Official Title of Study:

Protocol H125001: An Open-Label Phase 1/2 Study of JCARH125, BCMA-targeted Chimeric Antigen Receptor (CAR) T Cells, in Subjects With Relapsed or Refractory Multiple Myeloma

NCT Number: NCT03430011

Document Date (Date in which document was last revised): February 10, 2020

PROTOCOL H125001: AN OPEN-LABEL PHASE 1/2 STUDY OF JCARH125, BCMA-TARGETED CHIMERIC ANTIGEN RECEPTOR (CAR) T CELLS, IN SUBJECTS WITH RELAPSED AND/OR REFRACTORY MULTIPLE MYELOMA

Protocol Number:	H125001
Study ID:	EVOLVE
NCT Number:	NCT03430011
Date:	10 Feb 2020
Regulatory Sponsor:	Juno Therapeutics, Inc., a wholly-owned subsidiary of Celgene Corporation 400 Dexter Ave North, Suite 1200 Seattle, WA 98109 Phone: [redacted]
Medical Director:	[redacted] Sr. Medical Director Juno Therapeutics, Inc. Mobile: [redacted] E-mail: [redacted]
Statistician:	[redacted] Director, Biostatistics Juno Therapeutics, Inc. Phone: [redacted] E-mail: [redacted]
Study Manager:	[redacted] Sr. Clinical Trial Manager Juno Therapeutics, Inc. Mobile: [redacted] E-mail: [redacted]
Safety Reporting:	[redacted]

CONFIDENTIAL

This trial will be conducted in compliance with the protocol, International Council for Harmonisation Good Clinical Practice (ICH GCP), and applicable state, local, and federal regulatory requirements.

SIGNATURE PAGE

Protocol H125001: An Open-Label Phase 1/2 Study of JCARH125, BCMA-targeted Chimeric Antigen Receptor (CAR) T Cells, in Subjects with Relapsed and/or Refractory Multiple Myeloma

We, the undersigned, have read this protocol and agree that it contains all necessary information required to conduct the study.

Sponsor Signatures: Date:

_____ _____

[redacted]
Sr. Medical Director

_____ _____

[redacted]
Director, Biostatistics

_____ _____

[redacted]
Sr. Clinical Trial Manager

I have read this protocol and agree to conduct the study as outlined herein, in accordance with the Declaration of Helsinki, the International Council for Harmonisation (ICH) E6 Guideline for Good Clinical Practice, US FDA regulations, Institutional Review Board regulations, and all national, state, and local laws and/or requirements of the pertinent regulatory authorities.

_____ Date
Investigator Printed Name

_____ _____
Investigator Signature

PROTOCOL SYNOPSIS

Protocol Number: H125001	**Product Name: JCARH125**
Protocol Title: Protocol H125001: An Open-Label Phase 1/2 Study of JCARH125, BCMA-targeted Chimeric Antigen Receptor (CAR) T Cells, in Subjects with Relapsed and/or Refractory Multiple Myeloma	
Sponsor: Juno Therapeutics, Inc., a wholly owned subsidiary of Celgene Corporation	**Study Phase:** Phase 1/2

Study Rationale:

Substantial progress in the treatment of multiple myeloma (MM) has been made over the past 2 decades with the development of proteasome inhibitors (eg, bortezomib and carfilzomib), immunomodulator drugs (IMiDs) (eg, lenalidomide, pomalidomide), and monoclonal antibodies (elotuzumab and daratumumab). However, MM remains incurable and nearly all patients eventually relapse with disease that becomes increasingly resistant to treatment with each additional line of therapy. High-dose therapy followed by autologous stem cell transplant performed either at the time of initial diagnosis or at relapse, is considered the standard of care for younger patients (less than 70 years of age) with newly diagnosed MM. Although high-dose therapy with ASCT is not curative, event-free survival and overall survival are prolonged compared to treatment with standard-dose myeloma treatments alone.

Autologous T cells transduced with a recombinant chimeric antigen receptor (CAR) are engineered to bind to a tumor-specific antigen. BCMA is an ideal target for CAR T cell therapy since its expression is highly restricted to MM cells and plasma cells, and therefore, the toxic effect of anti-BCMA CAR T cells on normal cells is minimal. Adoptive cellular therapy using CAR T cells targeting specifically expressed antigen on tumor cells has become one of the exciting breakthroughs in MM immunotherapy.

