FRED HUTCHINSON CANCER RESEARCH CENTER
UNIVERSITY OF WASHINGTON SCHOOL OF MEDICINE

PROTOCOL NO. 9457

A Phase 1b study of JCAR014, autologous T cells engineered to express a CD19-specific chimeric antigen receptor, in combination with durvalumab (MEDI4736) for relapsed/refractory B-cell non-Hodgkin lymphoma

Protocol No.	FHCRC 9457
Current Version:	14 May 2021
Previous Version:	20 November 2020

Study Team

Investigators:	**Professional Title**	**Telephone Number**
Jordan Gauthier, MD (Principal Investigator)	Assistant Professor, FHCRC	206-667-2713
Alexandre V Hirayama, MD	Post-Doctoral Research Fellow	206-667-6909
Statistician:		
Vicky Wu	Assistant Professor, FHCRC	206-667-3358
Research Staff:		
Martha Kahugu	Research Nurse	206-667-7582
Alisa Bradford	Research Coordinator	206-667-2834

EMERGENCY (24-HOUR) PHONE: 206-598-8902

PROTOCOL SYNOPSIS

Protocol Number: FHCRC 9457	**Product Names:** JCAR014 and durvalumab
Title of Study: A Phase 1b study of JCAR014, autologous T cells engineered to express a CD19-specific chimeric antigen receptor, in combination with durvalumab (MEDI4736) for relapsed/refractory B-cell non-Hodgkin lymphoma	
	Phase of Development: Phase 1b

Study Objectives:

Primary:

- To evaluate the safety of JCAR014 in combination with durvalumab in adult patients with relapsed/refractory (R/R) B-cell non-Hodgkin lymphoma (NHL)
- To determine the maximum tolerated dose (MTD) of durvalumab in combination with JCAR014
- To characterize the pharmacokinetic (PK) profile of JCAR014

Secondary:

- To assess the antitumor activity of JCAR014 in combination with durvalumab in R/R B-cell NHL
- To estimate the duration of response (DOR), progression-free survival (PFS), and overall survival (OS) in patients treated with JCAR014 in combination with durvalumab
- To characterize the PK profile of durvalumab
- To assess the immunogenicity of JCAR014 and durvalumab

Exploratory:

- To assess the pharmacodynamic effects of JCAR014 and durvalumab in blood and within the tumor

Background:

B-cell NHL: B-cell malignancies comprise a heterogeneous group of tumors including multiple NHL subtypes. Patients with B-cell NHL, including diffuse large B-cell lymphoma (DLBCL), commonly relapse or have refractory disease and remain incurable despite multi-modality treatments.

The majority (> 95%) of B-cell lymphomas express the B-cell lineage marker CD19, a 95-kDa glycoprotein present on the surface of B cells from early development until differentiation into plasma cells. CD19 is an attractive immunotherapeutic target because it is present on the surface of most B-cell malignancies but not on most normal tissues.

Approximately 30% of B-cell lymphomas have been shown to express programmed cell death ligand 1 (PD-L1), a protein involved in tumor immunosuppression of tumor-infiltrating lymphocytes and potentially of adoptively transferred T cells, such as chimeric antigen receptor (CAR)-modified T cells. Secretion of interferon gamma by CAR T cells may stimulate B-cell lymphomas to upregulate PD-L1 expression. In addition, B-cell lymphomas have a varying degree of infiltrating immune cells that also express PD-L1 and may contribute to the immunosuppressive microenvironment of the tumor.

JCAR014: JCAR014 consists of autologous T cells that express a CAR composed of a murine-derived, CD19-specific single-chain variable fragment (scFv) genetically fused to the 4-1BB and CD3ζ signaling endodomains. The JCAR014 cell product is prepared by modifying T cells ex vivo using a replication-incompetent, self-inactivating lentiviral vector that encodes the CD19 CAR and a truncated human epidermal growth factor receptor (EGFRt) that facilitates analysis of transduction efficiency and in vivo tracking of transduced cells by flow cytometry. JCAR014 is administered intravenously (IV) in a 1:1 ratio of CD4+ and CD8+ CAR-expressing (EGFRt+) T cells. JCAR014 T cells exhibit CD19-specific tumor cell recognition, resulting in tumor cell lysis and CAR T cell cytokine secretion and proliferation.

Durvalumab: Durvalumab is a human IgG1κ monoclonal antibody (mAb) that binds to PD-L1 and inhibits the binding of PD-L1 to programmed cell death protein 1 (PD-1) and CD80. Durvalumab contains a triple mutation in the constant domain of the IgG1 heavy chain that inhibits binding of complement protein C1q and the Fcγ receptors

involved in triggering effector function such as antibody-dependent cell-mediated cytotoxicity or phagocytosis. Durvalumab is administered by IV infusion.

Study Purpose and Rationale: To date, JCAR014 has been studied in adult patients with CD19+ B-cell NHL and acute lymphoblastic leukemia (ALL) with encouraging results. The complete remission (CR) rate in ALL is > 90% and the overall response rate (CR and partial response [PR]) in NHL is approximately 67%. There is a need to improve the antitumor efficacy of this approach. Improvements in the expansion and persistence of CAR-T cells and in antitumor activity have been made by modifying the lymphodepleting chemotherapy regimen; however, expression of PD-L1 by the tumor, the lymphoma microenvironment, or the activated CAR-T cell mass may limit the antitumor activity of JCAR014. Preliminary data suggest that CAR-T cells, upon antigen stimulation, upregulate expression of PD-1 and PD-L1, thus becoming targets for suppression by PD-L1 expressed on the tumor, the tumor microenvironment, or by the CAR-T cell mass itself.

In vitro studies have shown that durvalumab antagonizes the inhibitory effects of PD-L1 on primary human T cells, resulting in their restored proliferation and production of interferon gamma in response to T-cell receptor stimulation. Durvalumab has been evaluated in a total of 1883 patients with cancer, with evidence of antitumor activity and an acceptable safety profile when administered via IV infusion at 10 mg/kg every 2 weeks. More recently, a similar safety profile has been observed when administered at 20 mg/kg every 4 weeks.

This Phase 1 study is intended to evaluate the safety, tolerability, in vivo expansion, and antitumor activity of CAR-T cells (JCAR014) in combination with a PD-L1 antagonist (durvalumab) in R/R B-cell NHL.

Study Design: This is an open-label, single-center, Phase 1b study to determine the safety, PK, and antitumor activity of JCAR014 in combination with durvalumab in adult patients with R/R DLBCL (including transformed DLBCL and primary mediastinal B-cell lymphoma [PMBCL]).

Patients will be enrolled into one of two treatment groups (Group 1 or Group 2). Within each group, durvalumab dose escalation/de-escalation will follow a modified toxicity probability interval (mTPI) algorithm, with a target dose-limiting toxicity (DLT) rate of 30% and an equivalence interval of 25%–35% (Appendix F). A dose level will be considered unsafe, with no additional patients enrolled at that dose level, if it has an estimated 95% or more probability of exceeding the target DLT rate of 30% (i.e., P[DLT > 30%|data] > 95%) with at least three patients treated at that dose level. Dose escalation in each group will occur independently according to the mTPI algorithm as applied to each group.

Initial Study Design:

Group 1 (first dose of durvalumab after JCAR014):

Patients in Group 1 receive the first infusion of durvalumab after treatment with JCAR014. The first treated cohorts of patients in Group 1 received durvalumab no earlier than 21 days after the JCAR014 infusion (Group 1 – late). Patients in Group 1 receiving JCAR014 (up to 2 x 10^6 CAR-T cells/kg) are assessed for DLT from the time of the first durvalumab infusion until 28 days after the first durvalumab infusion. According to the mTPI algorithm, durvalumab at Dose Level 1 (225 mg, n = 3 evaluable) and Dose Level 2 (750 mg, n = 3 evaluable) were found to have acceptable safety.

Group 2 (first dose of durvalumab before JCAR014):

Patients in Group 2 receive the first dose of durvalumab 1 day prior to administration of JCAR014. DLTs in Group 2 are assessed from the time of the pre-JCAR014 dose of durvalumab until 28 days after treatment with JCAR014 (up to 2 x 10^6 CAR T cells/kg). According to the mTPI algorithm, durvalumab at Dose Level 1 (7.5 mg, n = 1 evaluable), Dose Level 2 (22.5 mg, n = 1 evaluable), Dose Level 3 (75 mg, n = 3 evaluable), Dose Level 4 (225 mg, n = 6 evaluable, including one DLT), and Dose Level 5 (750 mg, n = 6 evaluable, including one DLT) were found to have acceptable safety.

In Group 1 and Group 2, patients subsequently receive durvalumab at approximately 28 day intervals at the current highest safe durvalumab dose level (750 mg) identified in dose escalation studies in either Group 1 or Group 2.

Amended Study Design:

Analyses of efficacy and pharmacodynamic data from patients previously treated in Group 1 (day 21 durvalumab start) and Group 2 (day -1 durvalumab start) indicated that durvalumab ≤ 750 mg starting no earlier than day 21

(Group 1 – late) may be superior to starting on day -1 (Group 2). Furthermore, data from the trial sponsor indicated that durvalumab 1500 mg is unlikely to provide an advantage in PD-L1 blockade compared to durvalumab 750 mg, suggesting that escalation to durvalumab 1500 mg in this trial may be unnecessary. Because JCAR014 CAR-T cells are declining in blood at day 21 after JCAR014 infusion, we elected to revise the protocol to add a cohort in Group 1 who receive durvalumab as early as 7 days after JCAR014 infusion (Group 1 – early) and nominate 750 mg as the maximum durvalumab dose in all Groups. Patients in Group 1 – early receiving JCAR014 (up to 2 x 10^6 CAR-T cells/kg) are treated in cohorts of 3 patients and assessed for DLT from the time of the first durvalumab infusion until 28 days after the first durvalumab infusion. Durvalumab dose de-escalation/re-escalation decisions follow the mTPI algorithm in cohorts of 3 patients.

Amended groups:

Group 1 – late: start durvalumab no earlier than 21 days after JCAR014.

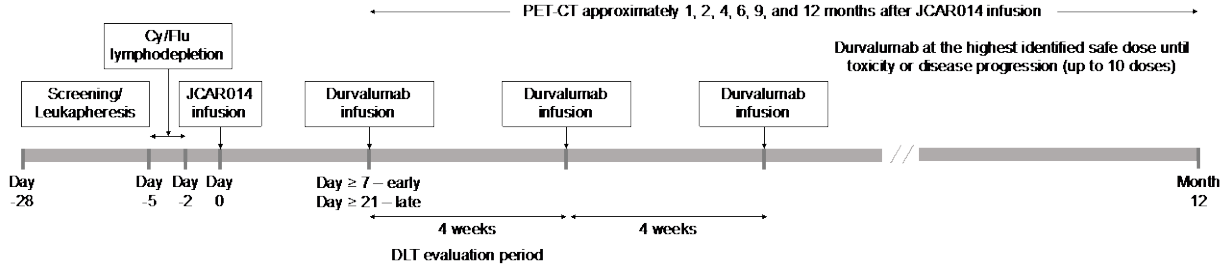
Group 1 – early: start durvalumab no earlier than 7 days after JCAR014.

Group 2: start durvalumab one day prior to JCAR014.

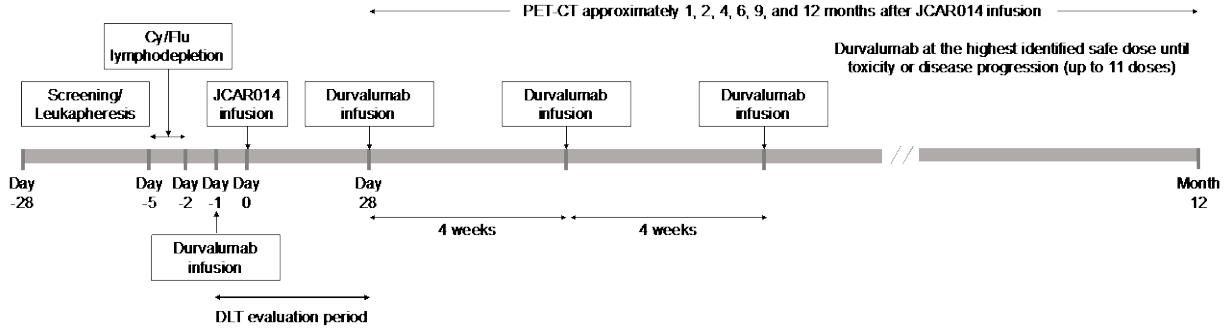
In all groups, patients subsequently receive durvalumab 750 mg at approximately 28 day intervals.

If durvalumab 750 mg has acceptable safety in Group 1 – early (day 7 start) according to the mTPI algorithm, patients will then be treated alternately in Group 1 – early and Group 1 – late until 6 evaluable patients have been treated in each of the 3 groups: Group 2; Group 1 – late; Group 1 – early. The Steering Committee (SC) will then evaluate available safety, toxicity, efficacy, and pharmacodynamic data to determine which group/s should be subsequently expanded. Allocation of the subsequent patients will be alternated if more than one cohort is expanded. The maximum number of evaluable patients in the trial will be 42.

Group 1 (post-JCAR014 treatment with durvalumab):



Group 2 (pre-JCAR014 treatment with durvalumab):



The study was gated such that the first six patients were treated with durvalumab at intervals of at least 2 weeks and subsequent patients were scheduled for treatment with durvalumab at intervals of at least 1 week. If a patient's durvalumab infusion is delayed for clinical or logistical reasons, and JCAR014 cell manufacturing and/or lymphodepletion chemotherapy are in progress for the next patient planned for treatment with the same dose level of durvalumab, the 1 week interval between durvalumab infusions is not required. Patients may commence treatment with lymphodepletion and/or JCAR014 before durvalumab dose assignment.

In both groups, JCAR014 may be dose de-escalated after review by the SC if the SC determines that the observed data indicate that dose de-escalation of JCAR014 is required. In this case, a separate group may be enrolled at a

stable dose of durvalumab (to be determined by the SC) and dose re-escalation of JCAR014 may occur via the mTPI algorithm. Enrollment in this group will commence after amendment to the protocol and discussion with the FDA.

All eligible patients will undergo leukapheresis to enable JCAR014 production. Lymphodepleting chemotherapy (fludarabine [Flu] and cyclophospamide [Cy]) will be administered approximately Day -5 to Day -2 prior to JCAR014 administration, and will consist of either a single dose of cyclophosphamide 60 mg/kg administered on Day -5 and three daily doses of fludarabine 25 mg/m^2/day on Days -4 to -2 or with concurrent cyclophosphamide (300 mg/m^2/day) and fludarabine (30 mg/m^2/day) on days -4 through -2. The first dose of durvalumab will be administered on Day -1 for patients in Group 2 only, and approximately day 7 or 21 for patients in Group 1. All patients will receive JCAR014 on Day 0. In both groups, durvalumab will be administered approximately every 4 weeks for the greater of either 10 post-JCAR014 cycles or 4 cycles beyond identification of CR (for patients in whom studies demonstrating transition to CR occur late after JCAR014 infusion). Durvalumab cycles may be ceased if there is unacceptable toxicity, disease progression, or the patient or PI/designee determine it is not in the patient's best interest to continue durvalumab. Patients with disease progression at restaging who have evidence of biological activity after durvalumab infusion that could be associated with subsequent antitumor effect (e.g., a mixed response, tumor stability, or evidence of JCAR014 expansion and/or persistence) may receive additional post-JCAR014 cycles of durvalumab up to the maximum number allowed for Group 1 or Group 2.

The planned dose levels of durvalumab and JCAR014 (intermediate dose levels may be evaluated) are as follows:

Dose Level	Durvalumab		JCAR014 (Group 1 and Group 2)
	Group 1	Group 2	
-1	75 mg	—	—
1	225 mg	7.5 mg	Up to 2 x 10^6/kg CAR T cells
2	750 mg	22.5 mg	—
3	—	75 mg	—
4	—	225 mg	—
5	—	750 mg	—

After the JCAR014 infusion, patients will be monitored for in vivo T-cell expansion/persistence and will have serum samples collected for cytokine profiling. Standard safety laboratory studies will be monitored until 12 months post-JCAR014 infusion or 90 days after the final durvalumab infusion, whichever is longer. Safety and tolerability will be assessed from study entry until the end of treatment and primary follow-up (12 months post-JCAR014 infusion or 90 days after last durvalumab infusion, whichever is longer). Long-term follow-up to assess delayed adverse events will begin after the primary follow-up and will continue for up to 15 years after the JCAR014 infusion. Toxicities will be graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03, with the exception of cytokine release syndrome (CRS), which will be graded according to a system based on modified criteria (Davila 2014, Lee 2014). PK (in vivo expansion and persistence) will be assessed from the time of JCAR014 infusion until cells are no longer detectable by flow cytometry or quantitative polymerase chain reaction (qPCR).

For a subset of patients with accessible tumor who consent to optional biopsies, a fresh tumor biopsy may be obtained prior to lymphodepleting chemotherapy, within the first 4 weeks after administration of JCAR014, and approximately within the first 4 weeks after the first post-JCAR014 administration of durvalumab. If biopsy within this period is not suitable for logistical, research or clinical reasons, biopsies may be completed at a different time. In the event of persistent mass, relapse or progression, a biopsy may be collected at that time point. These samples will be evaluated for the extent of JCAR014 migration and PD-1 and PD-L1 expression. Additional markers of immune cell phenotype and analysis of the tumor microenvironment may be explored in response to emerging data.

Disease response will be determined by positron emission tomography (PET)/computed tomography (CT) at approximately 1, 2, 4, 6, 9, and 12 months after the JCAR014 infusion (at the end of the JCAR014 cycle, the end of the first post-JCAR014 durvalumab cycle, approximately every other durvalumab cycle until 6 months after the JCAR014 infusion, then every 3 months until 12 months after the JCAR014 infusion or 90 days after the last durvalumab dose, whichever is later). At the time of the 1-month post-JCAR014 response assessments (and at

other timepoints as clinically indicated until the patient achieves a CR), patients with bone marrow lymphoma at baseline may have repeat a bone marrow aspirate and biopsy that will be analyzed for lymphoma by flow cytometry; samples may also be analyzed for other exploratory endpoints.

Patients may be eligible for retreatment with JCAR014 ± durvalumab if at least 3 months have elapsed since the last dose of durvalumab. Retreatment data will not be included in the dose-finding portion of the study.

The SC, comprising the PI and/or designee and FHCRC statistician and medical director/s from Juno Therapeutics and MedImmune, will regularly assess the safety, PK, and efficacy of the combination of JCAR014 and durvalumab administration throughout the study. In addition, an independent Data Safety Monitoring Board (DSMB) will review cumulative study data approximately quarterly over the course of the study to evaluate safety, protocol conduct, and scientific validity and integrity of the trial.

After the primary follow-up phase (12 months post-JCAR014 infusion or 90 days after the last durvalumab infusion, whichever is longer), patients will be asked to participate in long-term follow-up in accordance with Food and Drug Administration guidelines.

Study Population: The target study population consists of adult patients with R/R B-cell NHL.

Patients must meet all of the following criteria to be enrolled in this study:

Inclusion Criteria:

1) Male or female ≥ 18 years of age at the time of screening consent
2) Relapsed or refractory, PET-positive DLBCL not otherwise specified (NOS), high grade B cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements, PMBCL, or DLBCL transformed from indolent histology with one of the following:
   a) Persistent disease after first-line chemo-immunotherapy
   b) Relapse after first-line chemo-immunotherapy and not eligible for autologous hematopoietic stem cell transplant (HCT)
   c) Relapse or persistent disease after at least two lines of therapy or after autologous HCT
3) Evidence of CD19 expression on any prior or current tumor specimen or a high likelihood of CD19 expression based on disease histology
4) Karnofsky performance status ≥ 60%
5) Adequate organ function, defined as:
   a) Assessed by the Investigator to have adequate bone marrow function to receive lymphodepleting conditioning chemotherapy
   b) Serum creatinine < 1.5 x age-adjusted upper limit of normal (ULN)
   c) Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) < 3 x ULN and total bilirubin ≤ 2 x ULN
   d) Adequate pulmonary function, defined as CTCAE Grade ≤ 1 dyspnea and SaO_2 ≥ 92% on room air. Patients with clinically significant pulmonary dysfunction, as determined by medical history and physical exam should undergo pulmonary function testing and must have a forced expiratory volume in 1 second (FEV1) of ≥ 50% of predicted value or diffusing capacity of the lung for carbon monoxide (DLCO; corrected) ≥ 40% of predicted value
   e) Adequate cardiac function, defined as left ventricular ejection fraction (LVEF) ≥ 35% as assessed by echocardiogram or multiple uptake gated acquisition (MUGA)
6) Women of reproductive potential (defined as all women physiologically capable of becoming pregnant) must agree to use suitable methods of contraception for 90 days after the last dose of study therapy (durvalumab or JCAR014 infusion)
7) Males who have partners of reproductive potential must agree to use an effective barrier contraceptive

method for 90 days after the last dose of study therapy (durvalumab or JCAR014)

8) Ability to understand and provide informed consent

Exclusion Criteria:

1) Subjects with known active central nervous system (CNS) involvement by malignancy. Subjects with prior CNS disease that has been effectively treated will be eligible if treatment was completed at least 3 months prior to enrollment and there is no evidence of disease or stable abnormalities on repeat imaging.
2) Planned use of corticosteroids (> 10 mg/day prednisone or equivalent) or other systemic immunosuppression within 4 days prior to leukapheresis or within 72 hours prior to JCAR014 infusion. Topical and/or inhaled steroids are permitted.
3) Prior treatment with any CD19 CAR T-cell therapy
4) Prior allogeneic HCT
5) Known active hepatitis B, hepatitis C, or human immunodeficiency virus (HIV) infection
6) Pregnant or breastfeeding women
7) Known exclusion criteria for leukapheresis, JCAR014, or durvalumab therapy
8) Prior treatment with PD-1, PD-L1, cytotoxic T lymphocyte-associated protein 4 (CTLA-4) targeted therapy, or tumor necrosis factor receptor superfamily (TNFRSF) agonists including CD134 (OX40), CD27, CD137 (4-1BB), and CD357 (glucocorticoid-induced tumor necrosis factor receptor family-related protein [GITR])
9) Active or prior documented autoimmune or inflammatory disorders (including inflammatory bowel disease [e.g., ulcerative colitis, Crohn's disease], celiac disease, or other serious chronic gastrointestinal conditions associated with diarrhea, autoimmune vasculitis, systemic lupus erythematosus, Wegener syndrome [granulomatosis with polyangitis], myasthenia gravis, Graves' disease, rheumatoid arthritis, hypophysitis, uveitis, etc.) within 3 years prior to the planned start of treatment. The following are exceptions to this criterion:
    a) Vitiligo
    b) Alopecia
    c) Hypothyroidism (e.g., following Hashimoto syndrome) stable on hormone replacement
    d) Psoriasis not requiring systemic treatment
    e) Other conditions considered to be low risk of serious deterioration by the Principal Investigator (PI)
10) History of any one of the following cardiovascular conditions within the past 6 months: Class III or IV heart failure as defined by the New York Heart Association (NYHA), cardiac angioplasty or stenting, myocardial infarction, or unstable angina. History of other clinically significant cardiac disease that, in the opinion of the PI or designee, is a contraindication to lymphodepleting chemotherapy, JCAR014 infusion, or durvalumab infusion is also excluded.
11) History or presence of clinically relevant CNS pathology, such as epilepsy, seizure, paresis, aphasia, stroke, severe brain injuries, dementia, Parkinson's disease, cerebellar disease, or psychosis. History of other organic brain syndrome that, in the opinion of the PI or designee, is a contraindication to lymphodepleting chemotherapy, JCAR014 infusion, or durvalumab infusion is also excluded.
12) History of solid organ transplantation
13) Uncontrolled infection

14) Receipt of live, attenuated vaccine within 28 days prior to the first dose of durvalumab (Note: enrolled patients should not receive live vaccine during the study and for 180 days after the last dose of durvalumab.)

Test Product, Dose, and Mode of Administration:

JCAR014 will be administered as an IV infusion and will consist of a single dose of 2 x 10^6/kg EGFRt+ T cells. Dose de-escalation to a lower dose of EGFRt+ T cells may be recommended by the SC based on ongoing safety evaluation.

Durvalumab will be administered as an IV infusion at 7.5, 22.5, 75, 225, or 750 mg. Continued dosing at an every 4 week (Q4W) interval is allowed after clearance of the DLT evaluation period. A maximum of 10 doses of durvalumab in Group 1 and 11 doses of durvalumab in Group 2 will be administered. Intermediate dose levels may be evaluated.

Safety Assessments: Adverse events, serious adverse events, and laboratory abnormalities (type, frequency, and severity) will be collected. Adverse events of special interest will include CRS, neurological toxicity, macrophage activation syndrome (MAS), tumor lysis syndrome (TLS), hepatic function abnormalities, pneumonitis, infusion reactions, hypersensitivity reactions, colitis and other gastrointestinal disorders (diarrhea, enterocolitis), and other immune-related adverse events (irAEs), defined as adverse events of an immune nature (i.e., inflammatory) in the absence of a clear alternative etiology. DLTs will be assessed in Group 1 for 28 days after the first durvalumab administration and in Group 2 for 28 days after JCAR014 administration.

DLT Definition:

The following treatment-related (JCAR014 or durvalumab) events will be considered DLTs:

1. Death within 4 weeks of the study treatment
2. Grade ≥ 3 neurotoxicity of greater than 7 days duration
3. Grade ≥ 3 neurotoxicity that does not revert to Grade 1 or baseline within 28 days
4. Grade ≥ 3 seizures that do not resolve to grade ≤ 2 within 3 days
5. Grade ≥ 4 cytokine release syndrome
6. Grade 3 cytokine release syndrome that does not resolve to grade ≤ 2 within 7 days
7. Grade ≥ 3 non-infectious colitis or non-infectious pneumonitis
8. Grade ≥ 3 irAE or other grade ≥ 3 autoimmune toxicity (excluding B-cell aplasia)
9. Any increase in aspartate transaminase (AST) or ALT > 3 x ULN and concurrent increase in total bilirubin > 2 x ULN that is unrelated to CRS and has no other probable reason to explain the combination of increases
10. Grade ≥ 3 allergic reaction to the JCAR014 infusion
11. Any Grade 3 or 4 event deemed unexpected by the Investigator and considered a DLT upon evaluation by the SC

Efficacy Assessments: PET/CT assessment of response will be performed at approximately 1, 2, 4, 6, 9, and 12 months following the JCAR014 infusion. The Investigator's assessment using Lugano criteria will be used to evaluate the protocol-specified response endpoints.

Pharmacokinetics and Biomarker Assessments:

1. PK assessment of JCAR014 cells by flow cytometry and JCAR014 transgene DNA by PCR in blood and bone marrow
2. PK assessment of durvalumab
3. Quantification of anti-drug antibodies (ADAs) directed against durvalumab
4. Quantification of ADAs directed against JCAR014
5. Assessment of cellular immune responses against JCAR014
6. Characterization of JCAR014 cells and other immune cells in the blood by flow cytometry
7. Quantification of PD-L1 on JCAR014 cells by immunohistochemistry and flow cytometry
8. Quantification of soluble PD-L1 in serum
9. Assessment of soluble proteins (e.g., cytokines and chemokines) in the blood
10. Evaluation of tumor biopsies for CD19 and PD-L1 expression, presence of JCAR014, and attributes of tumor and tumor microenvironment (e.g., presence of regulatory T cells, expression of tumor immune checkpoint markers)
11. Assessment of replication-competent lentivirus (RCL)

Statistical Methods:

The target toxicity rate for the MTD is 30%. An mTPI method will be used to guide dose escalation, and the MTD for each group will be estimated using isotonic regression based on the DLT evaluable analysis set. The DLT evaluable analysis set includes all patients who have received JCAR014 cell product that conforms to dose or composition standards and full infusion of the first dose of durvalumab, and who have either experienced a DLT or were followed for the full DLT evaluation period.

Analysis of other primary, secondary, and exploratory endpoints will be descriptive based on the appropriate analysis set and may include summary statistics such as means, standard deviations, and 95% confidence intervals, if applicable. Kaplan-Meier curves and median time-to-event data will be presented for time-to-event variables (e.g., DOR, PFS, and OS), if appropriate.

Adverse events and laboratory abnormalities will be described and summarized.

Analyses will be performed for each group separately.

Sample size: A maximum sample size of 42 is planned for Group 1 and Group 2 combined. The SC may decide to further increase the sample size beyond 21 per group by adding additional patients. If a third group is enrolled, a maximum sample size of 63 is allowed for the trial.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF APPENDICES

LIST OF ABBREVIATIONS

Abbreviation or Term	Definition/Explanation
ADA	anti-drug antibody
AE	adverse event
AESI	adverse event of special interest
ALL	acute lymphoblastic leukemia
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the curve
CAR	chimeric antigen receptor
CBC	complete blood count
CCO	Clinical Coordinators Office
CFR	Code of Federal Regulations
CL	clearance
CLL	chronic lymphocytic leukemia
C_{max}	maximum concentration
CMC	Chemistry, Manufacturing, and Controls
CNS	central nervous system
CPF	Cell Processing Facility
CR	complete response or complete remission
CRA	Clinical Research Associate
CRF	case report form
CRM	continuous reassessment method
CRP	C-reactive protein
CRS	cytokine release syndrome
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTL	Cell Therapy Laboratory
CTLA-4	cytotoxic T lymphocyte-associated protein 4
Cy/Flu	cyclophosphamide + fludarabine
DCR-24w	disease control rate at 24 weeks
DLBCL	diffuse large B-cell lymphoma
DLCO	diffusing capacity of the lung for carbon monoxide

Abbreviation or Term	Definition/Explanation
DLT	dose-limiting toxicity
DOR	duration of response
DSMB	Data Safety Monitoring Board
ECG	electrocardiogram
ECHO	echocardiogram
EDC	electronic data capture
EEG	electroencephalogram
EGFR	epidermal growth factor receptor
EGFRt	truncated epidermal growth factor receptor
FDA	Food and Drug Administration
FEV1	forced expiratory volume in 1 second
FHCRC	Fred Hutchinson Cancer Research Center
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GI	gastrointestinal
GLP	Good Laboratory Practice
HCC	hepatocellular carcinoma
HCT	hematopoietic stem cell transplant
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
IBC	Institutional Biosafety Committee
ICF	informed consent form
ICH	International Conference on Harmonisation
ICU	intensive care unit
IFNγ	interferon gamma
IHC	immunohistochemistry
IL-6	interleukin 6
IND	Investigational New Drug
IP	investigational product
irAE	immune-related adverse event
IRB	Institutional Review Board
IRO	Institutional Review Office

Abbreviation or Term	Definition/Explanation
IV	intravenous(ly)
LDH	lactate dehydrogenase
LTFU	long-term follow-up
LVEF	left ventricular ejection fraction
mAb	monoclonal antibody
MAS	macrophage activation syndrome
MHC	major histocompatibility complex
MMSE	Mini Mental State Examination
MTD	maximum tolerated dose
mTPI	modified toxicity probability interval
MUGA	multiple uptake gated acquisition
NCI	National Cancer Institute
NHL	non-Hodgkin lymphoma
NIH	National Institutes of Health
NOAEL	no-observed-adverse-effect level
NOS	not otherwise specified
NSCLC	non-small cell lung cancer
NYHA	New York Heart Association
ORR	objective response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
PCP	pneumocystis pneumonia
PCR	polymerase chain reaction
PD	progressive disease
PD-1	programmed cell death protein 1
PD-L1	programmed cell death ligand 1
PD-L2	programmed cell death ligand 2
P[DLT]	probability of dose-limiting toxicity
PET	positron emission tomography
PFS	progression-free survival
PI	Principal Investigator
PK	pharmacokinetic(s)

Abbreviation or Term	Definition/Explanation
PMBCL	primary mediastinal B-cell lymphoma
PO	per os
PR	partial response
PT	prothrombin time
PTT	partial thromboplastin time
Q2W	every 2 weeks
Q4W	every 4 weeks
Q28D	every 28 days
qPCR	quantitative polymerase chain reaction
R/R	relapsed/refractory
RCL	replication-competent lentivirus
SAE	serious adverse event
SCCA	Seattle Cancer Care Alliance
SCCHN	squamous cell carcinoma of the head and neck
scFv	single-chain variable fragment
sCRS	severe cytokine release syndrome
SEM	standard error of the mean
SC	Steering Committee
SNP	single nucleotide polymorphism
SOP	standard operating procedure
TCR	T-cell receptor
TIL	tumor-infiltrating lymphocyte
TLS	tumor lysis syndrome
T_{max}	time to peak concentration
TNBC	triple-negative breast cancer
TNFα	tumor necrosis factor alpha
ULN	upper limit of normal
UPN	Unique Patient Number

1. BACKGROUND

1.1 B-Cell Non-Hodgkin Lymphoma

It is estimated that approximately 72,000 new cases of non-Hodgkin lymphoma (NHL) will be diagnosed and approximately 20,000 patients will die of their disease in 2015 (Siegel 2015). In the United States, approximately 85% of NHL cases are categorized as B-cell lymphomas and 15% are categorized as T/NK-cell lymphomas (NCCN 2014). The most common histologic type of lymphoma is diffuse large B-cell lymphoma (DLBCL), representing approximately 30% of the annual incidence of NHL. The addition of anti-CD20 antibody therapy with rituximab to standard CHOP chemotherapy has improved the outcome for patients with DLBCL (Coiffier 2002). The goal of treatment is to obtain a complete remission (CR) as demonstrated by a negative positron emission tomography (PET) scan. Patients with advanced stage disease usually receive six to eight cycles of R-CHOP or six cycles of dose-adjusted EPOCH-R. Patients who fail to achieve a PET-negative CR or those who relapse following CR are treated with salvage therapy with plans for high-dose chemotherapy and autologous hematopoietic cell transplantation (HCT) for those who respond to the salvage regimen. High-dose therapy with HCT can cure 20% to 50% of chemotherapy-responsive patients and is considered the standard of care for patients responding to salvage chemotherapy who are medically fit for transplant. Unfortunately, patients who relapse early after primary therapy with a regimen containing rituximab have a worse prognosis even with salvage high-dose therapy and autologous HCT (Gisselbrecht 2010).

