of assessments for subjects randomized to Arm A that cross over to JCAR017 treatment. For detailed procedures please refer to the procedures described for Arm B visit, noting that not all Arm B assessments are required, with the below correspondence:

Visit for patients crossing over to JCAR017	Section for Reference
Pre-Treatment Evaluation	Section 6.1.1
LD Chemotherapy	Section 6.2.3.2
JCAR017 infusion – Day 1	Section 6.2.4.2
Days 2, 3, 4, 11	Section 6.2.5
Day 8	Section 6.2.6
Day 15	Section 6.2.7
Day 22	Section 6.2.8
Day 29 – Month 1	Section 6.2.9
Month 2	Section 6.2.11
Month 3	Section 6.2.14

Visit for patients crossing over to JCAR017	Section for Reference
Month 6	Section 6.3.1.1.1 (Month 6) or Section 6.3.1.2
Month 9	Section 6.3.1.1.2 (Month 12) or Section 6.3.1.2
Month 12	Section 6.3.1.1.2 (Month 24)
Survival Follow-up	Section 6.3.7

6.3.3. 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
- Neurological examination
- MMSE
- Vital signs
- ECOG performance status assessment
- Clinical laboratory evaluations
- PET scan
- CT/MRI scan
- Tumor biopsy (see the JCAR017-BCM-003 laboratory manual)
- Bone marrow aspirate and biopsy (see the JCAR017-BCM-003 laboratory manual)
- Electroencephalogram
- CSF assessment
- Brain imaging
- RCL peripheral blood
- PK by ddPCR [redacted]
- Research samples (see the JCAR017-BCM-003 laboratory manual):
  [redacted]
  - Plasma samples
  - Peripheral blood for detection of B-cell aplasia by flow cytometry (Arm B)
- Leukapheresis

Additionally, if the Investigator requests any of the following procedures, research samples may be requested:

- Lumbar puncture or Ommaya reservoir tap for CSF assessment

- Fluid sampling
- Tissue sampling
- Autopsy

6.3.4. Assessments at Time of Death (Subjects Receiving JCAR017)

In case an autopsy is performed, blood and tissue samples may be collected if feasible for central analysis of markers related to safety and efficacy of the CAR T cells.

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 the assessments listed for the Month 36 (EOS) visit (Table 3) will be performed. Subjects from Arm A who cross over to JCAR017 and subsequently voluntarily withdraw prematurely from the study, will have a visit scheduled as soon as possible, and all the assessments listed for the Month 12 (EOS) visit (Table 4) will be performed.

6.3.6. Second Primary Malignancy Follow-up Period

Second primary malignancies will be monitored as events of interest and must be reported as serious adverse events regardless of the treatment arm and cohort the subject was in. This includes any new malignancies, regardless of causal relationship to IP(s), occurring throughout the subject's entire participation in the study. If a subject develops a second primary malignancy, the Sponsor will request a tumor sample (refer to JCAR017-BCM-003 laboratory manual) and blood samples (See also Section 6.4.10 and Section 6.4.11) for further testing.

6.3.7. Survival Follow-up

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

6.3.8. Long-term Follow-up

Because this protocol involves gene transfer, long-term follow-up for lentiviral vector safety, disease status, and survival will continue after EOS under a separate LTFU protocol thereafter for up to 15 years after the JCAR017 infusion (European Medicines Agency [EMA], 2009; FDA, 2010; FDA, 2006).

All subjects who either complete the 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.

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 neurological (as detailed in Section 6.4.5). In addition, symptom-directed exams should be performed.

6.4.2. Vital Signs

Vital signs include temperature, respiratory rate, heart rate, blood pressure. On the day of JCAR017 administration, special monitoring is to be performed, refer to Section 7.4.5 for the details.

6.4.3. Pulse Oximetry

Oxygen saturation (SaO_2) will be assessed by pulse oximetry as per Table 3 and Table 4.

6.4.4. Height and Weight

Height in centimeters (cm) or inches (in) and body weight to the nearest kilogram (kg) or pound (lb) in indoor clothing, but without shoes will be measured according to Table 3 and Table 4.

6.4.5. Routine Neurologic and Mini Mental State Examinations

A routine neurologic examination should include, at minimum, a physical exam to assess cranial nerves, motor and sensory skills, coordination and balance, and the Mini Mental State Examination (MMSE; see Appendix F). The MMSE may be administered by an appropriately trained provider as per investigator judgment (ie, physician, nurse); a neurologist is not required. Efforts should be made to have the same provider perform the MMSE on a given subject to maintain consistency of assessment. If subjects in Arm B develop neurologic symptoms suspicious of and/or diagnosed as neurologic toxicity, subjects will have daily MMSE exams until resolution of symptoms, unless the subject is medically incapacitated and/or medically unable to complete the MMSE.

6.4.6. Cerebrospinal Fluid Assessment

Cerebrospinal fluid (CSF) assessment and CNS imaging should be performed if CNS involvement is suspected at screening or at any time during the study as clinically indicated (eg, if new CNS symptoms occur, or if clinical signs or suspicion of CNS lymphoma exist). Cerebrospinal fluid will be analyzed for cell count, differential cytology, glucose and protein levels. Cerebrospinal fluid cultures (bacterial, fungal, viral) should be performed as clinically indicated for suspicion of infection.

6.4.7. Eastern Cooperative Oncology Group Performance Status

Eastern Cooperative Oncology Group (ECOG) performance status (see Appendix B) will be used to evaluate subject eligibility at screening and will be assessed throughout the study at time points specified in Table 3 and Table 4.

6.4.8. Multi-gated Acquisition Scan / Echocardiogram

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

6.4.9. Electrocardiogram

A standard 12-lead ECG should be obtained. ECG 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.

6.4.10. Replication-Competent Lentivirus Testing (Subjects receiving JCAR017)

Replication-competent lentivirus (RCL) testing will be performed on genomic DNA obtained by a peripheral blood draw, and if positive, confirmed on [redacted] Details regarding sample collection and processing are provided in the JCAR017-BCM-003 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 3 and Table 4. If all samples collected within the first year after the dose of JCAR017 are negative, subsequent samples will be collected and archived. [redacted]

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 LTFU protocol.

If a subject develops a second primary malignancy, the Sponsor will request a sample for assessment of RCL.

6.4.11. Viral Vector Sequence Testing (Subjects receiving JCAR017)

Persistence of JCAR017 vector sequences will be monitored at timepoints indicated in Table 3 and Table 4. Details regarding sample collection and processing are provided in the JCAR017-BCM-003 laboratory manual. The presence of vector HIV gag DNA sequences will be determined by evaluation of blood samples by ddPCR. [redacted]

If a subject develops a second primary malignancy, the Sponsor will request a sample for assessment of viral vector sequence testing.

6.4.12. Clinical Laboratory Evaluations

Screening and other laboratory evaluations (see Appendix G) will be performed according to Table 3 and 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. A central laboratory will be used; however, clinical management of study subjects will be based on local assessments.

6.5. Efficacy Assessment

Efficacy will be assessed according to the Celgene Lugano Classification guidelines based on radiographic tumor evaluation by diagnostic quality CT/MRI scans (chest, neck, abdomen, and pelvis) and PET scans (see Appendix C). These guidelines are based on the "Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification" (Cheson, 2014). Assessment of bone marrow involvement by lymphoma will be performed by PET scan only; bone marrow aspirates and biopsies will not be required for assessment of disease response. Efficacy assessments will be performed at Weeks 9 (after 3 cycles of SOC for Arm A and 5 weeks after JCAR017 infusion for Arm B) and 18 (8 weeks after the start of HDCT for Arm A and 14 weeks after JCAR017 infusion for Arm B) and Months 6, 9, 12, 18, 24 and 36.

Subjects in Arm B who received bridging chemotherapy should have a PET performed prior to start of lymphodepleting chemotherapy. This assessment will be only used for evaluation of PET disease status, not counted as a formal efficacy assessment.

6.5.1. Pseudoprogression

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

6.6. Pharmacokinetics

6.6.1. Pharmacokinetics of JCAR017

Assessment of JCAR017 PK will be determined by ddPCR to detect vector HIV gag DNA sequences [redacted]. Peripheral blood will be collected as indicated in Table 3 and Table 4.

Detailed information regarding the collection, handling, and shipment of PK assessment samples is provided in the JCAR017-BCM-003 laboratory manual.

6.7. Biomarkers, [redacted]

[redacted]

6.7.2. Exploratory Biomarkers

[redacted]

- [redacted] efficacy and severity of CRS and neurotoxicity.
- Plasma may be analyzed for presence of cell-free DNA (cfDNA) as a surrogate for tumor burden and correlated with clinical efficacy.

[redacted]

6.7.3. Additional and Optional Research

Additional and optional research as described below may be performed using left-over samples originally collected for another test required in this study or using samples collected specifically for [redacted] testing. The research may involve genetic tests using DNA or RNA and may lead to the development of new diagnostic tests.

6.7.3.1. Additional Research

Additional research related to the study drug and/or disease may be performed. The results of this additional research could help to improve the diagnosis and/or the treatment of this disease in the future.

6.7.3.2. Optional Research

Optional research not related to the study drug or the subject's disease may be performed. The subject's decision to participate in this optional research will not impact their ability to participate in the main study.

6.8. Subject Reported Outcomes or Quality of Life or Health Economics

Subject-reported quality-of-life outcomes will be administered according to Table 3.

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. [redacted] EORTC QLQ-C30 and FACT-Lym "Additional concerns" subscale will be used to assess the subject's health as well as physical, social, emotional, and functional well-being. Reasons for missing subject reported outcomes questionnaires should also be captured so that the appropriate imputation method can be employed to correct for missing data in the analysis.

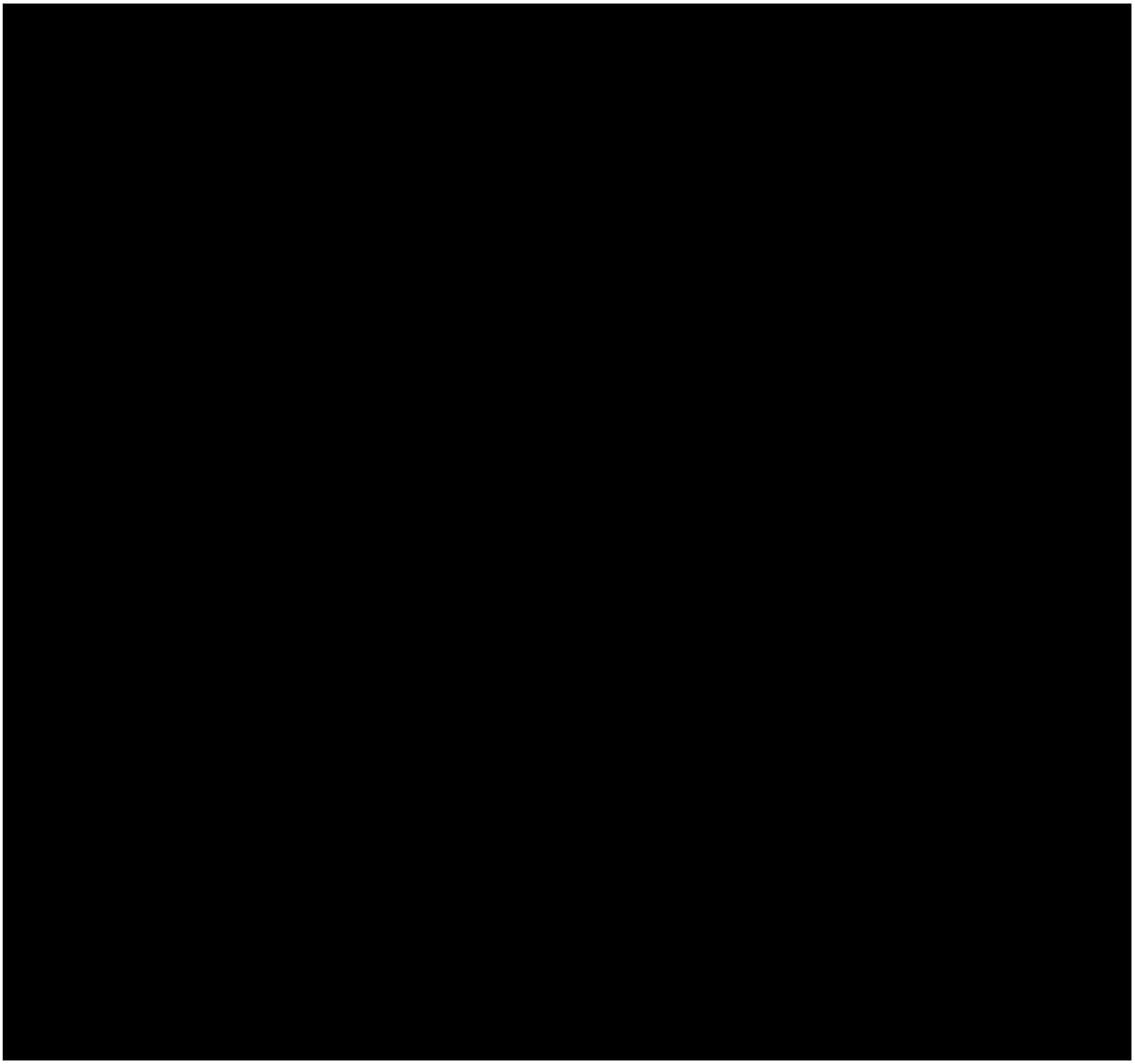
The questionnaire will be completed by the subjects before any clinical assessments are performed and treatments administered at any given visit. If subjects refuse to complete all or any part of a questionnaire, this will be documented. Questionnaires should be completed in the language most familiar to each subject, and subjects should be given adequate time and space to complete the questionnaire. Site personnel should review questionnaires for completeness and ask subjects to complete any missing responses.

6.8.1. EORTC QLQ-C30

The European Organization for Research and Treatment of Cancer – Quality of Life C30 Questionnaire (EORTC QLQ-C30) questionnaire will be used as a measure of health-related quality of life. The EORTC QLQ-C30 is composed of both multi-item scales and single item measures. These include five functional scales (physical, role, emotional, cognitive and social), three 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 EORTC QLQ-C30 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 two items assessing global health status/ HRQoL utilize a 7-point scale ranging from 1("Very Poor") to 7 ("Excellent") (Aaronson, 1993). See Appendix H.

[redacted]



6.8.3. FACT-Lym

The Functional Assessment of Cancer Therapy-Lymphoma (FACT-Lym) that 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 because the topics covered by these subscales are instead assessed by the EORTC QLQ C30 items and subscales. 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 J.

6.8.4. Hospital Resource Utilization

Hospital resource utilization will be assessed based on the numbers of hospitalizations, intensive care unit (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. Description of Investigational Product(s)

7.1.1. JCAR017

See Section 1.2 for JCAR017 description.

JCAR017 will be supplied by the Sponsor and labeled appropriately as investigational product for this study. 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.

7.2. Lymphodepleting Chemotherapy

Fludarabine and cyclophosphamide will be sourced locally by the clinical site. Please refer to local fludarabine and cyclophosphamide prescribing information for more details on available formulations, preparation, storage conditions (eg, refrigeration), the approved indications, known precautions, warnings, and adverse reactions of fludarabine and cyclophosphamide (see current version of Prescribing Information). The fludarabine and cyclophosphamide dosing schedule and dose adjustments to be followed for this study are described in Section 7.4.2.

7.3. Reference therapies

Standard of care regimen defined as R-DHAP, R-ICE and R-GDP followed by HDCT will be sourced locally by the clinical site. Please refer to local SOC and HDCT components prescribing information for more details on available formulations, preparation, storage conditions (eg, refrigeration), the approved indications, known precautions, warnings, and adverse reactions of the SOC and HDCT components (see current version of Prescribing Information). The SOC and HDCT dosing schedule to be followed for this study are described in Section 7.4.1.

7.4. Treatment Administration and Schedule

7.4.1. Reference Therapies

Standard of care regimen will be administered as per investigator decision. Subjects should receive 3 cycles of SOC followed by HDCT and an HSCT.

1. R-DHAP: Rituximab 375 mg/m² - Day 1, dexamethasone 40 mg – Days 1 to 4, cytarabine 2 x 2000 mg/m² - Day 2, cisplatin 100 mg/m² - Day 1
2. R-ICE: Rituximab 375 mg/m² - Day 1, ifosfamide 5000 mg/m² - Day 2, etoposide 100 mg/m² - Days 1 to 3, carboplatin area under the curve (AUC) 5 (maximum dose 800 mg) – Day 2
3. R-GDP: Rituximab 375 mg/m² - Day 1, dexamethasone 40 mg – Days 1 to 4, gemcitabine 1000 mg/m² - Days 1 and 8, cisplatin 75 mg/m² - Day 1

The standard HDCT to be used in this study prior to the HSCT is BEAM defined as carmustine (BCNU) 300 mg/m² - Day 1, etoposide 200 mg/m² - Days 2 to 5, cytarabine 200 mg/m² - Days 2 to 5, melphalan 140 mg/m² - Day 6.

Standard of care regimen, schedule of the regimen, dose adjustment for toxicities and premedication will be done as per site standard, local label and investigator's decision. In Japan, due to unavailability of intravenous BCNU, ranimustine (MCNU) will be used at the same dosage and schedule as BCNU.

7.4.2. 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. Refer to the most recent package inserts for further details on administration of these agents.

Lymphodepleting chemotherapy can start 5 to 7 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 7 days after LD chemotherapy upon discussion with Celgene. Refer to Section 6.2.3.2 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 upper limit of normal (ULN) OR calculated creatinine clearance (by Cockcroft-Gault, see Appendix D) is ≤ 30 mL/min.

The recommended administration is as follows:

- The IV hydration is 1 L of 0.9% sodium chloride (NaCl) given at 500 mL/hr starting 2 hours prior to cyclophosphamide
- Fludarabine IV 30 mg/m^2 over 30 minutes
  - If creatinine clearance (CrCl) is between 50 to 70 mL/min: Reduce dose by 20% for each daily dose
  - If CrCl is between 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.

7.4.3. JCAR017 Premedication

Subjects should be premedicated with 500 to 650 mg paracetamol/acetaminophen per os (PO) and 25 to 50 mg diphenhydramine hydrochloride (PO or IV) 30 to 60 minutes prior to JCAR017 infusion. In case the diphenhydramine 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.

7.4.4. JCAR017 Preparation and Cell Thawing

See the JCAR017 Product administration manual for details.

7.4.5. JCAR017 Administration

JCAR017 will be infused at a dose of 100 x 10^6 JCAR017-positive viable transduced T cells (CAR+ T cells) on Day 29 (2 to 7 days after completion of LD chemotherapy) for subjects randomized in Arm B. For subjects from Arm A crossing over to JCAR017, refer to the schedule on Table 4. Each JCAR017 dose includes CD4+ CAR+ T cells and CD8+ CAR+ T cells. The subject must be continuously monitored during each administration of JCAR017. Vital signs (temperature, respiratory rate, heart rate, blood pressure, and SaO_2 by pulse oximetry) will be measured approximately every 15 minutes, starting from 15 minutes prior to the first IV administration until one hour after the last IV administration, and hourly for the next 2 hours. If the subject's vital signs are not stable 4 hours following the final administration, vital signs should be monitored as clinically indicated until stable.

See the JCAR017 Product Administration Manual for complete information.

7.4.6. Non-Conforming Product

7.4.6.1. Protocol Product Deviation Plan

The JCAR017 Protocol Product Deviation Plan (PPDP) defines an assessment and decision-making process, which could result in a recommendation to treat a subject with a drug product that does not meet the specification for certain non-safety related attributes (non-conforming JCAR017). In this process, the 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. Quality Assurance then assesses the recommendation and is ultimately responsible for the drug product lot disposition. Documentation of the non-conforming drug product is submitted to local health authorities and is provided to the Investigator to submit per institutional review board/ ethics committee (IRB/EC) requirements. The JCAR017 PPDP is a stand alone document.

7.4.6.2. Exception Use of Non-conforming Product

Once a decision is made for the exception use of non-conforming JCAR017, country-specific requirements will be followed for the release of a non-conforming JCAR017 product to treat a subject enrolled in a JCAR017 clinical trial. For example, approval from local health authorities and/or IRBs/ECs will be obtained where required. In the European Union (EU), requirements provided in Section 11.54 of the EU Guideline on good manufacturing practice specific to advanced therapy medicinal products will be followed. Any subject will need to provide consent prior to receiving the non-conforming JCAR017 product. Please refer to Section 9 for the details regarding analyses of these subjects.

7.4.7. Overdose

Overdose, as defined for this protocol, refers to SOC regimen and HDCT, 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
- PO: Any amount 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 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 case report form (CRF) (see Section 10 for the reporting of AEs associated with overdose).