Study Objectives:

Phase 1 Dose-Escalation

Primary:

- To evaluate the safety and tolerability of JCARH125 in subjects with relapsed/refractory (R/R) MM
- To determine the recommended Phase 2 dose(s) (RP2D) of JCARH125 in subjects with R/R MM

Secondary:

- To evaluate the expansion and persistence (ie, pharmacokinetics [PK]) of JCARH125 in peripheral blood
- To assess preliminary antitumor activity of JCARH125, as determined by the overall response rate (ORR) and complete response (CR)/stringent complete response (sCR) rate according to the International Myeloma Working Group (IMWG) Uniform Response Criteria

Phase 1 Anakinra Cohort - Prophylactic Treatment with Anakinra

Primary

- To evaluate the safety and tolerability of JCARH125 at the dose level 3 and/or dose level 3a and to explore the incidence and onset of Grade ≥ 2 cytokine release syndrome (CRS) in subjects with R/R MM who receive prophylactic treatment with anakinra

Secondary

- To evaluate the expansion and persistence (ie, PK) of JCARH125 in subjects who receive prophylactic treatment with anakinra in peripheral blood

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- To assess preliminary antitumor activity of JCARH125 in subjects who receive prophylactic treatment with anakinra, as determined by the ORR and CR/sCR rate according to the IMWG Uniform Response Criteria

Phase 2 Expansion

Primary:

- To evaluate the antitumor activity of JCARH125, as determined by the ORR according to the IMWG criteria, at the RP2D(s) in subjects with R/R MM

Secondary:

- To evaluate the CR/sCR rate assessed according to the IMWG criteria
- To assess the duration of response (DOR) following treatment with JCARH125
- To evaluate the safety and tolerability of JCARH125 in subjects with R/R MM
- To evaluate overall survival (OS) and progression -free survival (PFS)
- To assess time to response to JCARH125
- To evaluate expansion and persistence (ie, PK) of JCARH125 in peripheral blood
- To assess health -related quality of life (HRQoL) and health economics and outcomes research (HEOR)

Phase 2a Prior BCMA-directed Anti-myeloma Therapy Cohort

Primary:

- To evaluate the antitumor activity of JCARH125 at the RP2D(s) in subjects with R/R MM who have relapsed following prior treatment with a BCMA-directed anti-myeloma therapy, including T-cell engager (TCE), antibody-drug conjugate (ADC), or CAR T-cell therapy

Secondary:

- To evaluate the CR/sCR rate assessed according to IMWG criteria
- To assess the duration of response (DOR) following treatment with JCARH125
- To evaluate the safety and tolerability of JCARH125 in subjects with R/R MM
- To evaluate overall survival (OS) and progression free survival (PFS)
- To assess time to response to JCARH125
- To evaluate expansion and persistence (ie, PK) of JCARH125 in peripheral blood

Additional Exploratory Objectives

- [redacted]

Additional Exploratory Objectives in Phase 1 Anakinra Only

- [redacted]

Study Design:

This is an open-label, multicenter, Phase 1/2 study to determine the safety, PK, and antitumor activity of JCARH125 in adult subjects with R/R MM. The Phase 1 dose-escalation portion of the study will evaluate the

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safety and tolerability of increasing dose levels of JCARH125 to identify the RP2D. The Phase 2 expansion portion of the study will further evaluate the safety, PK, and antitumor activity of JCARH125 at the RP2D(s).

An additional phase 2 cohort will evaluate the safety and tolerability of JCARH125 at the RP2D(s) in subjects with R/R MM who have relapsed following prior treatment with a BCMA-directed anti-myeloma therapy including TCE, ADC, or CAR T-cell therapy.

The Phase 1 anakinra cohort will evaluate the safety and tolerability of JCARH125 at the dose level 3 and/or dose level 3a following prophylactic use of anakinra.

Phase 1 Dose Escalation:

The JCARH125 dose levels planned to be evaluated in Phase 1 are provided in the table below. Dose-escalation/de-escalation will follow a modified toxicity probability interval (mTPI-2) algorithm with a target dose-limiting toxicity (DLT) rate of 30% and an equivalence interval of 25% to 35%. Dose-escalation may be halted once a dose level with acceptable safety and satisfactory antitumor activity has been selected for evaluation in Phase 2. A maximum tolerated dose (MTD) may not be defined in this study.

Dose Level	JCARH125 Dose (CD3+CAR+ cells)
-1	25×10^6
1	50×10^6
2	150×10^6
2a[a]	300×10^6
3	450×10^6
3a[b]	600×10^6
4	800×10^6

[a] Introduced with Protocol Amendment 4 (10 September 2018) as a part of safety measures.
[b] Introduced with Protocol Amendment 5 (31 May 2019) as a possible intermediate dose level.

Note: Additional intermediate dose levels may be evaluated based on ongoing safety and efficacy data.

For a dose level to be considered safe, at least 3 DLT-evaluable subjects must have completed the 21-day DLT evaluation period and the level estimated to be safe per the mTPI-2 algorithm. The decision to open a dose level for enrollment will be made by the Sponsor based on results from the mTPI-2 algorithm after consultations with the Principal Investigators at each site as appropriate.

The first 3 subjects treated in the study will be treated with JCARH125 at Dose Level 1 (50×10^6 CD3+CAR+ cells). Within the first dose cohort, treatment of the first 3 subjects will be staggered by a minimum of 14 days. At each higher dose level, treatment of the first 3 subjects within the dose cohort will be staggered by a minimum of 7 days. Staggering of subjects in a dose cohort may be lifted after a minimum of 3 subjects have been treated in that dose cohort, have completed the 21-day DLT evaluation period, and the dose level is determined to be safe according to the mTPI-2 algorithm.