Patients who are unable to undergo autologous HCT or those who relapse following autologous HCT have a poor prognosis with a median survival of 6 to 12 months. Allogeneic HCT may be considered in patients who have appropriate donors and chemotherapy-sensitive disease that can be rendered into CR or near CR prior to the transplant (Rezvani 2008). Evidence for a graft-versus-lymphoma effect for DLBCL is more limited, perhaps because Class I major histocompatibility complex (MHC) is absent on a high proportion of DLBCL (Challa-Malladi 2011), and long-term survival is achieved in only 30% to 40% of patients who have minimal disease at the time of allogeneic HCT. Thus, patients with relapsed aggressive lymphoma who have previously had an autologous HCT or those medically unable to receive autologous HCT have a poor prognosis and are in need of novel treatments.

1.2 CD19 as a Drug Target in B-Cell Non-Hodgkin Lymphoma

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 (Stamenkovic 1988, Brentjens 2011). CD19 is an attractive therapeutic target because it is expressed homogeneously by most B-cell malignancies, including B-cell NHL (Li 1993, Li 1996, Davila 2012). Importantly, the CD19 antigen is not expressed on hematopoietic stem cells or on any normal tissue apart from those of the B-cell lineage.

1.3 PD-L1 as a Drug Target in B-Cell Non-Hodgkin Lymphoma

Programmed cell death protein 1 (PD-1, or CD279) is a member of the immunoglobulin superfamily of molecules involved in regulation of T-cell activation. It is found mainly on activated T cells where its engagement inhibits activation, resulting in downstream effects on cytokine production, proliferation, cell survival, and transcription factors associated with effector T-cell function (Freeman 2000, Carter 2002, Bennett 2003, Saunders 2005, Nurieva 2006, Fife 2008).

PD-1 has two ligands. The first, programmed cell death ligand 1 (PD-L1), is constitutively expressed on many hematopoietic cells, but may be up-regulated in hematopoietic and non-hematopoietic cells. Regulation of PD-L1 is mediated, in part, by type I and type II interferons. The second, programmed cell death ligand 2 (PD-L2), was identified in 2001 (Latchman 2001, Tseng 2001). Its expression is far more restricted and is confined to hematopoietic cells.

PD-L1 is part of a complex system of receptors and ligands that are involved in controlling T-cell activation. PD-L1 acts at multiple sites in the body to help regulate normal immune responses and is utilized by tumors to help evade detection and elimination by the host immune system tumor response. In the lymph nodes, PD-L1 on antigen-presenting cells binds to PD-1 or CD80 on activated T cells and delivers an inhibitory signal to the T cell (Keir 2008, Park 2010). This results in reduced T-cell activation and fewer activated T cells in circulation. In the tumor microenvironment, PD-L1 expressed on tumor cells and infiltrating immune cells binds to PD-1 and CD80 on activated T cells reaching the tumor. Binding of PD-L1 to PD-1 delivers an inhibitory signal to those T cells, preventing them from killing target cancer cells and protecting the tumor from immune elimination (Zou 2008).

Approximately 30% of B-cell lymphomas have been shown to express PD-L1 (Andorsky 2011). Additionally, B-cell lymphomas have a varying degree of infiltrating immune cells that also express PD-L1 and contribute to the immunosuppressive microenvironment of the tumor (Myklebust 2013). A significant frequency of primary mediastinal B-cell lymphomas have genomic rearrangements associated with overexpression of PD-L1 transcripts (Twa 2014). High levels of soluble PD-L1 have also been associated with poor overall survival in DLBCL suggesting that targeting this axis may have therapeutic utility (Rossille 2014).

One published report (Andorsky 2011), as well as immunohistochemistry (IHC) studies conducted by Ventana/MedImmune, demonstrate expression of PD-L1 in a subset of NHL patient tumor biopsies. Andorsky et al. reported that PD-L1 is expressed by tumor cells in approximately 30% of the NHL biopsies analyzed. A more complete analysis was performed by MedImmune/Ventana. In this study, a series of 84 formalin-fixed, paraffin-embedded biopsy sections from NHL patients were analyzed by IHC for the expression of PD-L1. The majority of samples, 46, were of the DLBCL subtype, 18 were of the follicular lymphoma (FL) subtype, and the remaining 20 were of the mantle cell lymphoma (MCL) subtype. The percentage of tumor cells demonstrating PD-L1–specific staining of the cell membrane was estimated by visual inspection in DLBCL and MCL samples, but not FL samples, as it was not possible to

distinguish FL cells from normal infiltrating lymphocytes. Where PD-L1 staining on tumor cell membranes was identified, staining intensity was scored between 1 (low) and 3 (high). The percentage of infiltrating lymphocytes demonstrating PD-L1–specific staining of the cell membrane was estimated by visual inspection in all samples.

In the 46 DLBCL samples, 32 samples (70%) demonstrated PD-L1 staining on ≥ 5% of tumor cells. The mean percentage of PD-L1–expressing tumor cells within these 32 samples (± standard error of the mean [SEM]) was 27% ± 5%, with a range of 5%-100%. The intensity of staining varied across the 32 positive samples, with 38% of samples demonstrating high intensity staining. There was no correlation between the percentage of tumor cells expressing PD-L1 and the intensity of staining. PD-L1 was also detected on ≥ 5% of infiltrating lymphocytes in 40 of the 46 samples (87%). The mean percentage of PD-L1–expressing infiltrating lymphocytes in these 40 samples was 57% ± 4%, with a range of 5%-100%. In general, samples with high tumoral expression of PD-L1 also demonstrated high levels of infiltrating lymphocyte PD-L1 expression; however, there was a subset of samples that demonstrated high expression on infiltrating lymphocytes in the absence of notable tumoral expression.

The percentage of MCL samples demonstrating PD-L1 expression on ≥ 5% tumor cells was only 10% (2 of 20), notably lower than that in the DLBCL samples. The mean percentage of PD-L1–expressing cells in these two positive samples was 5% ± 1%, also lower than that observed in the DLBCL samples. In contrast, 100% of the MCL samples demonstrated PD-L1 expression on ≥ 5% infiltrating lymphocytes; however, the mean percentage of PD-L1–positive infiltrating lymphocytes across the samples was also lower in the MCL samples (13.3% ± 3%; range, 5%-60%).

Seventeen of 18 FL samples (94%) demonstrated PD-L1 expression on ≥ 5% infiltrating lymphocytes, and the mean percentage of PD-L1–expressing infiltrating lymphocytes in these samples was more comparable to that observed in the DLBCL samples (35% ± 6%; range, 5%-80%).

Of the 84 NHL samples examined, 75 (89%) demonstrated PD-L1 expression on greater than 5% of tumor cells or infiltrating lymphocytes. These data suggest that the expression of PD-L1 is a common feature of NHL tumors.

1.4 Adoptive CAR T-Cell Therapy for B-Cell Non-Hodgkin Lymphoma

CD19-specific chimeric antigen receptors (CARs) are single chain variable fragments (scFv) from CD19-specific monoclonal antibodies (mAbs) fused to a transmembrane domain and cytoplasmic signaling domains. The CAR is expressed on the T-cell surface and redirects the transfected T cells to recognize CD19-expressing lymphoma cells, leading to tumor cell lysis, cytokine secretion, and T-cell proliferation (Sadelain 2013). In clinical studies, CD19-targeted CARs have demonstrated encouraging activity in adult and pediatric patients with relapsed/refractory (R/R) B-cell acute lymphoblastic leukemia (ALL), B-cell NHL, and chronic

lymphocytic leukemia (CLL) (Kalos 2011, Porter 2011, Davila 2014, Maude 2014, Kochenderfer 2015, Lee 2015).

Recent studies in B-cell NHL demonstrating activity of CD19-targeted CAR T cells have employed T-cell products that are unselected for T-cell subsets (Kochenderfer 2014b, Schuster 2014, Kochenderfer 2015). JCAR014 differs from these products in that it consists of CD4+ and CD8+ CD19-targeted CAR T cells administered in a 1:1 ratio. It is known that CD4+ T cells enhance CD8+ effector T-cell persistence, memory formation, and trafficking to antigen-rich tissues. Activated CD8+ T cells have also shown poor survival in the absence of CD4+ T-cell help, and CD4+ T-cell help is required during recall expansion of memory CD8+ T cells (Toes 1999, Bos 2010). Likewise, CAR+ CD4+ T cells enhance CAR+ CD8+ cytolytic effector T-cell function both in vitro and in vivo (Adusumilli 2014). Thus, since JCAR014 is enriched with CD4+ and CD8+ CD19-targeted CAR T cells, persistence, trafficking to the tumor, and antitumor activity may be improved and more reproducible compared to unselected CAR T-cell investigational drug products.

Emerging data indicate that in vivo expansion of CD19-targeted CAR T cells strongly correlates with antitumor response (Gardner 2014, Kochenderfer 2014b, Schuster 2014, Turtle 2015). The antitumor activity of CAR T cells in NHL has been lower than that observed in ALL patients. The effect of the tumor microenvironment or bone marrow lymphoma involvement (i.e., more accessible target antigen) on CAR-T cell expansion and function may be important for antitumor activity in NHL.

1.5 Investigational Drug Products

1.5.1 JCAR014

1.5.1.1 Description of JCAR014 Drug Product

JCAR014 consists of autologous T cells that express a CAR composed of a murine-derived, CD19-specific scFv genetically fused via a modified IgG4 hinge spacer and a CD28 transmembrane domain to the 4-1BB and CD3ζ signaling endodomains. The JCAR014 cell product is prepared by modifying T cells ex vivo using a replication-incompetent, self-inactivating lentiviral vector that encodes the CD19 CAR and a truncated human epidermal growth factor receptor (EGFRt) downstream of a T2A ribosomal skip element. Expression of EGFRt allows accurate measurement of transduction efficiency, selection, and in vivo tracking of transduced cells by flow cytometry. JCAR014 is administered intravenously (IV) in a 1:1 ratio of CD4+ and CD8+ CAR-expressing (EGFRt+) T cells.

The methods employed to derive CD19 CAR T cells from the patient's $CD8^+$ and $CD4^+$ T cells enriched from peripheral blood mononuclear cells (PBMCs), and release tests of the cell products prior to infusion are outlined in the Chemistry, Manufacturing and Controls (CMC) section of the Investigational New Drug (IND) application to the Food and Drug Administration (FDA). Modifications to the CMC section during the course of the study will be submitted for FDA review.

1.5.1.2 Clinical Experience with JCAR014

JCAR014 is currently being evaluated in a first-in-human Phase 1/2 trial in adult patients with relapsed or refractory CD19+ ALL, CLL, and NHL (2639 study; ClinicalTrials.gov #NCT01865617). This trial is the first clinical trial in which patients with CD19+ B-cell malignancies receive T cells composed of a defined composition of CD8+ and CD4+ T cells engineered to express a CD19-specific CAR. The cell product for infusion is formulated in a 1:1 ratio of CD8+:CD4+ CAR+ T cells and infused at one of three dose levels (2×10^5, 2×10^6, or 2×10^7 CAR T cells/kg) after lymphodepleting chemotherapy. Different lymphodepleting chemotherapy regimens have been sequentially evaluated; cyclophosphamide (2 to 4 g/m^2) plus etoposide (100 to 200 mg/m^2/d for 3 days), cyclophosphamide alone (2 to 4 g/m^2), cyclophosphamide (30 to 60 mg/kg) plus fludarabine (25 mg/m^2/d for 3 to 5 days), and concurrent cyclophosphamide (300 mg/m^2/day) and fludarabine (30 mg/m^2/day) on each of 3 days.

We reported data from patients treated with JCAR014, which demonstrated elimination of marrow disease by flow cytometry in 93% of patients with B-ALL, and a complete response rate in NHL of 64% after treatment with lymphodepletion containing cyclophosphamide and fludarabine and JCAR014 at 2×10^6 CAR-T cells/kg (Turtle et al, J Clin Invest, 2016; Turtle et al, Sci Trans Med, 2016). At ASH 2016, we presented response data in high-risk CLL patients, showing 25% CR in patients who received cyclophosphamide and fludarabine and JCAR014 at $\leq 2 \times 10^6$ CAR-T cells/kg (Turtle et al, ASH abstract #56, 2016).

At ASH 2016, we also reported toxicity data from 133 patients with B-ALL, NHL or CLL who received lymphodepletion chemotherapy followed by JCAR014 (Turtle et al, ASH abstract #1852, 2016). Ninety-five of 133 patients (71%) developed CRS, which was grade ≥ 4 in 8%. Neurologic toxicity occurred in 40% of patients and was grade ≥ 3 in 21%. Six patients (4.5%) died of complications related to severe CRS and/or neurologic toxicity. Only 1 of these patients died after receiving a regimen of cyclophosphamide and fludarabine lymphodepletion and CAR-T cells at a dose level that is now recommended for their disease status.

Among NHL patients in the cohort reported at ASH 2016 (Turtle et al, ASH abstract #1852, 2016), 58% developed grade 1-3 CRS and 6% developed grade 4 CRS. Two NHL patients died of complications related to CRS and/or neurotoxicity. Both patients received JCAR014 at 2×10^7 CAR-T cells/kg. One patient died from gastrointestinal bleeding and complications of CRS 23 days after receiving JCAR014, and a second developed neurotoxicity and an intracranial hemorrhage and died 13 days after the JCAR014 infusion. A JCAR014 dose of 2×10^7 CAR-T cells/kg was deemed excessively toxic for a first JCAR014 infusion.

In NHL patients treated with cyclophosphamide and fludarabine followed by JCAR014 at 2×10^6 CAR-T cells/kg (n = 42), grade 1-2 CRS occurred in 26 patients (62%), no patients developed grade 3 CRS, and only one developed grade 4 CRS. Ten patients (23%) had grade 1-2 neurotoxicity, 3 (7%) had grade 3 neurotoxicity, and none had grade 4 neurotoxicity. Neurotoxicity was reversible and no NHL patients died after receiving this regimen. Therefore,

cyclophosphamide and fludarabine lymphodepletion followed by JCAR014 at 2 x 10^6 CAR-T cells/kg is a regimen with acceptable toxicity in NHL patients.

1.5.2 Durvalumab (MEDI4736)

1.5.2.1 Description of Durvalumab Investigational Product

Durvalumab is a human IgG1κ mAb that binds to PD-L1 and inhibits the binding of PD-L1 to PD-1 and CD80. Durvalumab contains a triple mutation in the constant domain of the IgG1 heavy chain that inhibits binding of complement protein C1q and the Fcγ receptors involved in triggering effector function such as antibody-dependent cell-mediated cytotoxicity or phagocytosis. Durvalumab is administered by IV infusion.

A summary of durvalumab product information is provided in Table 1.

Table 1: Summary of Durvalumab Data and Guidance for Investigator

Category	Description
Investigational product:	Durvalumab, a human IgG1κ mAb directed against PD-L1, and with reduced binding to C1q and the Fcγ receptors
Therapeutic indication:	Durvalumab is being developed for the treatment of patients with advanced solid tumors and hematologic malignancies
Dosage forms and strengths:	Durvalumab is formulated at 50 mg/mL. The investigational product is supplied as a vialed liquid solution in clear 10R glass vials closed with an elastomeric stopper and a flip-off cap overseal. Each vial contains 500 mg (nominal) of active investigational product at a concentration of 50 mg/mL
Method of administration:	The product is to be diluted with 0.9% (w/v) saline for IV infusion.

1.5.2.2 Nonclinical Experience with Durvalumab

Durvalumab has shown the following activity as an anti–PD-L1 molecule:

- Durvalumab binds to PD-L1 and blocks its interaction with PD-1 and CD80.
- Durvalumab can relieve PD-L1–mediated suppression of human T-cell activation in vitro.
- Durvalumab inhibits tumor growth in a xenograft model via a T-cell–dependent mechanism.
- A surrogate anti-mouse PD-L1 antibody resulted in improved survival in a syngeneic tumor model as monotherapy and resulted in complete tumor regression in > 50% of treated mice when given in combination with chemotherapy.
- In the same study, anti-mouse PD-L1 antibody-treated mice were completely tumor-free 3 months after tumor implantation and demonstrated long-term immunity during re-challenge.
- In a subsequent study in the same syngeneic model, the combination of an anti-mouse PD-L1 antibody and anti–CTLA-4 antibody resulted in complete tumor regression in all treated mice.

- Prevalence of PD-L1 expression on the surface of human tumors, ranging from approximately 0% to 35%, was demonstrated in a broad survey of samples derived from solid tumor types of interest.

The cynomolgus monkey is considered to be the only relevant nonclinical species for evaluation of local and systemic toxicities of durvalumab. This is based on similar binding and potency of durvalumab against human and cynomolgus monkey PD-L1 and lack of binding to rodent PD-L1. To underscore the pharmacological relevance of the cynomolgus monkey, durvalumab was found to suppress soluble PD-L1 in serum and fully occupy membrane PD-L1 on various leukocyte subsets at doses ≥ 0.1 mg/kg (lowest dose tested), with a dose-related duration of suppression and occupancy.

In general, IV administration of durvalumab to cynomolgus monkeys in nonclinical safety studies was not associated with adverse effects that were considered of relevance to humans. Adverse findings in the non-Good Laboratory Practice (GLP) pharmacokinetic (PK)/pharmacodynamic and dose range-finding study (four doses over 5 weeks) and a GLP 4-week repeat-dose toxicity study were consistent with anti-drug antibody (ADA)-associated morbidity and mortality in individual animals. Similar observations have been reported by MedImmune in cynomolgus monkeys administered human mAbs unrelated to durvalumab. Given that immunogenicity of human mAbs and consequent ADA-mediated adverse effects in nonclinical species are generally not predictive of responses in humans, the observed ADA-associated morbidity and mortality in these studies were not taken into consideration for the determination of the no-observed-adverse-effect level (NOAEL) of durvalumab. Based on the lack of any other treatment-related adverse effects, the NOAELs for durvalumab in these studies were considered to be the 100 mg/kg dose for the non-GLP dose range-finding study, and the 200/100 mg/kg dose (200 mg/kg loading dose followed by four weekly doses of 100 mg/kg) in the GLP 4-week repeat-dose toxicity study. Finally, in the pivotal 3-month GLP toxicity study, IV administration of durvalumab to cynomolgus monkeys was not associated with any treatment-related adverse effects. Therefore, the NOAEL for durvalumab in this study was considered to be the 200/100 mg/kg dose (200 mg/kg loading dose followed by 13 weekly doses of 100 mg/kg), the highest dose tested. In addition to the in vivo toxicology data, no unexpected membrane binding of durvalumab was observed in GLP tissue cross-reactivity studies using normal human and cynomolgus monkey tissues.

1.5.2.3 Clinical Experience with Durvalumab

A total of 1,883 subjects have been enrolled and treated in 30 ongoing durvalumab clinical studies, including 20 sponsored and 10 collaborative studies. Of the 1,883 subjects, 1,279 received durvalumab monotherapy and 440 received durvalumab in combination with other agents. No studies have been completed and none were terminated prematurely due to toxicity.

Data from the largest clinical study to date, Study CD-ON-MEDI4736-1108, examining durvalumab monotherapy across numerous types of advanced solid tumors, are presented below. Data from other ongoing studies are presented in the durvalumab Investigator's Brochure.

Study CD-ON-MEDI4736-1108

Study CD-ON-MEDI4736-1108 is a Phase 1/2, first-in-human, multicenter, open label, dose-escalation, and dose-expansion study to determine the MTD or optimal biologic dose, safety, PK, immunogenicity, and antitumor activity of durvalumab in adult patients with advanced solid tumors refractory to standard therapy or for which no standard therapy exists. A total of 736 subjects with advanced solid tumors have been treated in Study CD-ON-MEDI4736-1108. Of these subjects, 694 have received durvalumab at 10 mg/kg every 2 weeks (Q2W), either in the dose-escalation or dose-expansion phase of the study. The 10 mg/kg Q2W cohort comprises subjects with non-small cell lung cancer (NSCLC), squamous cell carcinoma of the head and neck (SCCHN), gastroesophageal cancer, hepatocellular carcinoma (HCC), pancreatic adenocarcinoma, triple-negative breast cancer (TNBC), bladder cancer, uveal melanoma, and advanced cutaneous melanoma. Subjects in the 10 mg/kg Q2W dose cohort were exposed to a median of six doses of durvalumab (range, 1–27).

The safety profile of durvalumab as monotherapy and combined with other anticancer agents was consistent with the pharmacology of the target and other agents in the immune checkpoint inhibitor class. The safety profile of durvalumab monotherapy in the 694 subjects with advanced solid tumors treated at 10 mg/kg Q2W in Study CD-ON-MEDI4736-1108 has been broadly consistent with that of the overall 1,279 subjects who have received durvalumab monotherapy (not including subjects treated with blinded investigational product) across the clinical development program. No tumor types appeared to be associated with unique adverse events (AEs). The majority of treatment-related AEs were manageable with dose delays, symptomatic treatment, and in the case of events suspected to have an immune basis, the use of established treatment guidelines for immune-mediated toxicity. As of 07 May 2015, among the 694 subjects treated with durvalumab 10 mg/kg Q2W in Study CD-ON-MEDI4736-1108, a total of 378 subjects (54.5%) experienced a treatment-related AE, with the most frequent (occurring in ≥ 5% of subjects) being fatigue (17.7%), nausea (8.6%), diarrhea (7.3%), decreased appetite (6.8%), pruritus (6.3%), rash (6.1%), and vomiting (5.0%). A majority of the treatment-related AEs were Grade 1 or Grade 2 in severity with ≥ Grade 3 events occurring in 65 subjects (9.4%). Six subjects had treatment-related Grade 4 AEs (upper gastrointestinal hemorrhage, increased aspartate aminotransferase [AST], dyspnea, neutropenia, colitis, diarrhea, and pneumonitis) and one subject had a treatment-related Grade 5 event (pneumonia). Treatment-related serious adverse events (SAEs) that occurred in ≥ 2 subjects were colitis and pneumonitis (three subjects each). A majority of the treatment-related SAEs were ≥ Grade 3 in severity and resolved with or without sequelae. Adverse events that resulted in permanent discontinuation of durvalumab were considered treatment-related in 18 subjects (2.6%), with colitis being the most frequent treatment-related AE resulting in discontinuation (three subjects). A majority of the treatment-related AEs resulting in discontinuation of durvalumab were ≥ Grade 3 in severity and resolved with or without sequelae.

Partial efficacy data are available for Study CD-ON-MEDI4736-1108. Tumor assessments were based on RECIST v1.1 (Eisenhauer 2009). A total of 456 of 694 subjects with advanced solid

tumors treated with durvalumab 10 mg/kg Q2W were evaluable for response (defined as having ≥ 24 weeks of follow-up, measurable disease at baseline, and at least one follow-up scan, or discontinued due to disease progression or death without any follow-up scan). In PD-L1−unselected patients, the objective response rate (ORR), based on investigator assessment per RECIST v1.1, ranged from 0% in uveal melanoma to 20.0% in bladder cancer, and the disease control rate at 24 weeks (DCR-24w) ranged from 4.2% in TNBC to 39.1% in advanced cutaneous melanoma. PD-L1 status was known for 383 of the 456 response-evaluable subjects. Across the PD-L1−positive tumors, ORR was > 10% for bladder cancer, advanced cutaneous melanoma, HCC (33.3% each); NSCLC (26.7%); and SCCHN (18.2%). Moreover, in the PD-L1−positive subset, DCR-24w was > 10% in advanced cutaneous melanoma (66.7%), NSCLC (36.0%), HCC and bladder cancer (33.3% each), and SCCHN (18.2%).

As of 09 February 2015, PK data were available for 378 subjects in the dose-escalation and dose-expansion phases of Study CD-ON-MEDI4736-1108 following treatment with durvalumab 0.1 to 10 mg/kg Q2W or 15 mg/kg every 3 weeks (Q3W). The maximum observed concentration (C_{max}) increased in an approximately dose-proportional manner over the dose range of 0.1 to 15 mg/kg. The area under the concentration-time curve from 0 to 14 days (AUC_{0-14}) increased in a greater than dose-proportional manner over the dose range of 0.1 to 3 mg/kg and increased dose-proportionally at ≥ 3 mg/kg. These results suggest that durvalumab exhibits nonlinear PK, likely due to saturable target-mediated clearance (CL), at doses < 3 mg/kg and approaches linearity at doses ≥ 3 mg/kg. Near complete target saturation (soluble programmed cell death ligand 1 [sPD-L1] and membrane bound) is expected with durvalumab ≥ 3 mg/kg Q2W. Exposures after multiple doses showed accumulation consistent with PK parameters estimated from the first dose. Of the 338 subjects for whom ADA were available, 8 were detected ADA-positive, with an impact on PK/pharmacodynamics in one subject.

2. STUDY PURPOSE AND RATIONALE

2.1 Rationale for Combination of JCAR014 with Durvalumab

CD19-targeted CAR T cells have been tested in adult patients with CD19+ B-cell NHL with a high overall response rate, but a lower than desirable rate of complete remission. While changes to the conditioning regimen or to the CAR T-cell product may improve the expansion and persistence of CAR T cells, expression of checkpoint proteins may decrease the function of the modified T cells, thereby limiting antitumor activity.

PD-L1 is expressed in lymphoma, both on the tumor and in the tumor microenvironment, and likely plays a role in tumor-associated immunosuppression (Andorsky 2011). Immunohistochemical studies conducted by MedImmune suggest that PD-L1 expression is a common feature of NHL tumors, with expression being found on greater than 5% of tumor cells or infiltrating lymphocytes in 75 of 84 (89%) NHL samples examined. Evidence also exists that PD-L1 is upregulated in response to IFNγ (Chen 2012, Abiko 2015). As such, PD-L1 expression may be induced or further upregulated on tumor cells and other infiltrating cells at the site of CAR T-cell action due to secretion of IFNγ by activated CAR-T cells. Expression of PD-L1 by

lymphoma cells may play a role in tumor-associated immunosuppression within the tumor microenvironment.

Blockade of the PD-1/PD-L1 axis has been explored in NHL (Lesokhin 2014). Preliminary results of a Phase 1 study of the PD-1 antagonist mAb nivolumab in NHL showed that PD-1 inhibition had an acceptable safety profile at similar dose levels (1 and 3 mg/kg) used for the treatment of solid tumors. Among 29 treated patients with B-cell NHL, 72% experienced drug-related AEs, including two patients (7%) with SAEs of pneumonitis. The clinical study included 11 patients with DLBCL, and evidence of clinical activity was observed. One patient achieved a CR and three additional patients achieved a partial response (PR). Progression-free survival (PFS) at 24 weeks was 24% for the cohort of patients with DLBCL.

It is well established that tumor-infiltrating lymphocytes (TILs) express PD-1, and preliminary data collected at Juno also suggest that CAR-T cells, upon stimulation through the CAR, upregulate expression of PD-1 and PD-L1, but not PD-L2. Thus, both TILs and CARs are targets of suppression by PD-L1. With these data in mind, CAR-T cells given in combination with agents that block T-cell suppression through the PD-1 pathway may have enhanced antitumor activity due to improved expansion of CAR-T cells and prolonged duration of CAR-T cell persistence and function.

Monoclonal blocking antibodies to PD-1 or PD-L1 have been shown to be safe and effective in patients with various cancers, and may be useful in reversing the PD-L1–mediated immunosuppression in patients treated with CAR-T cells. Durvalumab is a human IgG1κ mAb that binds to PD-L1 and inhibits the binding of PD-L1 to PD-1. In vitro studies have shown that durvalumab antagonizes the inhibitory effects of PD-L1 on primary human T cells, resulting in their enhanced proliferation and production of IFNγ in response to T-cell receptor stimulation. Thus, blockade of the PD-1/PD-L1 axis with durvalumab may improve the antitumor activity of JCAR014 in patients with aggressive NHL lymphoma by both blocking suppression of the CAR-T cells as well as reinvigorating exhausted CAR-T cells and TILs. This Phase 1 study is intended to evaluate the safety, tolerability, in vivo expansion, and antitumor activity of CAR-T cells (JCAR014) in combination with a PD-L1 antagonist (durvalumab) in R/R B-cell NHL.

2.2 JCAR014 Dose Rationale

This trial will employ lymphodepleting chemotherapy with cyclophosphamide and fludarabine prior to CAR-T cell administration. In the 2639 study, JCAR014 has been generally tolerated as monotherapy at dose levels ranging from 2 x 10^5 to 2 x 10^6 CAR+ T cells/kg in 14 patients with NHL conditioned with cyclophosphamide and fludarabine (see Section 1.5.1.2); toxicity was encountered in three of six patients treated with 2 x 10^7 CAR+ T cells/kg, which exceeded the MTD. Antitumor activity has been observed in patients with NHL at all doses of JCAR014 tested.

2.3 Rationale for Lymphodepleting Chemotherapy

Clinical trials of T-cell therapy for melanoma at the National Cancer Institute (NCI) demonstrated that administering lymphodepleting chemotherapy such as fludarabine and cyclophosphamide, or fludarabine, cyclophosphamide, and total body irradiation, prior to the transfer of 10^{10} to 10^{11} polyclonal melanoma-specific T cells improved the survival of a subset of the transferred T cells and antitumor efficacy (Dudley 2002, Dudley 2005, Dudley 2008). The size of the T-cell pool is subject to homeostatic regulation, and the induction of lymphopenia results in less competition for cytokines such as IL-15 and IL-7 that promote lymphocyte proliferation and survival, and thus leads to the proliferation of residual T cells including those that are adoptively transferred. Lymphodepleting chemotherapy may also eliminate $CD4^+$ $CD25^+$ regulatory T cells, and activate antigen-presenting cells that may promote the function of transferred T cells. Studies in murine models subsequently confirmed the human data indicating that lymphodepletion improves the persistence and antitumor efficacy of transferred effector T cells (Wrzesinski 2007).

Data have been presented for over 50 patients with NHL who were treated with three different CD19-targeted CAR-T cell products; however, there is no consensus on the optimal lymphodepleting chemotherapy regimen to use.