7.5. Method of Treatment Assignment

At Day 1, subjects will be randomized via an IRT system to one of the 2 arms (Arm A or Arm B). Details of the use of the IRT system are found in the IRT user manual.

7.6. Packaging and Labeling

7.6.1. Product Tracking

7.6.1.1. Reference Therapies

Manufacturer details and batch numbers will be used for the reference therapies components tracking.

7.6.1.2. Lymphodepleting Chemotherapy

Manufacturer details and batch numbers will be used for the products tracking.

7.6.1.3. JCAR017

The identity of the IP 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.

7.6.2. Product Packaging and Labeling

7.6.2.1. Lymphodepleting Chemotherapy

Fludarabine and cyclophosphamide will be provided by the clinical sites and labeled as per their local procedures.

7.6.2.2. Reference Therapies

Standard of care regimen and HDCT components will be provided by the clinical sites and labeled as per their local procedures.

7.6.2.3. JCAR017

The label(s) for IP will include, but may not be limited to, Sponsor name, address and telephone number, the protocol number, IP name, dosage form and strength (where applicable), amount of IP 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.

7.6.3. 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.

7.7. Investigational Product Accountability and Disposal

7.7.1. 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.

7.7.2. Drug Disposal and Destruction

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

7.8. Investigational Product Compliance

7.8.1. Reference Therapies

For the SOC and HDCT regimen, the administered dosage of the different components will be recorded in the source documents and on the appropriate CRFs. Additionally, if the study subject misses a dose, this information should be documented in the study subject's CRF and source documents.

Where provided by Celgene Corporation an accurate accounting of the dispensing and return for each study subject will be maintained in the source documents on an ongoing basis by a member of the study site staff. Disposal and/or destruction of unused or remaining reference therapies will be performed as per local procedures.

7.8.2. Lymphodepleting Chemotherapy

For the LD chemotherapy, the administered dosage of the different components will be recorded in the source documents and on the appropriate CRFs. Additionally, if the study subject misses a dose, this information should be documented in the study subject's CRF and source documents.

Where provided by Celgene Corporation an accurate accounting of the dispensing and return for each study subject will be maintained in the source documents on an ongoing basis by a member

of the study site staff. Disposal, and/or destruction of unused or remaining Fludarabine and/or Cyclophosphamide will be performed as per local procedures.

7.8.3. JCAR017

The administered dosage of JCAR017 will be recorded in source documents and on the appropriate CRFs. The investigator(s) or designee is responsible for taking an inventory of each shipment of investigational 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 IP 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 IP for each study subject will be maintained in source documents on an ongoing basis by a member of the study site staff.

Additionally, if any IP is lost or damaged or if the study subject misses a dose, 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 IP.

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 randomization. All medications will be recorded from the randomization and until 90 days after JCAR017 or 90 days after last dose of chemotherapy. From 91 days after JCAR017 or 91 days after last dose of chemotherapy until the EOS visit, concomitant medications given for AEs related to the study treatment or any protocol-mandated procedures will be recorded. For subjects receiving LD chemotherapy but not JCAR017, concomitant medications associated with AEs will be recorded for 30 days following the last dose of LD chemotherapy.

Table 5: Reporting Periods for Concomitant Medications, Procedures and Transfusions

Arm	Start	End	Required Reporting
Arm A and B	Informed Consent	Randomization	Medications given, procedures and transfusions performed for a clinically significant condition related to protocol-mandated procedures or for active medical history conditions should be reported as described in the CRF completion guidelines
Arm A	Randomization	90 days after last dose of chemotherapy	All medications, procedures and transfusions
Arm B and cross over	Randomization (Arm B) and Pre-treatment evaluation (cross over)	90 days after JCAR017 infusion	
Arm A, B and cross over	End of previous period	End of study	Only medications, procedures and transfusions ongoing at the time of AEs related to any protocol-mandated procedures, SOC/HDCT or JCAR017

Abbreviations: AEs = adverse events, CRF = case report form, HDCT = high-dose chemotherapy, SOC = standard of care.

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.

Due to the large amount of data generated during hospitalizations, a targeted concomitant medication collection approach will be utilized for the CRF. The medications which should NOT be entered in the Concomitant Medications CRF during inpatient and ICU stays are defined in the CRF Completion Guidelines.

Over the course of this study, additional medications may be required to manage aspects of the disease state of the subjects (refer to Section 8.1.1), including side effects from trial treatments or

disease progression. Supportive care, including, but not limited to antiemetic medications, may be administered at the discretion of the Investigator.

Prophylactic treatment/measures are strongly recommended for subjects at risk for tumor lysis syndrome (TLS), per institutional or clinical standards. The use of red blood cells and platelet transfusions, and/or granulocyte colony-stimulating factors is permitted per institutional or clinical standards. Prophylactic anticoagulation to prevent thromboembolic events is permitted as per institutional or clinical standards.

All concomitant treatments, including blood and blood products, used from 30 days prior to first dose of any IP until 30 days after the last dose of IP, must be reported on the CRF.

Intrathecal treatment (IT) with methotrexate and/or cytarabine is allowed for prophylaxis and for treatment of subjects with secondary CNS involvement. Subjects with secondary CNS involvement who received IT treatment with methotrexate and/or cytarabine should have a minimum of 7 days wash-out period prior to the start of lymphodepleting chemotherapy.

Local radiation is allowed to a single lesion or subset of lesions if other non-irradiated PET-positive lesions are present and if completed at least 7 days prior to the start of lymphodepleting chemotherapy.

Radiotherapy is allowed after completion of per protocol treatment in both arms to sites of previous PET positive disease.

For information regarding other drugs that may interact with any study treatment and affect its metabolism, pharmacokinetics, or excretion, please see the IB and/or local package insert.

Vaccination with a killed vaccine is permitted at any time in consultation with the Medical Monitor.

8.1.1. Bridging Chemotherapy (Subjects Receiving JCAR017)

In Arm B, bridging chemotherapy with one of the protocol-defined SOC regimen (Section 7.4.1) is allowed for disease control while JCAR017 is being manufactured if deemed necessary by the investigator (ie, after leukapheresis and prior to lymphodepleting chemotherapy). Bridging therapy given after leukapheresis to maintain disease control must be stopped at least 7 days prior to LD chemotherapy.

For subjects from Arm A who cross over to JCAR017, bridging with non-investigational therapy is allowed if completed at least 7 days prior to the start of lymphodepleting chemotherapy.

Local radiation is allowed to a single lesion or subset of lesions if other non-irradiated PET-positive lesions are present and if completed at least 7 days prior to the start of lymphodepleting chemotherapy.

8.2. Prohibited Concomitant Medications and Procedures

The following medications are considered exclusionary or should be used with caution during the study. The sponsor must be notified if a subject receives any of these during the study.

- Any investigational antineoplastic therapy

- Any concurrent chemotherapy, immunotherapy, biologic or hormonal therapy for cancer treatment (except IT prophylaxis and treatment for secondary CNS involvement);
- Concurrent use of hormones for non-cancer-related conditions (eg, insulin for diabetes and hormone replacement therapy) is acceptable;
- 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;

Note: Use of immunosuppressive medications for the management of IP-related AEs or in subjects with contrast allergies is acceptable. In addition, use of inhaled and intranasal corticosteroids is permitted; therapeutic doses of steroids may be used in life-threatening situations and for other medical conditions when indicated.

8.2.1. Subjects Infused with JCAR017

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

- Steroids: therapeutic doses (> 20 mg/day of prednisone or equivalent) unless used for treatment of CRS and NT. Therapeutic doses may be used in life-threatening situations and for other medical conditions when indicated, or after loss of detectable JCAR017 cells. Pre-treatment containing steroids may be given for necessary medications (eg, intravenous immunoglobulin [IVIG]) after discussion with the Sponsor. Pre-medication with steroids for JCAR017 administration 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 antineoplastic agent after lack of adequate response to study treatment or progression of lymphoma:

- Immunosuppressive therapies (eg, calcineurin inhibitors, methotrexate or other chemotherapeutics, mycophenolate, rapamycin, thalidomide, immunosuppressive antibodies such as anti-TNF, anti-IL6, or anti-IL6R)
- Non-protocol-specified antineoplastic agents, excluding IT prophylaxis and treatment for secondary CNS involvement. Lymphodepleting 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- epidermal growth factor receptor (EGFR) targeted treatments, unless intended for treatment of uncontrolled JCAR017 proliferation
- Experimental agents

The Sponsor must be notified if a subject receives any of these medications during the study.

Please refer to the locally approved fludarabine and cyclophosphamide labels for the list of medications which should be avoided from concomitant use.

8.3. Required Concomitant Medications and Procedures

To minimize the risk of infusion reactions, all subjects should be premedicated with acetaminophen and diphenhydramine prior to JCAR017 infusion (see Section 7.4.3). Supportive care for the management of CRS is detailed in Appendix L. In some cases, tocilizumab, an anti-IL-6R-antibody, may be required to treat toxicities such as CRS. Please refer to the currently approved Actemra®/ RoActemra® package insert. As per label, up to 4 doses of tocilizumab can be given for treatment of CRS. The recommendation is to follow the local labeled guidance. However, for JCAR017 investigators, 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 patient and to resupply in case tocilizumab is given. The preferred dose to intervene in subjects with CRS is 8 mg/kg. Another anti-IL-6 agent, if available in the country, 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.

In some cases, steroids (eg, dexamethasone) may also be given for the treatment of CRS or NT.

9. STATISTICAL CONSIDERATIONS

9.1. Overview

This is a global randomized multicenter phase 3 trial evaluating the efficacy and safety of JCAR017 versus SOC in subjects with high-risk, second-line, transplant-eligible relapse/refractory aggressive B-cells NHL.

The primary objective is to demonstrate that subjects treated with JCAR017 have a larger benefit on EFS than subjects treated with SOC salvage strategies. Key secondary objectives are to demonstrate hierarchically additional efficacy benefit on CRR, PFS and OS.

The ORCHARRD trial (van Imhoff, 2016) reports a median PFS (with failure to achieve a response after 2 cycles included as an event) in the overall population of approximately 3 months, with a median OS of approximately 13.5 months, with significantly shorter PFS and OS in high risk subjects of approximately 2 months median PFS and 11 months median OS. Event-free survival at 2 years for the R-DHAP and O-DHAP arms were 18% and 16%, respectively.

Date of randomization will be defined as Day 1. Baseline value will be defined as the last value on the randomization date (+3 days) or before the date/time of randomization (date if date/time not collected). If multiple values of the same variable are eligible for the baseline, the average of these values will be used as the baseline. For subjects who are not randomized, the baseline will be the last available value. For subjects crossing over to receive JCAR017, secondary baseline is defined as the last value on or before the date/time of start of LD chemotherapy (date if date/time not collected).

9.2. Study Population Definitions

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

9.2.1. Screened Analysis Set

All subjects who signed informed consent form.

9.2.2. Intention-to-Treat Analysis Set

All subjects randomized to a treatment arm. Reporting on the Intention-to-Treat (ITT) analysis set will be done against the planned treatment.

9.2.3. Per-Protocol Analysis Set

All subjects of the ITT analysis set characterized by:

- Having a minimal exposure to treatment:
    - Arm A: one cycle of SOC (consisting on the administration of all the medications of the reference therapy);
    - Arm B: per protocol dose (CD8+ and CD4+) of conforming JCAR017;
- Having a baseline assessment and at least one post-baseline response assessment;

- Without important protocol deviations.

Reporting on the per-protocol (PP) analysis set will be done against the actual treatment received.

9.2.4. Safety Analysis Set

All subjects who take at least one dose of study treatment. Reporting done on safety analysis set will be done against actual treatment received.

9.2.5. Pharmacokinetic Analysis Set

All subjects who take conforming JCAR017 who have both pre-infusion and at least one post-infusion PK measurement.

[redacted]

9.2.6. Cross over Analysis Set (Arm A)

All subjects of the ITT analysis set randomized in Arm A who cross over to JCAR017 treatment.

9.2.7. JCAR017-Treated Analysis Set

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

9.2.8. Health-related Quality of Life Analysis Set

The health-related quality of life (HRQoL) analysis set for each instrument, will include all subjects from the ITT population who completed a baseline and at least one post-baseline HRQoL assessment. A subject will be considered compliant on each instrument based on the manual of this instrument.

Reporting on HRQoL analysis set will be done against actual treatment received.

9.3. Sample Size and Power Considerations

Sample size calculation, robustness and sensitivity is based on EAST 6.3 software (Cytel Inc.).

9.3.1. Sample Size Calculation

It is hypothesized that subjects treated with SOC have median EFS of 3 months. Subjects receiving experimental treatment JCAR017 are expected to have an increase of ~ 81% in the median EFS (equivalent to a hazard ratio of 0.55 under the exponential distribution assumption)

compared to subjects treated with SOC, bringing the median EFS in the experimental group to 5.455 months.

An interim analysis for superiority of JCAR017 over SOC on EFS will be performed at 60% information time (approximately 71 EFS events). O'Brien-Fleming boundary alpha spending function is used.

Given these assumptions, using a log rank test with 2.5% one-sided significance level, 119 EFS events will provide at least 90% power to reject the null hypothesis of HR greater than or equal to 1.

The null hypothesis will be rejected if the p-value associated to the test is smaller than or equal to 0.004 at the time of the interim analysis for efficacy (ie, when 71 EFS events are observed) or smaller than or equal to 0.024 at the time of the primary efficacy analysis (ie., when 119 EFS events are observed). The significance thresholds will be adjusted based on the actual number of EFS events observed at the time of each efficacy analysis in order to ensure the nominal significance level is maintained.

Given an expected randomization rate of up to 12 subjects per month (2, 4, 6, 8 and 10 subjects randomized during 1st, 2nd, 3rd, 4th, 5th month and 12 subjects per months after 6th month) and a 20% drop out rate before first response assessment and a yearly dropout rate of 10% (30% cumulative), a sample size of 182 subjects is expected to be randomized and 215 subjects to be screened (screen failure rate of 15%). The estimated accrual duration is 17.6 months, which is the midpoint between the estimated minimal accrual time (15.1 months) and the suggested maximum (20 months); minimal and suggested maximum accrual times are estimated by the sample size software and are based on the assumptions described above. Interim analysis for efficacy is expected to be performed at around 14.7 months after study start and final analysis at around 21.4 months after study start. The approximated time for the interim analysis for efficacy and for the final analysis are based on the assumptions for alpha, power, HR (or improvement in median survival), interim looks, accrual models and drop-out rates and are estimated by the sample size software.

If null hypothesis of HR equal to 1 is rejected for EFS, hypothesis testing on CRR (and subsequently on PFS and OS) will be performed hierarchically; the hierarchical testing strategy is used in order to control the overall type I error rate. If the null hypothesis can be rejected for the primary endpoint but at least one null hypothesis for key secondary endpoint cannot be rejected at the interim analysis for efficacy, then hypothesis testing on all key secondary endpoints will be re-evaluated at the primary efficacy analysis (Glimm, 2010).

Considered independently, performed at the same time of the primary efficacy analysis and with the same randomization and dropout model, expected power will be respectively over 98% for CRR assuming a rate of 22% in Arm A and 51% in Arm B, over 96% for PFS assuming a median of 3 months in Arm A and 6 months in Arm B (HR = 0.5), and approximatively 37% for OS assuming a rate at 2 years of 41% in Arm A and 56% in Arm B (HR = 0.65).

In addition, an interim analysis for futility will be conducted when ~30 evaluable subjects (~15 subjects per arm and having received their assigned treatment) have their 9 weeks response assessment (after 3 cycles of SOC for Arm A and 5 weeks after the JCAR017 infusion) or have been confirmed with disease progression prior to this timepoint. No formal statistical test will be

performed for this interim analysis, and therefore no type I error adjustment is implemented in the sample size calculation.

9.3.2. Sample Size Robustness and Sensitivity

The robustness and the sensitivity of the proposed sample size has been evaluated under several conditions via simulations. Power extracted out of the simulations were rounded up to the next integer. Please note that number of subjects randomized is set to 182 and that maximum number of EFS events at primary efficacy analysis is set to 119.

If the HR is below the expected value and median EFS in Arm A is set to 3 months, power at the primary efficacy analysis is above 90% (see Table 6). If the HR is above the expected value but on or below 0.6 and median EFS in Arm A is set to 3 months, power at the primary efficacy analysis is at an acceptable level (see Table 6). If expected HR is strictly above 0.6 with median EFS in Arm A set to 3 months, power at the primary efficacy analysis (ie, when 182 subjects are randomized and 119 events are observed) is below acceptable levels, indicating that the number of EFS events triggering the primary efficacy analysis is insufficient to reject the null hypothesis with a high likelihood.

When EFS events are not distributed according to an exponential distribution but according to a Weibull distribution (with shape parameter set at the same value in Arm A and Arm B, ensuring proportional hazard assumption is maintained), targeting the same absolute clinical benefit (median EFS at 3 months in Arm A and median EFS at 5.455 months in Arm B) underpowered and overpowered situations may occur. In case the shape parameter is above 1 (indicating that hazards in both arms are increasing with time but with constant hazard ratio), HR is below the expected value and power at the primary efficacy analysis is above 90% (see Table 7). In case the shape parameter is below 1 (indicating that hazards in both arms are decreasing with time but with hazard ratio constant), power is at an acceptable level as long as shape parameter is strictly above 0.75 (see Table 7).

Table 6: Power Estimated via Simulation for other HR Assumptions

Hazard Ratio	Median EFS in Arm A	Median EFS in Arm B	Events at Interim/Primary Efficacy Analysis	Power at Primary Efficacy Analysis
0.5	3 months	6 months	71 / 119	96%
0.525	3 months	~5.7 months	71 / 119	93%
0.575	3 months	~5.2 months	71 / 119	84%
0.6	3 months	5 months	71 / 119	78%
0.65	3 months	~4.6 months	71 / 119	64%

Table 7: Power Estimated via Simulation with Weibull Distribution

Shape Parameter	Median EFS in Arm A	Median EFS in Arm B	Events at Interim/Primary Efficacy Analysis	Power at Primary Efficacy Analysis
1.25	3 months	5.455 months	71 / 119	98%
1.1	3 months	5.455 months	71 / 119	94%
0.9	3 months	5.455 months	71 / 119	82%
0.8	3 months	5.455 months	71 / 119	73%
0.75	3 months	5.455 months	71 / 119	68%

9.4. Background and Demographic Characteristics

Subject's age, height, weight, and continuous baseline variables will be summarized using descriptive statistics (number of non-missing values, mean, median, standard deviation, interquartile range, range), while sex, race and other categorical variables will be provided using frequency tabulations for the ITT, PP and safety analysis set for each arm and as per histology. Medical history data, including prior cancer therapies will be summarized using frequency tabulations by Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and preferred term (PT) for the ITT, PP and safety analysis set for each arm and as per histology.

9.5. Subject Disposition

Subject disposition will be summarized using frequency and percent in the screened, ITT, PP and safety analysis set for screening, treatment and follow-up period. Summary of subjects randomized by site will be provided. Summary of subjects with protocol deviations and important protocol deviations will be provided per arm. Summary of subjects who are randomized for study treatment but not able to successfully generate a JCAR017 cell product, along with the reason(s) for manufacturing failure, will be summarized.

9.6. Efficacy Analysis

Primary analysis will be based on the ITT analysis set. Per-protocol and safety analysis set will be used for supportive analyses when required.

For time-to-event endpoints such as EFS, PFS, DOR, and OS, the K-M product limit method will be used to extract summary information about survivorship. At least medians together with two-sided 95% confidence intervals will be reported and it will be calculated and extracted from K-M curves.

In addition, the event rates at specific time-points will be computed, along with the standard errors and associated two-side 95% confidence intervals (Greenwood's formula; Klein, 1997).

The rank preserving structural failure time (RPSFT), the inverse probability of censoring weighting (IPCW) and the 2-stage Weibull approaches, will be considered for PFS and OS in order to adjust for cross over bias (Colleoni, 2011; Ishak, 2014; Jin, 2012; Korhonen, 2012; Motzer, 2010; Sternberg, 2013; Latimer, 2014).

The RPSFT approach, relies on a simple model for survival times that assumes that the effect of treatment is multiplicative on time, that it conveys benefit immediately, and that the size of the benefit is the same regardless of whether subjects were randomized or crossed over to treatment (Ishak, 2014).

The IPCW approach reweights the influence of subjects who could have crossed over but did not, despite being otherwise similar to those who did cross over (ie, omits survival time after cross over from analyses by censoring subjects at the time of the treatment switch). The method usually relies on using time-dependent (and possibly time-fixed) risk factors to determine subjects' probability of cross over which serve as weights. It assumes that there are sufficient numbers of subjects who did and did not cross over in all risk factor profiles where cross over occurred (Ishak, 2014).