Encouraging antitumor activity has been observed in 11 patients with NHL who received lymphodepleting chemotherapy with a combination of high doses of cyclophosphamide (60 to 120 mg/kg) and fludarabine (25 mg/m^2/day for 5 days) (Kochenderfer 2015). However, significant cardiac toxicity, neurotoxicity, and death were reported at the highest CAR-T cell dose level (5 x 10^6 CAR+ T cells/kg). When the CAR-T cell dose was reduced to 1 x 10^6 CAR+ T cells/kg and a lower dose regimen of cyclophosphamide (300 mg/m^2/day for 3 days) and fludarabine (30 mg/m^2/day for 3 days) was used, the severe cardiac and neurotoxicity was eliminated, and although transient neurotoxicity (aphasia and ataxia) was still evident, encouraging antitumor activity was observed (Kochenderfer 2014a).

Current data with JCAR014 show improved CAR-T cell expansion, persistence, and antitumor activity in patients conditioned with high-dose cyclophosphamide (60 mg/kg) and fludarabine (25 mg/m^2/day for 3 to 5 days) compared with those treated with cyclophosphamide alone or in combination with etoposide (see Section 1.5.1.2). However, similar to the data presented by Kochenderfer et al., cardiac toxicity, neurotoxicity, and death were observed with high cell doses (2 x 10^7 CAR+ T cells/kg). Current data in 14 patients support the tolerability of monotherapy at doses of 2 x 10^5 (n = 3) and 2 x 10^6 CAR+ T cells/kg (n = 11) after Cy/Flu conditioning. CAR-T cell expansion was also observed in a small number of patients who were retreated with a second dose of JCAR014 after Cy/Flu conditioning, whereas no appreciable expansion was observed in patients retreated with JCAR014 after conditioning with regimens other than cyclophosphamide and fludarabine (personal communication, Turtle et al).

2.4 Durvalumab Dose Rationale

The dose level and treatment schedule for durvalumab (up to 20 mg/kg Q4W) is based on a safe dose established in Study CD-ON-MEDI4736-1108, a Phase 1/2 study to evaluate the safety, tolerability, and PK of durvalumab in patients with advanced solid tumors (see Section 1.5.2.3). To our knowledge, anti–PD-L1 antibodies have not previously been administered in combination with CAR-T cells, such as JCAR014, in human patients. Inhibition of PD-L1 prior to the administration of JCAR014 has the potential to affect the proliferative rate and adverse event profile of JCAR014. Similarly, the stimulation of CAR-T cells and the secretion of cytokines have the potential to affect the adverse event profile of durvalumab due to the activation of endogenous TILs upon lifting checkpoint inhibition. Thus, the combination of JCAR014 and durvalumab has the potential to cause both immune-related adverse events (irAEs), defined as AEs of an immune nature (i.e., inflammatory) in the absence of a clear alternative etiology, as well as AEs unique to JCAR014 or the combination.

A fixed dosing regimen will be used for this study and is based on a population PK model that was developed for durvalumab using monotherapy data from Study CD-ON-MEDI4736-1108 (292 patients; dose regimens = 0.1 to 10 mg/kg Q2W or 15 mg/kg every 3 weeks). Population PK analysis indicated only a minor impact of body weight on the PK of durvalumab (coefficient of ≤ 0.5). The impact of body weight-based (10 mg/kg Q2W) and fixed dosing (750 mg Q2W) of durvalumab was evaluated by comparing predicted steady state PK concentrations (5th, median, and 95th percentiles) using the population PK model. A fixed dose of 750 mg and 1500 mg was selected to approximate 10 mg/kg and 20 mg/kg, respectively (based on median body weight of approximately 75 kg). A total of 1000 patients were simulated using a body weight distribution of 40 to 120 kg. Simulation results demonstrated that body weight-based and fixed dosing regimens yield similar median steady state PK concentrations with slightly less overall between-patient variability with fixed dosing regimen.

The proposed initial durvalumab dose level in Group 1 will utilize a dose of durvalumab equivalent to that shown to have an acceptable safety profile (225 mg or 3 mg/kg IV Q4W) and approximately one order of magnitude below the recommended dose (1500 mg or 20 mg/kg Q4W). A further 1.5 order of magnitude reduction in the initial durvalumab dose level in Group 2 to 7.5 mg Q4W (equivalent to ~0.1 mg/kg) is planned in order to start below a dose that would provide maximal inhibition of PD-L1 throughout the interval of dosing. Dose escalation will then follow a modified toxicity probability interval (mTPI) scheme with careful safety monitoring.

2.5 Rationale for Dosing Schedules with JCAR014 and Durvalumab

In vitro studies have shown that durvalumab antagonizes the inhibitory effects of PD-L1 on primary human T cells, resulting in their enhanced proliferation and production of IFNγ. Thus, blockade of the PD-1/PD-L1 axis with durvalumab may be able to improve the antitumor activity of CAR-T cells such as JCAR014 in patients with aggressive NHL lymphoma by either

reinvigorating exhausted CAR-T cells or blocking suppression of the CAR-T cells that are subsequently infused.

After treatment with CAR-T cells, most patients with lymphoma have a partial response and, although CAR-T cells may persist, the cells decline in number in the peripheral blood and fail to mediate further resolution of the lymphoma. Administration of a PD-L1 inhibitor after treatment with JCAR014 (Group 1) may reverse the suppression of the CAR-T cells that may have occurred from PD-L1 expression on the tumor, or on cells in the tumor microenvironment, including the CAR-T cells. Administering a PD-L1 inhibitor prior to treatment with JCAR014 (Group 2) may prevent the induction of suppression of the CAR-T cells at the tumor site or by the tumor microenvironment, resulting in superior antitumor efficacy.

3. STUDY OBJECTIVE AND ENDPOINTS

The objectives and corresponding endpoints for the study are presented in Table 2.

Table 2: Study Objectives and Endpoints

Objective	Endpoint(s)
Primary	
• To evaluate the safety of JCAR014 in combination with durvalumab in adult patients with R/R B-cell NHL	• Type, frequency, and severity of AEs and laboratory abnormalities • DLT rates
• To determine the maximum tolerated dose (MTD) of durvalumab in combination with JCAR014	• MTD estimated per isotonic regression
• To characterize the PK profile of JCAR014	• Maximum concentration (Cmax), time to maximum concentration (Tmax), area under the curve (AUC), and other relevant PK parameters of JCAR014
Secondary	
• To assess the antitumor activity of JCAR014 in combination with durvalumab in R/R B-cell NHL	• Rate of CR, rate of PR, and objective response rate (ORR, defined as the proportion of patients with a best response of either CR or PR) by Investigator assessment using Lugano criteria
• To estimate the duration of response (DOR), PFS, and overall survival (OS) in patients treated with JCAR014 in combination with durvalumab	• DOR, defined as the time from first response to progressive disease (PD) or death • PFS, defined as the time from date of first study treatment (JCAR014 or durvalumab) to PD or death • OS, defined as the time from date of first study treatment to death
• To characterize the PK profile of durvalumab	• Cmax, Tmax, AUC, and other relevant PK parameters of durvalumab

Objective	Endpoint(s)
• To assess the immunogenicity of JCAR014 and durvalumab	• Measurement of antibodies and cellular immune responses to JCAR014 and ADAs directed against durvalumab
Exploratory	
• To assess the pharmacodynamic effects of JCAR014 and durvalumab in blood and within the tumor	• B-cell depletion in circulation, profile of soluble circulating proteins such as cytokines and chemokines, and changes in the level of detectable soluble PD-L1 in serum • Assessment by immunohistochemistry and/or gene expression of changes in the phenotype of tumor cells (e.g., expression of PD-L1) and of the tumor microenvironment (e.g., infiltration by CAR-T cells) assessed in biopsies • Assessment of the phenotype and/or genetic profile of endogenous immune cells and CAR-T cells in blood • Evaluations may be made pre-JCAR014 and post-JCAR014 and/or pre-durvalumab and post-durvalumab

4. STUDY DESIGN AND INVESTIGATIONAL PLAN

4.1 Overall Study Design

This is an open-label, single-center, Phase 1b study to determine the safety, PK, and antitumor activity of JCAR014 in combination with durvalumab in adult patients with R/R DLBCL (including transformed DLBCL and primary mediastinal B-cell lymphoma [PMBCL]).

Patients will be enrolled into one of two treatment groups (Group 1 or Group 2). Within each group, dose escalation/de-escalation of durvalumab will follow a modified toxicity probability interval (mTPI) algorithm (Ji 2010) with a target DLT rate of 30% and an equivalence interval of 25%–35%. A dose level will be considered unsafe, with no additional patients enrolled at that dose level, if it has an estimated 95% or more probability of exceeding the target DLT rate of 30% (i.e., P[DLT>30%|data] > 95%) with at least three patients treated at that dose level. Dose escalation in each group will occur independently according to the mTPI algorithm as applied to each group.

Initial Study Design:

Group 1 (first dose of durvalumab after JCAR014):

Patients in Group 1 receive the first infusion of durvalumab after treatment with JCAR014. The first treated cohorts of patients in Group 1 received durvalumab no earlier than 21 days after the JCAR014 infusion (Group 1 – late). Patients in Group 1 receiving JCAR014 (up to 2 x 10^6 CAR-T cells/kg) are assessed for DLT (see Section 4.3) from the time of the first durvalumab

infusion until 28 days after the first durvalumab infusion. According to the mTPI algorithm, durvalumab at Dose Level 1 (225 mg, n = 3 evaluable) and Dose Level 2 (750 mg, n = 3 evaluable) were found to have acceptable safety.

Group 2 (first dose of durvalumab before JCAR014):

Patients in Group 2 receive the first dose of durvalumab 1 day prior to administration of JCAR014. DLTs in Group 2 are assessed from the time of the pre-JCAR014 dose of durvalumab until 28 days after treatment with JCAR014 (up to 2 x 10^6 CAR T cells/kg). According to the mTPI algorithm, durvalumab at Dose Level 1 (7.5 mg, n = 1 evaluable), Dose Level 2 (22.5 mg, n = 1 evaluable), Dose Level 3 (75 mg, n = 3 evaluable), Dose Level 4 (225 mg, n = 6 evaluable, including one DLT), and Dose Level 5 (750 mg, n = 6 evaluable, including one DLT) were found to have acceptable safety.

In Group 1 and Group 2, patients subsequently receive durvalumab at approximately 28 day intervals at the current highest safe durvalumab dose level (750 mg) identified in dose escalation studies in either Group 1 or Group 2.

Amended Study Design:

Analyses of efficacy and pharmacodynamic data from patients previously treated in Group 1 (day 21 durvalumab start) and Group 2 (day -1 durvalumab start) indicated that durvalumab ≤ 750 mg starting no earlier than day 21 (Group 1 – late) may be superior to starting on day -1 (Group 2). Furthermore, data from the trial sponsor indicated that durvalumab 1500 mg is unlikely to provide an advantage in PD-L1 blockade compared to durvalumab 750 mg, suggesting that escalation to durvalumab 1500 mg in this trial may be unnecessary. Because JCAR014 CAR-T cells are declining in blood at day 21 after JCAR014 infusion, we elected to revise the protocol to add a cohort in Group 1 who receive durvalumab as early as 7 days after JCAR014 infusion (Group 1 – early) and nominate 750 mg as the maximum durvalumab dose in all Groups. Patients in Group 1 – early receiving JCAR014 (up to 2 x 10^6 CAR-T cells/kg) are treated in cohorts of 3 patients and assessed for DLT from the time of the first durvalumab infusion until 28 days after the first durvalumab infusion. Durvalumab dose de-escalation/re-escalation decisions follow the mTPI algorithm in cohorts of 3 patients.

Amended groups:

Group 1 – late: start durvalumab no earlier than 21 days after JCAR014.

Group 1 – early: start durvalumab no earlier than 7 days after JCAR014.

Group 2: start durvalumab one day prior to JCAR014.

In all groups, patients subsequently receive durvalumab 750 mg at approximately 28 day intervals.

If durvalumab 750 mg has acceptable safety in Group 1 – early (day 7 start) according to the mTPI algorithm, patients will then be treated alternately in Group 1 – early and Group 1 – late until 6 evaluable patients have been treated in each of the 3 groups: Group 2; Group 1 – late;

Group 1 – early. The Steering Committee (SC) will then evaluate available safety, toxicity, efficacy, and pharmacodynamic data to determine which group/s should be subsequently expanded. Allocation of the subsequent patients will be alternated if more than one cohort is expanded. The maximum number of evaluable patients in the trial will be 42.

Study schematics for patients treated in Group 1 and Group 2 are provided in Figure 1 and Figure 2, respectively.

Figure 1: Study Schema for Patients in Group 1 (Post-JCAR014 Treatment with Durvalumab)

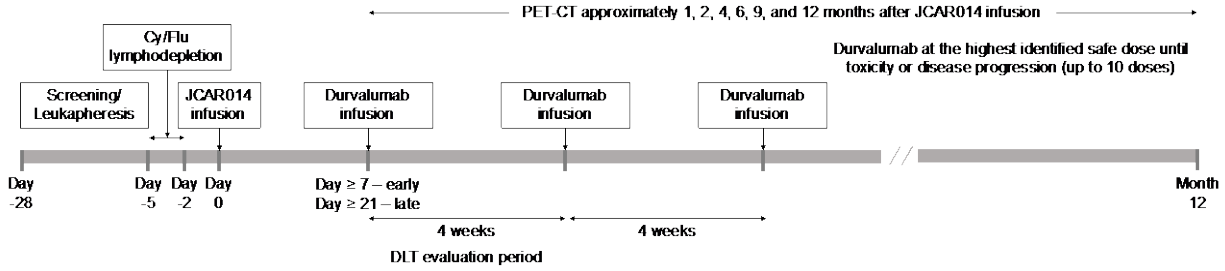
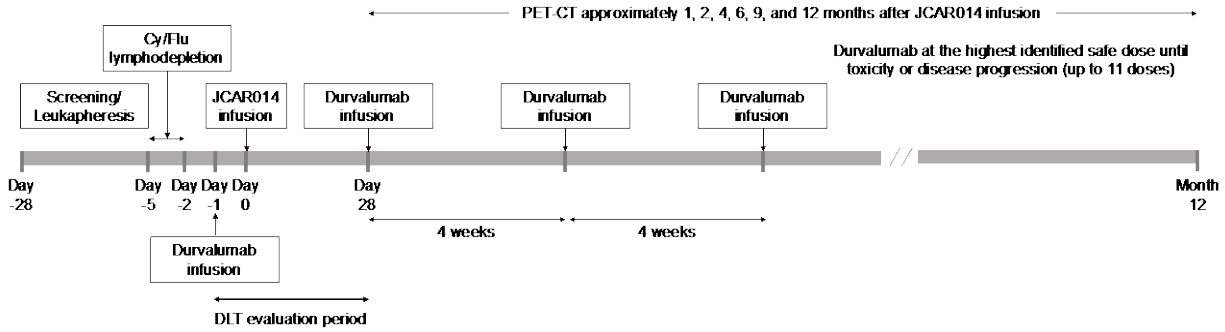


Figure 2: Study Schema for Patients in Group 2 (Pre-JCAR014 Treatment with Durvalumab)



In both groups, JCAR014 may be dose de-escalated after review by the SC if the SC determines that the observed clinical safety data indicate that dose de-escalation of JCAR014 is required. In this case, a separate group may be enrolled at a stable dose of durvalumab (to be determined by the SC) and dose re-escalation of JCAR014 may occur via the mTPI algorithm. Enrollment in this group will commence after amendment to the protocol and discussion with the FDA.

All eligible patients will undergo leukapheresis to enable JCAR014 production. Lymphodepleting chemotherapy will be administered prior to JCAR014 administration, and will consist of either a single dose of cyclophosphamide 60 mg/kg administered on Day -5 and three daily doses of fludarabine 25 mg/m^2/day on Days -4 to -2 or concurrent cyclophosphamide (300 mg/m^2/day) and fludarabine (30 mg/m^2/day) on days -4 through -2. The first dose of durvalumab will be administered on Day -1 for patients in Group 2 only, and approximately day 7 or 21 for patients in Group 1. All patients will receive JCAR014 on Day 0. In both groups, durvalumab

will be administered approximately every 4 weeks for the greater of either 10 post-JCAR014 cycles or 4 cycles beyond identification of CR (for patients in whom studies demonstrating transition to CR occur late after JCAR014 infusion). Durvalumab cycles may be ceased if there is unacceptable toxicity, disease progression, or the patient or PI/designee determine it is not in the patient's best interest to continue durvalumab. Patients with disease progression at restaging who have evidence of biological activity after durvalumab infusion that could be associated with subsequent anti-tumor effect (e.g. a mixed response, tumor stability, or evidence of JCAR014 expansion and/or persistence) may receive additional post-JCAR014 cycles of durvalumab up to the maximum number allowed for Group 1 or Group 2.

The planned dose levels for durvalumab and JCAR014 are listed in Table 3. Intermediate doses may be evaluated upon recommendation by the SC.

Table 3: Planned Dose Levels for Durvalumab and JCAR014

Dose Level	Durvalumab		JCAR014 (Group 1 and Group 2)
	Group 1	Group 2	
-1	75 mg	—	—
1	225 mg	7.5 mg	Up to 2 x 10^6/kg CAR-T cells
2	750 mg	22.5 mg	—
3	—	75 mg	—
4	—	225 mg	—
5	—	750 mg	—

After the JCAR014 infusion, patients will be monitored for in vivo T-cell expansion/persistence and will have serum samples collected for cytokine profiling. Standard safety laboratory studies will be monitored until 12 months post-JCAR014 infusion or 90 days after the final durvalumab infusion, whichever is longer. Safety and tolerability will be assessed from study entry until the end of treatment and primary follow-up (12 months post-JCAR014 infusion or 90 days after the last durvalumab infusion, whichever is longer). Long-term follow-up to assess delayed AEs will begin after the primary follow-up and will continue for up to 15 years after the JCAR014 infusion. Toxicities will be graded using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03, with the exception of CRS, which will be graded according to a system based on modified criteria (Davila 2014, Lee 2014). PK (in vivo expansion and persistence) will be assessed from the time of JCAR014 infusion until cells are no longer detectable by flow cytometry or quantitative polymerase chain reaction (qPCR).

For a subset of patients with accessible tumor who consent to optional biopsies, a fresh tumor biopsy may be obtained prior to lymphodepleting chemotherapy, within the first 4 weeks after administration of JCAR014, and approximately within the first 4 weeks after the first post-JCAR014 administration of durvalumab. If biopsy within this period is not suitable for

logistical, research or clinical reasons, biopsies may be completed at a different time. In the event of persistent mass, relapse or progression, a biopsy may be collected at that time point. These samples will be evaluated for the extent of JCAR014 migration and PD-1 and PD-L1 expression. Additional markers of immune cell phenotype and analysis of the tumor microenvironment may be explored in response to emerging data.

Disease response will be determined by positron emission tomography (PET)/computed tomography (CT) at approximately 1, 2, 4, 6, 9, and 12 months after the JCAR014 infusion (at the end of the JCAR014 cycle, the end of the first post-JCAR014 durvalumab cycle, approximately every other durvalumab cycle until 6 months after the JCAR014 infusion, then every 3 months until 12 months after the JCAR014 infusion or 90 days after the last durvalumab dose, whichever is later). At the time of the 1-month post-JCAR014 response assessments, patients with bone marrow lymphoma at baseline may have a repeat bone marrow aspirate and biopsy that will be analyzed for lymphoma by flow cytometry; samples may also be analyzed for other exploratory endpoints. Bone marrow and aspirates may be collected and analyzed at other timepoints as clinically indicated until the patient achieves a CR.

Patients may be eligible for retreatment with JCAR014 at the same cell dose ± durvalumab at or below the highest tested safe dose if at least 3 months have elapsed since the last dose of durvalumab. Subjects undergoing retreatment will follow the same assessment schedule; however, durvalumab-related assessments will not be conducted in subjects who receive retreatment with JCAR014 only. Retreatment data will not be included in the dose-finding portion of the study.

After the primary follow-up phase (12 months post-JCAR014 infusion or 90 days after the last durvalumab infusion, whichever is longer), patients will be asked to participate in long-term follow-up in accordance with Food and Drug Administration guidelines.

4.2 Dose Escalation Scheme

Dose escalation will follow the mTPI decision table in Appendix F. The PI or designee will submit an updated list of treated subjects and DLT events to FHCRC Statistics, who will then confirm the assigned durvalumab dose and treatment group.

4.3 Dose-Limiting Toxicity Criteria

The following treatment-related (JCAR014 or durvalumab) events will be considered DLTs:

1. Death within 4 weeks of the study treatment
2. Grade ≥ 3 neurotoxicity of greater than 7 days duration
3. Grade ≥ 3 neurotoxicity that does not revert to Grade 1 or baseline within 28 days
4. Grade ≥ 3 seizures that do not resolve to grade ≤ 2 within 3 days
5. Grade ≥ 4 cytokine release syndrome (grading is shown in Table 5)

6. Grade 3 cytokine release syndrome that does not resolve to grade ≤ 2 within 7 days
7. Grade ≥ 3 non-infectious colitis or non-infectious pneumonitis
8. Grade ≥ 3 irAE or other grade ≥ 3 autoimmune toxicity (excluding B-cell aplasia)
9. Any increase in aspartate transaminase (AST) or ALT > 3 x ULN and concurrent increase in total bilirubin > 2 x ULN that is unrelated to CRS and has no other probable reason to explain the combination of increases
10. Grade ≥ 3 allergic reaction to the JCAR014 infusion
11. Any Grade 3 or 4 event deemed unexpected by the Investigator and considered a DLT upon evaluation by the Steering Committee

4.4 Protocol Enrollment

Enrollment is expected to take approximately 18 to 24 months. Study treatment with initial follow-up is expected to be approximately 15 months. All patients who receive treatment with JCAR014 will be followed for up to 15 years after the JCAR014 dose for safety evaluations (see Section 8.1.13). The anticipated duration of the study is approximately 3 years.

4.5 Removal of Patients from Study

4.5.1 Patient Withdrawal from Further Study Treatment

Patients who receive JCAR014 and/or durvalumab and are subsequently withdrawn from further study treatment (e.g., due to toxicity) will not be withdrawn from the study. They will remain on study and continue to have all scheduled follow-up evaluations per the Schedule of Events (see Appendix A). A patient's treatment may be discontinued for any of the following reasons:

- CR
- Undetectable levels of JCAR014 (< 10 copies/µg DNA in blood by PCR) on two consecutive evaluations
- Progressive disease
- AE
- Investigator decision
- Patient decision
- Other

Patients who receive treatment with JCAR014 and/or durvalumab, achieve a CR, and then relapse may be eligible for retreatment (see Section 8.1.12).

4.5.2 Patient Withdrawal from Study

A patient may be discontinued from the study for any of the following reasons:

- Patient did not receive any study therapy (JCAR014 or durvalumab)
- Patient withdrawal of consent
- Study termination by the Principal Investigator (PI), the FHCRC Institutional Review Board (IRB), or the FDA
- Lost to follow-up
- Death
- Other

Patients who are withdrawn from the study because of failure to generate a JCAR014 dose that meets the required quality control and criteria for product release may re-enroll in the study at a later time provided that the patient meets all eligibility criteria.

4.5.3 Termination of the Study

The study may be terminated at any time by the PI, the study Sponsor, the FHCRC IRB, or the FDA.

4.5.4 Replacement of Study Patients

Patients who are enrolled for leukapheresis and/or treatment with lymphodepleting chemotherapy, JCAR014, and durvalumab, but do not receive at least one dose of JCAR014 or durvalumab will be replaced. In addition, patients enrolled in the dose-escalation phase who do not complete the DLT evaluation period for reasons other than DLT will be considered non-evaluable and will be replaced with another patient at the same dose level.

5. STUDY POPULATION

The target study population consists of adult patients with R/R DLBCL. Patients must meet all of the inclusion and exclusion criteria to be enrolled in this study.

5.1 Criteria for Screening

5.1.1 Inclusion Criteria

1) Male or female ≥ 18 years of age at the time of screening consent
2) Relapsed or refractory DLBCL, not otherwise specified (NOS); high grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements; primary mediastinal B-cell lymphoma (PMBCL); or DLBCL transformed from indolent histology with one of the following:
    a) Persistent disease after first-line chemo-immunotherapy
    b) Relapse after first-line chemo-immunotherapy and not eligible for autologous hematopoietic stem cell transplant (HCT)

c) Relapse or persistent disease after at least two lines of therapy or after autologous HCT

3) Ability to understand and provide informed consent

5.1.2 Exclusion Criteria

1) Subjects with known active central nervous system (CNS) involvement by malignancy. Subjects with prior CNS disease that has been effectively treated will be eligible if treatment was completed at least 3 months prior to enrollment and there is no evidence of disease or stable abnormalities on repeat imaging
2) Planned use of corticosteroids (> 10 mg/day prednisone or equivalent) or other systemic immunosuppression within 4 days prior to leukapheresis. Topical and/or inhaled steroids are permitted.
3) Prior treatment with any CD19 CAR-T cell therapy
4) Prior allogeneic HCT
5) Known active hepatitis B, hepatitis C, or human immunodeficiency virus (HIV) infection
6) Pregnant or breastfeeding women
7) Known exclusion criteria for leukapheresis, JCAR014, or durvalumab therapy

5.2 Criteria for Leukapheresis and Pre-therapy Evaluation

5.2.1 Inclusion Criteria

1) Screening evaluation appropriate for leukapheresis and T-cell collection
2) Evidence of CD19 expression on any prior or current tumor specimen or a high likelihood of CD19 expression based on disease histology

5.2.2 Exclusion Criteria

1) Subjects with known active central nervous system (CNS) involvement by malignancy. Subjects with prior CNS disease that has been effectively treated will be eligible if treatment was completed at least 3 months prior to enrollment and there is no evidence of disease or stable abnormalities on repeat imaging
2) Prior treatment with PD-1, PD-L1, cytotoxic T lymphocyte-associated protein 4 (CTLA-4) targeted therapy, or tumor necrosis factor receptor superfamily (TNFRSF) agonists including CD134 (OX40), CD27, CD137 (4-1BB), and CD357 (glucocorticoid-induced tumor necrosis factor receptor family-related protein [GITR])

3) Active or prior documented autoimmune or inflammatory disorders (including inflammatory bowel disease [e.g., ulcerative colitis, Crohn's disease], celiac disease, or other serious chronic gastrointestinal conditions associated with diarrhea, autoimmune vasculitis, systemic lupus erythematosus, Wegener syndrome [granulomatosis with polyangitis], myasthenia gravis, Graves' disease; rheumatoid arthritis, hypophysitis, uveitis, etc.) within 3 years prior to the planned start of treatment. The following are exceptions to this criterion:
    a) Vitiligo
    b) Alopecia
    c) Hypothyroidism (e.g., following Hashimoto syndrome) stable on hormone replacement
    d) Psoriasis not requiring systemic treatment
    e) Other conditions considered to be low risk of serious deterioration by the PI
4) History of any one of the following cardiovascular conditions within the past 6 months: Class III or IV heart failure as defined by the New York Heart Association (NYHA), cardiac angioplasty or stenting, myocardial infarction, or unstable angina. History of other clinically significant cardiac disease that, in the opinion of the PI or designee, is a contraindication to lymphodepleting chemotherapy, JCAR014 infusion, or durvalumab infusion is also excluded.
5) History or presence of clinically relevant CNS pathology, such as epilepsy, seizure, paresis, aphasia, stroke, severe brain injuries, dementia, Parkinson's disease, cerebellar disease, or psychosis. History of other organic brain syndrome that in the opinion of the PI or designee is a contraindication to lymphodepleting chemotherapy, JCAR014 infusion or durvalumab infusion
6) History of solid organ transplantation

5.3 Criteria for Lymphodepletion Chemotherapy, JCAR014 and Durvalumab Therapy

5.3.1 Inclusion Criteria

1) Successful collection of T cells for JCAR014 manufacturing
2) Documentation of CD19 expression on any prior or current tumor biopsy
3) Internal review of histology
4) Detectable PET-positive disease
5) Karnofsky performance status ≥ 60%
6) Adequate organ function, defined as:
    a) Assessed by the Investigator to have adequate bone marrow function to receive lymphodepleting conditioning chemotherapy

b) Serum creatinine < 1.5 x age-adjusted ULN

c) ALT and AST < 3 x ULN and total bilirubin ≤ 2 x ULN

d) Adequate pulmonary function, defined as CTCAE Grade ≤ 1 dyspnea and SaO_2 ≥ 92% on room air. Patients with clinically significant pulmonary dysfunction, as determined by medical history and physical exam should undergo pulmonary function testing and must have a forced expiratory volume in 1 second (FEV1) ≥ 50% of predicted value or diffusing capacity of the lung for carbon monoxide (DLCO; corrected) ≥ 40% of predicted value

e) Adequate cardiac function, defined as left ventricular ejection fraction (LVEF) ≥ 35% as assessed by echocardiogram (ECHO) or multiple uptake gated acquisition (MUGA)

7) Women of reproductive potential (defined as all women physiologically capable of becoming pregnant) must agree to use suitable methods of contraception for 90 days after the last dose of study therapy (durvalumab or JCAR014)

8) Males who have partners of reproductive potential must agree to use an effective barrier contraceptive method for 90 days after the last dose of study therapy (durvalumab or JCAR014)

5.3.2 Exclusion Criteria

1) Subjects with known active CNS involvement by malignancy. Subjects with prior CNS disease that has been effectively treated will be eligible if treatment was completed at least 3 months prior to enrollment and there is no evidence of disease or stable abnormalities on repeat imaging.

2) Uncontrolled infection

3) Receipt of live, attenuated vaccine within 28 days prior to the first dose of durvalumab (Note: enrolled patients should not receive live vaccine during the study and for 180 days after the last dose of durvalumab)

4) Planned use of corticosteroids (> 10 mg/day prednisone or equivalent) or other systemic immunosuppression is not permitted within 72 hours prior to JCAR014 infusion. Topical and/or inhaled steroids are permitted.

5.4 Reproductive Potential and Contraception Requirements

Any female patient who does not meet at least one of the following criteria will be considered to have reproductive potential:

- Post-menopausal for at least 12 consecutive months (i.e., no menses), or
- Undergone a sterilization procedure (hysterectomy, salpingectomy, or bilateral oophorectomy; tubal ligation is not considered a sterilization procedure)

Pregnancy test for females of reproductive potential must be negative within 14 days before leukapheresis and within 28 days before lymphodepleting chemotherapy.

Female patients with reproductive potential who are not sexually abstinent and male patients who are sexually active with females of reproductive potential must agree to use a suitable method of contraception for the duration of the study (from screening through 90 days after the last dose of study therapy [durvalumab or JCAR014]), for example:

- Condom with spermicidal agent
- Diaphragm or cervical cap with spermicidal agent
- Intrauterine device
- Hormonal contraceptives in combination with either a condom, diaphragm, or cervical cap

6. STUDY TREATMENTS

Minor variations to the outlined schedules for logistical or clinical reasons are permissible.

6.1 Leukapheresis

Following enrollment on the study, a leukapheresis collection will be performed on each patient to obtain PBMCs for the production of the JCAR014 investigational product. The leukapheresis will be performed by the Seattle Cancer Care Alliance (SCCA) Apheresis Unit using standard operating procedures (SOPs) for obtaining PBMCs. If a technical issue arises during the procedure or in the immediate processing of the product such that it cannot be used for JCAR014 production, the patient may undergo a second collection procedure.

Patients ineligible for a vein-to-vein apheresis may elect to have a percutaneous central venous access catheter inserted to support this collection.

The leukapheresis product will be delivered to the Cell Processing Facility (CPF) at the FHCRC or the Cell Therapy Laboratory (CTL) at the SCCA. CAR-T cell manufacturing will be conducted in accordance with the IND. A portion of the cells at any point in manufacturing may be collected for research.

Quality control and release testing will be performed on the CAR-T cell product prior to its release for patient infusion.