In the 2-stage Weibull approach, the EFS event can be used as a secondary baseline and patients in Arm A are treated as an observational dataset. Treatment effect received by subjects in Arm A who switched compared subjects who did not switch will be estimated by fitting a Weibull model (excluding patients in Arm B) with covariates measured at the secondary baseline and a time-varying covariate indicating treatment switch from Arm A to JCAR017.

For binary endpoints such as CRR and ORR, the frequency distribution (n, %) will be provided as summary information. The point estimate together with two-sided exact 95% confidence intervals (CI) will be provided. Cochran-Mantel-Haenszel (CMH) test with stratification factors as strata will be used for analysis and calculation of p-values.

9.6.1. Primary Efficacy Analysis

The primary endpoint is EFS, defined as the time from randomization to death due to any cause, PD, failure to achieve CR or PR by 9 weeks post-randomization, or start of a new antineoplastic therapy due to efficacy concerns, whichever occurs first.

Start of a new antineoplastic therapy due to efficacy concerns will be based on investigator's assessment and related data will be collected in the electronic case report form (eCRF). Start of a new antineoplastic therapy will be captured from time of randomization to date of imaging (or other objective finding) that serves as the basis of starting a new antineoplastic therapy.

Primary response assessment will be based on central assessment performed by the IRC and supportive response assessment will be based on investigator assessment. Response assessment will be evaluated primarily per the Celgene Lugano Classification guidelines based on "The Lugano Classification" (Cheson, 2014).

Event-free survival will be analyzed with a stratified Cox-PH model if the proportional hazards assumption hold (unstratified Cox-PH model as supportive analysis). The stratification factors to be used in the Cox-PH model correspond to the stratification at the time of randomization; in addition, the model will include treatment as the only covariate for analysis. If the proportional hazards assumption is not fulfilled, piecewise Cox-PH model will be used. Details on the evaluation of HR assumption and application of the Cox-PH model will be described in the statistical analysis plan (SAP).

Full set of censoring rules for EFS will be detailed in the SAP.

9.6.2. Key Secondary Efficacy Analysis

For CRR, CMH test with stratification factors as strata will be used for analysis and calculation of p-values. For PFS and OS, similar analysis strategy than for EFS will be used. However, as subjects from Arm A have the possibility to cross over to JCAR017, RPSFT method, IPCW method and 2-stage Weibull approach will be used for the analysis of these time-to-event data.

- Complete response rate (CRR) is defined as the proportion of subjects achieving a CR from randomization up to 3 years post-randomization. Subjects with unknown or missing response will be counted as non-responder in the analysis. Any responses after a start of a new antineoplastic therapy will not be considered. Response after cross over will be analyzed descriptively on the cross over population.
- Progression free survival (PFS) is defined as the time from randomization to PD or death from any cause, whichever occurs first.
- Overall survival (OS) is defined as the time from randomization to death due to any cause.

Full set of censoring rules for PFS and OS will be detailed in the SAP.

9.6.3. Other Efficacy Analyses

- Overall response rate is defined as the proportion of subjects achieving an objective response of PR or CR according to the Lugano Classification during the treatment period. Subjects with unknown or missing response will be counted as non-responder in the analysis. Any responses after a start of a new antineoplastic therapy will not be considered. Response after cross over from Arm A to JCAR017 will be analyzed descriptively on the cross over population.
- Duration of response (DoR) is defined as the time from first response to disease progression, start of new antineoplastic therapy or death and will be summarized using K-M estimates. In case a subject does not have PD, start of a new antineoplastic therapy or death prior to data cutoff date, DOR will be censored at the date of the last adequate response assessment.
- Progression-free survival on the next line of treatment (PFS-2) is defined as time from randomization to objective tumor progression on next-line treatment or death from any cause. Subjects alive and for whom a second objective disease progression has not been observed will be censored at the last time known to be alive and without second objective disease progression. Recurrent event approach based on a Prentice, Williams and Peterson model will be used for the analysis of PFS-2.
- Subjects receiving HSCT up to 3 years post-randomization will be summarized via counts and percents. Subjects receiving HSCT, response rates will be summarized at 3 months post-HSCT.
- For subjects who cross over from Arm A to JCAR017, descriptive statistics of EFS, OS, PFS, DoR, CRR, ORR will be provided.

9.6.4. Subgroup Analyses

Efficacy subgroup analyses will be performed on at least the flowing variables:

- Secondary age-adjusted International Prognostic Index (sAAIPI) status: 0 or 1 versus 2 or 3
- Prior response status: refractory versus relapse to last prior therapy. The status is refractory if a subject achieved PD, SD, PR or CR with relapse within 3 months to last prior therapy; otherwise the status is relapsed
- Age: < 40, ≥ 40 to < 65, ≥ 65 to < 75 and ≥ 75 years at the time of randomization
- Sex: male versus female
- Ethnicity: Hispanic or Latino versus not Hispanic or Latino
- Region: Europe, US and Japan
- Race: white versus other races
- ECOG performance status at screening: 0 and 1
- Prior chemotherapy response status: chemorefractory versus chemosensitive to last therapy. The status is chemorefractory if a subject achieved SD or PD to last chemotherapy-containing regimen; otherwise the status is chemosensitive
- Central nervous system (CNS) disease status: known as CNS disease versus no known CNS disease at the time of randomization
- Histological and molecular subtype:
  - NHL type: DLBCL, FL3B, high grade B-cell lymphoma with DLBCL histology, PMBCL or THRBCL
  - DLBCL subtype: DLBCL NOS de novo or DLBCL from transformed indolent NHL
  - DLBCL subtype based on cell of origin: GCB or ABC, non-GCB
- Bridging therapy status: impact of bridging therapy treatment effect versus SOC will be evaluated in subjects receiving bridging

Subgroup analyses will only be performed if there are enough subjects in each subgroup (more than 10 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.

9.7. Safety Analysis

Safety analysis will include all subjects in the Safety analysis set.

9.7.1. Treatment Exposure

Study treatment and extent of exposure summaries will be provided on the safety population. Descriptive statistics will be provided for treatment exposure and duration, cumulative dose,

number of days dosed, average daily dose, dose intensity, treatment compliance, relative dose intensity per treatment arms, per regimen and agent when relevant. Dose modification will be summarized per arm.

9.7.2. Adverse Events

Adverse events will be coded using MedDRA SOC and preferred term (PT).

The severity of each adverse event will be graded by the Investigator using Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 or higher, unless otherwise specified in the protocol.

Related AEs are those for which the Investigator selects "Related" to JCAR017 or SOC on the AE reported in CRF. Adverse events will be identified and captured as SAEs if they meet the definition for SAE.

Treatment-emergent adverse events (TEAEs) are defined as AEs occurring or worsening on or after the date of randomization and within 90 days after last dose of chemotherapy (Arm A), or within 90 days after the infusion of JCAR017 (Arm B or subjects in Arm A crossing over to JCAR017) or start of new antineoplastic therapy, whichever occurs first as well as those AEs made known to the investigator at any time thereafter that are suspected of being related to study treatment. Adverse event summaries will provide the number and percentage of subjects with at least one TEAEs by SOC and PT for:

- TEAEs
- TEAEs by severity grade
- Grade 3 or more TEAEs
- Grade 5 TEAEs
- TEAEs by maximum CTCAE grade
- TEAEs suspected to be related to JCAR017 or SOC
- Grade 3 or more TEAEs suspected to be related to JCAR017 or SOC
- SAEs
- SAEs suspected to be related to JCAR017 or SOC
- AEs leading to treatment discontinuation, study discontinuation or death
- Adverse events of special interest (AESI)
- Grade 3 or more AESI

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 overall. In summaries by severity grade, the most severe grade will be used for those AEs that occur more than once in an individual subject during the study. AEs will be summarized in clinical, histological and molecular subgroups of interest.

Corresponding supportive subject-level listing will be provided.

9.7.3. Laboratory Evaluations

9.7.3.1. Numeric Laboratory Results

Summaries of numeric laboratory data will be based on central assessment and will be reported using conventional units for hematological tests, serum chemistry tests and for other laboratory tests including coagulation, inflammatory markers and immunoglobulins. Baseline, raw values, and changes from baseline will be summarized per arm using descriptive statistics for each laboratory test specified in the study protocol.

9.7.3.2. Graded Laboratory Values

Central laboratory data will be graded according to NCI CTCAE, Version 4.03 (or higher) 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. Summary data (count and percent) within each grade will be provided per arm. Cross-tabulation table of post-baseline grade and worst post baseline grade versus baseline grade will be provided for selected hematology, serum chemistry and coagulation parameters per arm.

9.7.3.3. Summaries of Laboratory Abnormalities

Laboratory results will be programmatically classified as below normal range, within normal range and above normal range if the numeric laboratory result is below the lower limit of normal range, within normal range or above the upper limit of normal range. Shift tables per treatment arm will be presented for selected hematology, serum chemistry and coagulation parameters showing change in results from the baseline value (below normal range, within normal range, and above normal range) to each post-baseline visit and to the worst post-baseline value (below normal range, within normal range, and above normal range).

9.8. Interim Analysis

Two interim analyses, one for futility and one for efficacy, will be performed. In addition, the rate of EFS events will be monitored during the course of the study at predefined timepoints to potentially increase the sample size, if required. In order to prevent bias being introduced into the study conduct and analyses, an independent and external statistical group will be responsible for performing these interim analyses and monitoring of EFS events for sample size increase. A data safety monitoring board (DSMB) will be responsible of reviewing such analyses and provide recommendation to the sponsor.

9.8.1. Futility Interim Analysis

The purpose of the first interim analysis is to stop for futility in case of no efficacy signal on CRR at 9 weeks after randomization (after 3 cycles of SOC for Arm A and 5 weeks after the JCAR017 infusion) for JCAR017 treated subject compared to SOC. The futility interim analysis will be conducted when ~30 evaluable subjects (~15 subjects per arm and having received their assigned treatment) have their 9 weeks response assessment (after 3 cycles of SOC for Arm A and 5 weeks after the JCAR017 infusion) or have been confirmed with disease progression prior to this timepoint. Screening and treatment will continue while this interim analysis is being conducted. The study may be terminated if the CRR in JCAR017 arm is lower than the CRR in

the SOC arm. No formal statistical test will be performed, and no type I error adjustment is implemented for this futility interim analysis.

9.8.2. Efficacy Interim Analysis

A second interim analysis will be performed at 60% information time (ie, at around 71 EFS events). The purpose of this interim analysis is to demonstrate superiority of JCAR017 versus SOC on EFS. O'Brien-Fleming boundary are used for defining the efficacy boundaries. The null hypothesis will be rejected if the p-value associated to the test is smaller than or equal to 0.004. Screening and randomization will continue while this interim analysis is being conducted. In case of efficacy demonstrated on primary endpoint, recruitment of subjects will continue.

9.8.3. Monitoring of EFS Events and Sample Size Increase

Monitoring of EFS events will be performed in an aggregate manner during the study course at predefined timepoint (at 100 subjects randomized and at the time of the efficacy interim analysis). Predictive probability of observing the required 119 EFS events or more at the expected primary analysis (ie, at around 21.4 months) will be computed at these predefined timepoint. In case this predictive probability is too low (below 50% at first monitoring and below 80% at second monitoring of the EFS events), then sample size will be increased with a limit of up to 40 additional subjects (with a 1:1 ratio).

Additional information on the estimation of the EFS probability curve and computation of the predictive distribution for the EFS events will be mentioned in the SAP.

9.9. Other Topics

9.9.1. Randomization

Subjects will be randomized at 1:1 ratio into one of the two arms: Arm A or Arm B. Randomization will be based on a permuted-blocks randomization method, with the following stratification factors:

1. Best overall response to first-line therapy: refractory (defined as SD, PD, PR or CR with relapse before 3 months) versus relapse (CR with relapse on or after lasting at least 3 months);
2. Secondary age adjusted International Prognostic Index (sAAIPI): 0 or 1 versus 2 or 3.

9.9.2. Data Safety Monitoring Board

An independent data safety monitoring board (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 selected 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 screening of the first subject on the protocol and will meet approximately quarterly throughout the trial and as needed to address any safety issues that may

arise. Subject safety will be evaluated as specified in DSMB charter. The DSMB will provide advice to the Sponsor as outlined in the DSMB charter. The effectiveness of the risk mitigation plan will be reviewed by the DSMB at each meeting. Operational details for the DSMB will be detailed in the DSMB charter.

9.9.3. 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

9.9.4. Independent Review Committee

An independent review committee (IRC) will be established to review data related to disease response assessments during the study and determine remission and relapse for the primary analysis. An IRC charter will detail the IRC data flow and review process in alignment with the response definitions in Appendix C. Subject management will be based upon local investigator assessments. The designation of remission and relapse for the primary analysis and other related key secondary and secondary efficacy endpoints will be based only on the evaluations made by the IRC. Operational details for the IRC will be detailed in the IRC charter agreed upon between Celgene and the IRC before initiation of any IRC review.

9.9.5. Exploratory Analysis

[redacted]

- [redacted] pharmacokinetic [redacted] for JCAR017
- The effect of treatments directed at sCRS and neurotoxicity on duration and severity of sCRS and neurotoxicity
- [redacted]
- Safety: Detection of RCL

9.9.6. Health-Related Quality of Life

All HRQoL analyses will be conducted on the HRQoL analysis set. The PRO/QoL compliance rate (%) will be calculated for each instrument in two ways: as the number of subjects compliant at each visit over the number of expected subjects (alive and on study) at that particular visit and over the ITT population. As the power for the study was calculated based on the primary endpoint, all PRO analyses should be interpreted as descriptive. Missing values will be addressed according to questionnaire guidelines. Reasons for missing questionnaires will be captured so that the appropriate imputation method can be applied according to questionnaire guidelines. For those domains, the analyses will be conducted as detailed in the SAP.

The primary domains of interest for the HRQoL analysis are global health/quality of life (GH/QoL), fatigue, physical functioning and cognitive functioning and FACT-Lym "Additional

Concerns" subscale (FACT-Lym). [redacted]

9.9.7. Hospital Resource Utilization

Hospital resource utilization (HRU) will be summarized per arm using number and duration of hospitalizations, reasons for hospitalization, unit of admission, intensive care unit (ICU) inpatient stay, non-ICU inpatient stay and number of outpatient visits. Intensive care unit and non-ICU inpatient stay is defined as the sum of duration of all ICU and non-ICU stays respectively.

A supportive by-subject listing will be provided.

9.9.8. Pharmacokinetics[redacted]

Description of the statistical analysis for PK [redacted] will be specified in the SAP.

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 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 7.4.7 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 and cyclophosphamide (flu/cy) and SOC (R-DHAP, R-ICE, R-GDP) 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 8. If they meet the seriousness criteria, they will be reported to Drug Safety as provided in Section 10.5.

Table 8: Recording Periods for Adverse Events

	Start	End	Required Recording
Arm A and B	Signing of informed consent	Randomization	AEs related to any protocol mandated procedure* Each AE with a change in toxicity grade will be recorded in the CRF as a separate AE record
Arm B and cross over	Randomization (Arm B) and Pre-treatment evaluation (cross over)	90 days after JCAR017 infusion	All AEs Each AE with a change in toxicity grade will be recorded in the eCRF as a separate AE record
Arm A	Randomization	90 days after last dose of chemotherapy	
Arm A, B and cross over	End of previous period	End of study	Only AEs related to any study procedure or JCAR017 or SOC/HDCT 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
Arm A, B and cross over	Randomization	End of study	The following conditions should be reported as SAEs, regardless of relationship to study drug: • Second primary malignancies • New onset or exacerbation of a pre-existing neurologic disorder • New onset of a rheumatologic or other autoimmune disorder • New onset of a hematologic disorder • Rare and unexpected disorders with an unknown etiology (eg, Guillain-Barré, Stevens-Johnson syndrome).

Abbreviations: AEs = adverse events, eCRF = electronic case report form, HDCT = high-dose chemotherapy, SAEs = serious adverse events, SOC = standard of care.
* Any clinically significant conditions/events unrelated to study procedures should be reported either in the medical history or as an adverse event as described in the CRF completion guidelines (CCGs).

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 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.

For CRS and neurotoxicity reporting requirements in the CRF, please refer to the CRF completion guidelines (CCGs).

Any medical condition already present prior to randomization 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.

AEs 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 8 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. Any confirmed detectable result from RCL testing or any result from a second primary malignancy that suggest malignant transformation due to insertional oncogenesis will be reported as an SAE within 24 hours of the investigator being notified of the positive result.

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, JCAR017 and SOC/HDCT and HSCT, action taken regarding LD chemotherapy, JCAR017 and SOC/HDCT and HSCT, and outcome.

10.2.2. Severity/Intensity

For both AEs and SAEs, the Investigator must assess the severity/ intensity of the event. CRS must be graded using the modified CRS grading scale (Appendix L).

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

AEs 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 the LD chemotherapy, JCAR017 or the SOC regimen 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 IP 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 IP caused the adverse event. 'Reasonable possibility' means there is evidence to suggest a causal relationship between the IP 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 IP 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 IP as a result of an AE or SAE, as applicable (eg, discontinuation, interruption, or dose reduction of IP, 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.

SAEs 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 IP 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 βhCG or positive pregnancy test) occurring at any time after receipt of lymphodepleting chemotherapy, infusion of JCAR017 or SOC/HDCT in either a female subject of childbearing potential or a female partner 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 IP 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 taking IP becomes pregnant, the male subject taking IP 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 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 or SOC/HDCT and HSCT) 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 a serious adverse event (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 IP (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 8.

10.6. Potential Risks and Management of Treatment Toxicities

A summary of potential risks and management of treatment toxicity is provided below for the IP. See respective IB for a complete discussion of potential risks associated with JCAR017.

10.6.1. Management of Toxicities Associated with JCAR017

Cytokine release syndrome (CRS) and neurologic toxicities (NT) are associated with CAR T-cell therapies. Celgene has developed specific toxicity management guidelines (TMG) for CRS and NT associated with Celgene cellular products based on current clinical experience across the clinical development programs (Appendix L). 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 eCRF to inform future modifications of the management guidelines.

10.6.1.1. Cytokine Release Syndrome

Administration of JCAR017 is associated with cytokine release syndrome (CRS). 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. With JCAR017, CRS usually occurs within two weeks after infusion (Abramson, 2017b).

- 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.

- Neurological toxicity has been observed concurrently with CRS.
- With other CAR T cell products, CRS has been reported in a few cases to be associated with findings of macrophage activation syndrome/hemophagocytic lymphohistiocytosis (MAS/HLH), and the physiology of the syndromes may overlap.

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

10.6.1.2. Fever

The possibility of CRS should be considered for all subjects with fever (≥ 38°C or ≥ 100.4°F) following JCAR017 treatment. 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.

10.6.1.3. 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, 2017b) 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 generally occur as CRS is resolving or after CRS resolution.

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

10.6.1.4. 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, cytopenias, 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.

10.6.1.5. 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 pre-medicated with acetaminophen and diphenhydramine (see Section 7.4.3). 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 administration 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 administration; 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

10.6.1.6. Tumor Lysis Syndrome

Both lymphodepleting chemotherapy and JCAR017 may cause tumor lysis syndrome (TLS) in subjects with high disease burden. Subjects should be closely monitored for laboratory evidence of TLS (hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia) (see Appendix E), 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.

10.6.1.7. 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, 2013; Grupp, 2013). Serum immunoglobulin levels will be obtained from all subjects prior to and at various time points following JCAR017 treatment. Hypogammaglobulinemic subjects (serum immunoglobulin G (IgG) < 500 mg/dL) should be considered for intravenous immunoglobulin replacement therapy per institutional guidelines.

10.6.1.8. Uncontrolled T Cell Proliferation

JCAR017 T cells could theoretically proliferate out of control. If uncontrolled JCAR017 T cell proliferation occurs, subjects may be treated with high dose steroids (eg, methylprednisolone 1 to 3 g/day, tapered over 7 days) or lymphodepleting doses of cyclophosphamide (1 to 3 g/m^2 IV). If

an Investigator suspects uncontrolled JCAR017 proliferation, the Sponsor 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.

10.6.1.9. Replication-Competent Lentivirus, Clonality and Insertional Oncogenesis

Lentiviral vectors used in gene transfer are engineered to be replication-defective; however, generation of replication-competent lentiviruses (RCLs) 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 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 (Wang, 2009; Scholler, 2012; McGarrity, 2013). 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.

10.6.1.10. Cytopenias

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

10.6.1.11. Infections

Life-threatening and fatal infections have been observed. Severe infections may include bacterial, fungal (including *pneumocystis jirovecii*), and viral infections (eg, CMV, 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.

10.6.2. Risks Associated with Lymphodepleting Chemotherapy

Subjects receiving JCAR017 will receive fludarabine and cyclophosphamide prior to treatment with JCAR017 to facilitate lymphodepletion and CAR T cell engraftment. Refer to the package

inserts or summary of product characteristics for specific details surrounding the risks of fludarabine and cyclophosphamide.

10.6.3. Risks Associated with Reference Therapies

Subjects randomized to Arm A will receive reference therapy as defined in Section 7.3. Management of toxicities related to the reference therapies should be performed as per local institution practice.

10.6.4. Second Primary Malignancies

New malignancies must be reported as SAEs. This includes any second primary malignancy, regardless of the treatment arm the subject is in. 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 randomization 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.). In the event a subject develops a second primary malignancy, the Sponsor may request a sample for detection of CAR T cell sequence, where applicable (refer to Section 6.3.6).

10.7. 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 Brochure.

In the United States, all suspected unexpected serious adverse reactions (SUSARs) will be reported in an expedited manner in accordance with 21 CFR 312.32.

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 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; In Japan, Celgene KK shall notify the Heads of the Institutes in addition to the Investigators:

- Any AE suspected of being related to the use of IP 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.
- In Japan, measures taken in foreign countries to ensure subject safety, study reports that indicate potential risk of cancer, etc., or biannual SAE report according to the local regulations.

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.

10.8. Adverse Events 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-related reaction;
- Cytokine release syndrome (CRS);
- Neurological toxicity (NT);
- Macrophage activation syndrome (MAS);
- Tumor lysis syndrome (TLS)
- Prolonged cytopenias
- Hypogammaglobulinemia
- Infections
- Autoimmune disorders
- Second primary malignancy (SPM)

Further information regarding the list of AESI can be found in the SAP.

11. DISCONTINUATIONS

11.1. Treatment Discontinuation

The following events are considered sufficient reasons for discontinuing a subject from the investigational product(s):

- Adverse Event
- Withdrawal by subject
- Death
- Lost to follow-up
- Physician decision
- 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 the Sponsor. 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
- Manufacturing failure
- Withdrawal by subject
- Death
- Lost to follow-up
- 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 Celgene/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, IP 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 International Council for Harmonisation (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 laws 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 (ICF) 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 laws.

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/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.

IP 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 consented 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/ 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 screening and randomization;
- 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/Documents

The Investigator must ensure that the records and documents pertaining to the conduct of the study and the distribution of the investigational product are complete, accurate, filed and retained. Examples of source documents include: hospital records; clinic and office charts; laboratory notes; memoranda; subject's diaries or 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 screening/randomization 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;
- IP 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 screening 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 will include on-site visits with the Investigator and his/her staff as well as any appropriate communications by mail, email, fax, or telephone. During monitoring visits, the facilities, investigational product storage area, CRFs, subject's source documents, and all other study documentation will be inspected/reviewed by the Celgene representative in accordance with the Study 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, EMA, Health Canada) 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.

15.3. Product Quality Complaint

A Product Quality Complaint (PQC) is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, purity, or performance of any drug product manufactured by or on behalf of Celgene Corporation after it is released for distribution. Product Quality Complaints may reduce the usability of the product for its intended function or affect performance of the product and therefore pose a significant risk to the patient. Examples of PQCs include (but are not limited to): mixed product, mislabeling, lack of effect, seal/packaging breach, product missing/short/overage, contamination, suspected falsified, tampered, diverted or stolen material, and general product/packaging

damage. If you become aware of a suspected PQC, you are obligated to report the issue immediately. You can do so by emailing [redacted] or by contacting the Celgene Customer Care Center [redacted].

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.

17. REFERENCES

Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst. 1993 Mar 03;85(5):365-76.

Abramson S, Palomba ML, Arnason, JE, Lunning MA, Solomon SR, Farazi T, et al. Lisocabtagene maraleucel (liso-cel) treatment of patients (pts) with relapsed/refractory (R/R) B-cell non-Hodgkin lymphoma (NHL) and secondary CNS lymphoma: Initial results from TRANSCEND NHL 001. J Clin Oncol. 2019 May 20;37(15):7515.

Abramson JS, Gordon LI, Palomba ML, Lunning MA, Arnason JE, Forero-Torres A, et al. Updated safety and long term clinical outcomes in TRANSCEND NHL 001, pivotal trial of lisocabtagene maraleucel (JCAR017) in R/R aggressive NHL. J Clin Oncol. 2018 May 20; 36(15):7505-7505.

Abramson JS, Palomba ML, Gordon L, Lunning MA, Arnason JE, Wang M, et al. High CR rates in relapsed/refractory (r/r) aggressive B-NHL treated with the CD19-directed CAR T cell product JCAR017 (TRANSCEND NHL 001). Hematological Oncology. 2017a May;35(S2):138.

Abramson JS, Palomba ML, Gordon LI, Lunning MA, Arnason JE, Wang M, et al. High Durable CR Rates in Relapsed/Refractory (R/R) Aggressive B-NHL Treated with the CD19-Directed CAR T Cell Product JCAR017 (TRANSCEND NHL 001): Defined Composition Allows for Dose-Finding and Definition of Pivotal Cohort. Blood. 2017b Dec 7;130:581.

Abramson JS, Palomba L, Gordon LI, Lunning M, Arnason J, Forero-Torres A, et al. Transcend NHL 001: Immunotherapy with the CD19-directed CAR T cell product JCAR017 results in high complete response rates in relapsed or refractory B-cell non-Hodgkin lymphoma. Blood. 2016 Dec 01;128(22):4192.

[redacted]

Brentjens RJ, Riviere I, Park JH, Davila ML, Wang X, Stefanski J, et al. Safety and persistence of adoptively transferred autologous CD19-targeted T cells in patients with relapsed or chemotherapy refractory B-cell leukemias. Blood. 2011 Nov 3;118(18):4817-28.

[redacted]

Cairo MS, Bishop M. Tumour lysis syndrome: new therapeutic strategies and classification. Br J Haematol. 2004 Oct;127(1):3-11.

Camicia R, Winkler HC, Hassa PO. Novel drug targets for personalized precision medicine in relapsed/refractory diffuse large B-cell lymphoma: a comprehensive review. Mol Cancer. 2015 Dec 11;14(1):207.

Cheson BD, Ansell S, Schwartz L, Gordon LI, Advani R, Jacene HA, et al. Refinement of the Lugano Classification lymphoma response criteria in the era of immunomodulatory therapy. Blood. 2016 Nov 24;128(21):2489-96.

Cheson BD, Fisher RI, Barrington SF, Cavalli F, Schwartz LH, Zucca E, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol. 2014 Sep 20;32(27):3059-68.

Cheson BD, Pfistner B, Juweid ME, Gascoyne RD, Specht L, Horning SJ, et al. Revised response criteria for malignant lymphoma. J Clin Oncol. 2007 Feb 10;25(5):579-86.

[redacted]

Colleoni M, Giobbie-Hurder A, Regan MM, Thürlimann B, Mouridsen H, Mauriac L, et al. Analyses adjusting for selective cross over show improved overall survival with adjuvant letrozole compared with tamoxifen in the BIG 1-98 Study. J Clin Oncol. 2011 Mar 20; 29(9): 1117–1124.

Couzin J, Kaiser J. Gene therapy. As Gelsinger case ends, gene therapy suffers another blow. Science. 2005 Feb 18;307(5712):1028.

Crump M, Neelapu SS, Farooq U, Van Den Neste E, Kuruvilla J, Westin J, et al. Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR-1 study. Blood. 2017 Oct 19; 130(16):1800-8.

Crump M, Kuruvilla J, Couban S, MacDonald DA, Kukreti V, Kouraoukis CT, et al. Randomized comparison of gemcitabine, dexamethasone, and cisplatin versus dexamethasone, cytarabine, and cisplatin chemotherapy before autologous stem-cell transplantation for relapsed and refractory aggressive lymphomas: NCIC-CTG LY.12. J Clin Oncol. 2014 Nov 1;32(31):3490-6.

Davila ML, Riviere I, Wang X, Bartido S, Park J, Curran K, et al. Efficacy and toxicity management of 19-28z CAR T cell therapy in B cell acute lymphoblastic leukemia. Sci Transl Med. 2014 Feb 19;6(224):224ra25.

Davila ML, Kloss CC, Gunset G, Sadelain M. CD19 CAR-targeted T cells induce long-term remission and B Cell Aplasia in an immunocompetent mouse model of B cell acute lymphoblastic leukemia. PLoS One. 2013 Apr 09;8(4):e61338.

Davila ML, Brentjens R, Wang X, Riviere I, Sadelain M. How do CARs work?: Early insights from recent clinical studies targeting CD19. Oncoimmunology. 2012 Dec 01;1(9):1577-83.

Donahue RE, Kessler SW, Bodine D, McDonagh K, Dunbar C, Goodman S, et al. Helper virus induced T cell lymphoma in nonhuman primates after retroviral mediated gene transfer. J Exp Med. 1992 Oct 01;176(4):1125-35.

Dreyling M, Ghielmini M, Rule S, Salles G, Vitolo U, Ladetto M, et al. Newly diagnosed and relapsed follicular lymphoma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2017 Jul 1;28(suppl 4):iv62-iv71.

Dreyling M, Campo E, Hermine O, Jerkeman M, Le Gouill S, Rule S, Shpilberg O, Walewski J, Ladetto M. Newly diagnosed and relapsed follicular lymphoma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2016 Sep;27(suppl 5):v83-v90.

European Medicines Agency. Guideline on follow-up of patients administered with gene therapy medicinal products. European Medicines Agency [Internet]. European Medicines Agency. 2009 Dec 11. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_001375.jsp&mid=WC0b01ac058002958d.

[redacted]

Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer. 2015 Mar 01;136(5):E359-86.

Food and Drug Administration. Briefing Document — Testing for replication competent retrovirus (RCR)/lentivirus (RCL) in retroviral and lentiviral vector based gene therapy products — Revisiting current FDA recommendations. Food and Drug Administration. 2010. Available from: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/CellularTissueandGeneTherapiesAdvisoryCommittee/UCM232592.pdf.

Food and Drug Administration. Guidance for industry: supplemental guidance on testing for replication competent retrovirus in retroviral vector based gene therapy products and during follow-up of patients in clinical trials using retroviral vectors. Food and Drug Administration [Internet]. Food and Drug Administration. 2006 Oct. Available from: http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/ucm072961.htm.

Gardner RA, Finney O, Annesley C, Brakke H, Summers C, Leger K, et al. Intent-to-treat leukemia remission by CD19 CAR T cells of defined formulation and dose in children and young adults. Blood. 2017 Jun 22;129(25):3322-3331.

Gisselbrecht C, Glass B, Mounier N, Singh Gill D, Linch DC, Tmeny M, et al. Salvage regimens with autologous transplantation for relapsed large B-cell lymphoma in the rituximab era. J Clin Oncol. 2010;28(27):4184-90.

Glimm E, Maurer W, Bretz F. Hierarchical testing of multiple endpoints ingroup-sequential trials. Statist. Med. 2010 Jan 30;29(2):219-228.

Grupp SA, Kalos M, Barrett D, Aplenc R, Porter DL, Rheingold SR, et al. Chimeric antigen receptor-modified T cells for acute lymphoid leukemia. N Engl J Med. 2013 Apr 18;368(16):1509-18.

[redacted]

Hacein-Bey-Abina S, Von Kalle C, Schmidt M, McCormack MP, Wulffraat N, Leboulch P, et al. LMO2-associated clonal T cell proliferation in two patients after gene therapy for SCID-X1. Science. 2003 Oct 17;302(5644):415-9. Erratum in Science. 2003;302(5645):568.

Hamlin PA, Zelenetz AD, Kewalramani T, Qin J, Satagopan JM, Verbel D et al. Age-adjusted International Prognostic Index predicts autologous stem cell transplantation outcome for patients with relapsed or primary refractory diffuse large B-cell lymphoma. Blood. 2003; 102(6):1989-96.

Hay KA, Hanafi LA, Li D, Gust J, Liles WC, Wurfel MM, et al. Kinetics and biomarkers of severe cytokine release syndrome after CD19 chimeric antigen receptor-modified T Cell therapy. Blood. 2017 Nov;130:2295-2306.

[redacted]

Hitz F, Connors JM, Gascoyne RD, Hoskins P, Moccia A, Savage KJ, et al. Outcome of patients with primary refractory diffuse large B cell lymphoma after R-CHOP treatment. Ann Hematol 2015 Aug;94:1839–1843.

[redacted]

Ishak KJ, Proskorovsky I, Korytowsky B, Sandin R, Faivre S, Valle J. Methods for adjusting for bias due to crossover in oncology trials. Pharmacoeconomics. 2014 Jun;32(6):533-46.

Jin H, Tu D, Zhao N, Shepherd LE, Goss PE. Longer-term outcomes of letrozole versus placebo after 5 years of tamoxifen in the NCIC CTG MA.17 trial: Analyses adjusting for treatment crossover. J Clin Oncol. 2012 Mar 1;30(7):718-21.

[redacted]

[redacted]

Klein JP, Moeschberger ML. Survival Analysis: Techniques for Censored and Truncated Data. 1997.

Kochenderfer JN, Somerville RPT, Lu T, Shi V, Bot A, Rossi J, et al. Lymphoma remissions caused by anti-CD19 chimeric antigen receptor T cells are associated with high serum interleukin-15 levels. J Clin Oncol. 2017 Jun 1;35(16):1803-1813.

Kochenderfer JN, Dudley ME, Kassim SH, Somerville RP, Carpenter RO, Stetler-Stevenson M, et al. Chemotherapy-refractory diffuse large B-cell lymphoma and indolent B-cell malignancies can be effectively treated with autologous T cells expressing an anti-CD19 chimeric antigen receptor. J Clin Oncol. 2015 Feb 20;33(6):540-9.

Korhonen P, Zuber E, Branson M, Hollaender N, Yateman N, Katiskalahti T, et al. Correcting overall survival for the impact of crossover via a rank-preserving structural failure time (RPSFT) Model in the RECORD-1 trial of everolimus in metastatic renal-cell carcinoma. J Biopharm Stat. 2012;22(6):1258-71.

[redacted]

Latimer NR, Adams KR, Lambert PC, Crowther MJ, Wailoo AJ, Morden JP, et al. Adjusting for treatment switching in randomized controlled trials – A simulation study and a simplified two-stage method. Stat Methods Med Res. 2017 Apr;26(2):724-751.

Lee DW, Santomasso BD, Locke FL, Ghobadi A, Turtle CJ, Brudno JN, et al. ASTCT consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells. Biol Blood Marrow Transplant. 2019 Apr;25(4):625-38.

Lee DW, Gardner R, Porter DL, Louis CU, Ahmed N, Jensen M, et al. Current concepts in the diagnosis and management of cytokine release syndrome. Blood. 2014 Jul 10;124(2):188-95. Erratum in: Blood. 2015;126(8):1048.

Lenz G, Wright G, Dave SS, Xiao W, Powell J, Zhao H, et al. Stromal gene signatures in large-B-cell lymphomas. N Engl J Med. 2008 Nov 27;359(22):2313-23.

Li YS, Wasserman R, Hayakawa K, Hardy RR. Identification of the earliest B lineage stage in mouse bone marrow. Immunity. 1996 Dec;5(6):527-35.

Li YS, Hayakawa K, Hardy RR. The regulated expression of B lineage associated genes during B cell differentiation in bone marrow and fetal liver. J Exp Med. 1993 Sep 1;178(3):951-60.

Li Z, Dullmann J, Schiedlmeier B, Schmidt M, von Kalle C, Meyer J, et al. Murine leukemia induced by retroviral gene marking. Science. 2002 Apr 19;296(5567):497.

Maloney DG, Abramson JS, Palomba ML, Gordon LI, Lunning MA, Arnason JE et al. Preliminary safety profile of the CD19-directed defined composition CAR T cell product JCAR017 in relapsed/refractory aggressive B-NHL patients: potential for outpatient administration. Blood. 2017 Dec7; 130:1552.

Maude SL, Frey N, Shaw PA, Aplenc R, Barrett DM, Bunin NJ, et al. Chimeric antigen receptor T cells for sustained remissions in leukemia. N Engl J Med. 2014 Oct 16;371(16):1507-17.

McGarrity GJ, Hoyah G, Winemiller A, Andre K, Stein D, Blick G, et al. Patient monitoring and follow-up in lentiviral clinical trials. J Gene Med. 2013 Feb;15(2):78-82.

Modlich U, Kustikova OS, Schmidt M, Rudolph C, Meyer J, Li Z, et al. Leukemias following retroviral transfer of multidrug resistance 1 (MDR1) are driven by combinatorial insertional mutagenesis. Blood. 2005 Jun 01;105(11):4235-46.

Moller MB, Christensen BE, Pedersen NT. Prognosis of localized diffuse large B-cell lymphoma in younger patients. Cancer. 2003 Aug 01;98(3):516-21.

Motzer RJ, Escudier B, Oudard S, Hutson TE, Porta C, Bracarda S, et al. Phase 3 Trial of everolimus for metastatic renal cell carcinoma: Final results and analysis of prognostic factors. Cancer. 2010 Sep 15;116(18):4256-65.

National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®): B-cell lymphomas; V.1.2019. Available from: https://www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf.

Neelapu SS, Locke FL, Bartlett NL, Lekakis L, Miklos D, Jacobson CA, et al. Axicabtagene Ciloleucel CAR T Cell Therapy in Refractory Large B-Cell Lymphoma. N Engl J Med. 2017 Dec 28;377(26)2531-44.

Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982 Dec;5(6):649-55.

Park JH, Geyer, MB, Brentjens RJ. CD19-targeted CAR T cell therapeutics for hematologic malignancies: interpreting clinical outcomes to date. Blood 2016;127(26):3312-20.

Porter DL, Levine BL, Kalos M, Bagg A, June CH. Chimeric antigen receptor-modified T cells in chronic lymphoid leukemia. N Engl J Med. 2011 Aug 25;365(8):725-33.

Rothe M, Modlich U, Schambach A. Biosafety challenges for use of lentiviral vectors in gene therapy. Curr Gene Ther. 2013 Dec;13(6):453-68.

[redacted]

Sadelain M, Brentjens R, Riviere I. The basic principles of chimeric antigen receptor design. Cancer Discov. 2013 Apr;3(4):388-98.

Schiefer AI, Kornauth C, Simonitsch-Klupp I, Skrabs C, Masel EK, Streubel B, et al. Impact of single or combined genomic alterations of TP53, MYC, and BCL2 on survival of patients with diffuse large B-cell lymphomas: A retrospective cohort study. Medicine (Baltimore). 2015 Dec;94(52):e2388.

Scholler J, Brady TL, Binder-Scholl G, Hwang WT, Plesa G, Hege KM, et al. Decade-long safety and function of retroviral-modified chimeric antigen receptor T cells. Sci Transl Med. 2012 May 02;4(132):132ra53.

Schulert GS, Grom AA. Pathogenesis of macrophage activation syndrome and potential for cytokine- directed therapies. Annu Rev Med. 2015;66:145-59.

Schuster SJ, Svoboda J, Chong EA, Nasta SD, Mato AR, Anak O, et al. Chimeric Antigen Receptor T Cells in Refractory B-Cell Lymphomas. N Engl J Med. 2017 Dec 28; 377(26):2545-54.

Siddiqi T, Abramson J, Li D, Brown W, DeVries T, Dave K, et al. Patient characteristics and pre-infusion biomarkers of inflammation correlate with clinical outcomes after treatment with the defined composition, CD19-targeted CAR T cell product, JCAR017. Blood 2017 Dec 07; 130(1):193.

Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA Cancer J Clin. 2016 Jan-Feb;66(1):7-30.

Sorror ML, Maris MB, Storb R, Baron F, Sandmaier BM, Maloney DG, et al. Hematopoietic cell transplantation (HCT)-specific comorbidity index: a new tool for risk assessment before allogeneic HCT. Blood. 2005 Oct 15;106(8):2912-9.

Stamenkovic I, Seed B. CD19, the earliest differentiation antigen of the B cell lineage, bears three extracellular immunoglobulin-like domains and an Epstein-Barr virus-related cytoplasmic tail. J Exp Med. 1988 Sep 01;168(3):1205-10.

Sternberg CN, Hawkins RE, Wagstaff J, Salman P, Mardiak J, Barrios CH et al. A randomised, double-blind phase III study of pazopanib in patients with advanced and/or metastatic renal cell carcinoma: final overall survival results and safety update. Eur J Cancer. 2013 Apr;49(6):1287-96.

Sugimoto M, Ito S, Mashima K, Umino K, Minakata D, Nakano H, et al. Retrospective evaluation of the MEAM regimen as a conditioning regimen before autologous peripheral blood stem cell transplantation for lymphoma in two centers with different dosing schedules of melphalan. Annals of Hematology. 2016 Sep 01;95(9):1513-9.