6.2 Lymphodepleting Chemotherapy

Patients will either be treated with a single dose of cyclophosphamide (60 mg/kg) followed by fludarabine (25 mg/m^2/day for 3 days) or with concurrent cyclophosphamide (300 mg/m^2/day) and fludarabine (30 mg/m^2/day) for 3 days prior to treatment with JCAR014. Refer to the most recent package inserts for specific details on administration of these agents. Dose reduction is permissible at the discretion of the PI or designee.

6.3 JCAR014 Treatment

JCAR014 should be administered at least 36 hours and preferably within 96 hours after completion of lymphodepleting chemotherapy. However, the JCAR014 infusion may be delayed to allow for resolution of AEs related to the disease, lymphodepleting chemotherapy, and durvalumab infusion, or for other factors.

Within a day of scheduled JCAR014 infusion the patient should undergo a clinical evaluation and determination of suitability to proceed with JCAR014 administration. Patients deemed not suitable for JCAR014 administration may receive JCAR014 with or without lymphodepletion chemotherapy at a later time if the clinical and/or laboratory contraindication to infusion subsequently improves. Discussion with the protocol PI or designee is required.

6.3.1 JCAR014 Administration

JCAR014 will be provided as a single cell product at the assigned cell dose. The JCAR014 infusion should be administered IV over approximately 20 to 30 minutes. All patients will be monitored during each T-cell infusion with vital signs and O_2 saturation being recorded before, during, and after the infusion (see Section 8.3.5).

6.3.2 Acute Infusion Reactions

Acute infusion reactions may occur with administration of JCAR014 or durvalumab. Guidelines for the treatment of acute infusion reactions are provided in Section 7.4.

6.4 Durvalumab Treatment

Durvalumab will be administered as an IV infusion at the assigned dose. Continued dosing at an approximately Q4W interval is allowed after clearance of the DLT evaluation period.

Within a day of scheduled durvalumab infusion the patient should undergo a clinical evaluation and clinical determination for suitability to proceed with durvalumab administration. Patients deemed not suitable for durvalumab administration may receive durvalumab with or without lymphodepletion chemotherapy at a later time if the clinical and/or laboratory contraindication to infusion subsequently improves. Discussion with the protocol PI or designee is required.

6.4.1 Durvalumab Drug Product

Durvalumab will be supplied as a 500 mg vial solution for infusion after dilution. The solution contains 50 mg/mL durvalumab, 26 mM histidine/histidine-hydrochloride, 275 mM trehalose dihydrate, and 0.02% (w/v) polysorbate 80; it has a pH of 6.0. The nominal fill volume is 10 mL. Durvalumab must be stored at 2°C to 8°C (36°F to 46°F).

6.4.2 Durvalumab Preparation and Administration

The dose of durvalumab for administration must be prepared by the Investigator's or site's designated investigational product (IP) manager using aseptic technique. Total time from needle puncture of the vial to the start of administration should not exceed:

- 24 hours at 2°C to 8°C (36°F to 46°F)
- 4 hours at room temperature

Durvalumab will be administered using an IV bag containing 0.9% (w/v) saline, with a final in-bag concentration ranging from 0.15 mg/mL to 20 mg/mL, and delivered through an IV administration set with a 0.2 µm or 0.22 µm in-line filter.

The IV bag size should be selected such that a final durvalumab in-bag concentration of 0.15 mg/mL to 20 mg/mL is achieved. The volumes of durvalumab, syringe accuracy, and acceptable bag volumes for each dose level are provided in Table 4.

Table 4: IV Bag Specifications for each Durvalumab Dose Level

Durvalumab dose (mg)	Durvalumab volume (mL)	Syringe accuracy (mL)	Acceptable IV bag sizes (mL)
7.5	0.15	0.01	50
22.5	0.45	0.01	50-100
75	1.5	0.1	50-500
225	4.5	0.1	50-1000
750	15	0.5	50-1000

A volume of IV bag diluent equal to the determined volume of durvalumab must be removed from the bag prior to addition of durvalumab. The determined volume of durvalumab is then added to the IV bag, and the bag is mixed by gentle inversion to ensure homogeneity of the dose in the bag. No incompatibilities between durvalumab and polyvinylchloride or polyolefin have been observed.

The standard infusion time is 1 hour; however, if there are interruptions during infusion, the total allowed time should not exceed 8 hours at room temperature. In the event that either preparation time or infusion time exceeds the specified time limits, a new dose must be prepared from new vials to ensure the patient receives the intended durvalumab dose. Durvalumab does not contain preservatives, and any unused portion must be discarded.

6.5 Recommended Supportive Care, Additional Treatment, and Monitoring

Prophylactic treatment/measures are strongly recommended for patients at risk for tumor lysis syndrome (TLS) according to institutional or clinical standards. Supportive care for the management of CRS is detailed in Section 7.1.

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

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

Prophylactic anti-seizure medication should be considered in some patients (see Section 7.2).

Hospitalization may be required after study treatment to manage any treatment-associated toxicities. Patients who do not have adequate support outside of the hospital or do not have reliable transportation to the clinic for scheduled evaluation or emergencies should be considered for hospitalization for the first 7 days of treatment in each cycle.

6.6 Concomitant Medications

Prescription medications taken by the patient at the time of a protocol-related AE that occurs from the time of informed consent until initiation of lymphodepleting chemotherapy will be recorded. All medications taken from the time of lymphodepleting chemotherapy until 30 days after the last dose of study therapy (durvalumab or JCAR014) will be recorded. From 30 days to 12 months after the the last dose of study therapy, only concomitant medications used at the time of JCAR014-related or durvalumab-related AEs will be recorded. Patients 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.

Vaccination with a killed vaccine is permitted at any time with consultation with the medical monitor.

7. POTENTIAL RISKS AND MANAGEMENT OF TREATMENT TOXICITIES

Administration of durvalumab is expected to enhance the persistence and activity of JCAR014 T cells. Similarly, cytokines released in response to JCAR014 administration may activate endogenous T cells, thus potentiating the immune-related adverse events associated with administration of immune therapies such as durvalumab. Thus, administration of the two agents in combination could exacerbate the adverse events expected from each agent alone.

A summary of potential risks and management of treatment toxicities is provided in the sections below.

7.1 Cytokine Release Syndrome

Administration of CAR-T cells such as JCAR014 may be associated with CRS. CRS may be characterized by high fever, fatigue, nausea, headache, dyspnea, tachycardia, rigors, hypotension, hypoxia, myalgia/arthralgia, anorexia, and neurologic abnormalities (e.g., altered mental status, aphasia, altered level of consciousness, and seizures or seizure-like activity). A modification of the CTCAE CRS grading scale has been established to better reflect JCAR014-associated CRS (Lee 2014), as detailed in Table 5.

If a patient becomes febrile or develops symptoms of CRS, cytokine and biomarker levels, serum ferritin, C-reactive protein (CRP), and/or markers of tumor lysis syndrome (e.g., chemistry, uric acid, lactate dehydrogenase [LDH]) may be measured, and persistence and/or phenotype of the transgene-expressing cells may be evaluated, as clinically indicated.

Any patient who develops clinical evidence of symptoms related to CRS will have a work-up to exclude infection or other causes, as clinically appropriate. Initial treatment should consist of supportive measures as dictated by the clinical and laboratory findings, and may include fluid replacement, medications to support blood pressure, antipyretics, oxygen supplementation, anti-seizure medications, and broad-spectrum antibiotics if infection cannot be excluded as a potential etiology for the signs and symptoms.

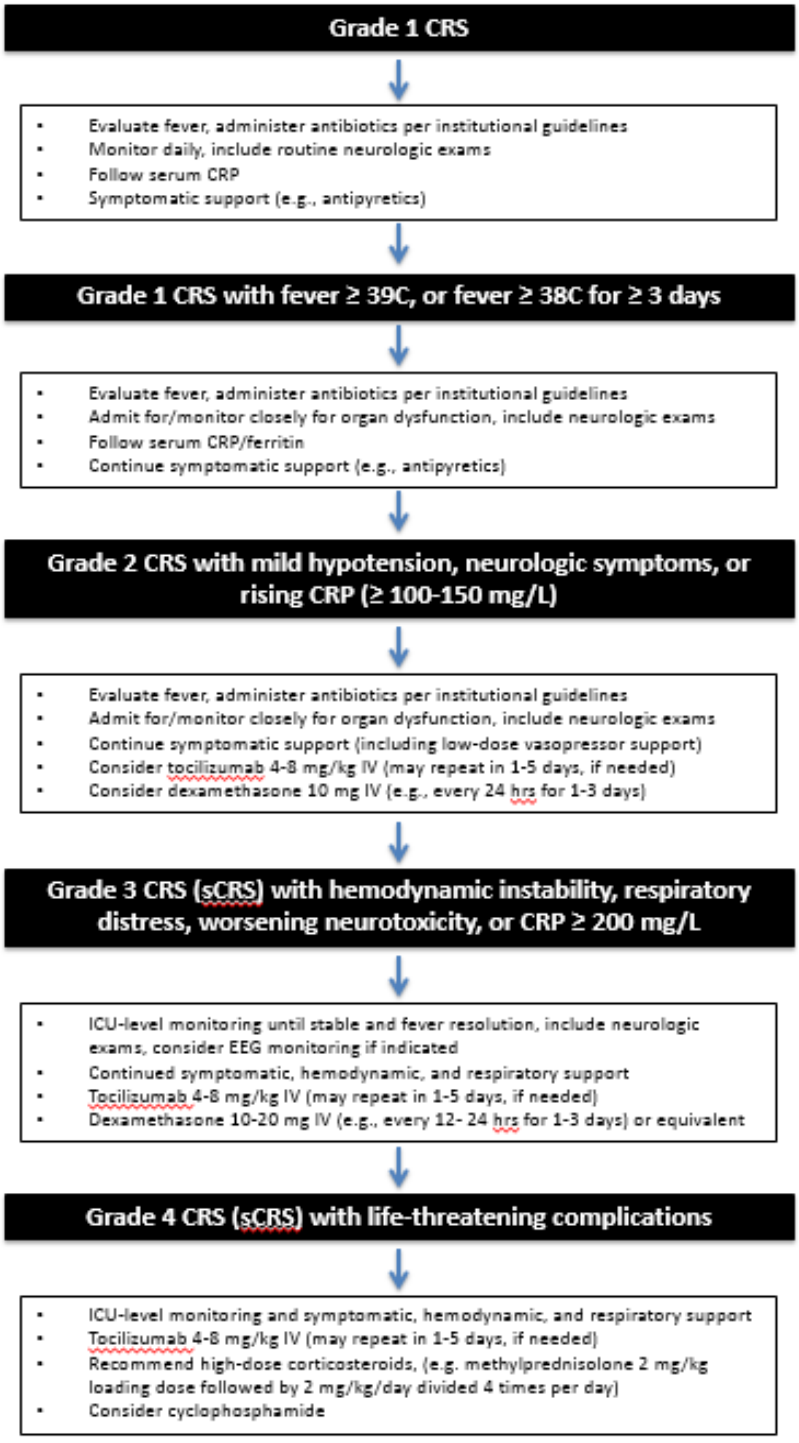
Grade ≥ 3 CRS (severe CRS; sCRS) and/or Grade 2 CRS with progressive symptoms and signs may be treated with tocilizumab 4-8 mg/kg IV with or without corticosteroids (e.g., dexamethasone 10 mg IV every 6 to 24 hours). An algorithm for management of CRS is shown in **Figure 3**. Other cytokine-directed therapies may be considered after discussion with the PI.

Table 5: Grading Criteria for CRS

Grade	Description of Symptoms
1: Mild	Not life-threatening, require only symptomatic treatment such as antipyretics and anti-emetics (e.g., fever, nausea, fatigue, headache, myalgia, malaise)
2: Moderate	Require and respond to moderate intervention: • Oxygen requirement < 40%, or • Hypotension responsive to fluids or low dose of a single vasopressor, or • Grade 2 organ toxicity (by CTCAE v4.03)
3: Severe	Require and respond to aggressive intervention: • Oxygen requirement ≥ 40%, or • Hypotension requiring high dose of a single vasopressor (e.g., norepinephrine ≥ 20 µg/min, dopamine ≥ 10 µg/kg/min, phenylephrine ≥ 200 µg/min, or epinephrine ≥ 10 µg/min), or • Hypotension requiring multiple vasopressors (e.g., vasopressin + one of the above agents, or combination vasopressors equivalent to ≥ 20 µg/min norepinephrine), or • Grade 3 organ toxicity or Grade 4 transaminitis (by CTCAE v4.03)
4: Life-threatening	Life-threatening: • Requirement for ventilator support, or • Grade 4 organ toxicity (excluding transaminitis)
5: Fatal	Death

Adapted from Lee et al., 2014 (Lee 2014)

Figure 3: Recommended Management of CRS



7.2 Neurologic Toxicities

Therapy with JCAR014 can be associated with neurologic toxicities, such as delirium, seizures, and/or focal neurologic deficits, which can preceed, accompany, or follow signs of CRS or occur in the absence of CRS.

For patients who have mild neurologic manifestations, symptomatic care and levetiracetam are recommended. Discussion with the PI or designee is recommended. For patients with worsening neurologic changes, the addition of corticosteroids should be considered (e.g., dexamethasone 10 mg IV every 6 to 24 hours). Tocilizumab (4-8 mg/kg IV) or other cytokine-directed therapies may be used based on clinical judgment; at this time, it is unclear if these approaches are of benefit to patients with neurotoxicity. Cerebrospinal fluid (CSF) assessments and CNS imaging should be considered if clinically indicated (see Section 8.3.6).

Levetiracetam (500 mg bid PO starting dose) or other anti-seizure medication should be considered prophylactically prior to treatment with JCAR014 for patients with a history of CNS irradiation or other intensive CNS-directed therapy. Levetiracetam or other anti-seizure medication should also be considered at the first appearance of symptoms consistent with CRS or neurologic toxicity (e.g., confusion, word-finding difficulties, disorientation). The use of continuous electroencephalogram (EEG) monitoring may be considered based on the patient's risk of toxicity and his/her clinical status.

7.3 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. While there are no definitive diagnostic criteria for MAS, it is typically diagnosed using published criteria for hemaphagocytic lymphohistiocytosis (Schulert 2015).

Patients treated with JCAR014 should be monitored for MAS, and cytokine-directed therapy or corticosteroids should be considered as clinically indicated.

7.4 Infusion Reactions

Administration of JCAR014 and durvalumab may cause infusion reactions. Possible risks associated with IV administration of JCAR014 and durvalumab are infection, redness, swelling,

pain, and induration at the administration site. Examples of other potential symptoms and signs associated with infusion reactions and their initial management are listed below:

- Fever, chills, and temperature elevations > 38.3°C may be managed with acetaminophen 650 mg PO every 4 to 6 hrs. All patients who develop fever or chills should have a blood culture drawn.
- Headache may be managed with acetaminophen.
- Nausea and/or vomiting may be managed with diphenhydramine 25 to 50 mg IV or other antiemetics (excluding corticosteroids).
- Hypotension should be managed initially by fluid administration.
- Hypoxemia should be managed initially with supplemental oxygen.

If the following signs appear during infusion of JCAR014, the infusion should be paused and the patient assessed. If assessment by the PI or designee indicates that the patient's condition is stable, then the infusion may be resumed.

- Systolic blood pressure < 80 mmHg OR > 30 mmHg fall from baseline
- Heart rate > 140/min OR increase from baseline > 40/min (confirmed by palpation or electrocardiogram [ECG])
- Respiratory rate > 35/min OR increase from baseline of > 10/min
- Arterial O_2 saturation < 88% on air OR fall from baseline > 5%

If a JCAR014 infusion is terminated due to acute toxicity, the residual T cells should be returned to FHCRC Therapeutic Products Program Quality Control Department for analysis. Investigation of possible causes of observed signs should proceed and, if necessary, additional medical treatment will be instituted.

Patients requiring discontinuation of the JCAR014 infusion may be eligible for re-treatment if the cause is deemed not related to the JCAR014 infusion.

Guidelines for the management of infusion reactions deemed related to durvalumab administration are provided in Appendix G.

7.5 Tumor Lysis Syndrome

Both lymphodepleting conditioning chemotherapy and JCAR014 may cause TLS in patients with high lymphoma burden. All patients will be considered at risk for TLS and should receive allopurinol prophylaxis before chemotherapy begins, unless contraindicated. Allopurinol should be continued for as long as the medical team determines appropriate after the JCAR014 infusion. Patients may receive additional hydration and urine alkalinization for the first 2 weeks after JCAR014 infusion.

If TLS develops, as defined by the Cairo Bishop criteria (Coiffier 2008), the Attending Physician will direct patient management with guidance from the study staff (Howard 2011). Conservative therapy, including allopurinol, urinary alkalinization, and IV fluid hydration may be instituted immediately for suspected TLS. Hyperkalemia may be treated with potassium-binding resins, diuresis, or insulin/dextrose therapy. Hyperphosphatemia may be treated with phosphate-binding resins. In severe cases, rasburicase (in non-G6PD-deficient individuals) or renal dialysis may be necessary.

7.6 B-Cell Aplasia

B-cell aplasia is an expected potential off-tumor, on-target toxicity associated with administration of CD19-targeted CAR-T cells. 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 patients prior to and at various timepoints following JCAR014 treatment. Hypogammaglobulinemic patients (serum IgG < 400 mg/dL) should be considered for intravenous immunoglobulin replacement therapy according to institutional guidelines.

The following should be considered for infection prophylaxis, as clinically indicated:

1) Antibiotic: while neutropenic
2) Antifungal: start fluconazole on the day of JCAR014 infusion and continue for approximately 21 days after JCAR014 infusion
3) Antiviral: start before chemotherapy and continue for at least 3 months after JCAR014 infusion
4) Pneumocystis jiroveci pneumonia (PJP) prophylaxis: start approximately day 21 after JCAR014 infusion and continue for at least 3 months after JCAR014 infusion

7.7 Persistent Uncontrolled T-cell Proliferation

In the unlikely event that clinically significant uncontrolled and persistent proliferation of JCAR014 T cells occurs in a study patient, initial therapy may involve treatment with corticosteroids. Anti-lymphocyte globulin, cytotoxic drugs, or administration of anti-EGFR monoclonal antibody (cetuximab), which has been shown to eliminate $EGFRt^{+}$ CD19 CAR-T cells in murine models, may be considered in serious cases. If an increase in CAR-T cells to greater than 10% of T cells at more than 3 months after the CAR-T cell infusion is observed, an analysis for clonal expansion by deep sequencing of the T-cell receptor (TCR) beta gene (Adaptive Biotechnology) may be conducted. All patients will be monitored for evidence of unexpected JCAR014 expansion and the emergence of a new malignancy, particularly of T-cell origin.

7.8 Replication-Competent Lentivirus

Per the FDA guidelines (Food and Drug Administration 2000, Food and Drug Administration 2006), all patients will be followed in this study for replication-competent lentivirus (RCL) and vector sequences for up to 15 years following the last dose of JCAR014.

7.9 Immune-Related Adverse Events

Based on the mechanism of action of durvalumab leading to T-cell activation and proliferation, there is the possibility of observing immune-related adverse events (irAEs) with JCAR014 and durvalumab combination therapy. Potential irAEs may be similar to those seen with the use of ipilimumab, nivolumab, or the combination thereof and may include immune-mediated pneumonitis/interstitial lung disease, diarrhea/enterocolitis, hepatitis, nephritis or renal dysfunction, rash, endocrinopathy, neurotoxicity, or peripheral neuromotor syndrome (Hodi 2010, Brahmer 2012, Topalian 2012, Wolchok 2013). Patients should be monitored for signs and symptoms of irAEs. In the absence of an alternate etiology (e.g., infection or disease progression), an immune-mediated etiology should be considered. In addition to the dose modifications shown in Appendix G, it is recommended that management of irAEs follow the guidelines outlined for ipilimumab (Weber 2012). The following guidelines are recommended for events considered related to durvalumab:

1. Patients should be evaluated to identify any alternative etiology.
2. In the absence of clear alternative etiology, all events of an inflammatory nature should be considered to be immune-related.
3. Symptomatic and topical therapy should be considered for low-grade events.
4. Systemic corticosteroids should be considered for a persistent low-grade event or for a severe event.
5. More potent immunosuppressives (e.g., infliximab, mycophenolate mofetil) should be considered for events not responding to systemic steroids.

If the Investigator has any question in regards to an AE being an irAE, the Investigator should contact the Juno medical monitor. Treatment modifications will not be required for AEs that are clearly not attributed to durvalumab (such as an accident) or for laboratory abnormalities that are not deemed to be clinically significant.

Following the DLT evaluation period, individual patient treatments may be interrupted or delayed based on toxicities observed during each subsequent 28-day period of treatment. General guidelines regarding treatment modification for irAEs deemed related to durvalumab are provided in Appendix G.

7.9.1 Hepatic Function Abnormalities

Hepatic function abnormalities meeting the definition of Hy's law (i.e., any increase in ALT or AST to greater than or equal to 3 x ULN and concurrent increase in total bilirubin to greater than 2 x ULN with no probable reason to explain the combination of increases) and considered related to either durvalumab alone or durvalumab in combination with JCAR014 is considered an adverse event of special interest (AESI). Concurrent findings are those that derive from a single blood draw or from separate blood draws taken within 8 days of each other. Follow-up investigations and inquiries will be initiated promptly to determine whether the findings are reproducible and/or whether there is objective evidence that clearly supports causation by a disease (e.g., cholelithiasis and bile duct obstruction with distended gallbladder, lymphoma, or hypotensive episode during CRS) or a medication or agent other than the investigational product (e.g., lymphodepleting chemotherapy). Guidelines for management of patients with hepatic function abnormalities deemed related to durvalumab are provided in Appendix G.

Hepatic abnormalities considered related to durvalumab and potentially meeting the definition of Hy's law will be reported as SAEs (see Section 9.3.3.2).

7.9.2 Pneumonitis

Adverse events of pneumonitis are also of special interest, as pneumonitis has been observed with anti–PD-1 and anti–PD-L1 mAbs, including durvalumab. Immune-mediated pneumonitis is characterized by inflammation focally or diffusely affecting the lung parenchyma that may be the result of effects of checkpoint inhibitors against the normal lung parenchyma (Chow 2013). Presentations of pneumonitis range from asymptomatic lung infiltrates to those that mimic severe bacterial pneumonia and can be fatal. For symptomatic patients, complaints and findings may include dyspnea, cough, tachypnea, pleuritic chest pain, and hypoxia. Initial work-up should include high-resolution CT scan, ruling out infection, and pulse oximetry. Pulmonary consultation is highly recommended. Guidelines for management of patients with pneumonitis deemed related to durvalumab are provided in Appendix G.

7.9.3 Infusion Reactions

Infusion-related reactions to durvalumab are of special interest and are defined, for the purpose of this protocol, as all AEs occurring from the start of investigational product infusion up to 24 hours after the infusion start time. Guidelines for management of patients with infusion reactions deemed related to durvalumab are provided in Appendix G.

7.9.4 Hypersensitivity Reactions

Hypersensitivity reactions as well as infusion-related reactions have been reported with anti–PD-L1 and anti–PD-1 therapy (Brahmer 2012). As with the administration of any foreign protein and/or other biologic agents, reactions following the infusion of mAbs can be caused by various mechanisms, including acute anaphylactic (immunoglobulin E-mediated) and anaphylactoid reactions against the mAb, and serum sickness. Acute allergic reactions may occur, may be

severe, and may result in death. Acute allergic reactions may include hypotension, dyspnea, cyanosis, respiratory failure, urticaria, pruritus, angioedema, hypotonia, urticaria, arthralgia, bronchospasm, wheeze, cough, dizziness, fatigue, headache, hypertension, myalgia, vomiting, and unresponsiveness.

Guidelines for management of patients with hypersensitivity (including anaphylactic reaction) and infusion-related reactions deemed related to durvalumab are provided in Appendix G.

7.9.5 Gastrointestinal Disorders

Diarrhea, colitis, enterocolitis, and pancreatitis are gastrointestinal irAEs that have been reported with durvalumab. Mild to severe diarrhea is the most frequently observed sign/symptom potentially associated with immune-mediated colitis, and may be accompanied by other signs and symptoms, including changes in bowel habits from baseline, abdominal pain, nausea/vomiting, or hematochezia. In severe cases, patients may experience significant dehydration, fever, peritoneal signs, bowel perforation, or ileus (Kaehler 2010). Immune-mediated pancreatitis, an important potential risk, is an inflammatory condition of the pancreas that typically manifests initially as asymptomatic elevations of amylase and lipase in patients treated with immune-checkpoint inhibitors. Clinical presentation frequently includes low-grade abdominal pain with accompanying fever and malaise (Di Giacomo 2010, Weber 2012). Guidelines for the management of patients with gastrointestinal disorders deemed related to durvalumab are in Appendix G.

7.9.6 Nephritis

The major clinical syndromes produced by immune-mediated renal injury include nephrotic syndrome, rapidly progressive glomerulonephritis, and acute renal failure (Cunard 2003). In association to immune-checkpoint inhibitors, two different forms of ipilimumab-induced renal damage are reported, acute kidney injury due to predominant acute granulomatous tubulointerstitial nephritis and nephrotic syndrome in lupus nephritis (Izzedine 2014). Signs and symptoms include increase in serum creatinine, decrease in urine output, peripheral edema, hematuria, and loss of appetite. Subjects should be monitored for elevated serum creatinine prior to and periodically during treatment.

7.10 Management of Other Toxicities

If a new onset CTCAE v4.03 Grade ≥ 3 toxicity is observed following study treatment, the patient will receive investigation and medical treatment appropriate for the physiological abnormalities.

Grade ≥ 3 toxicity that is attributed to the JCAR014 infusion, is unresponsive to supportive measures, or persists for > 7 days may be treated with corticosteroids (e.g., dexamethasone 10 mg IV every 4 to 12 hours), tocilizumab, or other cytokine-directed therapy after discussion with the PI or designee.

8. STUDY ASSESSMENTS AND PROCEDURES

8.1 Schedule of Events

A tabular schedule of events is provided in Appendix A. The proposed days of all treatments and assessments are approximate and may vary due to scheduling, clinical or other factors. Results of tests and procedures previously conducted as standard of care may be used for research purposes if conducted within the protocol-defined window.

8.1.1 Patient Enrollment

Eligible patients will be identified and registered into the system by the Clinical Coordinator's Office (CCO; Intake Office) and assigned a UPN (Unique Patient Number). The CCO will register the patient for the protocol through the Data Management Office.

Patients will initially sign a consent for screening and undergo eligibility blood tests. Eligible patients will then sign a consent for and undergo leukapheresis and restaging. Enrollment to the therapy portion of the study occurs at the conclusion of the pre-T-cell work-up when data are reviewed for all inclusion and exclusion criteria for therapy by the Immunotherapy attending physician and the patient signs consent for therapy.

A study number will be allocated to each patient and a log of enrolled patients will be maintained.

8.1.2 Screening

The following events will occur during the screening period:

1) Informed consent for screening
2) Medical history, including:
    a) Clinical and pathologic data at diagnosis and at the time of enrollment on the study
    b) Prior therapies and response to therapy
3) Height and weight
4) Physical examination
5) Karnofsky performance status
6) Recording of concomitant medications (see Section 6.6)
7) Safety laboratory evaluation:
    a) Complete blood count (CBC), differential, and platelet count
    b) Hepatic function panel with LDH and renal function panel with Mg
    c) Puget Sound Blood Center Recipient/Donor Battery Panel

d) Pregnancy test for females of reproductive potential

e) ABO blood typing and antibody screen

8) Collection of blood samples for research evaluations (see Appendix A and Appendix B)

8.1.3 Pre-Treatment Evaluation for Study Therapy

The following events will occur:

1) Informed consent for leukapheresis and restaging
2) The patient will undergo leukapheresis
3) Confirmation of diagnosis by internal pathology review of initial or subsequent biopsy or other pathologic material at the FHCRC/SCCA
4) Collection of archived tissue from most recent tumor biopsy (block or slides), if available
5) Updated medical history
6) Physical examination, including neurologic exam
7) Baseline chest x-ray
8) Baseline ECG
9) MUGA or cardiac ECHO
10) Mini Mental State Examination (MMSE; see Appendix D)
11) Baseline neuropsychological testing
12) Assessment of AEs (see Section 9.3.3)
13) Recording of concomitant medications (see Section 6.6)
14) Safety laboratory evaluations:
    a) CBC, differential, and platelet count
    b) Hepatic function panel with LDH and renal function panel with Mg
    c) Uric acid
    d) Serum ferritin
    e) CRP
    f) Prothrombin time (PT), partial thromboplastin time (PTT), fibrinogen, and D-dimer
    g) Human leukocyte antigen (HLA) typing will be initiated if results from previous test are not available
    h) Pregnancy test for females of reproductive potential within 14 days before leukapheresis and within 28 days before initiation of lymphodepleting chemotherapy

i) Thyroid stimulating hormone (TSH), Free T3, Free T4

15) Quantitative IgG

16) Collection of blood and biopsy samples for research evaluations (see Appendix A and Appendix B). If biopsies are performed for clinical reasons, additional samples may be collected for research.

a) Fresh tumor biopsy in patients who consent to optional biopsies

17) Restaging

a) Bone marrow aspirate and biopsy (may be omitted in patients who have had a marrow aspirate and biopsy within 30 days before the scheduled JCAR014 infusion AND have not received antitumor therapy in the interim)

b) Diagnostic-quality CT scan and a PET scan (may be omitted in patients who have had recent imaging within 30 days before the scheduled JCAR014 infusion AND who have not received antitumor therapy in the interim)

8.1.4 Administration of Lymphodepleting Chemotherapy

Patients will receive lymphodepleting chemotherapy with either a single dose of cyclophosphamide 60 mg/kg (administered on Day -5) and fludarabine 25 mg/m^2 daily for 3 days (administered on Days -4, -3, and -2) or with concurrent cyclophosphamide (300 mg/m^2/day) and fludarabine (30 mg/m^2/day (days -4 through -2). Alteration in the timing of chemotherapy is permissible for clinical or logistical reasons.

The following events will occur:

1) Informed consent for therapy
2) Safety laboratory evaluations daily during lymphodepleting chemotherapy:
   a) CBC, differential, and platelet count
   b) Hepatic function panel with LDH and renal function panel with Mg
   c) Uric acid
3) Assessment of AEs (see Section 9.3.3)
4) Recording of concomitant medications (see Section 6.6)
5) Administration of allopurinol for TLS prophylaxis, as clinically appropriate

8.1.5 Evaluations on the Day of Durvalumab Administration Prior to JCAR014 Administration (Day -1; Group 2 Only)

Patients in Group 2 will receive durvalumab on the day prior to JCAR014 administration. The following evaluations will occur at this visit:

1) Weight prior to the start of the durvalumab infusion
2) Physical examination prior to the start of the durvalumab infusion. If there is clinical suspicion of neurologic dysfunction, a neurologic examination should be performed.
3) ECG prior to the start of the durvalumab infusion
4) Safety laboratory evaluations prior to durvalumab infusion:
    a) CBC, differential, and platelets
    b) Hepatic function panel with LDH and renal function panel with Mg
    c) Uric acid
5) Collection of blood samples for research evaluations prior to and after durvalumab infusion (see Appendix A and Appendix B)
6) Evaluation of vital signs, including O_2 saturation, before, during, and after the infusion (see Section 8.3.5)
7) Assessment of AEs (see Section 9.3.3)
8) Recording of concomitant medications (see Section 6.6)

8.1.6 Evaluations on the Day of JCAR014 Infusion (Day 0; Groups 1 and 2)

The following evaluations will occur for patients in both groups on Day 0, the day of JCAR014 infusion:

1) Weight prior to the start of the JCAR014 infusion
2) Physical examination prior to the start of the JCAR014 infusion. If there is clinical suspicion of neurologic dysfunction, a neurologic examination should be performed.
3) Karnofsky performance status prior to the start of the JCAR014 infusion
4) ECG prior to the start of the JCAR014 infusion (patients in Group 1 only)
5) MMSE prior to the start of the JCAR014 infusion (Appendix D)
6) Safety laboratory evaluations prior to JCAR014 infusion:
    a) CBC, differential, and platelets
    b) Hepatic function panel with LDH and renal function panel with Mg
    c) Uric acid

d) Serum ferritin

e) CRP

f) PT, PTT, fibrinogen, and D-dimer

7) Collection of blood samples for research evaluations prior to JCAR014 infusion (see Appendix A and Appendix B)

8) Evaluation of vital signs, including O_2 saturation, before, during, and after the infusion (see Section 8.3.5)

9) Assessment of AEs (see Section 9.3.3)

10) Recording of concomitant medications (see Section 6.6)

8.1.7 Evaluations after the JCAR014 Infusion and prior to the First Post-JCAR014 Durvalumab Infusion (Groups 1 and 2)

The following evaluations will be performed between the JCAR014 infusion and the first post-JCAR014 durvalumab infusion. If no durvalumab is given, evaluations should be performed until 6 weeks after JCAR014 administration:

1) Physical examination 1 day after the JCAR014 infusion, twice weekly for the first 2 weeks after JCAR014 infusion, then at least weekly. If there is clinical suspicion of neurologic dysfunction, a neurologic examination should be performed.

2) MMSE on approximately Day 7 and Day 14 after JCAR014 infusion

3) Assessment of AEs (see Section 9.3.3)

4) Recording of concomitant medications (see Section 6.6)

5) Safety laboratory evaluations twice weekly for the first 2 weeks after JCAR014 infusion and then at least weekly:

   a) CBC, differential, and platelets (a CBC with differential should be drawn concurrently with JCAR014 persistence samples)

   b) Hepatic function panel with LDH and renal function panel with Mg

   c) Uric acid

   d) Serum ferritin

   e) CRP

   f) PT, PTT, fibrinogen, and D-dimer

   If patients become febrile or develop symptoms of CRS or TLS between the indicated timepoints, serum ferritin, CRP, or tumor lysis markers (e.g., chemistry, uric acid, LDH) may be measured at additional times, as clinically indicated.

6) Collection of blood and biopsy samples for research evaluations (see Appendix A and Appendix B). If biopsy or sampling of tissues is performed for clinical indications, then additional tissue may be obtained during the same procedure for research studies. The planned procedure should be discussed with the PI.
    a) If patients become febrile or develop possible signs of toxicity between the indicated timepoints, the persistence of transferred T cells and serum/plasma biomarkers may be measured at additional times, as clinically indicated. Samples may be cryopreserved for future analyses.
    b) For patients who consented to optional biopsies, a fresh tumor biopsy may be performed within the first 4 weeks after the JCAR014 infusion for research evaluations. Variation in timing of the biopsy due to logisitical or clinical reasons is acceptable. In the event of persistent mass, relapse or progression, a biopsy may be collected at that time point.
7) Restaging:
    a) CT and PET scans (see Section 8.1.10)
    b) Bone marrow aspirate and biopsy, if applicable (see Section 8.1.10)

8.1.8 Evaluation on the Day of each Post-JCAR014 Durvalumab Administration (Groups 1 and 2)

The following evaluations will occur on the day of each post-JCAR014 durvalumab infusion (e.g., approximately Days 28, 56, 84; first infusion may occur as early as Day 7 in Group 1):

1) Weight prior to the start of the durvalumab infusion
2) Physical examination prior to the start of the durvalumab infusion. If there is clinical suspicion of neurologic dysfunction, a neurologic examination should be performed.
3) Karnofsky performance status prior to the start of the durvalumab infusion
4) ECG prior to the start of the durvalumab infusion (first and third post-JCAR014 durvalumab cycles only)
5) MMSE (first post-JCAR014 durvalumab cycle only) (Appendix D)
6) Safety laboratory evaluations prior to durvalumab infusion:
    a) CBC, differential, and platelets
    b) Hepatic function panel with LDH and renal function panel with Mg
    c) Uric acid
    d) Serum ferritin
    e) CRP

f) PT, PTT, fibrinogen, and D-dimer

g) Quantitative IgG

7) Collection of blood samples for research evaluations prior to and after durvalumab infusion (see Appendix A and Appendix B).

8) Evaluation of vital signs, including O_2 saturation, before, during, and after the infusion (see Section 8.3.5)

9) Assessment of AEs (see Section 9.3.3)

10) Recording of concomitant medications (see Section 6.6)

8.1.9 Post-Infusion Evaluations during Cycles of Durvalumab Administration

8.1.9.1 First Post-JCAR014 Durvalumab Cycle (Groups 1 and 2)

Post-infusion evaluations during the first post-JCAR014 cycle of durvalumab will include the following:

1) Physical examination 1 day after the durvalumab infusion, twice weekly for the first 2 weeks after durvalumab infusion, then at least weekly. If there is clinical suspicion of neurologic dysfunction, a neurologic examination should be performed.

2) MMSE approximately 7 and 14 days after durvalumab infusion

3) Assessment of AEs (see Section 9.3.3)

4) Recording of concomitant medications (see Section 6.6)

5) Safety laboratory evaluations twice weekly for the first 2 weeks after durvalumab infusion and then at least weekly:

   a) CBC, differential, and platelets

   b) Hepatic function panel with LDH and renal function panel with Mg

   c) Uric acid

   d) Serum ferritin

   e) CRP

   f) PT, PTT, fibrinogen, and D-dimer

   If patients become febrile or develop symptoms of CRS or TLS between the indicated timepoints, serum ferritin, CRP, tumor lysis markers (e.g., chemistry, uric acid, LDH) may be measured at additional times, as clinically indicated.

6) Collection of blood and biopsy samples for research evaluations (see Appendix A and Appendix B). If biopsy or sampling of tissues is performed for clinical indications, then additional tissue may be obtained during the same procedure for research studies. The planned procedure should be discussed with the PI.
    a) If patients become febrile or develop possible signs of toxicity between the indicated timepoints, the persistence of transferred T cells and serum/plasma biomarkers may be measured at additional times, as clinically indicated. Samples may be cryopreserved for future analyses.
    b) For patients who consented to optional biopsies, a fresh tumor biopsy may be performed approximately within the first 4 weeks after the durvalumab infusion for research evaluations. Variation in timing of the biopsy due to logisitical or clinical reasons is acceptable. In the event of persistent mass, relapse or progression, a biopsy may be collected at that time point.
7) Restaging
    a) CT and PET scans (see Section 8.1.10)
    b) Bone marrow aspirate and biopsy, if applicable (see Section 8.1.10)
8) Quantitative IgG prior to the subsequent dose of durvalumab as clinically indicated.

8.1.9.2 Subsequent Durvalumab Cycles (Groups 1 and 2)

The following post-infusion evaluations will be performed in subsequent durvalumab cycles:

1) Physical examination approximately every 2 weeks. If there is clinical suspicion of neurologic dysfunction a neurologic examination should be performed.
2) Assessment of AEs (see Section 9.3.3)
3) Recording of concomitant medications
4) Safety laboratory evaluations approximately every 2 weeks
    a) CBC, differential, and platelet count
    b) Hepatic function panel with LDH and renal function panel
    c) Uric acid
    d) Serum ferritin
    e) CRP
    f) PT, PTT, fibrinogen, and D-dimer
5) Collection of blood and biopsy samples for research evaluations (see Appendix A and Appendix B). If biopsy or sampling of tissues is performed for clinical indications, then additional tissue may be obtained during the same procedure for research studies. The planned procedure should be discussed with the PI.

a) If patients become febrile or develop possible signs of toxicity between the indicated timepoints, the persistence of transferred T cells and serum/plasma biomarkers may be measured at additional times, as clinically indicated. Samples may be cryopreserved for future analyses.

b) For patients who consented to optional biopsies, a fresh tumor biopsy may be performed approximately within the first 4 weeks after the durvalumab infusion for research evaluations. Variation in timing of the biopsy due to logisitical or clinical reasons is acceptable. In the event of persistent mass, relapse or progression, a biopsy may be collected at that time point.

6) Restaging scans (see Section 8.1.10) should be coordinated to occur approximately 4 weeks after treatment with durvalumab and prior to the next cycle.

If clinically indicated, such as in the event of JCAR014 expansion and persistence with JCAR014-related toxicity, clinical assessments and safety laboratory evaluations may be performed in these subsequent cycles of durvalumab with the same frequency recommended in the first post-JCAR014 durvalumab cycle (see Section 8.1.9.1).

Post-infusion evaluations including physical examination, scans, and laboratory evaluations may be performed at an outside facility. Blood samples for research evaluations may be collected at an outside facility and shipped to Fred Hutchinson Cancer Research Center.

8.1.10 Restaging Studies and Response Assessment

The following evaluations will be performed for restaging and assessment of response:

1) A PET scan and a CT scan (preferably diagnostic quality) of the neck, chest, abdomen, and pelvis should be obtained approximately 1, 2, 4, 6, 9, and 12 months after the JCAR014 infusion. Scans should be performed until 12 months after JCAR014 or 90 days after the last dose of durvalumab, whichever is longer. This will result in restaging scans at the following timepoints relative to durvalumab:

   a) Prior to the first dose of durvalumab in Group 1 – late (may occur after first dose of durvalumab in the case of patients receiving durvalumab in Group 1 – early) and prior to the second dose of durvalumab in Group 2

   b) Approximately 4 weeks after the first post-JCAR014 durvalumab dose

   c) Approximately every other durvalumab cycle until 6 months post-JCAR014, then every 3 months until 12 months post-JCAR014 or 90 days after the last dose of durvalumab, whichever is later

   PET and CT scans may be performed before first dose of durvalumab in Group 1 – early. PET and CT scans are not required if progressive disease has been documented on previous imaging. PET scans are not required for patients with documented CR unless progression is suspected on CT, in which case, a PET scan should be performed.

2) Bone marrow aspirate and biopsy may be done at the time of the 1-month post-JCAR014 restaging assessment, and at other timepoints as clinically indicated, in patients with lymphoma involvement documented at baseline until the patient achieves a CR.

The Lugano Classification (as detailed in Appendix B) will be used to define tumor response. Evaluation of tumor response may be discontinued in patients who proceed to other antitumor therapies.

8.1.11 Follow-Up Evaluations

The following evaluations will occur every 30 days for the first 3 months following administration of the last dose of study therapy (durvalumab or JCAR014) and then every 3 months until 12 months after JCAR014 or 90 days after the last dose of durvalumab, whichever is longer:

1) Physical examination. If there is clinical suspicion of neurologic dysfunction, a neurologic examination should be performed.
2) ECG at 1 month after the last dose of study therapy (durvalumab or JCAR014)
3) Neuropsychological testing at approximately 2 months after JCAR014 administration
4) Assessment of AEs
5) Recording of concomitant medications (see Section 6.6)
6) Safety laboratory evaluations:
    a) CBC, differential, and platelet count
    b) Hepatic function panel with LDH and renal function panel with Mg
    c) Quantitative IgG, if clinically indicated
7) Collection of blood and biopsy samples for research evaluations (see Appendix A and Appendix B). If biopsy or sampling of tissues is performed for clinical indications, then additional tissue may be obtained during the same procedure for research studies. The planned procedure should be discussed with the PI.
    a) If patients become febrile or develop possible signs of toxicity between the indicated timepoints, the persistence of transferred T cells and serum/plasma biomarkers may be measured at additional times, as clinically indicated. Samples may be cryopreserved for future analyses. To evaluate re-expansion of JCAR014 and/or toxicity, research biomarker and/or T cell persistence samples may also be collected from patients who are planned for or have received subsequent treatment with a different CAR-T cell product.

During the follow-up period, physical examination, scans, and laboratory evaluations may be performed at an outside facility. Blood samples for research evaluations may be collected at an outside facility and shipped to Fred Hutchinson Cancer Research Center.

8.1.12 Retreatment

Patients may be eligible for retreatment with JCAR014 ± durvalumab if at least 3 months have elapsed since the last dose of durvalumab. Patients may be treated with the highest tested doses determined to be safe; the schedule of evaluations will follow the primary treatment schedule. Durvalumab-related assessments will not be conducted in patients who receive retreatment with JCAR014 only.

8.1.13 Long-Term Follow-Up

Enrolled patients who receive JCAR014 will be asked to participate in long-term follow-up (LTFU) for a minimum of 15 years according to the guidelines set forth by the FDA's Biologic Response Modifiers Advisory Committee that apply to gene transfer studies (see Appendix E).

8.1.14 Death

Death is an expected outcome during this study due to the nature of the disease being treated. All deaths must be reported.

During the informed consent process, the patient may be informed that in the event of their death, their next of kin may be asked if they consent to an autopsy being performed on the patient. Autopsy reports may be collected. The cause of death will be recorded if available.

If an autopsy is performed, tissue samples should be collected where feasible for evaluation of the presence of JCAR014 cells in brain, liver, kidney, lungs, bone marrow, blood, heart, reproductive organs, and any sites of disease.

8.2 Efficacy Assessments

Treatment response will be assessed by radiographic tumor evaluation at protocol-specified timepoints by diagnostic quality CT scans (chest, neck, abdomen, and pelvis) and PET scans, where feasible (see Section 8.1.10). Disease response will be determined using the Investigator's assessment according to the "Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification" (Cheson 2014) as described in Appendix C. Evaluation of tumor response may be discontinued in patients who proceed to other antitumor therapies.

8.3 Safety Assessments

Safety will be monitored by physical examination, laboratory evaluation, neurologic examination, as well as by collecting appropriate AEs. Details for AE collection and reporting are provided in Section 9.3.3.

8.3.1 Physical Examination

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

8.3.2 Clinical Laboratory Evaluation

Screening and other laboratory evaluations (see Table 6) will be performed according to Appendix A. Additional assessments should be performed between scheduled study visits as clinically required in order to diagnose and monitor AEs or expected events. The Investigator will assess the clinical significance of each applicable laboratory value that falls outside of the institutional reference range. This decision should be based upon the nature and degree of the observed laboratory abnormality. Values that are considered by the Investigator to be clinically significant and/or related to JCAR014 and/or durvalumab will be noted. The Investigator may choose to repeat any abnormal test once in order to rule out laboratory or sample collection error.

Table 6: Analytes for Clinical Laboratory Evaluation

Laboratory Panel	Analytes
Hepatic function panel	Albumin, total and direct bilirubin, alkaline phosphatase, ALT (SGPT), AST (SGOT), lactate dehydrogenase (LDH)
Renal function panel	Sodium, chloride, potassium, CO_2, anion gap, glucose, blood urea nitrogen (BUN), creatinine, albumin, calcium, phosphate, magnesium, GFR
CBC with differential and platelet count	WBC, RBC, hemoglobin, hematocrit, MCV, MCH, MCHC, platelet count, RDW-CV, % neutrophils, % lymphocytes, % eosinophils, % basophils, % immature granulocytes, neutrophils, lymphocytes, monocytes, eosinophils, basophils, immature granulocytes
Coagulation	PT, PTT, fibrinogen, and D-dimer
PSBC recipient/donor battery panel	HBsAg; anti-HIV-1, 2; anti-HBc; anti-HTLV-1, 2; anti-HCV
Inflammatory markers	CRP, ferritin
Immunoglobulins	IgG

8.3.3 Routine Neurological Examination

A routine neurological exam should include, at minimum, a physical exam to assess cranial nerves, motor and sensory function, and coordination and balance. In addition, the Mini Mental Status Examination (MMSE; see Appendix D) will be administered pre-treatment and at timepoints post-JCAR014 infusion and post-durvalumab infusion (see Appendix A). The MMSE may be administered by an appropriately trained provider (i.e., physician, nurse, study personnel); a neurologist is not required.

8.3.4 Formal Neuropsychological Tests

A formal neuropsychological test will be conducted pre-treatment and at approximately 2 months after JCAR014 administration. This evaluation will be performed by appropriately trained personnel and will include, at minimum, evaluation of information processing, attention, verbal fluency, executive function, and memory. Formal neuropsychological testing will be conducted in English-speaking subjects only.

8.3.5 Vital Signs

Vital signs include temperature, respiratory rate, heart rate, blood pressure, and SaO_2 by pulse oximetry. On the days of JCAR014 or durvalumab administration, vital signs, including SaO_2, should be measured at approximately the following times:

- Prior to the start of infusion
- Every 15 minutes (± 5 minutes) during the infusion
- Within 5 minutes after the end of infusion
- 30 minutes after the end of the infusion
- 60 minutes after the end of the infusion
- 2 hours after the end of the infusion

8.3.6 CSF Examination and CNS Symptom Assessment

CSF assessments and CNS imaging should be performed as clinically indicated (e.g., if new CNS symptoms occur, or if clinical signs or suspicion of CNS lymphoma exist). CSF will be analyzed for cell count and differential cytology, and where feasible for the presence of JCAR014. CSF cultures (bacterial, fungal, viral) should be performed as clinically indicated for suspicion of infection.

8.3.7 Karnofsky Performance Status

Karnofsky performance status (see Table 7) will be used to evaluate patient eligibility at screening and will be assessed throughout the study at timepoints specified in Appendix A.

Table 7: Karnofsky Performance Status Scale Definitions Rating (%) Criteria

Description	Score	Criteria
• Able to carry on normal activity and to work • No special care needed	100	Normal, no complaints; no evidence of disease
	90	Able to carry on normal activity; minor signs of symptoms of disease
	80	Normal activity with efforts; some signs or symptoms of disease
• Unable to work • Able to live at home and care for most personal needs • Varying amount of assistance needed	70	Cares for self; unable to carry on normal activity or do active work
	60	Requires occasional assistance, but is able to care for most of personal needs
	50	Requires considerable assistance and frequent medical care
• Unable to care for self • Requires equivalent of institutional or hospital care • Disease may be progressing rapidly	40	Disabled; requires special care and assistance
	30	Severely disabled; requires special care and assistance
	20	Very sick; hospital admission necessary; active supportive treatment necessary
	10	Moribund; fatal processes progressing rapidly
	0	Dead

8.3.8 MUGA/Echocardiogram

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

8.3.9 Electrocardiogram

A standard 12-lead ECG should be obtained.

8.4 Research Assessments

Peripheral blood, bone marrow biopsies and aspirates, and tumor biopsies may be collected for these biomarker studies. The volumes and timepoints for collection of these evaluations are listed in Appendices A and Appendix B.

8.4.1 Pharmacokinetic Assessments

Assessment of JCAR014 PK will be determined by quantitative PCR (qPCR) to detect the JCAR014 transgene and/or by flow cytometry to enumerate the number and immunophenotype of JCAR014 cells. Peripheral blood and bone marrow will be collected as indicated in Appendix A.

Assessment of durvalumab PK will be determined by a validated immunoassay on serum samples.

8.4.2 RCL Testing

In accordance with FDA guidelines (Food and Drug Administration 2000, Food and Drug Administration 2006), peripheral blood samples will be tested for RCL during screening and at 3, 6, and 12 months following the JCAR014 infusion. Additional blood samples will be collected annually for up to 15 years following JCAR014 administration (see **Appendix E**)

8.4.3 Immunogenicity Assessments

Humoral immune responses to JCAR014 will be assessed in selected patients. Samples from patients who have two consecutive negative assays for JCAR014 persistence or who have recovered endogenous B cells will be prioritized for humoral immune response analysis. Humoral responses will be evaluated by testing plasma in an anti-therapeutic antibody (ATA) assay in which binding to the extracellular region of JCAR014 is measured in patients who have B cell recovery or undetectable levels of JCAR014. Cellular immune responses to JCAR014 will be considered in patients who have two consecutive negative assays for JCAR014 or who have recovered endogenous B cells. Cellular responses to JCAR014 will be evaluated by assessing reactivity of patient peripheral T cells to JCAR014. Peripheral blood will be collected for these studies at the timepoints indicated in Appendix A.

The levels of ADA directed against durvalumab will be assessed using a validated immunoassay in serum samples.

8.4.4 Biomarker Assessments

Biomarker assessments may include immunophenotypic evaluation of JCAR014 and endogenous immune cell subsets, characterization of tumor and tumor microenvironment, assessment of serum biomarkers associated with CRS and immune cell function, and pharmacodynamic markers of therapeutic activity. Peripheral blood, lymphoma and bone marrow biopsies, bone marrow aspirates, and CSF (only if lumbar puncture indicated for clinical purposes) will be collected for these evaluations. Assays will be prioritized based on availability of tissue and the clinical situation.

Flow cytometry may be used to determine the phenotype of JCAR014 cells and to enumerate immune cell subsets in the blood, bone marrow, and CSF (if applicable). These studies aim to identify cellular markers correlated with JCAR014 function as well as safety and efficacy. As one component of this analysis, the absence of normal B cells in blood or bone marrow, if obtained, will be determined by flow cytometry as a pharmacodynamic marker of JCAR014 activity.

Serum/plasma biomarkers may be measured as a marker of immune activation. Potential correlations between cytokine production and efficacy and severity of CRS will be assessed.

Single nucleotide polymorphism (SNP), targeted mutational analysis, whole exome/genome sequencing, and/or gene expression analysis (e.g., RNA-Seq) may be conducted on JCAR014 cells pre-treatment, or isolated from peripheral blood and bone marrow aspirates post-treatment,

as well as tumor cells isolated from lymph node biopsies, in order to identify markers or signatures correlating with clinical response. T-cell receptor repertoire may also be assessed through sequencing analysis of the peripheral blood.

Soluble PD-L1 levels before and after treatment with durvalumab will be measured in serum samples.

The presence and distribution of specific cellular elements within the tumor and the tumor microenvironment may be assessed by immunohistochemistry on tumor biopsies to correlate the presence of these factors with response, duration of response, and/or JCAR014 persistence and function. Analyses to detect lymphoma cells in the peripheral blood may be performed. Lymphoma biopsy specimens may be collected for immunohistochemical evaluation of JCAR014 infiltration and prevalence, markers of JCAR014 phenotype and function, and location of JCAR014 relative to CD19+ tumor cells. Immunoregulatory pathways operative in the tumor microenvironment may influence the fate and function of adoptively transferred JCAR014 T cells. The data collected in these biomarker assessments may be used in aggregate to elucidate relationships between CAR T-cell function, persistence and efficacy, and molecules present in the tumor microenvironment.

9. ADVERSE EVENT REPORTING

9.1 Definitions

9.1.1 Adverse Event

An adverse event (AE) is the development of any untoward medical occurrence or the clinical deterioration of a pre-existing medical condition in a patient or clinical study patient administered a medicinal product (e.g., JCAR014 and/or durvalumab).

9.1.2 Serious Adverse Event

A serious adverse event (SAE) is defined as an AE occurring at any dose that meets one or more of the following criteria:

- Results in death
- Is life-threatening

  An AE or adverse reaction is considered “life-threatening” if, in view of the Investigator, its occurrence places the patient at immediate risk of death. It does not include an event that, had it occurred in a more severe form, might have caused death.

- Requires inpatient hospitalization or prolongation of an existing hospitalization (see NOTE below)
- Results in a persistent or significant disability/incapacity
- Is a congenital anomaly or birth defect

- Is an important medical event, as determined by the Investigator that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above.

  For reporting purposes, any suspected transmission via a medicinal product of an infectious agent is also considered a SAE and may be subject to expedited reporting requirements in some countries. Any organism, virus or infectious particle (for example prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent.

NOTE:

The following hospitalizations are not considered SAEs in this study:

- Admission to the hospital for social or situational reasons (e.g., no place to stay, live too far away to come for hospital visits)
- Hospitalization at the discretion of the Investigator for administration of study therapy (JCAR014 or durvalumab) or for ease of clinical monitoring
- Hospitalization for elective or pre-planned treatment for a pre-existing condition that is unrelated to the condition under study and has not worsened since signing informed consent

9.1.3 Adverse Events of Special Interest

An adverse event of special interest (AESI) is one of scientific and medical interest specific to the further understanding of the investigational product and which should be closely monitored. 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.

AESIs for durvalumab include, but are not limited to, events with a potential inflammatory or immune-mediated mechanism and which may require more frequent monitoring and/or interventions such as steroids, immunosuppressants, and/or hormone replacement therapy. These AESIs are being closely monitored in clinical studies with durvalumab monotherapy and combination therapy. An immune-related adverse event (irAE) is defined as an adverse event that is associated with drug exposure, is consistent with an immune-mediated mechanism of action, and where there is no clear alternate aetiology. Serologic, immunologic, and histologic (biopsy) data, as appropriate, should be used to support an irAE diagnosis. Appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the irAE.

If the Investigator has any questions in regards to an AE being an irAE, the Investigator should promptly contact the Juno Medical Director.

The following AEs are considered AESIs:

- Colitis
- Pneumonitis
- ALT/AST increases / hepatitis / hepatotoxicity
- Neuropathy / neuromuscular toxicity (i.e., events of encephalitis, peripheral motor and sensory neuropathies, Guillain-Barré, and myasthenia gravis)
- Endocrinopathy (i.e., events of hypophysitis, adrenal insufficiency, and hyper- and hypothyroidism)
- Dermatitis
- Nephritis
- Pancreatitis or laboratory abnormalities suggestive of pancreatitis, e.g., increased serum lipase, increased serum amylase

Further information on these risks (e.g., presenting symptoms) can be found in the current version of the durvalumab Investigator Brochure. More specific guidelines for their evaluation and treatment are described in detail in Appendix G.

9.2 Clinical Laboratory Abnormalities and Other Abnormal Assessments

Laboratory abnormalities (e.g., clinical chemistry, hematology, and urinalysis) and other abnormal assessment findings (e.g., ECG or vital signs) that meet at least one of the following criteria should be recorded as an AE or SAE:

- Investigator determines it is clinically significant
- Requires medical or surgical intervention
- Leads to product discontinuation, delay or interruption
- Associated with clinical signs and/or symptoms

Laboratory abnormalities without clinical significance should not be recorded as AEs or SAEs.

Whenever possible, the clinical diagnosis, rather than the laboratory result, should be reported by the Investigator (e.g., anemia versus low hematocrit).

Clinically significant abnormal laboratory values occurring during the study will be followed until repeat tests return to normal, stabilize, or are no longer clinically significant.

9.3 Assessment of Adverse Events and Serious Adverse Events

Each AE and SAE is to be evaluated for duration, severity, and causal relationship with JCAR014 and durvalumab.

9.3.1 Grading and Intensity of Adverse Events

The NCI CTCAE, version 4.03 (http://ctep.cancer.gov/reporting/ctc.html) will be used for grading and analysis of all AEs, with the exception of CRS, which will be graded according to the criteria outlined in Section 7.1. If CTCAE criteria do not exist for a given event, the Investigator should use one of the following:

- Grade 1: Mild – An event that is usually transient in nature and generally not interfering with activities, the AE is generally easily tolerated, does not require treatment.
- Grade 2: Moderate – An event that produces discomfort sufficient to interfere with some aspect of the patient's usual activity and may require medical intervention.
- Grade 3: Severe – An event that results in discomfort or disability which is incapacitating and preventing most normal daily activities and requires medical intervention and/or close follow up.
- Grade 4: Life-threatening – An event that could reasonably result in a potential threat to life.
- Grade 5: Fatal – The AE results in death.

9.3.2 Relationship to Study Drug

To ensure that investigative treatment-related conditions are distinguished from disease-related conditions, attribution of causality will be established in grading AEs. For each event, the Investigator or designee, in conjunction with data from the physician, research nurse, or other provider who examined and evaluated the research participant, will assign the attribution.

Attribution of AEs to study therapy (JCAR014 and/or durvalumab) should be determined using the following criteria:

- No (not related):

  The time course between administration of study therapy and the occurrence or worsening of the AE likely rules out a causal relationship and/or another cause (concomitant drugs, therapies, complications, etc.) is suspected and more plausible.

- Yes (related):

  The time course between administration of study therapy and the occurrence of or worsening of the AE is consistent with a causal relationship, and no other cause is likely.

9.3.3 Adverse Event Collection and Reporting

Whenever possible, AEs should be recorded as a diagnosis rather than listing of signs and symptoms. If an observed or reported sign or symptom is not considered a component of a disease or syndrome by the Investigator, it should be recorded as a separate AE. While CRS will

be collected as an AE, the individual signs and symptoms of CRS will be collected separately for analysis.

9.3.3.1 Non-Serious Adverse Event Reporting

From the time of initial consent up to initiation of lymphodepleting conditioning chemotherapy, AEs will not be recorded unless they are related to study procedures, or ongoing at the start of lymphodepleting chemotherapy.

All Grade 3 or greater AEs will be collected during and for 48 hours after leukapheresis.

All AEs that begin between the first dose of lymphodepleting conditioning chemotherapy and 30 days after the final dose of study treatment (JCAR014 or durvalumab) will be collected and recorded.

All AEs considered related to either JCAR014 or durvalumab should be collected and recorded until 12 months after JCAR014 infusion or 90 days after the final durvalumab infusion, whichever is longer.

The collection of AEs will stop at the commencement of new systemic antitumor therapy.

9.3.3.2 Serious Adverse Event Reporting

From the time of initial informed consent up to initiation of lymphodepleting chemotherapy, only protocol-related SAEs will be collected. All SAEs that occur after initiation of lymphodepleting chemotherapy up to 30 days following the final dose of study therapy (JCAR014 or durvalumab) must be collected and reported to Juno Therapeutics. After the 30 day post-treatment timeline, only SAEs considered related to study therapy (JCAR014 or durvalumab) must be reported to Juno Therapeutics.

All SAEs must be followed until the SAE has resolved or until the condition becomes chronic in nature, stabilizes (in the case of persistent impairment), or the patient dies.

All follow-up information must be submitted to Juno Therapeutics. Serious adverse events must also be reported to the reviewing IRB per IRB requirements (see Section 9.4); a copy of that report must be retained at the site and filed in the study files in accordance with the requirements of that institution.

Serious adverse events will be reported to the FDA and to the National Institutes of Health (NIH) Office of Biotechnology Biosafety Program within the appropriate reporting timelines in accordance with Federal Regulations (i.e., 21 CFR §312.32) and the NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules, respectively.

9.3.4 Death

Any death from the time the patient provides informed consent through 8 weeks after the final dose of study therapy (JCAR014 or durvalumab) should be reported as an SAE (Section 9.3.3.2).

Deaths that occur more than 8 weeks after the final dose of study therapy (JCAR014 or durvalumab) will be reported as SAEs only if considered related to JCAR014 or durvalumab.

If the patient's death is not related to progression of disease, the cause of death will be evaluated to determine if it was related to JCAR014 or durvalumab treatment.

9.3.5 Pregnancy

To ensure patient safety, each pregnancy occurring in a female patient or in the female partner of a male patient from the time of consent until 90 days after the final study treatment must be recorded. If the pregnancy is discovered following initiation of study therapy (JCAR014 or durvalumab), the pregnancy should be followed to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

9.4 IRB Reporting Requirements

Definitions associated with reportable events and reporting requirements can be found on the FHCRCs Institutional Review Office (IRO) extranet website.

The FHCRC PI and study personnel should meet regularly (in person or via teleconference) to review all reported events. The FHCRC IRB and IND Sponsor will be notified of reportable events by the FHCRC PI or study nurse according to current FHCRC IRB reporting obligations.

Reporting of unanticipated adverse effects to the FDA will be the responsibility of the sponsor (see Section 9.5)

Classification of an event as serious or non-serious determines the reporting procedures to be followed by the site for reporting the event to the Sponsor.
PI to Sponsor reporting requirements for adverse events are summarized below:

Classification		Reporting Time*	Reporting Action
SAE	Fatal or life-threatening	Within 24 hours of study team awareness	Email notification to Sponsor & PI
	All other SAEs	Within 2 business days of study team awareness	Email notification to Sponsor & PI

*In Title 21 CFR 312.64 the term "Immediate" is interpreted by the immunotherapy program in the Reporting Time column

9.5 FDA Reporting Requirements

As a study conducted under IND regulations, we will comply with the FDA regulations regarding safety reporting 21 CFR §312.32 including the following requirements:

- A sponsor must promptly review all information relevant to the safety of the drug 21 CFR §312.32 (b).
- A sponsor must notify the FDA in an IND safety report of potential serious risks, as soon as possible but in no case later than 15 calendar days after the sponsor determines that the information qualifies for reporting under 21 CFR §312.32 (c)(1). Information that is required to be reported includes, but is not limited to, (a) serious and unexpected adverse reactions and (b) an increased rate of occurrence of serious suspected adverse reactions.
- The IND safety report must be completed and sent to the FDA in a narrative format, on FDA Form 3500A, or an electronic format.
- A sponsor must also notify the FDA of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible but in no case later than 7 calendar days after the sponsor's initial receipt of the information 21 CFR §312.32 (c)(2).