Swerdlow SH, Campo E, Pileri SA, Harris NL, Stein H, Siebert R, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood. 2016 May 19;127(20):2375-90.

Teras LR, DeSantis CE, Cerhan JR, Morton LM, Jemal A, Flowers CR. 2016 US lymphoid malignancy statistics by World Health Organization subtypes. CACancer J Clin. 2016 Nov 12;66(6):443-59.

Tilly H, Gomes da Silva M, Vitolo U, Jack A, Meignan M, Lopez-Guillermo A, et al. Diffuse large B-cell lymphoma (DLBCL): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2015 Sep;26 Suppl 5:v116-25.

Tilly H, Vitolo U, Walewski J, da Silva MG, Shpilberg O, Andre M, et al. Diffuse large B-cell lymphoma (DLBCL): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2012 Oct;23 Suppl 7:vii78-82.

Turtle CJ, Riddell SR, Maloney DG. CD19-Targeted chimeric antigen receptor-modified T-cell immunotherapy for B-cell malignancies. Clin Pharmacol Ther. 2016a Sep;100(3):252-8.

Turtle CJ, Hanafi LA, Berger C, Hudecek M, Pender B, Robinson E, et al. Immunotherapy of non-Hodgkin's lymphoma with a defined ratio of CD8+ and CD4+ CD19-specific chimeric antigen receptor-modified T cells. Sci Transl Med. 2016b Sep 07;8(355):355ra116.

Van Den Neste E, Schmitz N, Mounier N, Gill D, Linch D, Trneny M, et al. Outcomes of diffuse large B-cell lymphoma patients relapsing after autologous stem cell transplantation: an analysis of patients included in the CORAL study. Bone Marrow Transplant. 2017 Feb;52(2):216-221.

Van Den Neste E, Schmitz N, Mounier N, Gill D, Linch D, Trneny M, et al. Outcome of patients with relapsed diffuse large B-cell lymphoma who fail second-line salvage regimens in the International CORAL study. Bone Marrow Transplant. 2016 Jan;51(1):51-7.

van Imhoff GW, McMillan A, Matasar MJ, Radford J, Ardeshna KM, et al. Ofatumumab versus rituximab salvage chemoimmunotherapy in relapsed or refractory diffuse large B-cell lymphoma: The ORCHARRD study. J Clin Oncol. 2016 Dec 28:JCO2016690198.

Wang X, Chang WC, Wong CW, Colcher D, Sherman M, Ostberg JR, et al. A transgene-encoded cell surface polypeptide for selection, in vivo tracking, and ablation of engineered cells. Blood. 2011 Aug 4;118(5):1255-63.

Wang GP, Levine BL, Binder GK, Berry CC, Malani N, McGarrity G, et al. Analysis of lentiviral vector integration in HIV+ study subjects receiving autologous infusions of gene modified CD4+ T cells. Mol Ther. 2009 May;17(5):844-50.

18. APPENDICES

APPENDIX A. TABLE OF ABBREVIATIONS

Table 9: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
ABC	Activated B-cell like
AE	Adverse event
AESI	Adverse event of special interest
ALL	Acute lymphoblastic leukemia
ALT	Alanine aminotransferase (SGPT)
AraC	Cytarabine
ASCT	Autologous stem cell transplant
ASTCT	American Society for Transplantation and Cellular Therapy
[redacted]	
AUC	Area under the curve
AST	Aspartate aminotransferase (SGOT)
BCNU	Carmustine
BEAM	Carmustine, etoposide, cytarabine, melphalan
β-hCG	Beta-human chorionic gonadotropin
CAR	Chimeric antigen receptor
CD	Cluster of differentiation
cfDNA	Cell-free DNA
CI	Confidence intervals
CLL	Chronic lymphocytic leukemia
CMH	Cochran-Mantel-Haenszel
CMR	Complete metabolic response
CNS	Central nervous system
COO	Cell of origin
CORAL	Collaborative trial in relapsed aggressive lymphoma
Cox-PH	Cox-proportional hazards
CR	Complete response
CRF	Case report form

Table 9: Abbreviations and Specialist Terms (Continued)

Abbreviation or Specialist Term	Explanation
CRP	C-reactive protein
CRR	Complete response rate
CRS	Cytokine release syndrome
CSF	Cerebrospinal fluid
CT	Computed tomography
CTCAE	Common terminology criteria for adverse events
ddPCR	Droplet digital polymerase chain reaction
DHAP	Dexamethasone, cytarabine, and cisplatin
DHL	Double-hit lymphoma
DL	Dose level
DLBCL	Diffuse large B-cell lymphoma
DLT	Dose-limiting toxicity
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic acid
DOR	Duration of response
DSMB	Data safety monitoring board
EBV	Epstein-Barr virus
EC	Ethics Committee
eCRF	Electronic case report form
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
EEA	European Economic Area
EEG	Electroencephalogram
EFS	Event-free survival
EGFRt	Truncated human epidermal growth factor receptor
EMA	European Medicines Agency
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer – Quality of Life C30 Questionnaire
EOS	End of study

Table 9: Abbreviations and Specialist Terms (Continued)

Abbreviation or Specialist Term	Explanation
[redacted]	
ET	Early termination
EU	European Union
[redacted]	
FACT-Lym	Functional Assessment of Cancer Therapy-Lymphoma
FCBP	Female of child bearing potential
FDA	Food and Drug Administration
FDG	Fluorodeoxyglucose
FL	Follicular lymphoma
FL3B	Follicular lymphoma Grade 3B
flu/cy	Fludarabine and cyclophosphamide
gagDNA	Glycosaminoglycan Deoxyribonucleic acid
GCB	Germinal center-like
GCP	Good Clinical Practice
GDP	Gemcitabine, dexamethasone, and cisplatin
GH	Global health
HBcAB	Hepatitis B core antibody
HBsAb	Hepatitis B surface antibody
HBsAg	Hepatitis B surface antigen
HCT-CI	Hematopoietic cell transplantation – specific comorbidity index
HDCT	High dose chemotherapy
HIV	Human immunodeficiency virus
HR	Hazard ratio
HRQoL	Health-related quality of life
HRU	Hospital resource utilization
HSCT	Hematopoietic stem cell transplant
IB	Investigator's brochure
ICF	Informed consent form

Table 9: Abbreviations and Specialist Terms (Continued)

Abbreviation or Specialist Term	Explanation
ICH	International Council for Harmonisation
ICU	Intensive care unit
IFN	Interferon
IHC	Immunohistochemistry
Ig	Immunoglobulin
IND	Investigational New Drug
IP	Investigational product
IPCW	Inverse probability of censoring weighting
IPI	International index prognostic
IRB	Institutional review board
IRC	Independent review committee
IRT	Interactive response technology
IT	Intrathecal
ITT	Intended-to-treat
IUD	Intrauterine device
IV	Intravenous
IVIG	Intravenous immunoglobulins
K-M	Kaplan-Meier
LD	Lymphodepleting
LDH	Lactate dehydrogenase
LTFU	Long-term follow-up
LVEF	Left ventricular ejection fraction
mAb	Monoclonal antibody
MAS	Macrophage activation syndrome
MCNU	Ranimustine
MedDRA	Medical Dictionary for Regulatory Activities
MMSE	Mini Mental State Examination
MRI	Magnetic resonance imaging
MUGA	Multi-gated acquisition scan
NaCl	Sodium chloride
NCCN	National Comprehensive Cancer Network

Table 9: Abbreviations and Specialist Terms (Continued)

Abbreviation or Specialist Term	Explanation
NCI	National Cancer Institute
NCIC	National Cancer Institute of Canada
NHL	Non-Hodgkin lymphoma
NK	Natural killer
NOS	Not otherwise specified
NT	Neurotoxicity
O-DHAP	Ofatumumab, dexamethasone, high dose cytarabine, and cisplatin
ORCHARRD	Ofatumumab versus rituximab salvage chemoimmunotherapy
ORR	Overall response rate
OS	Overall survival
[redacted]	
PCR	Polymerase chain reaction
PD	Progressive disease
PET	Positron emission tomography
PFS	Progression-free survival
PFS-2	PFS on next line of treatment
PK	Pharmacokinetics
PMBCL	Primary mediastinal large B-cell lymphoma
PO	Per os (oral)
PP	Per protocol
PPDP	Protocol Product Deviation Plan
PR	Partial response
PRO	Patient reported outcome
PT	Preferred term
R-CHOP	Rituximab- cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate and prednisone
R-DHAP	Rituximab- dexamethasone, high dose cytarabine (AraC), and cisplatin
R-GDP	Rituximab- gemcitabine, dexamethasone, and cisplatin
R-ICE	Rituximab- ifosfamide, carboplatin, and etoposide
RCL	Replication-competent lentivirus
RNA	Ribonucleic acid

Table 9: Abbreviations and Specialist Terms (Continued)

Abbreviation or Specialist Term	Explanation
RPFST	Rank preserving structural failure time
R/R	Relapsed or refractory
SAE	Serious adverse event
sAAIPI	Secondary age-adjusted International Prognostic Index
SaO_2	Oxygen saturation
SAP	Statistical analysis plan
SSC	Scientific steering committee
scFv	Single chain variable fragments
sCRS	Severe cytokine release syndrome
SD	Stable disease
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SOC	Standard of care
SOC	System organ class
SOP	Standard operating procedure
SPM	Second primary malignancy
SSC	Scientific steering committee
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse events
THL	Triple-hit lymphoma
THRBCL	T cell rich/histiocyte rich large B-cell lymphoma
TLS	Tumor lysis syndrome
TMG	Toxicity management guidelines
TNF	Tumor necrosis factor
TNM	Tumor, nodes, metastasis
ULN	Upper limit of normal
UK	United Kingdom
US/ USA	United States/ United States of America
WHO	World Health Organization

APPENDIX B. PERFORMANCE STATUS BY EASTERN COOPERATIVE ONCOLOGY GROUP SCALE

Table 10: 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.

(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 11: Criteria for Involvement of Site

Tissue Site	Clinical	FDG Avidity	Test	Positive Finding
Lymph nodes	Palpable	FDG-avid histologies	PET-CT	Increase FDG uptake
		Nonavid disease	CT	Unexplained node enlargement
Spleen	Palpable	FDG-avid histologies	PET-CT	Diffuse uptake, solitary mass, miliary lesions, nodules
		Nonavid disease	CT	> 13 cm in vertical length, mass, nodules
Liver	Palpable	FDG-avid histologies	PET-CT	Diffuse uptake, mass
		Nonavid disease	CT	Nodules
CNS	Signs, symptoms		CT	Mass lesion(s)
			MRI	Leptomeningeal infiltration, mass lesions
			CSF assessment	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 12: 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 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 Response (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 sum of perpendicular diameters (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 12: 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 Disease**	**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 12: 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). For the purpose of this trial, while score 3 might represent an early response 1 or 3 months after JCAR017 infusion, it likely reflects remaining active disease at later time points.
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.

(Cheson, 2014).

The integrated response assessment will be performed by the IRC as described in Table 13 and Table 14. Please refer to the Celgene "Guidelines for Efficacy Evaluation in PET-avid Non-Hodgkin Lymphoma" (based on the Lugano classification 2014) for the comprehensive interpretation used by the IRC. This is a stand-alone document.

Table 13: Integrated PET+CT Overall Time Point Response

PET-Staging Overall Response	CT-Staging Overall Response	PET + CT Overall TPR
CMR	CR/PR/SD/NE/PD	CR

Table 13: Integrated PET+CT Overall Time Point Response (Continued)

PET-Staging Overall Response	CT-Staging Overall Response	PET + CT Overall TPR
PMR	CR/PR/SD/NE/PD	PR
NMR	CR/PR/SD/NE/PD	SD
NE[1]	CR/PR/SD + prior PET response of CMR[2]	CR[3]
NE[1]	CR/PR/SD/NE + prior PET response of non-CMR[2]	NE
NA/NE[1]	PD	PD
PMD	CR/PR/SD/NE/PD	PD
NA	NE[4]	NE

Abbreviations: CMR = complete metabolic response, CR = complete response, CT = computed tomography, NA = not applicable, NE = not evaluable, NMR = non metabolic response, PD = progressive disease, PET = positron emission tomography, PMD = progressive metabolic response, PMR = partial metabolic response, PR = partial response, SD = stable disease, TPR = time point response, UNK= unknown.

[1] Non-evaluable PET or missing PET (the terms NE and UNK are equivalent).
[2] "Prior PET response" refers to the latest evaluable PET TPR not equivalent to NE. PET responses may be carried forward over multiple time points.
[3] CR may be carried forward until CT shows progression or is assessed as NE.
[4] No disease present.

Table 14: PET + CT + CNS Time Point Response

PET+CT TPR[1]	CNS TPR	CT + PET + CNS TPR
CR	CR	CR
CR	SD	PR
PR	CR	PR
PR	SD	PR
SD	CR	SD
SD	SD	SD
Any	SD	PD
PD	Any	PD
CR/PR/SD	NA[3]/NE[4]	CR/PR/SD
NE[4]	CR/SD	NE
NE[2]	CR/SD	CR/SD
NE[2,4]	NA[2]/NE[4]	NE

Abbreviations: CNS = central nervous system, CR = complete response, CT = computed tomography, NA = not applicable, NE = not evaluable, PET = positron emission tomography, PD = progressive disease, PR = partial response, SD = stable disease, TPR = time point response.

[1] Integrated PET and CT-staging TPR (see Table 13).

[2] No disease was identified.
[3] NA is used of an exam is not submitted for any timepoint or no disease is identified.
[4] At least one (1) lesion or area of disease cannot be adequately evaluated, or exam is missing but was previously received.

APPENDIX D. 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 E. CAIRO-BISHOP DEFINITIONS OF TUMOR LYSIS SYNDROME

Table 15: 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 hypouricemic agent(s).

Table 16: 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.

Table 17: Cairo-Bishop Grading System for TLS

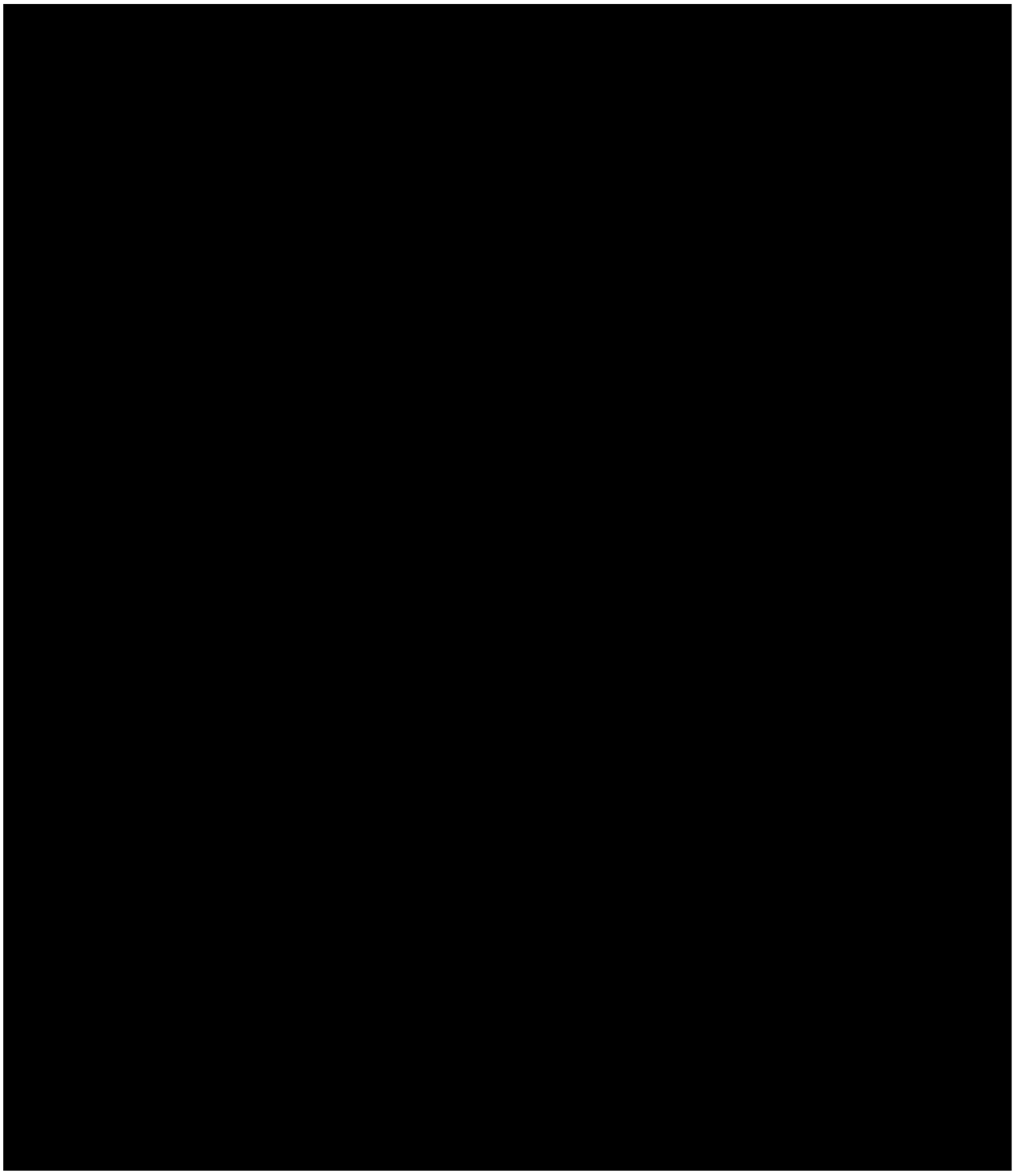
Grade	LTLS	Creatinine	Cardiac Arrhythmia	Seizure
0	-	≤ 1.5 × ULN	None	None
1	+	1.5 × ULN	Intervention not indicated	None
2	+	> 1.5 – 3.0 × ULN	Non-urgent medical intervention indicated	One brief generalized seizure; seizure(s) well controlled or infrequent; focal motor seizures not interfering with ADL

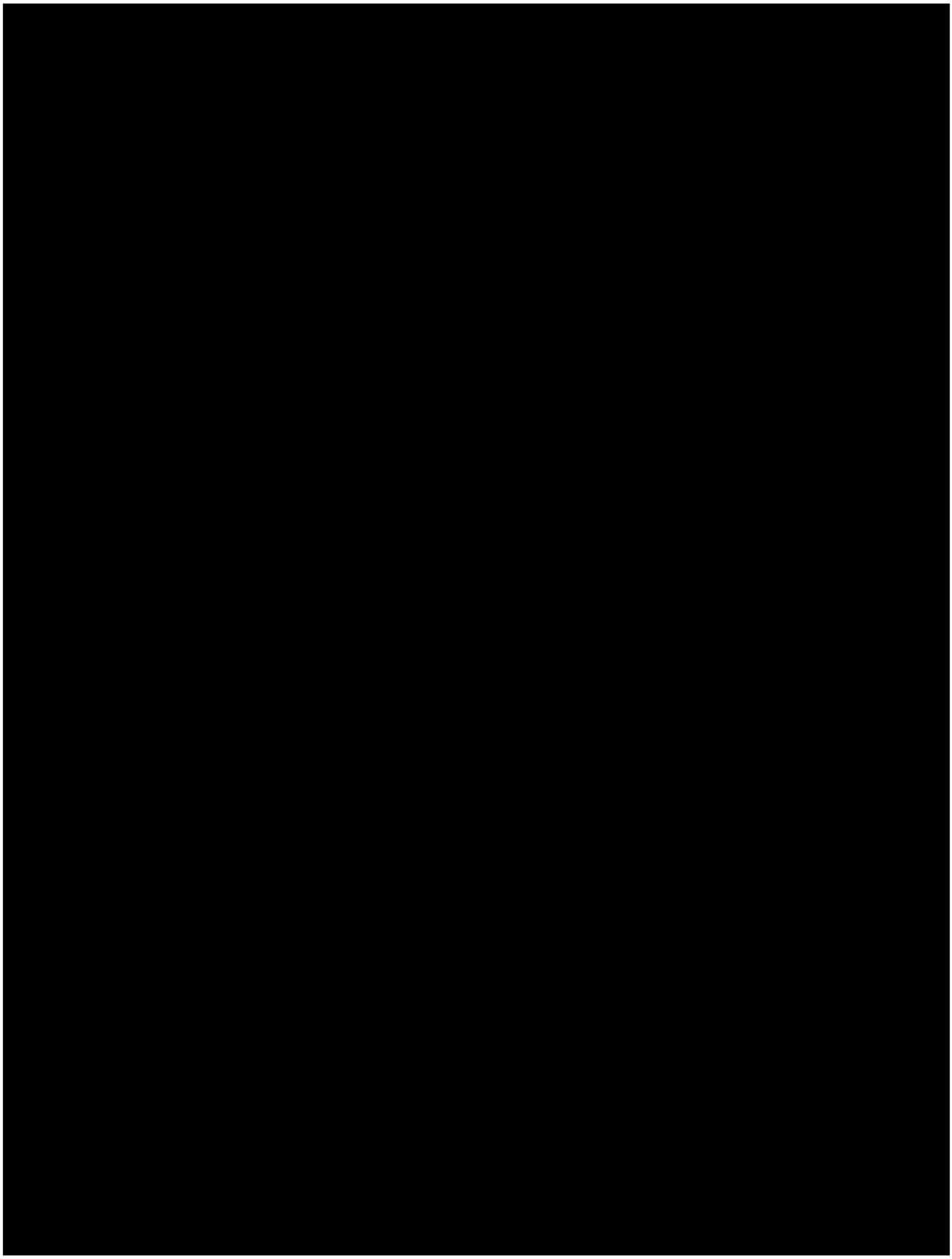
Table 17: Cairo-Bishop Grading System for TLS (Continued)