9.6 Steering Committee

The Steering Committee (SC), comprising the PI and/or designee and IND Sponsor, and representatives (medical director/s-) from Juno Therapeutics and MedImmune and statistician from FHCRC, will act in an advisory capacity to the PI/Sponsor throughout the trial, as needed. The decision to proceed to Group 2 will be made in consultation with the SC. The PI and IND Sponsor may override the algorithm's allocation of a patient to a particular dose level or schedule.

9.7 Data Safety Monitoring Plan

9.7.1 Definition of Risk Level

This Phase 1b trial involves genetic modification of somatic cells and requires an IND. At the FHCRC, this type of trial requires independent monitoring twice each year through the Clinical Research Support Office at the FHCRC, and through an independent Data Safety Monitoring Board (Section 9.7.3).

Institutional support of trial monitoring will be in accordance with the FHCRC/University of Washington Cancer Consortium Institutional Data and Safety Monitoring Plan. Under the provisions of this plan, FHCRC Clinical Research Support coordinates data and compliance monitoring conducted by consultants, contract research organizations, or FHCRC employees unaffiliated with the conduct of the study. Independent monitoring visits occur at specified intervals determined by the assessed risk level of the study and the findings of previous visits per the institutional DSMP.

In addition, protocols are reviewed at least annually and as needed by the Consortium Data and Safety Monitoring Committee (DSMC), FHCRC Scientific Review Committee (SRC) and the FHCRC/University of Washington Cancer Consortium Institutional Review Board (IRB). The review committees evaluate accrual, adverse events, stopping rules, and adherence to the applicable data and safety monitoring plan for studies actively enrolling or treating patients. The IRB reviews the study progress and safety information to assess continued acceptability of the risk-benefit ratio for human subjects. Approval of committees as applicable is necessary to continue the study.

The trial will comply with the standard guidelines set forth by these regulatory committees and other institutional, state and federal guidelines.

9.7.2 Monitoring and Personnel Responsible for Monitoring

The PI and IND Sponsor are responsible for every aspect of the design, conduct, and final analysis of the protocol. Regulations defining the responsibilities for assessment and reporting of AEs, SAEs, and unexpected AEs are defined by the Code of Federal Regulations: 21 CFR 312.32 and CTCAE Version 4.03 published by the Cancer Therapy Evaluation Program (CTEP), a division of the NCI/NIH.

This clinical study will rely upon the monitoring of the trial by the PI in conjunction with Study Physician(s), Physician Assistant(s) (PA), or Nurse Practitioner(s), Research Nurse(s), Research Coordinator(s), statistician, and an independent Study Monitor assigned by the FHCRC Clinical Research Support Office (CRS). Juno Therapeutics will perform targeted data verification of key study safety and outcome measures.

Continuous monitoring of the data and safety of this study should be performed by the Protocol Management Team (PMT), which consists of the PI and study personnel. Monitoring by the PMT should be performed at least monthly or more often if necessitated by the development of AEs, and should include review of the data on enrolled patients. The PMT will be responsible for implementation of the stopping rules for safety if necessary.

A case report form (CRF) should be completed for every patient who is registered for participation in the study. The PI or a Co-Investigator will sign and date the indicated places of the CRF. This signature will indicate that thorough inspection of the data therein has been made, and will certify the contents of the form.

9.7.3 Data Safety Monitoring Board

The study will be monitored by the Immunotherapy Integrated Research Center (IIRC) DSMB. The DSMB will be responsible for safeguarding the interests of trial participants and assessing the safety and efficacy of the interventions during the trial. This responsibility will be exercised by providing recommendations about stopping or continuing the trial. To contribute to enhancing the integrity of the trial, the DSMB may also formulate recommendations relating to

the selection, recruitment and retention of participants and their management; adherence to protocol-specified regimens; and the procedures for data management and quality control. The DSMB will be advisory to the study Sponsor and the PI, who will be responsible for prompt review of the DSMB recommendations to guide decisions regarding continuation or termination of the trial and whether amendments to the protocol or changes in study conduct are required. The DSMB is an independent, multidisciplinary group consisting of clinical experts and a statistician who collectively have experience in leukemia, lymphoma, hematology, biostatistics, and the conduct and monitoring of clinical trials. The DSMB will meet approximately every 6 months to review data. The current members are listed in the IIRC DSMB charter.

10. STATISTICAL PLAN

10.1 General Considerations

Results will be presented by dose level for each group separately using descriptive statistics. Data will be combined for all patients regardless of disease histology. Subgroup analyses by disease histology may be performed if the sample size in each subgroup is sufficient.

Data from retreated patients will be summarized separately.

10.2 Analysis Sets

10.2.1 Screened Analysis Set

The Screened analysis set will include all patients who have signed informed consent for screening.

10.2.2 Enrolled Analysis Set

The Enrolled analysis set will include all patients who meet all inclusion/exclusion criteria for leukapheresis and restaging, who are enrolled, and who undergo leukapheresis.

10.2.3 All Treated Analysis Set

The All Treated analysis set will include all patients who have received at least one dose of JCAR014 or one infusion of durvalumab.

10.2.4 DLT Evaluable Analysis Set

The DLT evaluable analysis set includes all patients who have received JCAR014 cell product that conforms to dose or composition standards and full infusion of the first dose of durvalumab, and who have either experienced a DLT or were followed for the full DLT evaluation period. Patients with JCAR014 levels < 10 copies/µg DNA in blood by PCR at time of durvalumab administration in Group 1 will not be DLT-evaluable unless a DLT is experienced or JCAR014 cell expansion after durvalumab administration is clinically significant as determined by the SC.

10.2.5 Efficacy Evaluable Analysis Set

The Efficacy Evaluable (EE) analysis set includes all patients who have received JCAR014 cell product that conforms to dose or composition standards and a full infusion of durvalumab on

Day 7-21 (Group 1) or Day-1 (Group 2), and who had at least one post-baseline disease assessment.

10.2.6 Pharmacokinetic Evaluable Set

The PK analysis set includes patients who have received JCAR014 (for analysis of JCAR014 PK) or durvalumab (for analysis of durvalumab PK) and who have the necessary baseline and on-study PK measurements to provide interpretable results for the specific parameters of interest.

10.3 Planned Analyses

10.3.1 Patient Disposition and Baseline Characteristics

An accounting of patients by disposition will be tabulated for each analysis set. Descriptive summaries of demographics and baseline characteristics will be presented for each analysis set.

Available demographic and baseline information on such patients will be listed and summarized.

10.3.2 Primary Endpoints

Analyses of the primary endpoints will be as follows:

1) Type, frequency, and severity of AEs and laboratory abnormalities

   All AEs will be listed and summarized (see Section 10.3.5.1 for details). Summaries of laboratory data will include, at a minimum, treatment-emergent laboratory abnormalities (see Section 10.3.5.2 for details). Summaries of AEs and laboratory abnormalities will be based on the All Treated analysis set.

2) DLT rates

   Observed DLT rates and AEs will be summarized based on the DLT Evaluable analysis set. Final DLT rates at each dose level will be estimated by isotonic regression (Ji 2010).

   The target toxicity rate for the MTD is 30%. The weighted least squares regression model will assume monotonic non-decreasing DLT rates with increasing dose and use the empirical (observed) DLT rates at each dose level as responses and dose level sample sizes as weights, along with the pool adjacent violators algorithm (PAVA) to estimate the DLT rate at each dose level using available software (e.g., Cytel EAST or the function pava() from the R package 'ISO'). Given the DLT estimates for each dose level, the MTD will be selected from all tried dose levels that have not been previously declared to be unsafe (i.e., P[DLT>30% data] > 95%) or unacceptably toxic according to the mTPI decision table (i.e., DU decision). With this constraint, the MTD will be determined as the dose level with the DLT estimate closest to the target toxicity level of 30%. In the case of dose levels with estimated toxicity of equal distance (tied dose levels) from the target toxicity of 30%, the following approach will be used (Ji 2010):

- Among all tied dose levels, the highest dose level with target toxicity ≤ 30% will be selected. For example, if one dose level has an estimated toxicity of 28% and the other has an estimated toxicity of 32%, the dose level with the estimated toxicity of 28% will be chosen as the MTD.
- If all tied dose levels have estimated toxicity > 30%, the lowest dose level will be selected. For example, if two dose levels have estimated toxicity of 32%, the lower dose level will be selected as the MTD.

3) Maximum concentration (C_{max}), time to peak concentration (T_{max}), area under the curve (AUC), and other relevant PK parameters of JCAR014 in blood and bone marrow

The PK profile of JCAR014 cells in blood, bone marrow, and CSF (in patients with samples) will be characterized, including C_{max}, T_{max}, AUC, and other relevant PK parameters. Expansion of JCAR014 in the blood will be determined ($C_{max}/C_{post\text{-}dose\ Day\ 2}$), along with the persistence of JCAR014 in the blood and bone marrow, based on both the qPCR assay (time above the lower limit of quantification) and flow cytometry (time above threshold JCAR014 level; see Section 8.4.1).

10.3.3 Secondary Endpoints

Definitions for secondary endpoints are provided in Section 0.

1) CR, PR, and OR rates

The rates of CR, PR, and OR will be summarized along with the 2-sided 95% exact Clopper-Pearson confidence intervals based on the EE analysis sets. In addition, ORR will be presented based on the All Treated analysis set, where patients with non-evaluable response will be treated as non-responders.

2) DOR, PFS, and OS

If a patient does not have an event for the DOR or PFS analyses, the patient will be censored at the date of the last adequate disease assessments on or prior to the earliest censoring event. The censoring reason can include ongoing follow-up, discontinuation or completion of the study, receipt of another anticancer treatment, and at least two consecutive missed scheduled disease assessments. For assessment of OS, data from surviving patients will be censored at the last time that the patient is known to be alive.

Kaplan-Meier (KM) methodology will be used to analyze DOR, PFS, and OS.

10.3.4 Exploratory Endpoints

The exploratory endpoints of the study are listed in Section 0; details of the exploratory analyses are provided in the statistical analysis plan (SAP).

10.3.5 Safety Analysis

10.3.5.1 Adverse Events

All AEs will be listed. The focus of AE summarization will be on treatment-emergent AEs (TEAEs). A TEAE is defined as an AE that occurs after the first study therapy infusion (JCAR014 or durvalumab) until 30 days after the final dose of study therapy, or an AE leading to discontinuation of study therapy. Any AE occurring after the initiation of another anticancer treatment will not be considered a TEAE.

Reporting of AEs will be based on the Medical Dictionary for Regulatory Activities (MedDRA) and CTCAE version 4.03. TEAEs will be summarized by system organ class (SOC), preferred term, and severity. A patient who reports multiple occurrence of TEAEs within the same SOC and preferred term is counted only once using the maximum severity grade for summaries. In addition, TEAEs will be summarized by treatment cycle.

10.3.5.2 Laboratory Data

All laboratory data will be listed. The focus of laboratory data summarization (including hematology, serum chemistry) will be on treatment-emergent laboratory abnormalities. A treatment-emergent laboratory abnormality is defined as an abnormality that, compared to baseline, worsens by at least one grade within 30 days after the final dose of study therapy (JCAR014 or durvalumab). The baseline value is defined as the last available recorded value on or prior to the date of the first dose of study therapy. In addition, laboratory abnormalities will be summarized by treatment cycle.

If baseline data are missing, then any graded abnormality (i.e., an abnormality that is Grade ≥ 1 in severity) will be considered treatment-emergent. Hematological and serum biochemistry data will be graded according to CTCAE version 4.03, when applicable. Grade 0 includes all non-missing values that do not meet the criteria for an abnormality of at least Grade 1. Grade 5 will not be used. Some laboratory tests have criteria for both increased and decreased levels; analyses for each direction (i.e., increased, decreased) will be presented separately.

10.4 Sample Size Considerations

A maximum sample size of 42 is planned for Group 1 and Group 2 combined. The SC may decide to further increase the sample size beyond 21 per group by adding additional patients. If a third group is enrolled, a maximum sample size of 63 is allowed for the trial.

10.5 Timing of Analyses

Data will be reviewed on a continual basis to evaluate DLT and antitumor activity to inform dose allocation. Dose allocation may stop early if all doses are either unsafe or ineffective.

Interim data may be analyzed and presented at scientific meetings.

The final analysis will occur when the study stopping criteria have been met and the follow-up period is complete, approximately 12 months after the last patient has come off treatment.

11. DATA MANAGEMENT

11.1 Data Collection System

An EDC system provided by Juno Therapeutics will be used for data collection. The EDC system will be a fully validated, secure system that conforms to 21 CFR Part 11 requirements. Access to the EDC system is role-based, and login credentials will be provided only after completion of the assigned role-based training.

11.2 Data Quality

Study site personnel will enter data into the CRFs in the EDC system. An independent monitor assigned through Clinical Research Support will perform regular monitoring of patient data per CRS policies. In addition, a Juno Therapeutics Clinical Research Associate (CRA) or designee will verify specific predetermined data points recorded in the CRFs with the source documents.

To ensure complete and accurate data, automated data validation checks programmed within the EDC system will flag missing and non-conformant data during data entry. Data review by the investigators and by the Juno Therapeutics project team may result in additional questions. Items flagged by the automated data validation checks and by the project team will appear as electronic queries on the applicable CRF in the EDC system for a specified user role to resolve. All data entry and subsequent data changes are logged in an audit trail in the EDC system.

Following database lock, an electronic copy of the final patient casebook will be provided to the study site for archival.

12. STUDY ADMINISTRATION

12.1 Regulatory and Ethical Considerations

12.1.1 Trial Conduct

This study is conducted by FHCRC in collaboration with Juno Therapeutics and MedImmune. Juno Therapeutics is funding the study, will undertake research investigations and will provide Durvalumab on behalf of MedImmune. MedImmune will undertake research investigations on this study. The IND Sponsor is Stanley Riddell, MD. The study will be conducted in compliance with the protocol approved by the Institutional Review Board, and according to Good Clinical Practice (GCP) standards any other applicable Federal, state, and/or local regulatory requirements. No deviation from the protocol will be implemented without the prior review and approval of the IRB except where it may be necessary to eliminate an immediate hazard to a patient. In such case, the deviation will be reported to the IRB as soon as possible.

12.1.2 Institutional Review Board Approval

It is the responsibility of the Investigator to ensure that the FHCRC IRB has reviewed and approved this protocol prior to initiating the study. The IRB must also review and approve the informed consent form (ICF), other written information provided to the patient, and all patient materials that may be used.

If the protocol, Investigator's Brochure, or ICF are amended during the study, the Investigator is responsible for ensuring that the IRB has reviewed and approved these amended documents and the study Sponsor has been notified. In addition, IRB approval of the amended documents must be obtained before implementation and before new patients are consented to participate in the study using the amended version of the ICF.

12.1.3 Institutional Biosafety Committee Approvals

JCAR014 consists of autologous T cells that have been manipulated via genetic modification in vitro to express a CAR directed against the CD19 cell surface marker. Since neither the patient's source material nor the final investigational drug product has been tested for the presence of communicable diseases in accordance with the provisions in 21 CFR §1271.90(a)(1), the JCAR014 investigational drug product should be handled according to institutional procedures for materials that may contain infectious materials (e.g., BioSafety Level 1 or 2).

It is the responsibility of the Investigator to ensure that the appropriate Institutional Biosafety Committee (IBC) has reviewed and approved this protocol and any other required materials prior to initiating the study if required per institutional policy.

12.1.4 Patient Informed Consent

Patients will be seen at the Seattle Cancer Care Alliance or the Fred Hutchinson Cancer Research Center (FHCRC) for consideration of treatment options for their disease. The protocol will be discussed thoroughly with the patient and other family members if appropriate, and all known and potential risks to the patient will be described. The procedure and alternative forms of therapy will be presented as objectively as possible, and the risks and hazards of the procedure explained to the patient. A summary of the clinic visit detailing what was covered will be dictated for the medical record.

Consent from the patient will be obtained using forms approved by the FHCRC IRB. Each informed consent form will be appropriately signed and dated by the patient or the patient's legally authorized representative and the person conducting the consent discussion, and also by an impartial witness if required by the IRB or local requirements. The process of obtaining the informed consent will be in compliance with all federal regulations, International Conference of Harmonisation (ICH) requirements (ICH E6 4.8) and local laws.

If the ICF is amended during the study, the Investigator must follow all applicable regulatory requirements pertaining to approval of the amended ICF by the IRB. The investigative site must

use the amended ICF for all new patients and repeat the consent process with the amended ICF for any ongoing patients.

12.2 Investigator Obligations

12.2.1 Investigator Responsibilities

The Investigator is responsible for ensuring that all study site personnel, including subinvestigators and other responsible study staff members, conduct the study in compliance with the Declaration of Helsinki and the ICH E6 Guideline for GCP, including the archiving of essential documents.

The Investigator will ensure adherence to the basic principles of Good Clinical Practice, as outlined in 21 CFR 312, Subpart D, "Responsibilities of Sponsors and Investigators," 21 CFR, Part 50, 1998, and 21 CFR, Part 56, 1998.

The Investigator, subinvestigators, and study staff will comply with 21 CFR, Part 54, 1998, providing documentation of any financial conflict of interest.

If necessary to amend either the protocol or the study ICF, the Investigator will be responsible for ensuring that the IRB reviews and approves the amended documents, and that patients are informed of applicable changes and updates. In accordance with applicable regulatory requirements, the Investigator is solely obligated to inform the IRB of progress of the study and notify the IRB of study closure.

12.3 Site Audits and Regulatory Inspections

Representatives of regulatory authorities, Juno Therapeutics, or the IRB may conduct inspections or audits of the clinical study. The Investigator agrees to provide to representatives of a regulatory agency or Juno access to records, facilities, and personnel for the effective conduct of any inspection or audit.

12.4 Public Notification of Study Conduct

Consistent with Section 113 of the Food and Drug Modernization Act of 1997 (FDAMA) and with requirements of the International Committee of Medical Journal Editors (ICMJE) as a condition of consideration for publication of study results, this protocol will be listed at the ClinicalTrials.gov website per the US FDA requirement and information at the website relating to study design and conduct will be appropriately updated during the course of the study.

12.5 Study Termination

Upon completion or early termination of the study, the following activities, when applicable, must be conducted by the Investigator:

- Data clarifications and/or resolutions;

- Accounting, reconciliation, and final disposition of used and unused study drug; and
- Review of site study records for completeness.

If the study is suspended or terminated for safety reasons, the Investigator will promptly inform the regulatory authorities of the suspension or termination of the study and the reasons for the action. The Investigator is also responsible for promptly informing the IRB and providing the reasons for the suspension or termination of the study.

12.6 Records

The medical record containing information regarding treatment of the patient will be maintained as a confidential document, within the guidelines of the FHCRC, the University of Washington Medical Center, and the SCCA. The investigators will ensure that data collected conform to all established guidelines for coding collection, key entry, and verification. Each patient is assigned a unique patient number to assure patient confidentiality. Patients will not be referred to by name or by any other personal identifier in any publication or external presentation. The Clinical Statistics Departments at FHCRC maintain a patient database to allow storage and retrieval of subject data collected from a wide variety of sources. The licensed medical records departments, affiliated with the institution where the patient receives medical care, maintains all original inpatient and outpatient chart documents.

The primary research records are kept in access controlled office spaces or password-protected computer-based applications; records will be retained, at a minimum, for the duration of time that durvalumab is commercially available in any region plus an additional 15 years. Information gathered from this study regarding patient outcomes and adverse events may be made available to the FDA, NIH, and Juno Therapeutics. All precautions to maintain confidentiality of medical records will be taken.

12.7 Confidentiality of Information

Patients' names will remain confidential and will not be included in the database. All study findings will be stored in electronic databases. The Investigator will maintain a personal patient identification list (patient and treatment numbers with the corresponding patient names) to enable records to be identified.

13. REFERENCES

1. Abiko K, Matsumura N, Hamanishi J, et al. IFN-gamma from lymphocytes induces PD-L1 expression and promotes progression of ovarian cancer. Br J Cancer 2015;112(9):1501-1509.
2. Adusumilli PS, Cherkassky L, Villena-Vargas J, et al. Regional delivery of mesothelin-targeted CAR T cell therapy generates potent and long-lasting CD4-dependent tumor immunity. Science Translational Medicine 2014;6(261):261ra151.
3. Andorsky DJ, Yamada RE, Said J, et al. Programmed death ligand 1 is expressed by non-hodgkin lymphomas and inhibits the activity of tumor-associated T cells. Clin Cancer Res 2011;17(13):4232-4244.
4. Bennett F, Luxenberg D, Ling V, et al. Program death-1 engagement upon TCR activation has distinct effects on costimulation and cytokine-driven proliferation: attenuation of ICOS, IL-4, and IL-21, but not CD28, IL-7, and IL-15 responses. J Immunol 2003;170(2):711-718.
5. Bos R and Sherman LA. CD4+ T-cell help in the tumor milieu is required for recruitment and cytolytic function of CD8+ T lymphocytes. Cancer Res 2010;70(21):8368-8377.
6. Brahmer JR, Tykodi SS, Chow LQ, et al. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. N Engl J Med 2012;366(26):2455-2465.
7. Brentjens RJ, Rivière I, Park JH, 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;118(18):4817-4828.
8. Carter L, Fouser LA, Jussif J, et al. PD-1:PD-L inhibitory pathway affects both CD4(+) and CD8(+) T cells and is overcome by IL-2. Eur J Immunol 2002;32(3):634-643.
9. Challa-Malladi M, Lieu YK, Califano O, et al. Combined genetic inactivation of beta2-Microglobulin and CD58 reveals frequent escape from immune recognition in diffuse large B cell lymphoma. Cancer Cell 2011;20(6):728-740.
10. Chen J, Feng Y, Lu L, et al. Interferon-gamma-induced PD-L1 surface expression on human oral squamous carcinoma via PKD2 signal pathway. Immunobiology 2012;217(4):385-393.
11. Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol 2014;32(27):3059-3068.
12. Chow LQ. Exploring novel immune-related toxicities and endpoints with immune-checkpoint inhibitors in non-small cell lung cancer. Am Soc Clin Oncol Educ Book 2013.
13. Coiffier B, Altman A, Pui CH, et al. Guidelines for the management of pediatric and adult tumor lysis syndrome: an evidence-based review. J Clin Oncol 2008;26(16):2767-2778.
14. Coiffier B, Lepage E, Briere J, et al. CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. N Engl J Med 2002;346(4):235-242.
15. Cunard R and Kelly CJ. 18. Immune-mediated renal disease. J Allergy Clin Immunol 2003;111(2 Suppl):S637-644.
16. Davila ML, Brentjens R, Wang X, et al. How do CARs work? Early insights from recent clinical studies targeting CD19. Oncoimmunology 2012;1(9):1577-1583.
17. Davila ML, Kloss CC, Gunset G, et al. 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;8(4):e61338.

18. Davila ML, Riviere I, Wang X, et al. Efficacy and toxicity management of 19-28z CAR T cell therapy in B cell acute lymphoblastic leukemia. Sci Transl Med 2014;6(224):224ra225.
19. Di Giacomo AM, Biagioli M and Maio M. The emerging toxicity profiles of anti-CTLA-4 antibodies across clinical indications. Semin Oncol 2010;37(5):499-507.
20. Dudley ME, Wunderlich JR, Robbins PF, et al. Cancer regression and autoimmunity in patients after clonal repopulation with antitumor lymphocytes. Science 2002;298(5594):850-854.
21. Dudley ME, Wunderlich JR, Yang JC, et al. Adoptive cell transfer therapy following non-myeloablative but lymphodepleting chemotherapy for the treatment of patients with refractory metastatic melanoma. J Clin Oncol 2005;23(10):2346-2357.
22. Dudley ME, Yang JC, Sherry R, et al. Adoptive Cell Therapy for Patients With Metastatic Melanoma: Evaluation of Intensive Myeloablative Chemoradiation Preparative Regimens. J Clin Oncol 2008.
23. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45(2):228-247.
24. Fife BT and Bluestone JA. Control of peripheral T-cell tolerance and autoimmunity via the CTLA-4 and PD-1 pathways. Immunol Rev 2008;224:166-182.
25. Food and Drug Administration. Guidance for Industry: Gene Therapy Clinical Trials — Observing Subjects for Delayed Adverse Events. 2006.
26. 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. 2000.
27. Freeman GJ, Long AJ, Iwai Y, et al. Engagement of the PD-1 immunoinhibitory receptor by a novel B7 family member leads to negative regulation of lymphocyte activation. J Exp Med 2000;192(7):1027-1034.
28. Gardner RA, Park JR, KellySpratt KS, et al. T Cell Products of Defined CD4:CD8 Composition and Prescribed Levels of CD19-CAR/EGFRt Transgene Expression Mediate Regression of Acute Lymphoblastic Leukemia in the Setting of Post-Allo-HSCT Relapse. Presented at the 56th Annual Meeting of the American Society of Hematology. 2014; San Francisco, CA.
29. Gisselbrecht C, Glass B, Mounier N, et al. Salvage regimens with autologous transplantation for relapsed large B-cell lymphoma in the rituximab era. J Clin Oncol 2010;28(27):4184-4190.
30. Grupp SA, Kalos M, Barrett D, et al. Chimeric antigen receptor-modified T cells for acute lymphoid leukemia. New England Journal of Medicine 2013;368(16):1509-1518.
31. Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med 2010;363(8):711-723.
32. Howard SC, Jones DP and Pui CH. The tumor lysis syndrome. N Engl J Med 2011;364(19):1844-1854.
33. Izzedine H, Gueutin V, Gharbi C, et al. Kidney injuries related to ipilimumab. Invest New Drugs 2014;32(4):769-773.
34. Ji Y, Liu P, Li Y, et al. A modified toxicity probability interval method for dose-finding trials. Clin Trials 2010;7(6):653-663.
35. Kaehler KC, Piel S, Livingstone E, et al. Update on immunologic therapy with anti-CTLA-4 antibodies in melanoma: identification of clinical and biological response patterns,

immune-related adverse events, and their management. Semin Oncol 2010;37(5):485-498.
36. Kalos M, Levine BL, Porter DL, et al. T cells with chimeric antigen receptors have potent antitumor effects and can establish memory in patients with advanced leukemia. Sci Transl Med 2011;3(95):95ra73.
37. Keir ME, Butte MJ, Freeman GJ, et al. PD-1 and its ligands in tolerance and immunity. Annu Rev Immunol 2008;26:677-704.
38. Kochenderfer JN, Dudley ME, Kassim S, 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. Journal of Clinical Oncology 2015;33(6):540-549.
39. Kochenderfer JN, Kassim SH, Somerville R, et al. Treatment of Chemotherapy-Refractory B-Cell Malignancies with Anti-CD19 Chimeric Antigen Receptor T Cells. Presented at the Annual Meeting of the American Society of Gene and Cell Therapy. 2014a; New Orleans, LA.
40. Kochenderfer JN, Somerville R, Lu L, et al. Anti-CD19 CAR T Cells Administered after Low-Dose Chemotherapy Can Induce Remissions of Chemotherapy-Refractory Diffuse Large B-Cell Lymphoma. Presented at the 56th Annual Meeting of the American Society of Hematology. 2014b; San Francisco, CA.
41. Latchman Y, Wood CR, Chernova T, et al. PD-L2 is a second ligand for PD-1 and inhibits T cell activation. Nat Immunol 2001;2(3):261-268.
42. Lee DW, Gardner R, Porter DL, et al. Current concepts in the diagnosis and management of cytokine release syndrome. Blood 2014;124(2):188-195.
43. Lee DW, Kochenderfer JN, Stetler-Stevenson M, et al. T cells expressing CD19 chimeric antigen receptors for acute lymphoblastic leukaemia in children and young adults: a phase 1 dose-escalation trial. Lancet 2015;385(9967):517-528.
44. Lesokhin AM, Ansell SM, Armand P, et al. Preliminary Results of a Phase I Study of Nivolumab (BMS-936558) in Patients with Relapsed or Refractory Lymphoid Malignancies. 56th Annual Meeting of the American Society of Hematology (2014), San Francisco, CA.
45. Li YS, Hayakawa K and Hardy RR. The regulated expression of B lineage associated genes during B cell differentiation in bone marrow and fetal liver. Journal of Experimental Medicine 1993;178(3):951-960.
46. Li YS, Wasserman R, Hayakawa K, et al. Identification of the earliest B lineage stage in mouse bone marrow. Immunity 1996;5(6):527-535.
47. Maude SL, Frey N, Shaw PA, et al. Chimeric antigen receptor T cells for sustained remissions in leukemia. New England Journal of Medicine 2014;371(16):1507-1517.
48. Myklebust JH, Irish JM, Brody J, et al. High PD-1 expression and suppressed cytokine signaling distinguish T cells infiltrating follicular lymphoma tumors from peripheral T cells. Blood 2013;121(8):1367-1376.
49. NCCN. NCCN Guidelines: Non-Hodgkin's Lymphomas. NCCN Clinical Practice Guidelines in Oncology 2014;1.2014.
50. Nurieva R, Thomas S, Nguyen T, et al. T-cell tolerance or function is determined by combinatorial costimulatory signals. EMBO J 2006;25(11):2623-2633.
51. Park JJ, Omiya R, Matsumura Y, et al. B7-H1/CD80 interaction is required for the induction and maintenance of peripheral T-cell tolerance. Blood 2010;116(8):1291-1298.

52. Porter DL, Levine BL, Kalos M, et al. Chimeric antigen receptor-modified T cells in chronic lymphoid leukemia. New England Journal of Medicine 2011;365(8):725-733.
53. Rezvani AR, Norasetthada L, Gooley T, et al. Non-myeloablative allogeneic haematopoietic cell transplantation for relapsed diffuse large B-cell lymphoma: a multicentre experience. Br J Haematol 2008;143(3):395-403.
54. Rossille D, Gressier M, Damotte D, et al. High level of soluble programmed cell death ligand 1 in blood impacts overall survival in aggressive diffuse large B-Cell lymphoma: results from a French multicenter clinical trial. Leukemia 2014;28(12):2367-2375.
55. Sadelain M, Brentjens R and Riviere I. The basic principles of chimeric antigen receptor design. Cancer Discovery 2013;3(4):388-398.
56. Saunders PA, Hendrycks VR, Lidinsky WA, et al. PD-L2:PD-1 involvement in T cell proliferation, cytokine production, and integrin-mediated adhesion. Eur J Immunol 2005;35(12):3561-3569.
57. Schulert GS and Grom AA. Pathogenesis of Macrophage Activation Syndrome and Potential for Cytokine-Directed Therapies. Annual Review of Medicine 2015;66:145-159.
58. Schuster SJ, Svoboda J, Nasta SD, et al. Phase IIa Trial of Chimeric Antigen Receptor Modified T Cells Directed Against CD19 (CTL019) in Patients with Relapsed or Refractory CD19+ Lymphomas. Presented at the 56th Annual Meeting of the American Society of Hematology. 2014; San Francisco, CA.
59. Siegel RL, Miller KD and Jemal A. Cancer Statistics 2015. Cancer: A Cancer Journal for Physicians 2015;65(1):5-29.
60. Stamenkovic I and 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. Journal of Experimental Medicine 1988;168(3):1205-1210.
61. Toes RE, Ossendorp F, Offringa R, et al. CD4 T cells and their role in antitumor immune responses. Journal of Experimental Medicine 1999;189(5):753-756.
62. Topalian SL, Hodi FS, Brahmer JR, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. N Engl J Med 2012;366(26):2443-2454.
63. Tseng SY, Otsuji M, Gorski K, et al. B7-DC, a new dendritic cell molecule with potent costimulatory properties for T cells. J Exp Med 2001;193(7):839-846.
64. Turtle CJ, Berger C, Sommermeyer D, et al. Immunotherapy with CD19-specific chimeric antigen receptor (CAR)-modified T cells of defined subset composition. Annual Meeting of the American Society for Clinical Oncology (2015), Chicago, IL.
65. Twa DD, Chan FC, Ben-Neriah S, et al. Genomic rearrangements involving programmed death ligands are recurrent in primary mediastinal large B-cell lymphoma. Blood 2014;123(13):2062-2065.
66. Weber JS, Kahler KC and Hauschild A. Management of immune-related adverse events and kinetics of response with ipilimumab. J Clin Oncol 2012;30(21):2691-2697.
67. Wolchok JD, Kluger H, Callahan MK, et al. Nivolumab plus ipilimumab in advanced melanoma. N Engl J Med 2013;369(2):122-133.
68. Wrzesinski C, Paulos CM, Gattinoni L, et al. Hematopoietic stem cells promote the expansion and function of adoptively transferred antitumor CD8 T cells. J Clin Invest 2007;117(2):492-501.
69. Zou W and Chen L. Inhibitory B7-family molecules in the tumour microenvironment. Nat Rev Immunol 2008;8(6):467-477.
70. Turtle CJ, Laïla-Aïcha Hanafi, Carolina Berger et al. CD19 CAR–T cells of defined CD4+:

CD8+ composition in adult B cell ALL patients. J Clin Invest, 2016; 126(6): 2123–2138.
71. Turtle CJ, Laïla-Aïcha Hanafi, Carolina Berger 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 Trans Med, 2016; **8** (355).

Appendix A Schedule of Evaluations

Table A-1: Schedule of Evaluations

Assessment	Protocol Section	Screening	Pretreatment Evaluation	Days -5 to -2	Day -1[b]	JCAR014 Treatment Cycle		First Post-JCAR014 Durvalumab Cycle		Subsequent Durvalumab Cycles[a]		Follow-Up Evaluations[c]
						Day 0	Post-JCAR014 Assessments (Days 1 to 27)	Day 21-28[f]	Post Durvalumab Assessments	Durvalumab Infusion (Approximately Days 56, 84, etc.)	Post-Durvalumab Assessments	
I/E criteria	5	X	X									
Confirm diagnosis			X									
Medical history[d]		X	X									
Height/weight[e]		X			X	X		X		X		
Physical exam	8.3.1	X	X		X	X	Day 1, twice weekly for first 2 weeks, then weekly	X	1 day post-infusion, twice weekly for first 2 weeks, then weekly	X	Approx every 2 weeks	X
Vitals including O_2 sat	8.3.5		X		X[g]	X[g]		X[g]		X[g]		
Karnofsky performance status	8.3.7		X			X		X		X		
Chest x-ray			X									
12-lead ECG[h]	8.3.9		X		X[h]	X[h,n]		X[h]		X[h,o]		1 month after the last dose of study therapy (JCAR014 or durvalumab)
MUGA/ECHO	8.3.8		X									
CT/PET scan[i]	8.1.10		X[j]				Approximately 1, 2, 4, 6, 9, and 12 months after the JCAR014 infusion (see Section 8.1.10)					
Pregnancy test		X[k]	X[k]									
HLA typing			X[p]									

Assessment	Protocol Section	Screening	Pretreatment Evaluation	Days -5 to -2	Day -1[b]	JCAR014 Treatment Cycle		First Post-JCAR014 Durvalumab Cycle		Subsequent Durvalumab Cycles[a]		Follow-Up Evaluations[c]
						Day 0	Post-JCAR014 Assessments (Days 1 to 27)	Day 21-28[f]	Post Durvalumab Assessments	Durvalumab Infusion (Approximately Days 56, 84, etc.)	Post-Durvalumab Assessments	
Leukapheresis	6.1		X									
Allopurinol prophylaxis	7.5			X[m]								
Lymphodepleting chemotherapy	6.2			X								
JCAR014 admin	6.3					X						
Durvalumab admin	6.4				X			X		X		
AEs	9.3.3		X	X	X	X	X	X	X	X	X	X
Con meds	5.6	X	X	X	X	X	X	X	X	X	X	X
Neurological exam	7.3.3		X		X[r]	X[r]	X[r]	X[r]	X[r]	X[r]	X[r]	X[r]
MMSE	Appendix D		X			X	Approx Day 7 and Day 14	X	Approx 7 and 14 days after durvalumab infusion			
Neuropsychological test	8.3.4		X									2 months after JCAR014 infusion

Assessment	Protocol Section	Screening	Pretreatment Evaluation	Days -5 to -2	Day -1[b]	JCAR014 Treatment Cycle		First Post-JCAR014 Durvalumab Cycle		Subsequent Durvalumab Cycles[a]		Follow-Up Evaluations[c]
						Day 0	Post-JCAR014 Assessments (Days 1 to 27)	Day 21-28[f]	Post Durvalumab Assessments	Durvalumab Infusion (Approximately Days 56, 84, etc.)	Post-Durvalumab Assessments	
CBC, differential, platelet count	8.3.2	X	X	X	X	X	Twice weekly for first 2 weeks, then at least weekly	X	Twice weekly for first 2 weeks, then at least weekly	X	Approx every 2 weeks	X
Hepatic function with LDH; renal function with Mg	8.3.2	X	X	X	X	X		X		X		X
Uric acid	8.3.2		X	X	X	X		X		X		
Serum ferritin	8.3.2		X			X		X		X		
CRP	8.3.2		X			X		X		X		
PT, PTT, fibrinogen, and D-dimer	8.3.2		X			X		X		X		
Quantitative IgG	8.3.2		X					X		X[t]		Approximately monthly[t]
PSBC recipient donor battery panel	8.3.2	X										
ABO blood typing; antibody screen		X										
Research Assessments												
Collection of archived tumor biopsy sample (if applicable)	8.4.4		X									
Fresh tumor biopsy (consenting patients only)	8.4.4		X				Within the first 4 weeks after JCAR014[w]		Within the first 4 weeks after durvalumab[w]			
BMA/BMB[l]	8.1.10		X[q]									

Assessment	Protocol Section	Screening	Pretreatment Evaluation	Days -5 to -2	Day -1[b]	JCAR014 Treatment Cycle		First Post-JCAR014 Durvalumab Cycle		Subsequent Durvalumab Cycles[a]		Follow-Up Evaluations[c]
						Day 0	Post-JCAR014 Assessments (Days 1 to 27)	Day 21-28[f]	Post Durvalumab Assessments	Durvalumab Infusion (Approximately Days 56, 84, etc.)	Post-Durvalumab Assessments	
						As clinically indicated at the time of restaging in patients with bone marrow lymphoma at baseline until patient achieves a CR						
B-cell reconstitution	8.4.4		X				Approx Day 14	X	Approx 14 days post-infusion	X		Approx 1, 2, 3, 4, 5, 6, 9, and 12 months after the JCAR014 infusion
T-cell subset screening	8.1.2	X										
T-cell persistence[s]	8.4.1					X	Approx 5, 7, 11, 14, 21 days post-infusion	X	Approx 5, 7, 11, 14, 21 days post-infusion	X	Approx 14 days post-infusion	Approx 1, 2, 3, 4, 5, 6, 9, and 12 months after the JCAR014 infusion
Serum biomarkers[s,u]	8.4.4		X		X	X	Approx 1, 4, 5, 7, 11, 14, 21 days post-infusion	X	Approx 1, 4, 5, 7, 11, 14, 21 days post-infusion	X		Approx 1 month after the last durvalumab infusion
RCL testing by VSVG qPCR	8.4.2		X							Approximately 3, 6, and 12 months after the JCAR014 infusion (see Section 8.4.2)		
JCAR014 humoral and cellular immune response[u]	8.4.3		X				Approx 14 days post infusion	X	Approx 14 days post infusion	X	Approx 14 days post infusion	Approx 1 and 2 months after JCAR014 infusion (if no post-JCAR014 durvalumab administered)
Endothelial activation studies	8.4.4		X			X	Approx 1 and 7 days post-infusion					

Assessment	Protocol Section	Screening	Pretreatment Evaluation	Days -5 to -2	Day -1[b]	JCAR014 Treatment Cycle		First Post-JCAR014 Durvalumab Cycle		Subsequent Durvalumab Cycles[a]		Follow-Up Evaluations[c]
						Day 0	Post-JCAR014 Assessments (Days 1 to 27)	Day 21-28[f]	Post Durvalumab Assessments	Durvalumab Infusion (Approximately Days 56, 84, etc.)	Post-Durvalumab Assessments	
Plasma biomarkers[s,u]	8.4.4		X		X	X	Approx 1, 4, 5, 7, 11, 14, 21 days post-infusion	X	Approx 1, 4, 5, 7, 11, 14, 21 days post-infusion	X	Approx 14 days post infusion	Approx 1 month after the last durvalumab infusion
IgH sequencing[u]	8.4.4		X				Approx Day 14	X	Approx 14 days post-infusion	X		Approx 1, 2, 3, 4, 5, 6, 9, and 12 months after the JCAR014 infusion
Durvalumab humoral immune response[u,z]	8.4.3				X			X		Day 0 of 4th, and 7th infusions		Approx 90 days after the last durvalumab infusion
Durvalumab PK[v,u]	8.4.1				X		Approx 14 days post-infusion[x]	X	Approx 14 days post-infusion[y]	Day 0 of 3rd, 4th, and 7th infusions		Approx 90 days after the last durvalumab infusion
Soluble PD-L1[u,z]	8.4.4		X		X		Approx 14 days post-infusion[x]	X	Approx 14 days post-infusion[y]	Day 0 of 2nd, and 4th infusions		
Additional optional Pharmacogenetic, Immunogenicity and Biomarker Research Laboratory Evaluations in Blood, BMB, BMA, and Tumor Tissue (archival or fresh)[s]	8.4.1 8.4.2 8.4.3	Details regarding the timepoints at which samples will be collected for these assays will be provided in a separate laboratory sample handling document.										

NOTE: The proposed days of all treatments and assessments are approximate and may vary due to scheduling, clinical or other factors.

[a] If JCAR014-related toxicity is observed during the first durvalumab cycle due to re-expansion of the CAR T cells, the schedule of assessments listed for the first durvalumab cycle may be followed

[b] Patients in Group 2 only

[c] Follow-up visits should be scheduled every 30 days for the first 3 months after the final dose of study therapy (durvalumab or JCAR014), then every 3 months up to 12 months after the JCAR014 infusion or 3 months after the final durvalumab infusion, whichever is later

[d] Medical history to include hematologic, histologic, and genetic findings at diagnosis and time of enrollment as well as prior therapies and response to therapy

[e] Height required only at Screening

[f] May occur as early as Day 7 for patients in Group 1 – early. Durvalumab infusion days for subsequent durvalumab cycles will be adjusted accordingly.

[g] Vital signs, including O_2 sat, obtained before the start of infusion; every 15 ± 5 min during infusion; within 5 min after the end of infusion; and 30 min, 60 min, and 2 hours after the end of infusion

[h] On days of JCAR014 or durvalumab administration, ECGs are to be obtained prior to infusion

[i] Diagnostic CT/PET scan to include neck chest, abdomen and pelvis, as clinically indicated by disease and status and according to the protocol. Staging evaluations may be ceased if the patient proceeds to other antitumor therapy (see Section 8.1.10)

[j] May be omitted in patients with imaging within 30 days before scheduled JCAR014 infusion who have not receive antitumor therapy since prior imaging

[k] Pregnancy tests to be conducted within 14 days before leukapheresis and within 28 days before initiation of lymphodepleting chemotherapy

[l] Bone marrow aspirates/biopsies should be sent for pathology analysis as clinically indicated. A 5-10 mL aliquot of the bone marrow aspirate in sodium heparin should be sent to the Turtle Lab for research. Fresh research bone marrow biopsy samples may be collected if requested by the PI or archived tissue may be used.

[m] May begin prior to lymphodepleting chemotherapy per standard institutional practice

[n] Patients in Group 1 only

[o] Third post-JCAR014 durvalumab cycle only

[p] Does not need to be repeated if results from previous test are available

[q] Not required for patients who have had a marrow aspirate and biopsy within 30 days before the scheduled JCAR014 infusion AND have not received antitumor therapy in the interim

[r] A neurologic examination should be performed if there is clinical suspicion of neurologic dysfunction

[s] May be evaluated at additional timepoints if clinically indicated

[t] Quantitative IgG to be measured approximately monthly (on days of durvalumab infusion as applicable) until levels are normal without IVIG replacement, as clinically indicated.

[u] Samples may be archived and assays performed in selected patients only.

[v] Pre and post durvalumab PK samples should be collected

[w] Biopsy may also be performed at a different timepoint if there is a persistent mass, progression or relapse

[x] Patients in Group 2 only

[y] Patients in Group 1 only

[z] Pre durvalumab infusion sample

Appendix B Maximum Blood Volume Collection for Research Laboratory Evaluations

Time	Volume (mL)[b,c]			
	Sodium heparin	EDTA	Citrate	Serum separator
Screening	30 – d	0	0	0
Pretreatment evaluation	55 – g, i	11 – j	15 – i, k	10 – f, h, i
Day -1 – 1	0	0	0	15 - f
JCAR014 Treatment Cycle				
Day 0 pre-infusion	35 – e, i	0	15 – i, k	5 - f
Day 1	15 – i	0	15 – i, k	5 - f
Day 4	15 - i	0	5 – i	5 – f
Day 5	20 – e	0	5 – i	5 – f
Day 7	20 – e	0	15 – i, k	5 – f
Day 11	20 – e	0	5 – i	5 – f
Day 14	75 – e, i	11 – j	5 – i	7.5 – f, h
Day 21	20 – e	0	5 – i	5 – f
Day 28 – a, m	75 – e, i	11 – j	5 – i	15 – f, h, i
First Post-JCAR014 Durvalumab Cycle				
Day 1	15 – i	0	5 – i	5 – f
Day 4	15 – i	0	5 – i	5 – f
Day 5	20 – e	0	5 – i	5 – f
Day 7	20 – e	0	5 – i	5 – f
Day 11	20 – e	0	5 – i	5 - f
Day 14	75 – e, i	11 – j	5 – i	7.5 – f, h
Day 21	20 – e	0	5 – i	5 – f
Day 28 – a	65 – e, i	11 – j	5 – i	15 – f, h, n
Subsequent Durvalumab Cycles				
Day 14	30 – e, i	0	5 – i	5 – f, h
Day 28 – a	75 – e, i	11 – j	5 – i	5 – f, h

Time	Volume (mL)[b,c]			
	Sodium heparin	EDTA	Citrate	Serum separator
Third, and Seventh Durvalumab Cycles				
Day 0	75 – e, i	11 – j	5 – i	7.5 – f, h
Fourth Durvalumab Cycles				
Day 0	75 – e, i	11 – j	5 – i	17.5 – f, h, i
Last Durvalumab Cycle				
Day 90	35 – e, i	5 – j	5 – i	7.5 – f, h
Follow-Up Evaluations				
Day 60	55 – e, i	11 – j	5 – i	10 – f, h
Day 90	35 – e, g, i	11 – j	5 – i	5 - i
Day 120	35 – e, i	11 – j	5 – i	5 - i
Day 150	35 – e, i	11 – j	5 – i	5 – i
Day 180	35 – e, g, i	11 – j	5 – i	5 – i
Day 270	35 – e, i	11 – j	5 – i	5 – i
Day 365	35 – e, g, i	11 – j	5 – i	5 - i

[a] Additional Day 0 pre-infusion samples may be drawn if there is a significant delay in administration of the first post-JCAR014 durvalumab infusion.

[b] Sample volumes reflect all assays expected for each visit day. If visit days are combined or not conducted, volumes will be revised accordingly in order to avoid duplication in sample collection.

[c] If multiple samples are collected at one time point, the first sample of the day will be used, unless there is a suspected problem with the first sample. Late-night samples may be counted as the next calendar day, as per inpatient standard.

[d] T-cell subset screening.

[e] T-cell persistence.

[f] Serum biomarkers, and durvalumab/ soluble PD-L1 assays (as specified in Appendix A).

[g] RCL testing by VSVG QPCR.

[h] JCAR014 humoral immune response.

[i] Optional archive/additional research studies.

[j] B-cell persistence and IgH sequencing (MRD tracking).

[k] Endothelial activation studies.

[l] Patients in Group 2 only.

[m] May occur as early as Day 7 for patients in Group 1 – early.

[n] Patients in Group 1 only.

Appendix C Response Criteria for Non-Hodgkin Lymphoma

Response	PET-CT-Based Criteria (Cheson 2014)
Complete response (CR)	Score 1, 2, or 3[a] with or without residual mass No evidence of FDG-avid disease in marrow
Partial response (PR)	Score 4 or 5[a] with reduced uptake compared with baseline and residual masses of any size Bone marrow with residual uptake higher than in normal marrow but reduced compared with baseline (Diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in marrow in the context of a nodal response, should consider further evaluation with MRI, biopsy, or interval scan.
Stable disease (SD)	Score 4 or 5[a] with no significant change in FDG uptake from baseline Bone marrow unchanged from baseline
Progressive disease (PD)	Score 4 or 5[a] with an increase in intensity of uptake from nadir New FDG-avid foci consistent with lymphoma (may need biopsy or repeat scan if uncertain about etiology of foci)

[a] Based on the Deauville 5-point Scale: 1 = no uptake; 2 = uptake ≤ mediastinum; 3 = uptake > mediastinum ≤ liver; 4 = moderately increased uptake > liver; 5 = markedly increased uptake > liver and/or new lesions related to lymphoma; X = new areas of uptake unlikely to be related to lymphoma

Appendix D Mini Mental State Examination

MMSE-2

Standard Version

Blue Form

Date of examination ___/___/___ Examiner _____

Name _____ Age _____ Sex _____

Years of school completed _____ Purpose of exam _____

Assessment of level of consciousness

Alert/ Responsive | Drowsy | Stuporous | Comatose/ Unresponsive

Instructions: Words in boldface type should be read aloud clearly and slowly to the examinee. Item substitutions appear in parentheses. Administration should be conducted privately and in the examinee's primary language. Unless otherwise specified, circle 0 if the response is incorrect or 1 if the response is correct. Begin by introducing the test:

Now I'd like to ask you some questions about your memory.

	RESPONSE	SCORE (circle one)
REGISTRATION		
Listen carefully. I am going to say three words. You say them back after I stop. Ready? Here they are... MILK [*pause*], **SENSIBLE** [*pause*], **BEFORE** [*pause*]. **Now repeat those words back to me.** [*Repeat up to 3 times, but score only the first trial.*]		
MILK		0 1
SENSIBLE		0 1
BEFORE		0 1
Now keep those words in mind. I am going to ask you to say them again in a few minutes.		
ORIENTATION TO TIME		
What day is today? What is the...		
year?		0 1
season?		0 1
month of the year?		0 1
day of the week?		0 1
date?		0 1
ORIENTATION TO PLACE*		
Where are we now? What is the...		
state (or province)**?**		0 1
county (or city/town)**?**		0 1
city/town (or part of city/neighborhood)**?**		0 1
building (name or type)**?**		0 1
floor of the building (room number or address)**?**		0 1

*Alternative place words that are appropriate for the setting and increasingly precise may be substituted and noted.

RECALL		
What were those three words I asked you to remember? [*Do not offer any hints.*]		
MILK		0 1
SENSIBLE		0 1
BEFORE		0 1

If administering the MMSE-2:SV, copy the MMSE-2:BV total raw score to the space provided at the top of page 2 and continue with administration.

MMSE-2:BV total raw score ☐ (16 max. points)

PAR • 16204 N. Florida Ave. • Lutz, FL 33549 • 1.800.331.8378 • www.parinc.com

9 8 7 6 Reorder #RO-6685 Printed in the U.S.A.

MMSE-2:BV total raw score ☐ (16 max. points)

ATTENTION AND CALCULATION [*Serial 7s*]

Now I'd like you to subtract 7 from 100. Then keep subtracting 7 from each answer until I tell you to stop.

What is 100 take away 7?	[93]	0	1
If needed, say: **Keep going.**	[86]	0	1
If needed, say: **Keep going.**	[79]	0	1
If needed, say: **Keep going.**	[72]	0	1
If needed, say: **Keep going.**	[65]	0	1

Score 1 point for each correct answer. An answer is considered correct if it is 7 less than the previous answer, even if the previous answer was incorrect.

NAMING

What is this? [*Point to eye.*]	0	1
What is this? [*Point to ear.*]	0	1

REPETITION

Now I am going to ask you to repeat what I say. Ready? IT IS A LOVELY, SUNNY DAY BUT TOO WARM. Now you say that. [*Wait for examinee response and record response verbatim. Repeat up to one time.*]

IT IS A LOVELY, SUNNY DAY BUT TOO WARM.	0	1

Detach the last page of this form. Tear the detached page in half along the horizontal perforation line. Use the upper half of the detached page, which has three shapes on it, as a stimulus form for the Comprehension task. Use the bottom half of the page as a stimulus form for the Reading ("CLOSE YOUR EYES") task. Use the upper back half of the detached page as a stimulus and response form for the Drawing (intersecting pentagons) task and the bottom half of the page (blank) as a response form for the Writing task.

COMPREHENSION

Listen carefully because I am going to ask you to do something. [*Show examinee the geometric figures stimulus page.*] **Look at these pictures and point to the circle, then point to the square, and then point to the triangle.**

Correct response	Observed response		
○		0	1
□		0	1
△		0	1

READING

[*Show examinee the word stimulus page.*] **Please do what this says to do.**

CLOSE YOUR EYES	0	1

WRITING

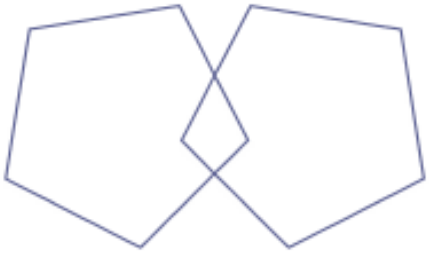
[*Place the blank piece of paper in front of the examinee and provide a pen or pencil.*] 0 1
Please write a sentence. [*If examinee does not respond, say:* **Write about where you live.**]
Score 1 point if the sentence is comprehensible and contains a subject and a verb. Ignore errors in grammar or spelling.

DRAWING

[*Display the intersecting pentagons on the stimulus form and provide a pen or pencil.*] **Please copy this design.** Score 1 point if the drawing consists of two 5-sided figures that intersect to form a 4-sided figure. 0 1

MMSE-2:SV total raw score ☐ (30 max. points)

CLOSE YOUR EYES



Appendix E Long-Term Follow-Up

Study participants should be asked to participate in long term follow-up, as directed by the FDA Guidance for Industry – Gene Therapy Clinical Trials: Observing Patients for Delayed Adverse Events (http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/ucm072957.htm#5).

Long term follow-up should commence approximately 1 year after the JCAR014 infusion. The planned recommendations for follow-up are as follows:

Years 1 - 15:

1. Recommendation that patients undergo at least annual history and physical examination with their primary physician:
   - Adverse event screening guidance for the primary physician in the form of a gene therapy LTFU-directed screening survey may be available.
   - A request for the study team to be notified of all new malignancies and unexpected illnesses.
   - The primary physician may be provided with a blood draw courier kit to enable samples to be returned to the Turtle Lab for archival purposes, and for analysis for transgene and vector persistence, and RCL, as dictated by studies of transferred T cell persistence.
2. A phone call survey or questionnaire to the participant may be used to screen for adverse events, and the patient may be offered the opportunity to return to FHCRC for an annual LTFU clinic visit.
3. Compliance with 21 CFR 312.32 in adverse event reporting.
4. Research studies:
   - Evaluation for transgene vector sequence by PCR of PBMC every 6 months for Years 1 to 5 and every year for Years 6-15 until the transgene becomes undetectable.
   - Annual testing of PBMC for RCL by VSVG qPCR. If there is no evidence of transgene persistence, RCL assays may be suspended after 1 year and samples may be archived.
5. Survival data and results from any available disease response evaluations (i.e., imaging studies [CT, PET/CT, MRI], bone marrow examinations, etc.) performed by the treating physician as standard of care may be collected.

Appendix F Modified Toxicity Probability Interval Decision Table

Number of toxicities	Number of patients treated at current dose																														
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30
0	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E
1	D	S	S	S	S	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E
2		DU	D	S	S	S	S	S	S	S	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E
3			DU	DU	D	S	S	S	S	S	S	S	S	S	S	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E
4				DU	DU	DU	D	D	S	S	S	S	S	S	S	S	S	S	S	S	E	E	E	E	E	E	E	E	E	E
5					DU	DU	DU	DU	DU	D	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	E	E	E	E	E
6						DU	DU	DU	DU	DU	DU	D	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	E
7							DU	DU	DU	DU	DU	DU	DU	D	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S
8								DU	DU	DU	DU	DU	DU	DU	DU	DU	D	S	S	S	S	S	S	S	S	S	S	S	S	S
9									DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	S	S	S	S	S	S	S	S	S	S	S
10										DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	D	S	S	S	S	S	S	S	S
11											DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	S	S	S	S	S	S
12												DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	S	S	S
13													DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	S
14														DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU
15															DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU
16																DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU
17																	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU
18																		DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU
19																			DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU
20																				DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU
21																					DU	DU	DU	DU	DU	DU	DU	DU	DU	DU
22																						DU	DU	DU	DU	DU	DU	DU	DU	DU
23																							DU	DU	DU	DU	DU	DU	DU	DU
24																								DU	DU	DU	DU	DU	DU	DU
25																									DU	DU	DU	DU	DU	DU

D, de-escalate to the next lower dose level; E, escalate to the next higher dose level; DU, current dose is unacceptably toxic; S, stay at the current dose level
Target toxicity (%) = 30%; Sample size = 30

Appendix G Durvalumab Dosing Modification for Toxicity Management

The following tables provide suggested management for toxicities that could be implemented at the discretion of the treating physician.

Table G-1 Durvalumab Treatment Modification and Toxicity Management Guidelines for Immune-related Adverse Events

Table G-2 Durvalumab Treatment Modification and Toxicity Management Guidelines for Infusion-related Reactions

Table G-3 Durvalumab Treatment Modification and Toxicity Management Guidelines for Non-immune-mediated Reactions

Table G-1 Durvalumab Treatment Modification and Toxicity Management Guidelines (TMGs) for Durvalumab

<table>
<tr><th></th><th>Dose Modifications</th><th>Toxicity Management</th></tr>
<tr>
<td>Immune-related adverse events (overall management for toxicities not noted below)</td>
<td>Drug administration modifications of study drug/study regimen will be made to manage potential irAEs based on severity of treatment-emergent toxicities graded per NCI CTCAE v4.03.
In addition to the criteria for permanent discontinuation of study drug/regimen based on CTC grade/severity (table below), permanently discontinue study drug/study regimen for the following conditions:
• Inability to reduce corticosteroid to a dose of ≤ 10 mg of prednisone per day (or equivalent) within 12 weeks after last dose of study drug/regimen
• Recurrence of a previously experienced Grade 3 treatment-related AE following resumption of dosing.
<table>
<tr><td>Grade 1</td><td>No dose modification</td></tr>
<tr><td>Grade 2</td><td>Hold study drug/study regimen dose until Grade 2 resolution to ≤ Grade 1
• If toxicity worsens, then treat as Grade 3 or Grade 4
• If toxicity improves to ≤ Grade 1, then treat at next scheduled treatment date</td></tr>
<tr><td>Grade 3</td><td>Depending on the individual toxicity, may permanently discontinue study drug/study regimen. Please refer to guidelines below</td></tr>
<tr><td>Grade 4</td><td>Permanently discontinue study drug/study regimen</td></tr>
</table>
Note: For Grade 3 and above asymptomatic amylase or lipase levels, hold study drug/regimen and if complete work-up shows no evidence of pancreatitis, may continue or resume study drug/regimen</td>
<td>It is recommended that management of irAEs follow the guidelines presented in this table:
• Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, concomitant medications, infections, etc.)
• In the absence of a clear alternative etiology, all events should be considered potentially immune-related
• Symptomatic and topical therapy should be considered for low-grade (Grade 1 or 2, unless otherwise specified) events
• For persistent (more than 3 to 5 days) low-grade (Grade 2) or severe (Grade ≥3) events, promptly start prednisone PO 1-2 mg/kg/day or IV equivalent
• If symptoms recur or worsen during corticosteroid tapering (≥ 4 weeks of taper), increase the corticosteroid dose (prednisone dose [e.g., up to 2-4 mg/kg/day or IV equivalent]) until stabilization or improvement of symptoms, then resume corticosteroid tapering at a slower rate
• More potent immunosuppressives – (refer to individual sections of the irAE for specific type of immunosuppressive) should be considered for events not responding to systemic steroids
• Discontinuation of study drug is not mandated for Grade 3/Grade 4 inflammatory reactions attributed to local tumour response (e.g., inflammatory reaction at sites of metastatic disease, lymph nodes, etc.). Continuation of study drug in this situation should be based upon a benefit/risk analysis for that patient</td>
</tr>
</table>

	Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
Pneumonitis/ILD	Grade of pneumonitis (CTCAE v4.03)	Any grade	• Monitor patients for signs and symptoms of pneumonitis or ILD (new onset or worsening shortness of breath or cough). Patients should be evaluated with imaging and pulmonary function tests, including other diagnostic procedures as described below • Suspected pneumonitis should be confirmed with radiographic imaging and other infectious and disease-related aetiologies excluded, and managed as described below • Initial work-up may include clinical evaluation, monitoring of oxygenation via pulse oximetry (resting and exertion), laboratory work-up and high-resolution CT scan. • Consider pulmonary and infectious disease consult
	Grade 1 (Asymptomatic, clinical or diagnostic observations only, intervention not indicated)	No dose modification required; however, consider holding study drug/study regimen dosing as clinically appropriate and during diagnostic work-up for other etiologies	For Grade 1 (radiographic changes only): • Monitor and closely follow up in 2-4 days for clinical symptoms, pulse oximetry (resting and exertion), and laboratory work-up and then as clinically indicated • Consider pulmonary and infectious disease consult
	Grade 2 (Symptomatic, medical intervention indicated, limiting instrumental ADL)	Hold study drug/study regimen dose until Grade 2 resolution to ≤ Grade 1 • If toxicity worsens, then treat as Grade 3 or Grade 4 • If toxicity improves to ≤ Grade 1, then the decision to reinitiate study drug/regimen at next scheduled treatment date will be based upon treating physician's clinical judgment.	For Grade 2 (mild to moderate new symptoms): • Monitor symptoms daily and consider hospitalization • Promptly start systemic steroids (e.g., prednisone 1-2 mg/kg/day or IV equivalent) • Reimaging as clinically indicated, consider Chest CT with contrast and repeat in 3-4 weeks • If no improvement within 2-3 days, additional work-up should be considered and prompt treatment with IV methylprednisolone 2-4 mg/kg/day started • If still no improvement within 3-5 days despite IV methylprednisone at 2-4/g/kg/day, promptly start immunosuppressive therapy (e.g. infliximab at 5 mg/kg IV, may be repeated at 2 and 6 weeks after initial doses at the discretion of the treating provider). Caution: Important to rule out sepsis and refer to infliximab label for general guidance before using infliximab • Once improving, gradually taper steroids over ≥ 4 weeks and consider prophylactic antibiotics, antifungal, or anti-PCP treatment (refer to current

	Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
			NCCN guidelines for treatment of cancer-related infections (Category 2B recommendation)[1] • Consider pulmonary and infectious disease consult – Consider as necessary discussing with Juno medical monitor
	Grade 3 or 4 (Grade 3: Severe symptoms; limiting self-care ADL; oxygen indicated Grade 4: life-threatening respiratory compromise, urgent intervention indicated [e.g., tracheostomy or intubation])	Permanently discontinue study drug/study regimen	For Grade 3 or 4 (severe or new symptoms, new/worsening hypoxia, life-threatening): • Promptly initiate empiric IV methylprednisolone 1-4 mg/kg/day or equivalent • Obtain pulmonary and infectious disease consult • Hospitalize the patient • Supportive care (oxygen, etc.) • If no improvement within 2-3 days, additional work-up should be considered and prompt treatment with additional immunosuppressive therapy (e.g. infliximab at 5 mg/kg IV, may be repeated at 2 and 6 weeks after initial doses at the discretion of the treating provider) started. Caution: rule out sepsis and refer to infliximab label for general guidance before using infliximab • Once improving, gradually taper steroids over ≥ 4 weeks and consider prophylactic antibiotics, antifungals, and in particular, anti-PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections (Category 2B recommendation)[2]
Diarrhea/ Enterocolitis	Grade of diarrhea (CTCAE v4.03)	Any grade	• Monitor for symptoms that may be related to diarrhea/enterocolitis (abdominal pain, cramping, or changes in bowel habits, such as increased frequency over baseline or blood in stool) or related to bowel perforation (such as sepsis, peritoneal signs, and ileus) • Permanently discontinue study drug for any grade of intestinal perforation • Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, infections including testing for clostridium difficile toxin, etc.) • Steroids should be considered in the absence of a clear alternative etiology, even for low-grade events, in order to prevent potential progression to higher-grade event