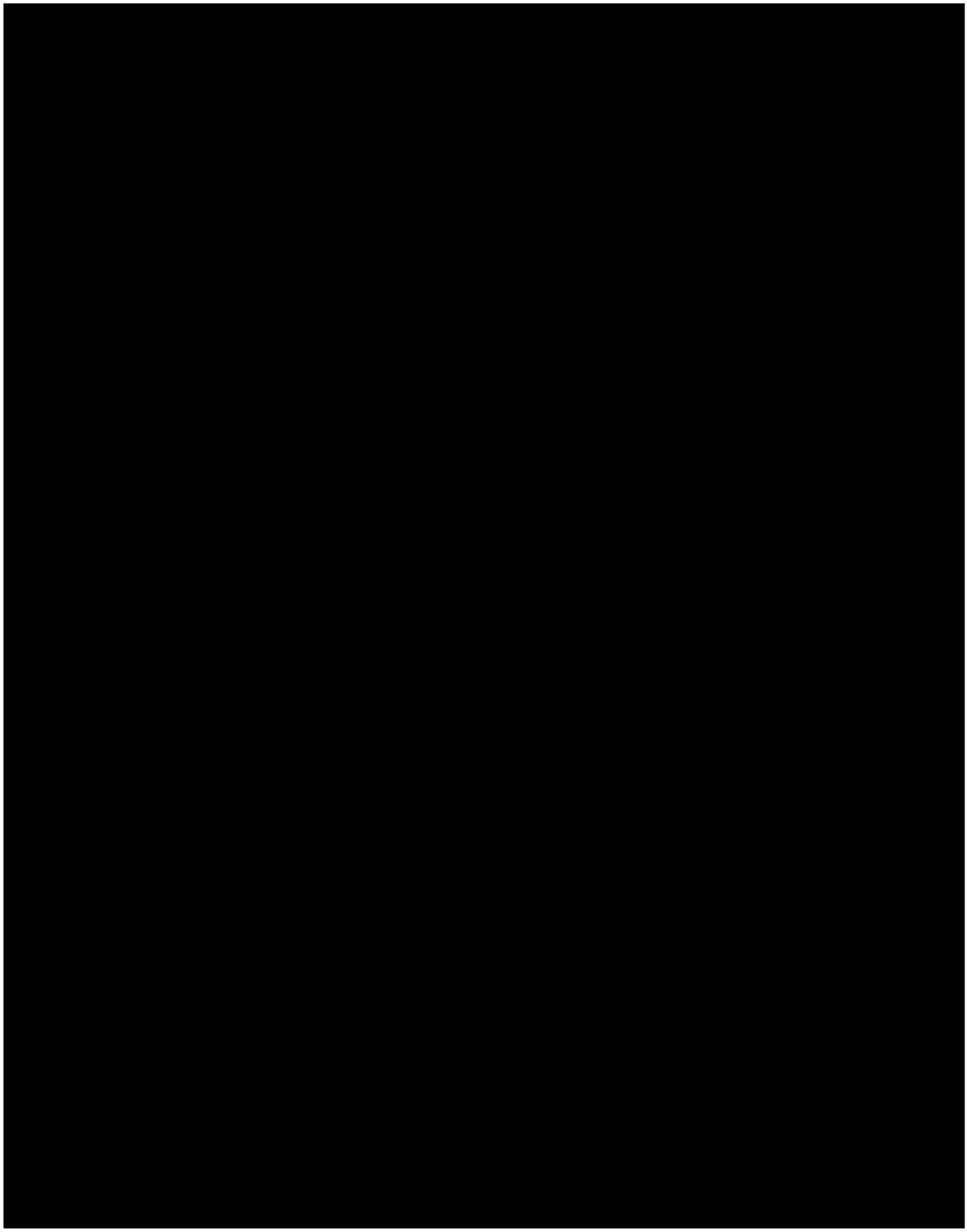
Grade	LTLS	Creatinine	Cardiac Arrhythmia	Seizure
3	+	> 3.0 – 6.0 × ULN	Symptomatic and incompletely controlled medically or controlled with device	Seizure in which consciousness is altered; poorly controlled seizure disorder; breakthrough generalized seizures despite medical intervention
4	+	> 6.0 × 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.
(Cairo, 2004).

APPENDIX F. MINI MENTAL STATE EXAMINATION







APPENDIX G. CLINICAL LABORATORY EVALUATIONS

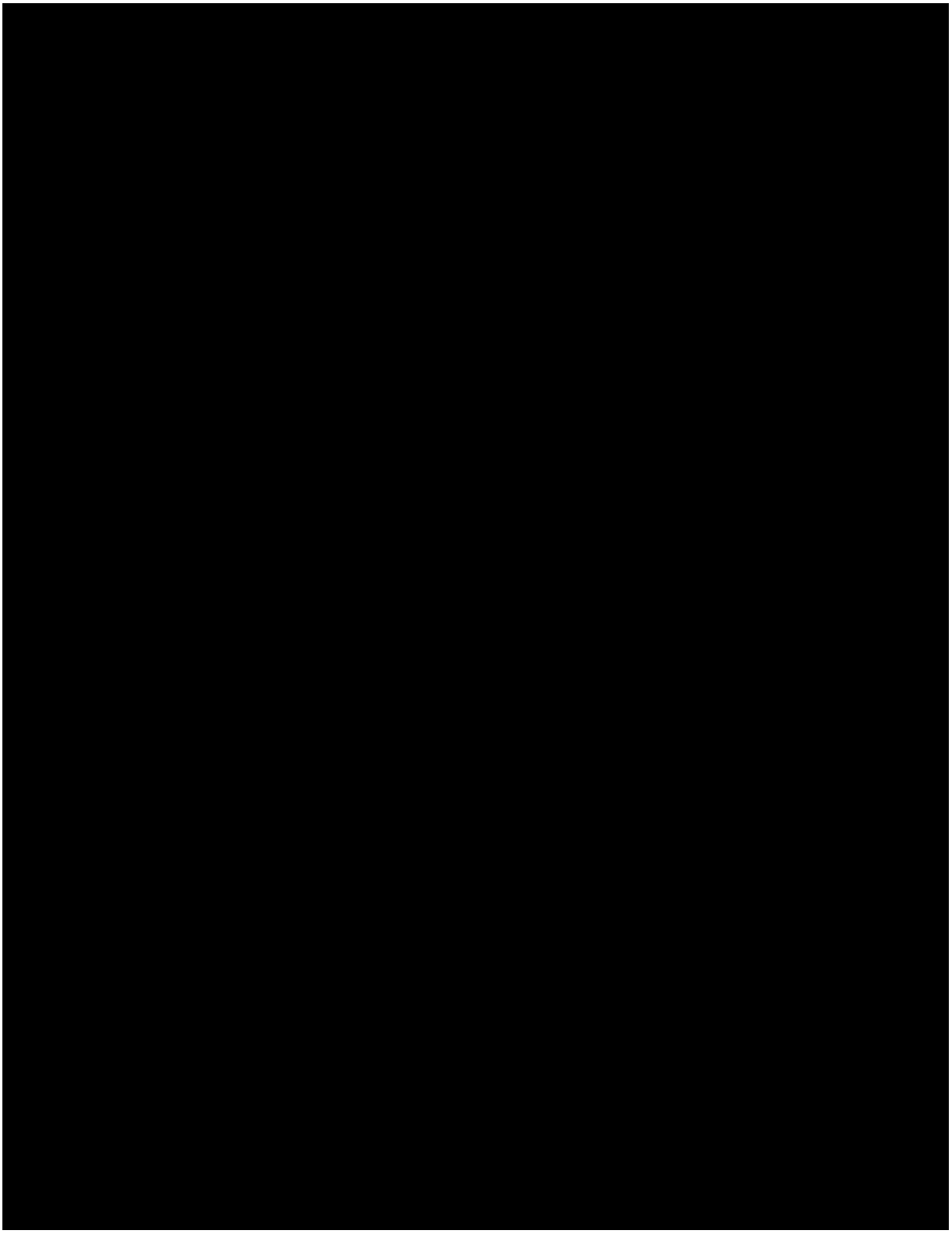
Table 18: Clinical Laboratory Evaluations

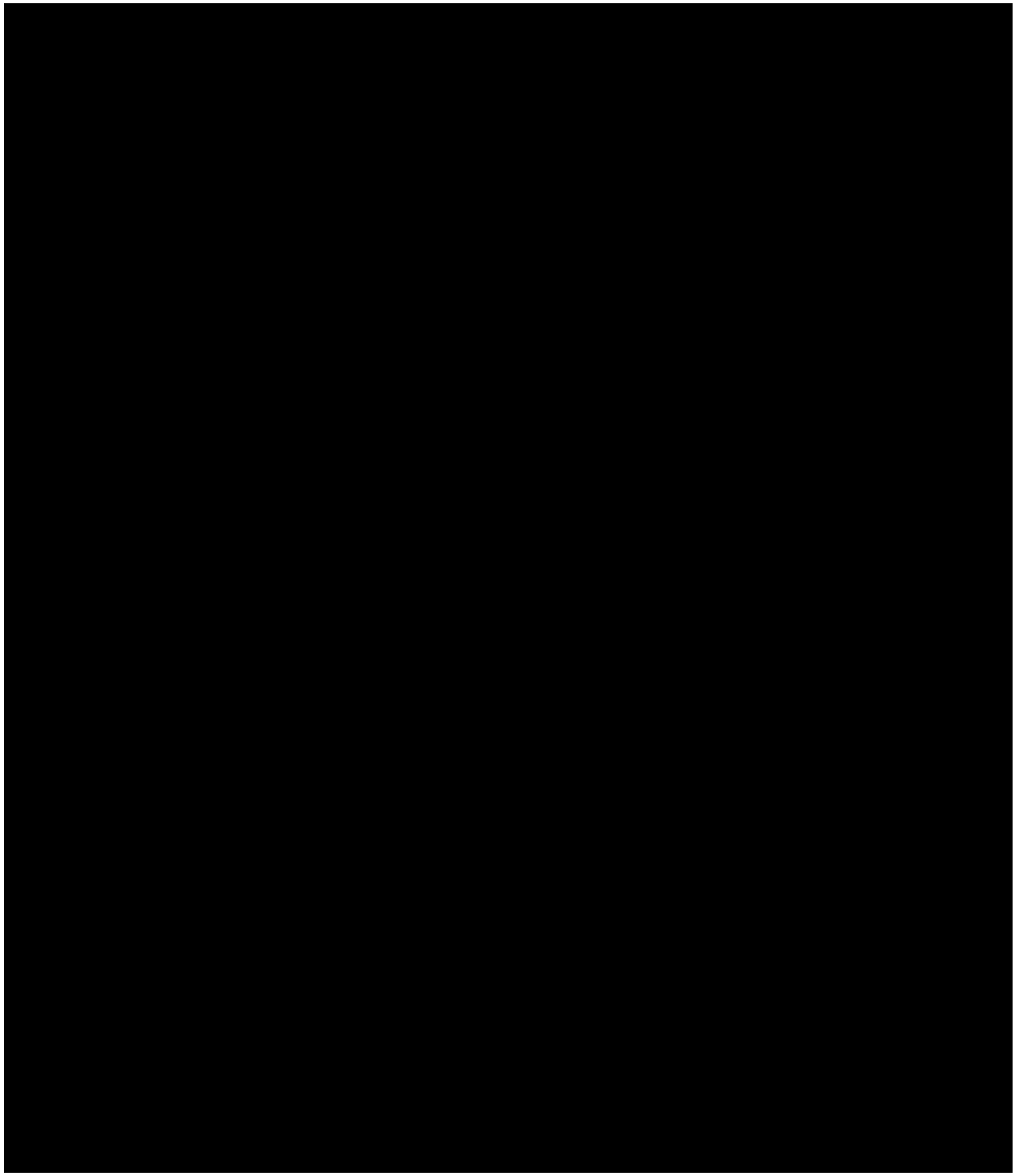
Laboratory Panel	Analytes
Hematology	CBC with differential
Coagulation	PT, aPTT, INR, fibrinogen, and D-dimer
Chemistry	Glucose, BUN, creatinine, sodium, potassium, chloride, calcium, total protein, albumin, total bilirubin, direct bilirubin, alkaline phosphatase, ALT (SGPT), AST (SGOT), magnesium, phosphate, bicarbonate, LDH, β2-microglobulin, uric acid, triglycerides
Immunoglobulins	IgG, IgM, IgA
Viral serology	HIV Hepatitis B (HBsAb, HBsAg, and HBcAb), Hepatitis C (Hep C Ab)
Inflammatory markers	CRP, ferritin
Disease characterization	Histology, cell of origin, immunochemistry, cytogenetics, molecular sub-typing
Cerebrospinal fluid*	RBCs, WBCs with differential, glucose, protein
Urinalysis*	Appearance, pH, specific gravity, protein Glucose, ketones, RBCs, WBCs Casts, crystals, or other components
Pregnancy*	ß-HCG (serum)

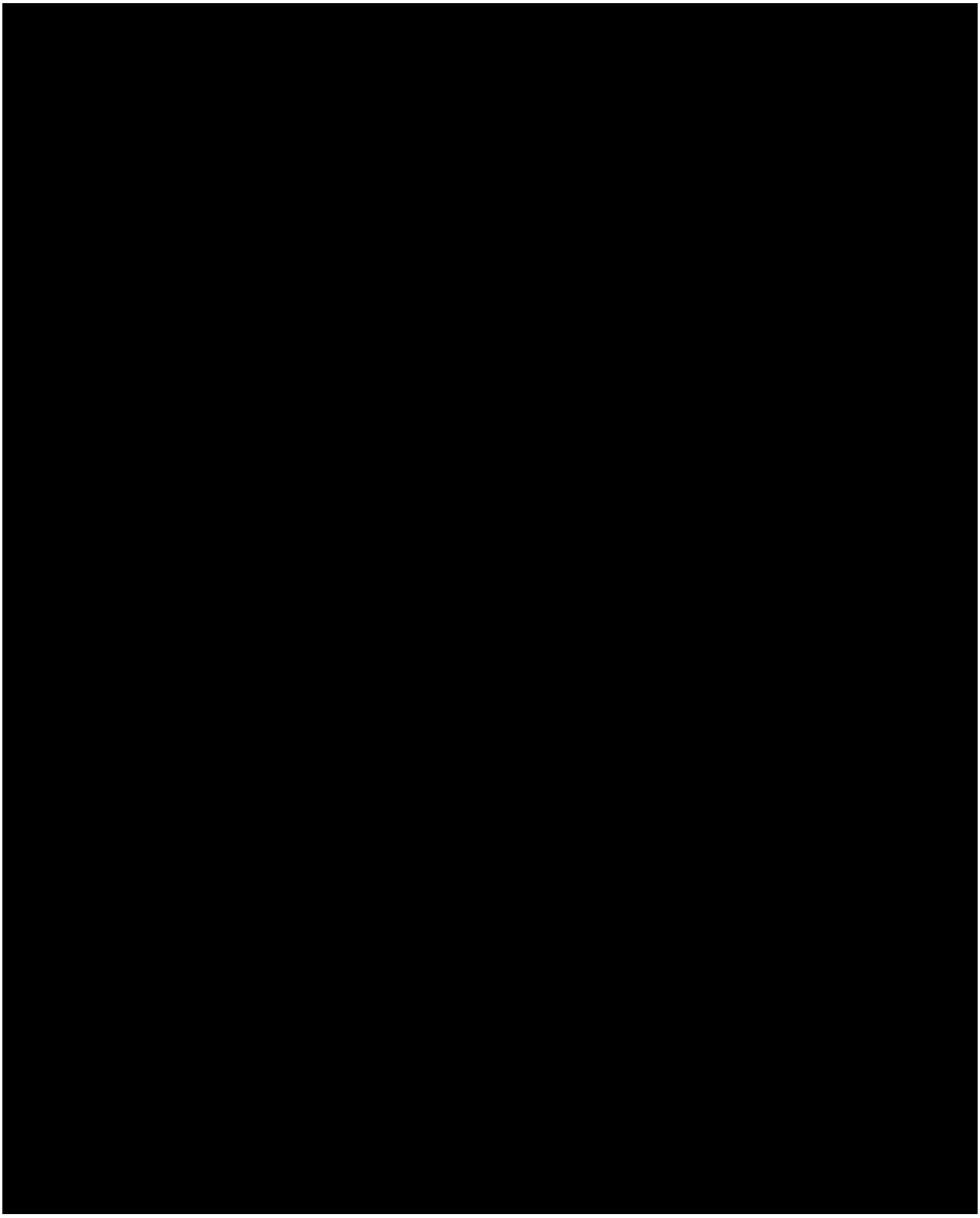
* Local assessment only.

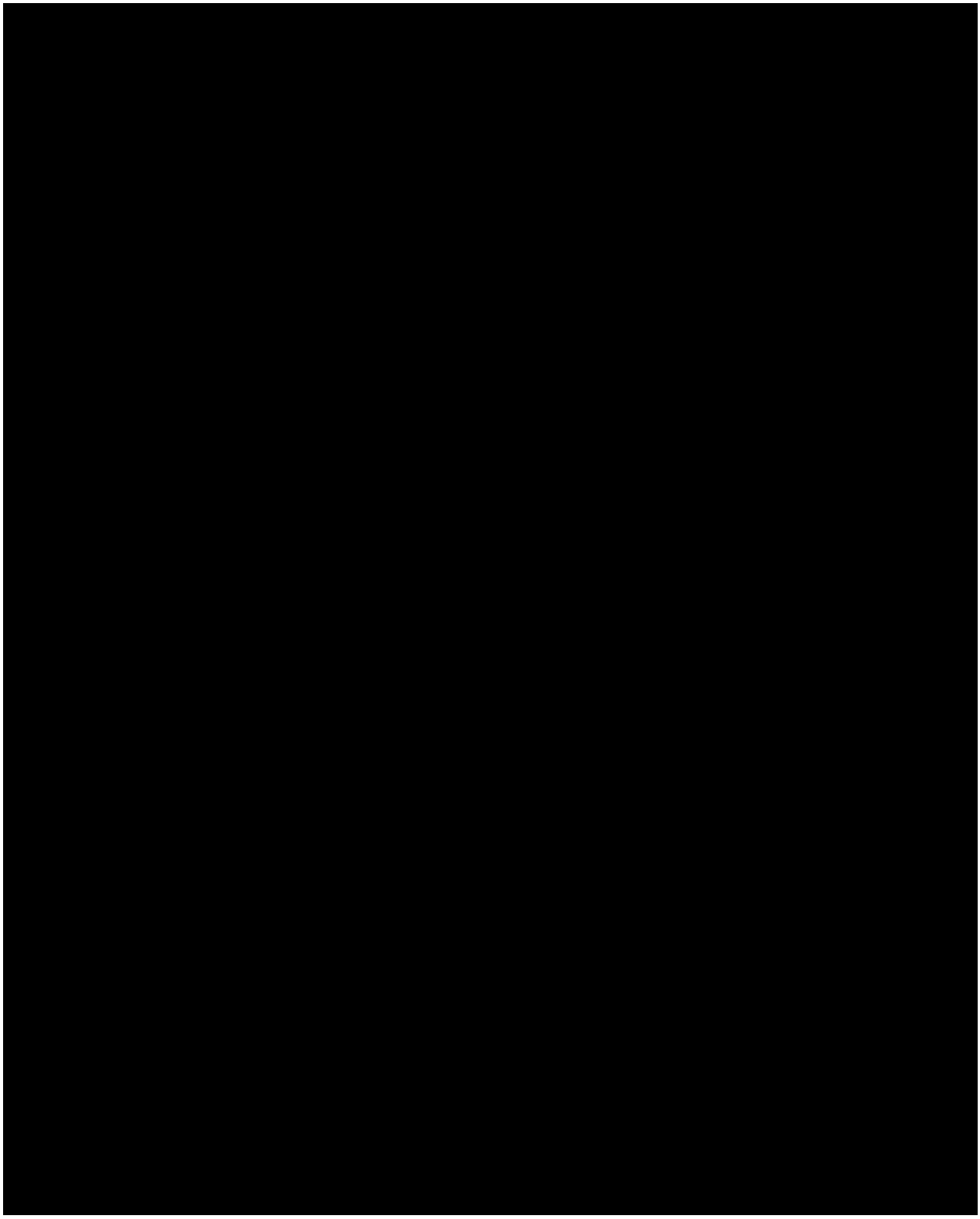
Abbreviations: ALT (SGPT) = alanine aminotransferase (serum glutamic pyruvic transaminase); aPTT = activated partial thromboplastin time; AST (SGOT) = aspartate aminotransferase (serum glutamic oxaloacetic transaminase); BUN = blood urea nitrogen; CBC = complete blood count; CRP = C-reactive protein; FISH = fluorescence in situ hybridization; HBcAb = Hepatitis B core antibody HBsAb = Hepatitis B surface antibody; HBsAg = Hepatitis B surface antibody; HIV= Human Immunodeficiency Virus; HLA = human leukocyte antigen; Ig = immunoglobulin; INR = international normalized ratio; LDH = lactate dehydrogenase; PT = prothrombin time; RBC = red blood cell; WBC = white blood cell.

APPENDIX H. SUBJECT REPORTED OUTCOMES: EORTC QLQ C-30

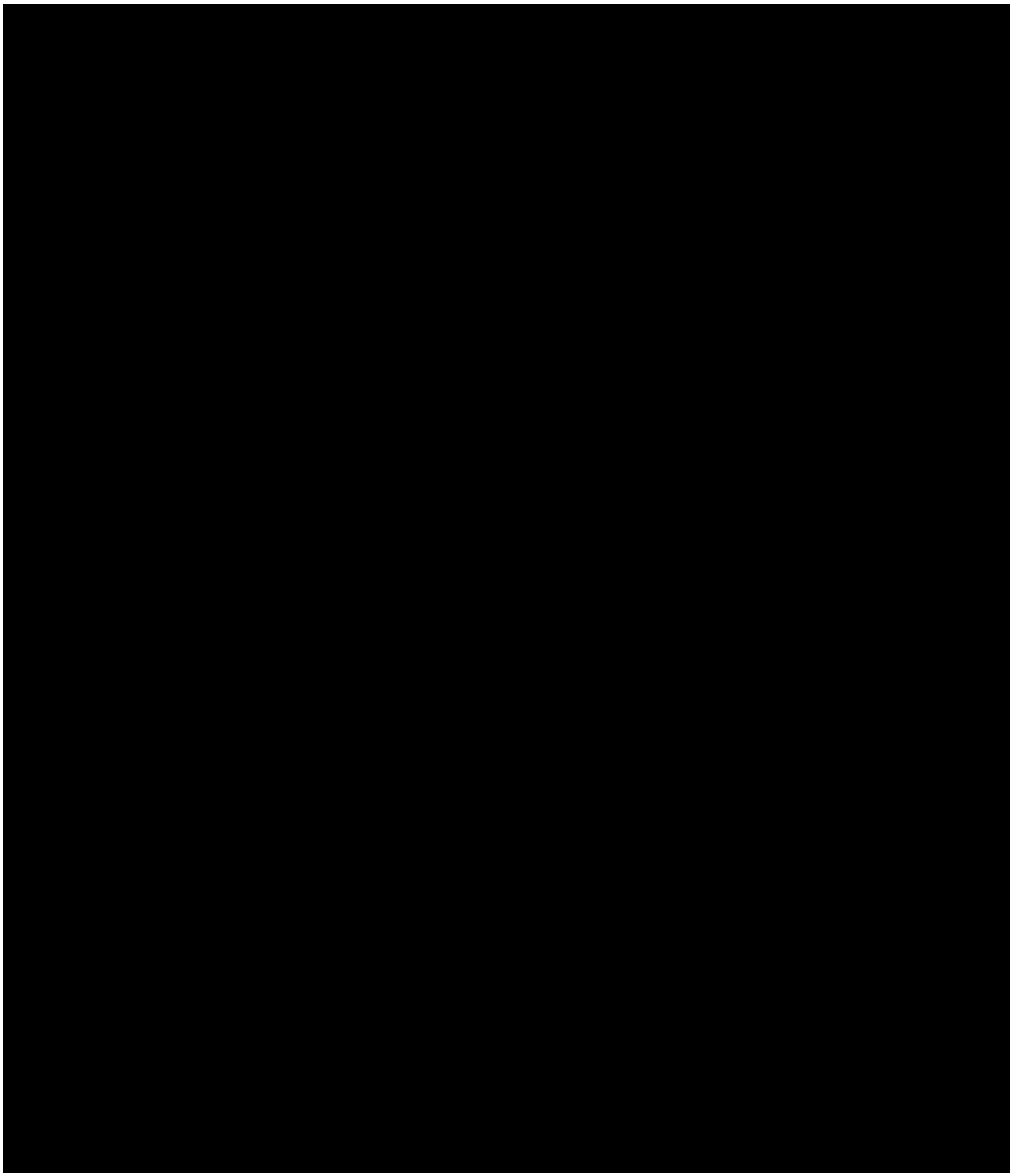








APPENDIX J. SUBJECT REPORTED OUTCOMES: FACT-LYM



APPENDIX K. HCT-CI SCORE CALCULATOR

Co-morbidity	Definition	Yes	Score
Arrhythmia	Atrial fibrillation[a] or		1
	Atrial flutter[a] or		
	Sick sinus syndrome[a] or		
	Ventricular arrhythmia[a]		
Cardiovascular	Coronary artery disease[a] or		1
	Congestive heart failure[a] or		
	Myocardial infarction[a] or		
	Ejection fraction ≤ 50%[b]		
Inflammatory bowel disease	Crohn's disease[a] or		1
	Ulcerative colitis[a] or		
Diabetes	Treated with insulin or oral hypoglycemic drugs[b]		1
Cerebro-vascular	Transient ischemic attacks[a] or		1
	Cerebro-vascular ischemic or hemorrhagic stroke[a]		
Depression/anxiety	Requiring psychological consultation and/or specific treatments[b]		1
Hepatic - mild	Chronic hepatitis[b] AND		1
	Bilirubin > ULN - 1.5 x ULN[b] or		
	AST/ALT > ULN - 2.5 x ULN[b]		
Obesity	Body mass index >35 (adults)[b] or		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 > 177 μmol/L)[b] or		2
	On dialysis[b] or		
	Prior renal transplantation[a]		
Pulmonary - Moderate	Dlco corrected for hemoglobin 66-80% of predicted[b] and/or		2
	FEV1 66-80% of predicted[b] or		
	Dyspnea on slight activity[b]		

Co-morbidity	Definition	Yes	Score
Pulmonary - Severe	Dlco corrected for hemoglobin ≤ 65% of predicted[b] and/or		3
	FEV1 ≤ 65% of predicted[b] or		
	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] AND		3
	Bilirubin > 1.5 x ULN[b] or		
	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.
(Sorror, 2005).

APPENDIX L. 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 Toxicity 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 chimeric antigen receptor (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 cytokine release syndrome (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 2.
- 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 mm Hg	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%	$FiO_2 \geq 40\%$	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.

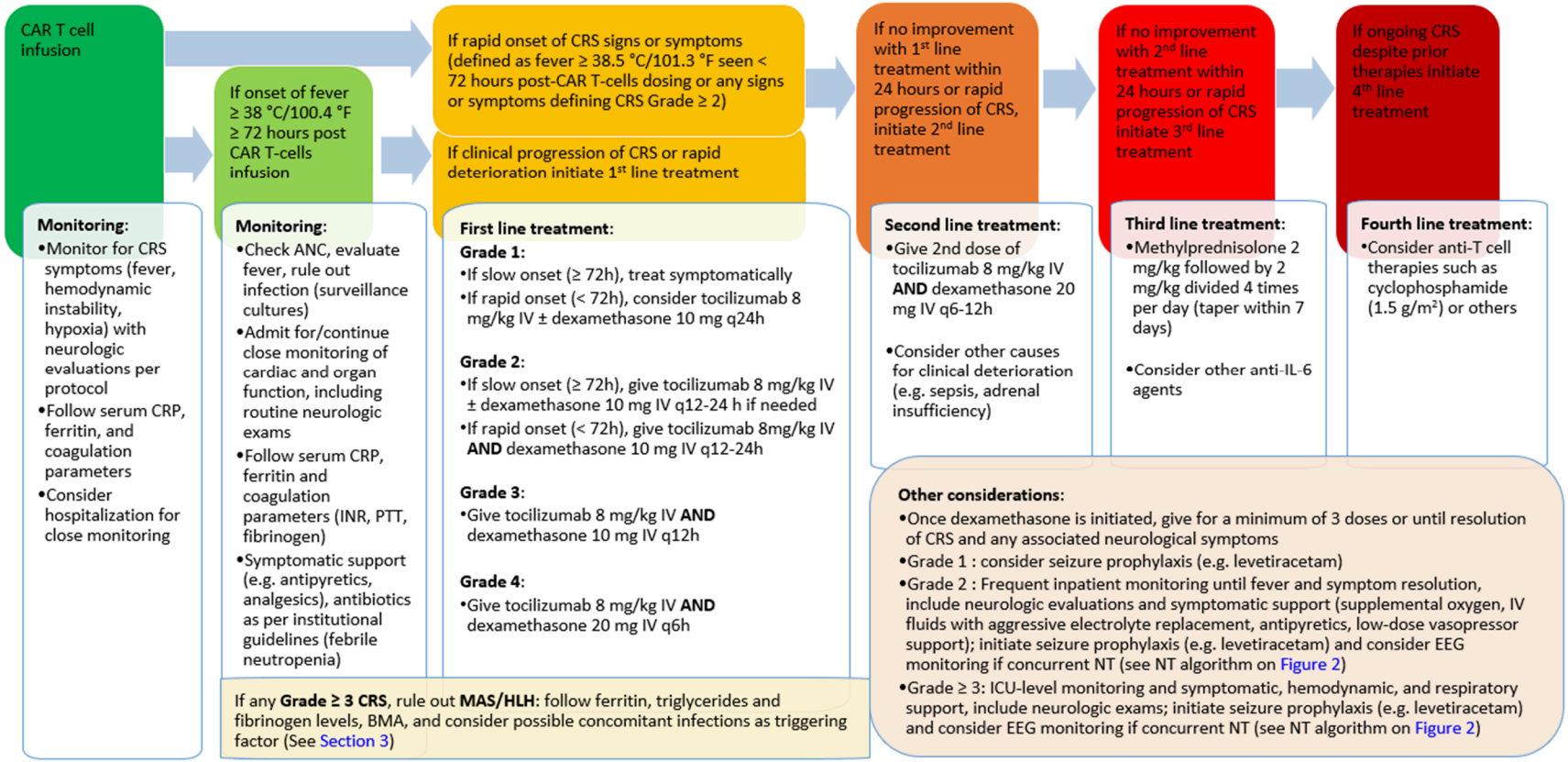
In some cases, tocilizumab, an anti-IL-6R-antibody, may be required to treat toxicities such as severe CRS. Please refer to the currently approved Actemra® prescribing information (US) or

RoActemra® Summary of Product Characteristics (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. RoActemra® 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 RoActemra® Summary of Product Characteristics [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 lymphohistiocytosis; 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).

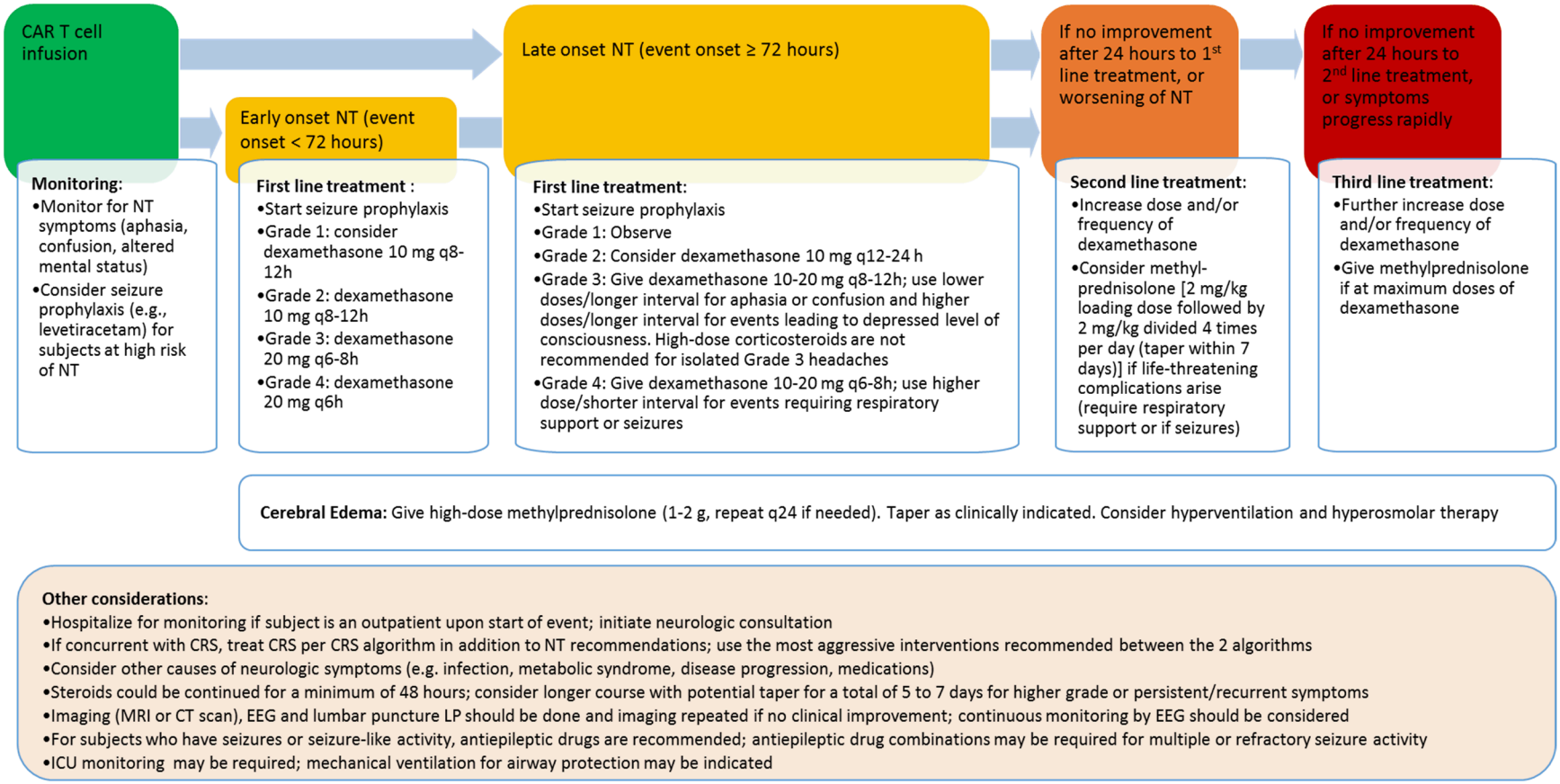
For subjects who have neurologic toxicity in the presence of CRS, the CRS should be managed following the guidelines provided in Figure 1.

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.

5. REFERENCES

Abramson JS, Palomba ML, Gordon LI, Lunning MA, Arnason JE, Wang M, et al. High durable CR rates in relapsed/refractory (r/r) aggressive B-NHL treated with the CD19-directed CAR T cell product JCAR017 (TRANSCEND NHL 001): defined composition allows for dose-finding and definition of pivotal cohort. Blood 2017 Dec 7;130(1) Abstract No. 581.

Actemra® [Prescribing Information]. South San Francisco, USA: Genentech Inc. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/125276s092lbl.pdf

Benedetti FD, Brogan P, Grom A, Quartier P, Schneider R, De Graaf K, et al. OP0204 Emapalumab, an interferon gamma (IFN-Y) blocking monoclonal antibody, in patients with macrophage activation syndrome (MAS) complicating systemic juvenile idiopathic arthritis (SJIA). Annals of Rheumatic Diseases. 2019;78:178.

Brudno JN, Kochenderfer JN. Toxicities of chimeric antigen receptor T cells: recognition and management. Blood 2016;127(26):3321-30.

Davila ML, Riviere I, Wang X, Bartido S, Park J, Curran K, et al. Efficacy and toxicity management of 19-28z CAR T cell therapy in B cell acute lymphoblastic leukemia. Sci Transl Med. 2014 Feb 19;6(224):224-5.

Frey N. Cytokine release syndrome: Who is at risk and how to treat. Best Pract Res Clin Haematol. 2017 Dec;30(4):336-40.

Gardner RA, Finney O, Annesley C, Brakke H, Summers C, Leger K, et al. Intent-to-treat leukemia remission by CD19 CAR T cells of defined formulation and dose in children and young adults. Blood 2017;129(25):3322-3331.

Gust J, Hay KA, Hanafi LA, Li D, Myerson D, Gonzalez-Cuyar LF, et al. Endothelial activation and blood-brain barrier disruption in neurotoxicity after adoptive immunotherapy with CD19 CAR-T Cells. Cancer Discov. 2017 Oct 12. [Epub ahead of print]

Hay KA, Hanafi LA, Li D, Gust J, Liles WC, Wurfel MM, et al. Kinetics and biomarkers of severe cytokine release syndrome after CD19 chimeric antigen receptor-modified T-cell therapy. Blood. 2017 Nov 23;130(21):2295-306.

Heipel M, Smith J, Brown W, Karimi M, Xie B, Li D, et al. Pharmacokinetic, pharmacodynamic and blood analytes associated with clinical response and safety in relapsed/refractory aggressive B-NHL patients treated with JCAR017 [abstract]. Blood. 2017 Dec 7; 130 Suppl 1:2835.

Karakike E, Giamarellos-Bourboulis EJ. Macrophage activation-like syndrome: A distinct entity leading to early death in sepsis. Front Immunol. 2019 Jan 31;10:55.

Lee DW, Gardner R, Porter DL, Louis CU, Ahmed N, Jensen M, et al. Current concepts in the diagnosis and management of cytokine release syndrome. Blood. 2014 Jul 10;124(2):188-195. Erratum in: Blood. 2015;126(8):1048.

Lee DW, Santomasso BD, Locke FL, Ghobadi A, Turtle CJ, Brudno JN, et al. ASTCT consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells. Biol Blood Marrow Transplant. 2019 Apr;25(4):625-38.

Lehmberg K, Nichols KE, Henter JI, Girschikofsky M, Greenwood T, Jordan M, et al. Consensus recommendations for the diagnosis and management of hemophagocytic lymphohistiocytosis associated with malignancies. Haematologica. 2015 Aug;100(8):997-1004.

Locke, FL, Neelapu SS, Bartlett NL, Lekakis LJ, Jabobson CA, Braunschweig I, et al. Preliminary results of prophylactic tocilizumab after axicabtagene ciloleucel (axi-cel; KTE-C19) treatment for patients with refractory, aggressive non-Hodgkin lymphoma (NHL). Blood 2017 Dec 7;130(1): Abstract 1547.

Neelapu SS, Locke FL, Bartlett NL, Lekakis LJ, Miklos DB, Jacobson CA, et al. Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma. N Engl J Med. 2017 Dec 28;377(26):2531-44.

Neelapu SS, Tummala S, Kebriaei P, Wierda W, Gutierrez C, Locke FL, et al. Chimeric antigen receptor T-cell therapy - assessment and management of toxicities. Nat Rev Clin Oncol. 2018 Jan; 15,(1):47–62.

Park JH. Managing Cytokine Release Syndrome. Clinical Care Options Oncology [Internet]. 2017; https://www.clinicaloptions.com/Oncology/Treatment Updates/Managing AEs/Modules/Managing_CRS.aspx.

Ramos-Casals M, Brito-Zerón P, López-Guillermo A, Khamashta MA, Bosch X. Adult haemophagocytic syndrome. Lancet. 2014 Apr 26;383(9927):1503-1516. Erratum in: Lancet. 2014 Apr 26;383(9927):1464.

RoActemra® [Summary of Product Characteristics]. Welwyn Garden City, United Kingdom: Roche Products Limited. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000955/WC500054890.pdf.

Siddiqi T, Abramson JS, Li D, Brown W, Devries T, Dave K, et al. Patient characteristics and pre-infusion biomarkers of inflammation correlate with clinical outcomes after treatment with the defined composition, CD19-targeted CAR T cell product, JCAR017. Blood. 2017; 130(1): Abstract 193.