[1] ASCO Educational Book 2015. Michael Pestow MD. "Managing Immune Checkpoint Blocking Antibody Side Effects" Section on Hepatotoxicity page 78
[2] ASCO Educational Book 2015. "Managing Immune Checkpoint Blocking Antibody Side Effects"

	Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
			• Use analgesics carefully; they can mask symptoms of perforation and peritonitis
	Grade 1 diarrhea (stool frequency of < 4 over baseline per day)	No dose modification	For Grade 1 diarrhea: • Close monitoring for worsening symptoms • Consider symptomatic treatment, including hydration, electrolyte replacement, dietary changes (e.g., American Dietetic Association colitis diet), loperamide and other supportive measures . Use of probiotics as per treating physician's clinical judgment. • If symptoms persist consider checking lactoferrin; if positive treat as Grade 2 below. If negative and no infection, continue Grade 1 management.
	Grade 2 diarrhea (stool frequency of 4-6 over baseline per day)	Hold study drug/study regimen until resolution to ≤ Grade 1 • If toxicity worsens, then treat as Grade 3 or Grade 4 • If toxicity improves to ≤ Grade 1 then treat at next scheduled treatment date	For Grade 2 diarrhea: • Consider symptomatic treatment including hydration, electrolyte replacement, dietary changes (e.g., American Dietetic Association colitis diet), and loperamide and/or budesonide • Promptly start prednisone 1-2 mg/kg/day or IV equivalent • If event is not responsive within 2-3 days or worsens despite prednisone at 1-2 mg/kg/day or IV equivalent, GI consult should be obtained for consideration of further work-up, such as imaging and/or colonoscopy to confirm colitis and rule out perforation, and prompt treatment with IV methylprednisolone 2-4 mg/kg/day started • If still no improvement within 2-3 days despite 1-2 mg/kg IV methylprednisolone, promptly start immunosuppressives (e.g. infliximab at 5 mg/kg IV, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider)[3]. Caution: Important to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab • Consult Juno medical monitor if no resolution to ≤ Grade 1 in 3-4 days • Once improving, gradually taper steroids over ≥ 4 weeks and consider prophylactic antibiotics, antifungals, and anti-PCP treatment (refer to current

	Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
			NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation])
	Grade 3 or 4 diarrhea (Grade 3: stool frequency of ≥ 7 over baseline per day Grade 4: life-threatening consequences)	Hold study drug/study regimen until resolution to Grade ≤1; study drug/study regimen can be resumed after completion of steroid taper. Permanently discontinue study drug/study regimen for Grade 3 if toxicity does not improve to Grade ≤1 within 14 days. Permanently discontinue study drug for 1) Grade 3 colitis in patients treated with CTLA-4 inhibitors or 2) Any grade large intestine perforation/Intestinal perforation in any patient treated with ICI.	For Grade 3 or 4 diarrhea: • Promptly initiate empiric IV methylprednisolone 1-2 mg/kg/day or equivalent • Monitor stool frequency and volume and maintain hydration • Urgent GI consult and imaging and/or colonoscopy as appropriate • If still no improvement within 2 days continue steroids and, promptly start further immunosuppressives agents (e.g. infliximab at 5 mg/kg 5 mg/kg IV, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider) • Caution: Ensure GI consult to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab • Once improving, gradually taper steroids over ≥ 4 weeks and consider prophylactic antibiotics, antifungals, and anti-PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation])
Hepatitis (elevated LFTs) **Infliximab should not be used for management of immune-related hepatitis**	Grade of LFT elevation (CTCAE v4.03) Any grade		• Monitor and evaluate liver function tests: AST, ALT, ALP, and total bilirubin • Evaluate for alternative etiologies (e.g., viral hepatitis, disease progression, concomitant medications)
	Grade 1 (AST or ALT > ULN to 3 × ULN and/or TB > ULN to 1.5 × ULN)	No dose modification If it worsens, treat as Grade 2 event	For Grade 1 AST or ALT and/or TB elevation: • Continue LFT monitoring per protocol

	Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
	Grade 2 (AST or ALT > 3 to 5 × ULN and/or TB >1.5-3.0 × ULN)	Hold study drug/study regimen dose until Grade 2 resolution to ≤ Grade 1 • If toxicity worsens, then treat as Grade 3 or Grade 4 • If improves to ≤ Grade 1, then treat at next scheduled treatment date	For Grade 2 AST or ALT and/or TB elevation: • Regular and frequent checking of LFTs (e.g., every 1-2 days) until elevations of these are improving or resolved. • If no resolution to ≤ Grade 1 in 1-2 days, discuss with Juno medical monitor. • If event is persistent (> 2-3 days) or worsens, promptly start prednisone 1-2 mg/kg/day or IV equivalent. • If still no improvement within 2-3 days despite 1-2 mg/kg/day of prednisone or IV equivalent, consider additional work-up and prompt treatment with IV methylprednisolone 2-4 mg/kg/day started. • If still no improvement within 2-3 days despite 1-2 mg/kg/day of IV methylprednisolone, promptly start immunosuppressives (mycophenolate mofetil 0.5-1g every 12 hours then taper in consultation with hepatology consult)).[3] Discuss with Juno medical monitor if mycophenolate mofetil is not available. **Infliximab should NOT be used.** • Once improving, gradually taper steroids over ≥ 4 weeks and consider prophylactic antibiotics, antifungals, and anti-PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation])
	Grade 3 (AST or ALT >5 to 20 × ULN and/or TB > 3.0 to 10 × ULN)	For elevations in transaminases ≤ 8 × ULN, or elevations in bilirubin ≤ 5 × ULN • Hold study drug/study regimen dose until resolution to ≤ Grade 1 or baseline • Resume study drug/study regimen administration at the next scheduled dose if elevations downgrade to ≤ Grade 1 or baseline within 14 days • Permanently discontinue study drug/study regimen if the elevations	For Grade 3 or 4 AST or ALT and/or TB elevation: • Promptly initiate empiric IV methylprednisolone at 1-2 mg/kg/day or equivalent • If still no improvement within 2-3 days despite 1-2 mg/kg/day methylprednisolone IV or equivalent, promptly start treatment with immunosuppressive therapy (mycophenolate mofetil 0.5-1g every 12 hours then taper in consultation with hepatology consult). Discuss with Juno medical monitor if mycophenolate is not available. **Infliximab should NOT be used.** • Hepatology consult, abdominal workup, and imaging as appropriate

[3] ASCO Educational Book 2015 "Managing Immune Checkpoint Blocking Antibody Side Effects", page 78 Section on Hepatotoxicity

	Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
		do not downgrade to ≤ Grade 1 or baseline within 14 days For elevations in transaminases > 8 × ULN or elevations in bilirubin > 5 × ULN, discontinue study drug/study regimen • Permanently discontinue study drug/study regimen for any case meeting Hy's law criteria (ALT > 3 × ULN + bilirubin > 2 × ULN without initial findings of cholestasis (i.e., elevated ALP) and in the absence of any alternative cause[4]	• Once improving, gradually taper steroids over ≥ 4 weeks and consider prophylactic antibiotics, antifungals, and anti-PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation])
	Grade 4 (AST or ALT > 20 × ULN and/or TB > 10 × ULN)	Permanently discontinue study drug/study regimen	
Nephritis or renal dysfunction (elevated serum creatinine)	Grade of elevated serum creatinine (CTCAE v4.03) Any grade		• Consult with Nephrologist • Monitor for signs and symptoms that may be related to changes in renal function (e.g., routine urinalysis, elevated serum BUN and creatinine, decreased creatinine clearance, electrolyte imbalance, decrease in urine output, proteinuria, etc.) • Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, infections, etc.) • Steroids should be considered in the absence of a clear alternative etiology even for low-grade events (Grade 2) in order to prevent potential progression to higher-grade event

[4] FDA Liver Guidance Document 2009 Guidance for Industry: Drug Induced Liver Injury – Premarketing Clinical Evaluation

	Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
	Grade 1 (serum creatinine > 1-1.5 × baseline; > ULN to 1.5 × ULN)	No dose modification	For Grade 1 elevated creatinine: • Monitor serum creatinine weekly and any accompanying symptom – If creatinine returns to baseline, resume its regular monitoring per study protocol. – If it worsens, depending on the severity, treat as Grade 2 or Grade 3 or 4 • Consider symptomatic treatment, including hydration, electrolyte replacement, diuretics, etc.
	Grade 2 (serum creatinine > 1.5-3.0 × baseline; > 1.5× to 3.0× ULN)	Hold study drug/study regimen until resolution to ≤ Grade 1 • If toxicity worsens, then treat as Grade 3 or Grade 4 • If toxicity improves to ≤ Grade 1, then treat at next scheduled treatment date	For Grade 2 elevated creatinine: • Consider symptomatic treatment, including hydration, electrolyte replacement, diuretics, etc. • Carefully monitor serum creatinine every 2-3 days and as clinically warranted • Consult Nephrologist and consider renal biopsy if clinically indicated • If event is persistent (> 3-5 days) or worsens, promptly start prednisone 1-2 mg/kg/day or IV equivalent • If event is not responsive within 3-5 days or worsens despite prednisone at 1-2 mg/kg/day or IV equivalent, additional workup should be considered and prompt treatment with IV methylprednisolone at 2-4 mg/kg/day started. • Once improving, gradually taper steroids over ≥ 4 weeks and consider prophylactic antibiotics, antifungals, and anti-PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]). • When event returns to baseline, resume study drug/study regimen and routine serum creatinine monitoring per study protocol.
	Grade 3 or 4 (Grade 3: serum dreatinine > 3.0 × baseline; > 3.0-6.0 × ULN Grade 4: serum creatinine > 6.0 × ULN)	Permanently discontinue study drug/study regimen	• Carefully monitor serum creatinine on daily basis • Consult Nephrologist and consider renal biopsy if clinically indicated • Promptly start prednisone 1-2 mg/kg/day or IV equivalent • If event is not responsive within 3-5 days or worsens despite prednisone at 1-2 mg/kg/day or IV equivalent, additional work-up should be considered and prompt treatment with with an immunosuppressive in consultation with a nephrologist

	Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
			• Once improving, gradually taper steroids over ≥ 4 weeks and consider prophylactic antibiotics, antifungals, and anti-PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]
Rash (excluding bullous skin formations)	Grade of skin rash (Refer to CTCAE v4.03 for definition of severity/grade depending on type of skin rash)	Any grade	Monitor for signs and symptoms of dermatitis (rash and pruritus) • Hold study drug if Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN), or other severe cutaneous adverse reaction (SCAR) is suspected • Permanently discontinue study drugs if SJS, TEN or SCAR is confirmed
	Grade 1	No dose modification	For Grade 1: • Consider symptomatic treatment, including oral antipruritics (e.g., diphenhydramine or hydroxyzine) and topical therapy (e.g., urea cream)
	Grade 2	For persistent (> 1 week) Grade 2 events, hold scheduled study drug/study regimen until resolution to ≤ Grade 1 or baseline • If toxicity worsens, then treat as Grade 3 • If toxicity improves, then resume administration at next scheduled dose	For Grade 2: • Obtain dermatology consult • Consider symptomatic treatment, including oral antipruritics (e.g., diphenhydramine or hydroxyzine) and topical therapy (e.g., urea cream) • Consider moderate-strength topical steroid • If no improvement of rash/skin lesions occurs within 3-5 days or is worsening despite symptomatic treatment and/or use of moderate-strength topical steroid, discuss with Juno medical monitor and promptly start systemic steroids prednisone 1-2 mg/kg/day or IV equivalent • Consider skin biopsy if persistent for > 1 week or recurs
	Grade 3	If toxicity improves to Grade ≤1 or baseline, then resume drug/study regimen after completion of steroid taper. • If toxicity worsens, then treat as Grade 4.	For Grade 3 or 4: • Consult dermatology • Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent • Consider hospitalization • Monitor extent of rash [Rule of Nines] • Consider skin biopsy (preferably more than 1) as clinically feasible
	Grade 4	Permanently discontinue study drug/study regimen	

	Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
			• Once improving, gradually taper steroids over ≥ 4 weeks and consider prophylactic antibiotics, antifungals, and anti-PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]) • Discuss with Juno medical monitor
Endocrinopathy (e.g., hyperthyroidism, hypothyroidism, hypopituitarism, adrenal insufficiency, etc.)	Any grade (Depending on the type of endocrinopathy, refer to CTCAE v4.03 for defining the CTC grade/severity)		• Consult endocrinologist • Monitor patients for signs and symptoms of endocrinopathies. Non-specific symptoms include headache, fatigue, behavior changes, changed mental status, vertigo, abdominal pain, unusual bowel habits, hypotension, and weakness. • Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression including brain metastases, infections, etc.) • Monitor and evaluate thyroid function tests: TSH, free T_3 and free T_4 and other relevant endocrine labs depending on suspected endocrinopathy. • If a patient experiences an AE that is thought to be possibly of autoimmune nature (e.g., thyroiditis, pancreatitis, hypophysitis, diabetes insipidus), the investigator should send a blood sample for appropriate autoimmune antibody testing • Investigators should ask subjects with endocrinopathies who may require prolonged or continued hormonal replacement, to consult their primary care physicians or endocrinologists about further monitoring and treatment after completion of the study.
	Grade 1 (Depending on the type of endocrinopathy, refer to CTCAE v4.03 for defining the CTC Grade 1)	No dose modification	For Grade 1 (including those with asymptomatic TSH elevation): • Monitor patient with appropriate endocrine function tests • If TSH < 0.5 × LLN, or TSH > 2 × ULN or consistently out of range in two subsequent measurements, include FT4 at subsequent cycles as clinically indicated and consider endocrinology consult.
	Grade 2 (Depending on the type of endocrinopathy, refer	For Grade 2 endocrinopathy other than hypothyroidism, hold study drug/study regimen dose until patient is clinically stable	For Grade 2 (including those with symptomatic endocrinopathy): • Isolated Type 1 diabetes mellitus may be treated with appropriate diabetic therapy and without corticosteroids. Only hold study drug/study regimen in

	Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
	to CTCAE v4.03 for defining the CTC Grade 2)	• If toxicity worsens, then treat as Grade 3 or Grade 4 • If toxicity improves to ≤ Grade 1, then treat at next scheduled treatment date	setting of hyperglycemia when diagnostic workup is positive for diabetic ketoacidosis. • Isolated hypothyroidism may be treated with replacement therapy without treatment interruption and without corticosteroids • Initiate hormone replacement as needed for management • Evaluate endocrine function, and as clinically indicated, consider pituitary scan • For patients with abnormal endocrine work-up, except for those with isolated hypothyroidism, consider short-term corticosteroids (e.g., 1-2 mg/kg/day methylprednisolone or IV equivalent) and prompt initiation of treatment with relevant hormone replacement (e.g., levothyroxine, hydrocortisone, or sex hormones). • Once improving, gradually taper steroids over ≥ 4 weeks and consider prophylactic antibiotics, antifungals, and anti-PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]) – For patients with normal endocrine work-up (lab or MRI scans), repeat labs/MRI as clinically indicated.
	Grade 3 or 4 (Depending on the type of endocrinopathy, refer to CTCAE v4.03 for defining the CTC grade/severity 3 or 4)	For Grade 3 or 4 endocrinopathy other than hypothyroidism, hold study drug/study regimen dose until endocrinopathy symptom(s) are controlled Resume study drug/study regimen administration if ≤ Grade 1 at the next scheduled dose	For Grade 3 or 4: • Consult endocrinologist • Isolated Type 1 diabetes mellitus may be treated with appropriate diabetic therapy and without corticosteroids. Only hold study drug/study regimen in setting of hyperglycemia when diagnostic workup is positive for diabetic ketoacidosis. • Isolated hypothyroidism may be treated with replacement therapy without treatment interruption and without corticosteroids • Promptly initiate empiric IV methylprednisolone 1-2 mg/kg/day or equivalent • Administer hormone replacement therapy as necessary. • For adrenal crisis, severe dehydration, hypotension, or shock: immediately initiate IV corticosteroids with mineralocorticoid activity • Once improving, gradually taper immunosuppressive steroids over ≥ 4 weeks and consider prophylactic antibiotics, antifungals, and anti-PCP treatment

	Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
			• (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]) • Discuss with Juno medical monitor
Amylase/Lipase increased	Grade 1	None	• For modest asymptomatic elevations in serum amylase and lipase, corticosteroid treatment is not indicated as long as there are no other signs or symptoms of pancreatic inflammation. • If isolated elevation of enzymes without evidence of pancreatitis, continue immunotherapy. • Assess for signs/symptoms of pancreatitis • Consider appropriate diagnostic testing (e.g, abdominal CT with contrast, MRCP if clinical suspicion of pancreatitis and no radiologic evidence on CT) • Consider other causes of elevated amylase/lipase • If evidence of pancreatitis, manage according to pancreatitis recommendations
	Grade 2, 3 or 4	In consultation with relevant pancreatic specialist consider continuing study drug/study regimen if no clinical/radiologic evidence of pancreatitis ± improvement in amylase/lipase.	
Acute Pancreatitis	Grade 1	None	• Consider gastroenterology referral
	Grade 2	Hold study drug/study regimen dose until resolution to Grade ≤1. Consider resumption of study drug/study regimen if no clinical/radiologic evidence of pancreatitis ± improvement in amylase/lipase in consultation with relevant pancreatic specialist	• Promptly start systemic steroids prednisone 1 to 2 mg/kg/day PO or IV equivalent – • IV hydration • Consider gastroenterology referral

	Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
	Grade 3 or 4	Permanently discontinue study drug/study regimen	• Promptly start systemic steroids prednisone 1 to 2 mg/kg/day PO or IV equivalent – • IV hydration • Consider gastroenterology referral
Immune-mediated neurotoxicity (to include, but not limited to, limbic encephalitis, autonomic neuropathy, excluding Myasthenia Gravis and Guillain-Barre)	Grade of neurotoxicity (Depending on the type of neurotoxicity, refer to CTCAE v4.03 for defining the CTC grade/severity)		
	Any grade		• Patients should be evaluated to rule out any alternative etiology (e.g., disease progression, infections, metabolic syndromes, and medications, etc.) • Monitor patient for general symptoms (headache, nausea, vertigo, behavior change, or weakness) • Consider appropriate diagnostic testing (e.g., electromyogram and nerve conduction investigations) • Symptomatic treatment with neurological consult as appropriate • For transverse myelitis, permanently discontinue for any grade.
	Grade 1	No dose modifications	See “Any grade” recommendations above.
	Grade 2	• Permanently discontinue study drug/study regimen if Grade 2 imAE does not resolve to Grade ≤1 within 30 days If toxicity worsens, then treat as Grade 3 or Grade 4	• Discuss with the Juno medical monitor • Obtain Neurology consult • Sensory neuropathy/neuropathic pain may be managed by appropriate medications (e.g., gabapentin, duloxetine, etc.) • Promptly start systemic steroids prednisone 1-2 mg/kg/day or IV equivalent • If no improvement within 2-3 days despite 1-2 mg/kg/day prednisone or IV equivalent, consider additional work-up and promptly treat with additional immunosuppressive therapy (e.g., IVIgG or other immunosuppressive depending on the specific imAE)

	Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
	Grade 3	• Permanently discontinue study drug/study regimen	For Grade 3 or 4: • Discuss with Juno medical monitor • Obtain Neurology consult • Consider hospitalization • Promptly initiate empiric IV methylprednisolone 1-2 mg/kg/day or equivalent • If no improvement within 2-3 days despite IV corticosteroids, consider additional work-up and promptly treat with additional immunosuppressants (e.g., IVIgG or other immunosuppressive depending on the specific imAE) • Once stable, gradually taper steroids over ≥ 4 weeks
	Grade 4	• Permanently discontinue study drug/study regimen	
Immune-mediated peripheral neuromotor syndromes, such as Guillain-Barre and Myasthenia Gravis		Any grade	• The prompt diagnosis of immune-mediated peripheral neuromotor syndromes is important, since certain patients may unpredictably experience acute decompensations which can result in substantial morbidity or in the worst case, death. Special care should be taken for certain sentinel symptoms which may predict a more severe outcome, such as prominent dysphagia, rapidly progressive weakness, and signs of respiratory insufficiency or autonomic instability • Patients should be evaluated to rule out any alternative etiology (e.g., disease progression, infections, metabolic syndromes, and medications, etc.). It should be noted that the diagnosis of immune-mediated peripheral neuromotor syndromes can be particularly challenging in patients with underlying cancer, due to the multiple potential confounding effects of cancer (and its treatments) throughout the neuraxis. Given the importance of prompt and accurate diagnosis, it is essential to have a low threshold to obtain a neurological consult • Neurophysiologic diagnostic testing (e.g., electromyogram and nerve conduction investigations, and "repetitive stimulation" if myasthenia is suspected) are routinely indicated upon suspicion of such conditions and may be best facilitated by means of a neurology consultation • Important to consider that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. Patients requiring treatment should be started with IVIG and followed by plasmapheresis if not responsive to IVIgG
	Grade 1	No dose modification	• Discuss with the Juno medical monitor

	Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
			• Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above • Obtain a neurology consult unless the symptoms are very minor and stable
	Grade 2	Hold study drug/study regimen dose until resolution to ≤ Grade 1 Permanently discontinue study drug/study regimen if it does not resolve to ≤ Grade 1 within 30 days or if there are signs of respiratory insufficiency or autonomic instability	Grade 2 • Discuss with the Juno medical monitor • Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above • Obtain a Neurology consult • Sensory neuropathy/neuropathic pain may be managed by appropriate medications (e.g., gabapentin, duloxetine, etc.) • MYASTHENIA GRAVIS – Steroids may be successfully used to treat Myasthenia Gravis. Important to consider that steroid therapy (especially with high doses) may result in transient worsening of myasthenia and should typically be administered in a monitored setting under supervision of a consulting neurologist. – Patients unable to tolerate steroids may be candidates for treatment with plasmapheresis or IVIG. Such decisions are best made in consultation with a neurologist, taking into account the unique needs of each patient. – If Myasthenia Gravis-like neurotoxicity present, consider starting acetylcholine esterase (AChE) inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis. • GUILLAIN-BARRE: – Important to consider that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. Patients requiring treatment should be started with IVIG and followed by plasmapheresis if not responsive to IVIgG.
	Grade 3	Hold study drug/study regimen dose until resolution to ≤ Grade 1 Permanently discontinue study drug/study regimen if Grade 3 irAE does not resolve to ≤ Grade 1 within 30 days or if there are signs of respiratory insufficiency or autonomic instability	For severe or life threatening (Grade 3 or 4) events: • Discuss with Juno medical monitor • Recommend hospitalization • Monitor symptoms and obtain neurological consult • MYASTHENIA GRAVIS

	Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
	Grade 4	Permanently discontinue study drug/study regimen	– Steroids may be successfully used to treat Myasthenia Gravis. It should typically be administered in a monitored setting under supervision of a consulting neurologist. – Patients unable to tolerate steroids may be candidates for treatment with plasmapharesis or IVIgG. – If Myasthenia Gravis-like neurotoxicity present, consider starting acetylcholine esterase (AChE) inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis. • GUILLAIN-BARRE: – Important to consider that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. Patients requiring treatment should be started with IVIG and followed by plasmapheresis if not responsive to IVIgG
Myocarditis	Any Grade	Discontinue drug permanently if biopsy proven immune-mediated myocarditis	• The prompt diagnosis of immune-mediated myocarditis is important, particularly in patients with baseline cardiopulmonary disease and reduced cardiac function • Consider, discussing with the study physician, as needed • Monitor patients for signs and symptoms of myocarditis (new onset or worsening chest pain, arrhythmia, shortness of breath, peripheral edema). As some symptoms can overlap with lung toxicities, simultaneously evaluate for and rule out pulmonary toxicity as well as other causes (e.g., pulmonary embolism, congestive heart failure, malignant pericardial effusion). Consult a cardiologist early, to promptly asses whether and when to complete a cardiac biopsy, including any other diagnostic procedures. • Initial work-up should include clinical evaluation, BNP, cardiac enzymes, ECG, echocardiogram (ECHO), monitoring of oxygenation via pulse oximetry (resting and exertion), and additional laboratory work-up as indicated. Spiral CT or cardiac MRI can complement ECHO to assess wall motion abnormalities when needed. • Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections)medications, or infections)

	Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
	Grade 1	No dose modifications required unless clinical suspicion is high, in which case hold study drug/study regimen dose during diagnostic work-up for other etiologies. If study drug/study regimen is held, resume after complete resolution to Grade 0.	• Monitor and closely follow up in 2 to 4 days for clinical symptoms, BNP, cardiac enzymes, ECG, ECHO, pulse oximetry (resting and exertion), and laboratory work-up as clinically indicated. • Consider using steroids if clinical suspicion is high.
	Grade 2, 3, or 4	If Grade 2 -- Hold study drug/study regimen dose until resolution to Grade 0. If toxicity rapidly improves to Grade 0, then the decision to reinitiate study drug/study regimen will be based upon treating physician's clinical judgment and after completion of steroid taper. If toxicity does not rapidly improve, permanently. discontinue study drug/study regimen. If Grade 3-4, permanently discontinue study drug/study regimen.	• Monitor symptoms daily, hospitalize. • Promptly start IV methylprednisolone 2 to 4 mg/kg/day or equivalent after Cardiology consultation has determined whether and when to complete diagnostic procedures including a cardiac biopsy. • Supportive care (e.g., oxygen). • If no improvement within 2-3 days despite IV methylprednisolone at 2 to 4 mg/kg/day, promptly start immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg IV, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. Infliximab is contraindicated for patients who have heart failure.

	Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
Myositis/Polymyositis	Any Grade		• Monitor patients for signs and symptoms of poly/myositis. Typically, muscle weakness/pain occurs in proximal muscles including upper arms, thighs, shoulders, hips, neck and back, but rarely affects the extremities including hands and fingers; also difficulty breathing and/or trouble swallowing can occur and progress rapidly. Increased general feelings of tiredness and fatigue may occur, and there can be new-onset falling, difficulty getting up from a fall, and trouble climbing stairs, standing up from a seated position, and/or reaching up. • If poly/myositis is suspected, a Neurology consultation should be obtained early, with prompt guidance on diagnostic procedures. Myocarditis may co-occur with poly/myositis; refer to guidance under Myocarditis. Given breathing complications, refer to guidance under Pneumonitis/ILD. Given possibility of an existent (but previously unknown) autoimmune disorder, consider Rheumatology consultation. • Consider, as necessary, discussing with the study physician. • Initial work-up should include clinical evaluation, creatine kinase, aldolase, LDH, BUN/creatinine, erythrocyte sedimentation rate or C-reactive protein level, urine myoglobin, and additional laboratory work-up as indicated, including a number of possible rheumatological/antibody tests (i.e., consider whether a rheumatologist consultation is indicated and could guide need for rheumatoid factor, antinuclear antibody, anti-smooth muscle, antisynthetase [such as anti-Jo-1], and/or signal-recognition particle antibodies). Confirmatory testing may include electromyography, nerve conduction studies, MRI of the muscles, and/or a muscle biopsy. Consider Barium swallow for evaluation of dysphagia or dysphonia. • Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections).
	Grade 1	None	• Monitor and closely follow up in 2 to 4 days for clinical symptoms and initiate evaluation as clinically indicated. • Consider Neurology consult. • Consider, as necessary, discussing with the study physician.

	Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
	Grade 2	Hold study drug/study regimen dose until resolution to Grade ≤1. Permanently discontinue study drug/study regimen if it does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency.	• Monitor symptoms daily and consider hospitalization. • Obtain Neurology consult, and initiate evaluation. • Consider, as necessary, discussing with the study physician. • If clinical course is rapidly progressive (particularly if difficulty breathing and/or trouble swallowing), promptly start IV methylprednisolone 2 to 4 mg/kg/day systemic steroids along with receiving input from Neurology consultant • If clinical course is *not* rapidly progressive, start systemic steroids (e.g., prednisone 1 to 2 mg/kg/day PO or IV equivalent); if no improvement within 2-3 days, continue additional work up and start treatment with IV methylprednisolone 2 to 4 mg/kg/day • If after start of IV methylprednisolone at 2 to 4 mg/kg/day there is no improvement within 2-3 days, consider starting another immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg IV, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab.
	Grade 3 or 4	For Grade 3: Hold study drug/study regimen dose until resolution to Grade ≤1. Permanently discontinue study drug/study regimen if Grade 3 imAE does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency. For Grade 4: Permanently discontinue study drug/study regimen.	• Monitor symptoms closely; recommend hospitalization. • Obtain Neurology consult • Consider discussing with the study physician, as necessary. • Promptly start IV methylprednisolone 2 to 4 mg/kg/day systemic steroids along with receiving input from Neurology consultant. • If after start of IV methylprednisolone at 2 to 4 mg/kg/day there is no improvement within 2-3 days, consider start of immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. • Consider whether patient may require IV IG, plasmapheresis.

Table G-2 Durvalumab Treatment Modification and Toxicity Management Guidelines for Infusion-Related Reactions

Severity Grade	Dose Modifications	Toxicity Management
Any Grade		• Management per institutional standard at the discretion of investigator • Monitor patients for signs and symptoms of infusion-related reactions (e.g., fever and/or shaking chills, flushing and/or itching, alterations in heart rate and blood pressure, dyspnea or chest discomfort, skin rashes, etc.) and anaphylaxis (e.g., generalized urticaria, angioedema, wheezing, hypotension, tachycardia, etc.)
Grade 1	The infusion rate of study drug/study regimen may be decreased by 50% or temporarily interrupted until resolution of the event	For Grade 1 or Grade 2: • Acetaminophen and/or antihistamines may be administered per institutional standard at the discretion of the investigator • Consider premedication per institutional standard prior to subsequent doses
Grade 2	The infusion rate of study drug/study regimen may be decreased by 50% or temporarily interrupted until resolution of the event (up to 4 hours). Subsequent infusions may be given at 50% of the initial infusion rate	
Grade 3/4	Permanently discontinue study drug/study regimen	For Grade 3 or 4: • Manage severe infusion-related reactions per institutional standards (e.g., IM epinephrine, followed by IV diphenhydramine and famotidine, and IV glucocorticoid)

Table G-3 Durvalumab Treatment Modification and Toxicity Management Guidelines for Non-Immune-Mediated Reactions

CTC Grade/Severity	Dose Modification	Toxicity Management
Any grade	Note: Dose modifications are not required for adverse events not deemed to be related to study treatment (i.e., events due to underlying disease) or for laboratory abnormalities not deemed to be clinically significant. Any durvalumab-related adverse event ≥ Grade 2 resulting in holding of durvalumab, please discuss with Juno medical monitor.	Treat accordingly as per institutional standard
1	No dose adjustment	Treat accordingly as per institutional standard
2	Hold study drug/study regimen until resolution to ≤ Grade 1 or baseline	Treat accordingly as per institutional standard
3	Hold study drug/study regimen until resolution to ≤ Grade 1 or baseline For AEs that downgrade to ≤ Grade 2 within 7 days or resolve to ≤ Grade 1 or baseline within 14 days, resume study drug/study regimen administration at next scheduled dose. Otherwise, discontinue study drug/study regimen	Treat accordingly as per institutional standard
4	Discontinue study drug/study regimen (note for Grade 4 labs, decision to discontinue would be based on accompanying clinical signs/symptoms and as per Investigator's clinical judgment and in consultation with the Juno medical monitor)	Treat accordingly as per institutional standard