Turtle CJ, Hanafi LA, Berger C, Gooley TA, Cherian S, Hudecek M, et al. CD19 CAR–T cells of defined CD4+:CD8+ composition in adult B cell ALL patients. J Clin Invest. 2016;126(6):2123-38.

APPENDIX M. SECONDARY AGE ADJUSTED INTERNATIONAL PROGNOSTIC INDEX (SAAIPI)

Assessments	Score
Serum Lactate Dehydrogenase (LDH) *Score 0 if LDH ≤ ULN mg/dL* *Score 1 if LDH >ULN mg/dL*	
Ann Arbor Stage *Score 0 if Stage I/II* *Score 1 if Stage III/IV*	
Karnofsky Performance Status (KPS) *Score 0 if KPS ≥ 80%* *Score 1 if KPS < 80%*	
sAAIPI score	

sAAIPI groups are low risk with score zero, low-intermediate risk with score 1, high-intermediate risk with score 2, and high risk with score 3.

Adapted from Hamlin, 2003.

Celgene Signing Page

This is a representation of an electronic record that was signed electronically in Livelink. This page is the manifestation of the electronic signature(s) used in compliance with the organizations electronic signature policies and procedures.

UserName: [redacted]
Title: [redacted]
Date: Thursday, 12 December 2019, 11:31 AM Eastern Daylight Time
Meaning: Approved, no changes necessary.
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– SUMMARY OF CHANGES –

AMENDMENT NO. 2.0

A GLOBAL RANDOMIZED MULTICENTER PHASE 3 TRIAL TO COMPARE THE EFFICACY AND SAFETY OF JCAR017 TO STANDARD OF CARE IN ADULT SUBJECTS WITH HIGH-RISK, TRANSPLANT-ELIGIBLE RELAPSED OR REFRACTORY AGGRESSIVE B-CELL NON-HODGKIN LYMPHOMAS (TRANSFORM)

INVESTIGATIONAL PRODUCT (IP):	**JCAR017**
PROTOCOL NUMBER:	**JCAR017-BCM-003**
ORIGINAL DATE:	**07 Mar 2018**
AMENDMENT No. 1.0 DATE:	**06 Feb 2019**
AMENDMENT No. 2.0 DATE:	**09 Dec 2019**
EudraCT NUMBER:	**2018-000929-32**

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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

A global protocol amendment was generated for Study JCAR017-BCM-003 [redacted]

- [redacted]
- [redacted]
- [redacted]

The updates introduced with this protocol amendment remain consistent with the scientific advice received [redacted] in December 2017.

[redacted]

Significant changes included in this amendment are summarized below:

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

  There is 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.

  Inclusion criterion #10 was updated to align with the summary of product characteristics (SmPC) and the United States (US) package insert (USPI) pregnancy guidance for cyclophosphamide.

  Revised Sections: 4.2. Inclusion Criteria (criteria #10 to #12), 5. Table of Events (Tables 3 and 4), 6.3.1.1.1. Month 6 (± 10 days), Section 6.3.1.1.2. Months 9, 12, 18, 24, and 36 (± 14 days), 10.4 Pregnancy

- **Exclusion criterion for known allergy to dimethyl sulfoxide (DMSO) or Dextran was added** [redacted]

  Revised Section: 4.3. Exclusion Criteria (criterion #19)

- **Toxicity Management Guidelines were updated to provide information on diagnosis and management of macrophage activation syndrome / hemophagocytic lymphohistiocytosis (MAS/HLH)**

  Cases of MAS/HLH have been described in patients treated with CAR T cell therapies. Guidelines on the background, diagnosis and management of MAS/HLH are provided.

  Revised Section: Appendix L

- **Exclusion of subjects with deep venous thrombosis (DVT) and/or pulmonary embolism (PE) within 3 months of leukapheresis and/or DVT or PE that requires ongoing therapeutic levels of anticoagulation and tumor invasion or venous or arterial vessels were updated**

  [redacted]

  Revised Sections: Section 4.3 Exclusion Criteria (criteria #15 and #16), Section 6.2.3.2 Arm B, Section 6.2.4.2 Arm B

This amendment includes the following minor changes that are not specific to the above major changes:

- Medical Monitor/Emergency Contact information updated – Medical Monitor/Emergency Contact information section
- 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 – Protocol Summary, Section 2 (Table 1 and Table 2)

[redacted]

- Addition made regarding the calculation of time of relapse for consistency with the note in Section 4.2 inclusion criterion #6 – Protocol Summary
- Update wording from enrollment to screening – Protocol Summary, Section 9.8.2, Section 9.9.2, Section 13.8, Section 14.3, Section 15.1

- Clarification made regarding the expected schedule for ifosfamide for R-ICE regimen - Protocol Summary, Section 7.4.1
- Update of the dose levels of JCAR017 to be displayed in 10^6 as per program decision – Protocol Summary, Section 1.2.4, Section 1.3.3, Section 7.4.5
- Clarification made that the efficacy assessments performed for the study by the independent review committee (IRC) will be done as per the Celgene "Guidelines for Efficacy Evaluation in PET-avid Non-Hodgkin Lymphoma" which is based on "The Lugano Classification" – Protocol Summary, Section 2 (Table 2), Section 6.5, Section 9.6.1
- Update of the list of adverse events of special interest – Protocol Summary, Section 10.8
- Update wording from enrollment to randomization/randomized – Protocol Summary, Section 3.1, Section 4.2, Section 4.3, Section 9.3.1, Section 9.8.2, Section 13.8, Section 14.3
- Number of subjects for the SCHOLAR-1 meta-analysis updated from 635 to 636 – Section 1.1
- Update made regarding the approvals of CD19-directed CAR T-cell therapies – Section 1.2.2
- Reference updated with latest data – Section 1.2.4
- Update made to have pharmacokinetic profile of JCAR017 its own objective – Section 2 (Table 1)

- Update made to clarify that stem cell collection in Arm A is not only to be performed in responding patients and that a prior collection can be used for the study – Section 3.1, Section 5 (Table 3), Section 6.2.2
- Overall study design figure updated to show "LD" in the black box – Section 3.1 (Figure 1)
- Clarification made to the inclusion criterion #5 regarding the tumor biopsy requirement for refractory subjects – Section 4.2 and Section 6.1.1
- Clarification made to the inclusion criterion #6 regarding the definition of refractory disease and relapsed disease – Section 4.2
- Clarification made to the inclusion criterion #7 regarding required Deauville score – Section 4.2
- Clarification made to the exclusion criterion #6 to clarify that subjects with transformation from chronic lymphocytic leukemia/small lymphocytic lymphoma (Richter transformation) are not allowed in the study – Section 4.3
- Update made to exclusion criterion #10 to clarify the virology results which exclude subjects from being eligible to the study – Section 4.3
- Screening period was extended from 21 to 28 days and randomization window was extended from 2 to 3 days – Section 5 (Table 3), Section 6.1.1, Section 6.2.1

[redacted]

- Addition of peripheral blood sample for detection of B-cell aplasia by flow cytometry – Section 5 (Tables 3 and 4), Section 6
- Update made to have body surface calculation done for Arm A as well at randomization – Section 5 (Table 3), Section 6.2.1
- Requirement added for daily MMSE for Arm B subjects in case of neurologic symptoms as supported by the investigator letter dated 11 Jul 2019 – Section 5 (Tables 3 and 4), Section 6.2, Section 6.4.5
- Clarification made regarding how visits are to be scheduled for Arm B subjects after Day 29 – Section 5 (Table 3), Section 6.2.5

[redacted]

- Clarification made on how Day 126 is to be scheduled for Arm A subjects – Section 6.2.14
- Removal of Month 5 from the list of visits as per Protocol Amendment 1.0 this visit was removed from the table of event – Section 6.3.1
- Removal of Month 5 from the list of visits as per Protocol Amendment 1.0 this visit was removed from the table of event – Section 6.3.1
- Update made regarding the replication-competent lentivirus (RCL) and viral vector collection - Section 6.3.1.2

[redacted]

- Update done to the list of the unscheduled evaluations – Section 6.3.3
- Update wording from new malignancies to second primary malignancies – Section 6.3.6, Section 6.4.10, Section 6.4.11, Section 10.2.1, Section 10.6.4
- Update done to the analysis performed on the cerebrospinal fluid for alignment with Appendix G - Section 6.4.6

[redacted]

- Clarification made about the use of a central laboratory for the study – Section 6.4.12
- Addition of sections about additional and optional research – Section 6.7.3
- Addition of details regarding the exception use of non-conforming product – Section 7.4.6.2
- Clarification made about the requirements for concomitant medication and procedures reporting align within the other JCAR017 studies – Section 8.1 and Table 5
- Clarification provided regarding the allowed local radiation and timing prior to lymphodepleting chemotherapy– Section 8.1

- Clarification provided regarding the allowed steroid doses – Section 8.2
- Clarification about the prohibited concomitant medications for subjects infused with JCAR017 – Section 8.2.1
- Clarification made regarding the baseline definition for statistical analysis – Section 9.1
- Update made to the per-protocol analysis set to further define the selected elements – Section 9.2.3

- Addition of 2 new analysis set: JCAR017-Treated Analysis Set and Health-related Quality of Life Analysis Set – respectively Section 9.2.7 and Section 9.2.8
- Minor rewording of the sample size calculation and sample size robustness and sensitivity description – Section 9.3, Section 17
- Clarifications made on the subgroup analyses – Section 9.6.4
- Minor rewording of the treatment exposure description – Section 9.7.1
- Clarifications made regarding the laboratory evaluations and how they will be used for the analyses – Section 9.7.3
- Clarifications made regarding the 2 different interim analyses – Section 9.8
- Update made to specify pharmacokinetic as part of the exploratory analysis – Section 9.9.5
- Clarifications added to the statistical analysis of patient reported outcomes – Section 9.9.6
- Clarifications added to the statistical analysis of hospital resource utilization – Section 9.9.7
- Addition of conditions to be reported as SAEs regardless of relationship to study drug – Section 10.1 (Table 8)
- Clarification of management of toxicities associated with JCAR017 – Section 10.6.1
- Some literature references were updated and added – Protocol body, Section 17
- Update to include the integrated positron emission tomography (PET) and computed tomography (CT) response assessment performed by IRC based on heath authority's requirement – Appendix C (Tables 13 and 14)
- New abbreviations added – Section 18, Appendix A
- Typographical errors corrected
- Style and formatting updated

– SUMMARY OF CHANGES –

AMENDMENT NO. 1.0

A GLOBAL RANDOMIZED MULTICENTER PHASE 3 TRIAL TO COMPARE THE EFFICACY AND SAFETY OF JCAR017 TO STANDARD OF CARE IN ADULT SUBJECTS WITH HIGH-RISK, TRANSPLANT-ELIGIBLE RELAPSED OR REFRACTORY AGGRESSIVE B-CELL NON-HODGKIN LYMPHOMAS (TRANSFORM)

INVESTIGATIONAL PRODUCT (IP):	**JCAR017**
PROTOCOL NUMBER:	**JCAR017-BCM-003**
ORIGINAL DATE:	**07 Mar 2018**
AMENDMENT No. 1.0 DATE:	**06 Feb 2019**
EudraCT NUMBER:	**2018-000929-32**

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(Mobile) [redacted]
E-mail: [redacted]

CELGENE THERAPEUTIC AREA HEAD SIGNATURE PAGE

{See appended electronic signature page}	
Signature of Celgene Therapeutic Area Head	**dd mmm yyyy**
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

A global protocol amendment was generated for Study JCAR017-BCM-003 [redacted]

- [redacted]
- [redacted]
- [redacted]

The updates introduced with this protocol amendment remain consistent with the scientific advice received [redacted] in December 2017.

[redacted]

Significant changes included in this amendment are summarized below:

- **Eligibility broadened to include additional subtypes of relapsed/refractory (R/R) aggressive non-Hodgkin lymphomas**

The addition of primary mediastinal (thymic) large B-cell lymphoma [PMBCL], T cell/histiocyte-rich large B-cell lymphoma [THRBCL] is based on the fact that these histologies have similar biological behavior, are treated according to the DLBCL treatment algorithm, and supporting preliminary data are available from Study 017001.

Revised Sections: Protocol Summary, Section 1.1 Disease Background, Section 1.3.2 Rationale for the Study Design, Section 4.2 Inclusion Criteria and Section 4.3 Exclusion Criteria

- **Event-free survival (EFS) and progression-free survival (PFS) definitions were modified**

"Event-free survival (EFS): Time from randomization to death from any cause, progressive disease (PD), failure to achieve complete response (CR) or partial response (PR) by 9 weeks post-randomization, or start of new antineoplastic therapy due to efficacy concerns, whichever occurs first"

"Progression-free survival (PFS): Time from randomization to PD or death from any cause, whichever occurs first"

Revised Sections: Protocol Summary, Section 2 Study Objectives and Endpoints, Section 9.6 Efficacy Analysis

- **Study Design was updated**

In Arm A standard of care (SOC), subjects will receive 3 cycles and the cycle time has been updated from 28 days to 21 days that is in line with clinical practice. Accordingly start of high dose chemotherapy (HDCT) has been moved from Day 85 to Day 71. The first efficacy assessment has been moved from Day 57 to Day 64; the second efficacy assessment has been moved from Day 113 to Day 126. Table of events was updated accordingly; main additional changes are listed below:

- Study Day 106 replaced by Day 102
- PET added for Arm B at Day 22 and PET and CT/MRI removed at Month 3 for Arm A.
- Month 5 visit has been removed
- Visit windows adjusted

Revised Sections: Protocol Summary, Section 3.1 Study Design, Section 5 Table of Events, Section 6 Procedures, Section 7.4.1 Reference Therapies

- **Crossover criteria were updated**

In order to ensure patients who responded to salvage chemotherapy will receive HDCT and HSCT and to reflect the new definition of EFS, cross over rules have been modified. Crossing over is now allowed after failure to achieve CR or PR by 9 weeks post-randomization, progression at any time, and start of a new antineoplastic therapy due to efficacy concerns after 18 weeks post- randomization.

Revised Sections: Protocol Summary, Section 3.1 Study Design, Section 6.3.2 Assessments for Subjects Crossing Over to JCAR017

- **Recommendation for the selection of subjects with secondary central nervous system (CNS) involvement was added. In addition, intrathecal (IT) treatment is now allowed for these patients.**

Existing note in inclusion criteria 5 was further detailed to clarify that 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. Details regarding IT administration was added.

Revised Section: Protocol Summary, Section 4.2 Inclusion Criteria, Section 4.3 Exclusion Criteria, Section 6.2.3.2 Arm B, Section 8.1 Permitted Concomitant Medications and Procedures, Section 8.2 Prohibited Concomitant Medications and Procedures

- **Definition of adequate organ function in inclusion criteria 8 was updated to ensure that subjects will be able to complete salvage chemotherapy followed by high dose chemotherapy (HDCT) and hematopoietic stem cell transplant (HSCT)**

Adequate bone marrow function was defined as absolute neutrophil count (ANC) $\geq 1.0 \times 10^9$ cells/L and platelets $\geq 50 \times 10^9$ cells/L in absence of bone marrow involvement. Creatinine clearance must be >45 mL/min and $FEV_1 \geq 50\%$.

Revised Section: Section 4.2 Inclusion Criteria

- **Use of systemic immunostimulatory agents added to the list of excluded medications in the exclusion criteria**

Revised Section: Section 4.3 Exclusion Criteria

- **Additional eligibility checklist prior to administration of HDCT/HSCT was added**

Revised Section: Section 6.2.10.1 Arm A

- **Change to allow radiotherapy after completion of per protocol treatment in both arms to sites of previous PET positive disease**

Revised Sections: Section 8.1 Permitted Concomitant Medications and Procedures, Section 8.2 Prohibited Concomitant Medications and Procedures.

- **Clarification was done on the methodology used for sample size calculation**

Revised Section: Section 9.3.1 Sample Size Calculation

- **Clarification was added that cetuximab is not indicated for the treatment of cytokine release syndrome (CRS) or neurotoxicity**

Revised Sections: Section 10.6.1.1 Cytokine Release Syndrome and Section 10.6.1.3 Neurologic Toxicities

- **Inclusion criterion 4 was restricted to Eastern Cooperative Oncology Group (ECOG) performance status ≤ 1**

[redacted]

Revised Sections: Section 4.2 Inclusion Criteria

- **Subjects with deep venous thrombosis (DVT) and/or pulmonary embolism (PE); and vascular tumor invasion will not be eligible**

[redacted]

Revised Section: Section 4.3 Exclusion Criteria and Section 8.1 Permitted Concomitant Medications and Procedures

This amendment includes the following minor changes that are not specific to the above major changes:

- IND number added – Cover page
- Medical monitor added – Medical Monitor/Emergency Contact information section
- Addition made for consistency with Section 9.6.1 to indicate that hazard ratio and its confidence interval will be estimated using a stratified Cox-proportional hazard – Protocol summary
- Update wording from enrolled to consented –Section 13.6
- Addition of 36 months after randomization timepoint to compare efficacy rates (EFS, PFS, OS) – Protocol Summary, Section 2

[redacted]

- Clarification made on how to calculate time of relapse for inclusion criteria 6 – Section 4.2
- Exclusion criterion 14 revised to include cerebral edema and remove paresis – Section 4.3

- Update of the method to be used to determine the presence of the viral vector from quantitative polymerase chain reaction (qPCR) to droplet digital polymerase chain reaction (ddPCR). [redacted] Detection of vector sequence in two consecutive visits will result in additional analysis on the pattern for vector integration sites – [redacted] Section 5 Table of Events, Section 6.1.1, Section 6.2.4.2, Section 6.2.5, Section 6.2.6, Section 6.2.7, Section 6.2.8, Section 6.2.9, Section 6.2.10, Section 6.2.11, Section 6.3.1, Section 6.3.3, Section 6.4.11 and Section 6.6.1

[redacted]

- Clarification made that assessments required at randomization must be done prior to receiving study treatment – Section 6.2.1
- Criteria for start of LD chemotherapy and infusion of JCAR017 has been updated to exclude patients with rapid disease progression – Section 6.2.3.2 and Section 6.2.4.2
- Clarification added in regard to vital signs for alignment with Section 7.4.5 JCAR017 Administration – Section 6.2.4.2
- Addition of pregnancy tests at Month 36 or end of study (EOS) – Section 5, Section 6.3.1.1.2 and Section 6.3.1.2

[redacted]

- Follow-up in case of disease recurrence or new malignancy was further detailed - Section 6.3.6 and Section 6.4.11
- The definition of timing of pseudoprogression was updated – Section 6.5.1
- Clarification added to explain that only the subscale of the Functional Assessment of Cancer Treatment-Lymphoma (FACT-Lym) questionnaire will be administered in the study because other topics are covered by the EORTC QLQ-C30 – Section 6.8.3
- Corrections done in the scheduling of R-ICE standard of care (SOC) regimen and HDCT – Protocol Summary, Section 7.4.1
- Clarification in regard to the standard of care scheduling and dose adjustment for toxicities that it will be done as per local label – Protocol Summary and Section 7.4.1
- Update from ASCT to HSCT – Section 7.4.1 and Section 9.6.3
- Deletion of radioisotope glomerular filtration rate (GFR) assessment as a criterion for withholding LD chemotherapy – Section 7.4.2
- Changes made to the recommendations for dose adjustment of fludarabine – Section 7.4.2

[redacted]

- Editorial change for the use of cetuximab from ‘indicated’ to ‘intended’ – Section 8.2
- Language was added for sites to have tocilizumab readily available prior to JCAR017 administration as required for treatment and management of CRS – Section 8.3

- Modification of definition of the Pharmacokinetic Analysis Set – Section 9.2.5
- Update of wording from enrolled to randomized – Protocol Summary, Section 9.3.1, Section 9.5 and Section 9.8.3
- Additional clarifications made in the analysis of adverse events– Section 9.7.2
- Correction of wording from blinded to aggregate – Section 9.8.3
- Clarification added to explain that additional information on the estimation of the EFS probability curve and computation of the predictive distribution for the EFS events will be mentioned in the Statistical Analysis Plan (SAP) – Section 9.8.3
- Adverse Event section modified to ease the reading – Section 10
- Management of Toxicities associated with JCAR017 section was updated: Tumor lysis syndrome and uncontrolled T cell proliferation were updated, cytopenias and infections were added - Section 10.6.1
- JCAR017 Management Guidelines for Cytokine Release Syndrome and Neurologic Toxicities updated from version 2.3 to version 3.1 – Section 18, Appendix L
- Some literature references were updated and added – Protocol body, Section 17
- New abbreviations added – Section 18, Appendix A
- New appendix added for the calculation of secondary age adjusted international prognostic index (sAAIPI) – Section 18, Appendix M
- Style and formatting updated