A maximum of 3 subjects will initially be treated at a dose level. If none of these 3 subjects experience a DLT, the dose may be escalated to the next higher dose level. If 1 of 3 subjects experiences a DLT at a dose level, then additional subjects will be enrolled at this dose level and dose-escalation/de-escalation decisions will be made per the mTPI-2 algorithm after the DLT data for these additional subjects are available. If 2 of 3 subjects experience a DLT at a dose level, then the dose will be de-escalated to the next lower dose level. If all 3 subjects experience a DLT at a dose level, the dose will be de-escalated and this dose and all higher doses will be removed from further evaluation in the trial.

To be considered evaluable for DLT, a subject must have received the conforming JCARH125 cell product at the assigned dose of JCARH125 and completed the 21-day evaluation period or experienced a DLT prior to completing the 21-day evaluation. Subjects who are not evaluable for DLT will be replaced.

Based on the cumulative safety and antitumor activity data from subjects treated in Phase 1, one or more dose levels will be selected for further evaluation in the Phase 2 portion of the trial (the RP2D); this dose level(s) will

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be selected by the Sponsor in collaboration with the Investigators. It is not necessary for the MTD to be determined per the mTPI algorithm in order to select the dose level(s) to be evaluated in Phase 2.

Phase 1 Anakinra Cohort - Prophylactic Treatment with Anakinra

Up to 14 subjects will be treated at the dose level 3 and/or dose level 3a with the addition of the prophylactic treatment with anakinra. The purpose is to investigate the potential benefit of prophylactic treatment with anakinra on the onset, incidence and severity of CRS.

All subjects who receive conforming JCARH125 product and receive at least 1 dose of prophylactic anakinra will be evaluated for safety and tolerability of JCARH125 following prophylactic treatment with anakinra. Subjects will receive 2 doses of 100 mg anakinra administered subcutaneously (SC) prior to JCARH125 infusion, one the night before and one 3 hours before JCARH125 infusion. Subjects will continue with anakinra for 5 consecutive days at a dose of 100 mg SC. In the case of CRS onset, anakinra 100 mg SC should be administered twice daily until CRS resolution. The anakinra dose should be administered at approximately the same time every day. In the case of worsening of CRS and/or in case of onset of neurological toxicity, the toxicity guidelines from the protocol should be followed.

If prophylactic treatment with anakinra reduces the incidence, severity or delays the time to onset of CRS, prophylactic treatment with anakinra may be implemented in the Phase 2 portion of the trial.

Phase 2 Expansion

In the Phase 2 portion of the study, subjects will be treated at the RP2D(s) identified in Phase 1. The primary analysis population for evaluation of JCARH125 efficacy (ie, the efficacy analysis set) will include all subjects treated at the RP2D(s) in Phase 2 expansion, subjects treated at the RP2D(s) in Phase 1 dose escalation, and subjects treated at the RP2D(s) in the Phase 1 anakinra cohort who have measurable disease as determined by the central laboratory at the last disease assessment prior to JCARH125 infusion and receive conforming product. The efficacy analysis set will include at least 75 subjects who are evaluable for both safety and efficacy.

Phase 2a – Prior BCMA-directed Anti-Myeloma Therapy Cohort

In the Phase 2a portion of the study, 3 separate cohorts of subjects with exposure to prior BCMA-directed anti-myeloma therapy cohort including TCE, ADC or CAR T-cell therapies will be treated at the RP2D(s) identified in Phase 1. All subjects who receive conforming JCARH125 product will be evaluated for safety and tolerability of JCARH125.

Cohort 1: 14 subjects who have been exposed to prior BCMA-directed CAR T-cell therapy

Cohort 2: 14 subjects who have been exposed to prior BCMA-directed TCE

Cohort 3: 14 subjects who have been exposed to prior BCMA-directed ADC therapy

Study Procedures and Evaluations for Subjects in Phase 1 dose escalation, Phase 1 anakinra cohort, Phase 2, and Phase 2a prior BCMA-directed anti-myeloma therapy cohort

A tumor biopsy sample (bone marrow biopsy, bone marrow aspirate and plasmacytoma biopsy if applicable) will be obtained from all subjects during initial screening. Subjects who meet all eligibility criteria will be enrolled and will undergo leukapheresis to enable JCARH125 product generation. Subjects may receive bridging therapy, excluding experimental and biological agents (daratumumab, eg), after leukapheresis and before lymphodepleting chemotherapy if deemed necessary by the treating physician for disease control during JCARH125 manufacturing. Bridging therapies must be discontinued at least 14 days prior to initiation of lymphodepletion and subjects must continue to meet eligibility criteria pertaining to measurable disease, adequate organ function, active infections, pregnancy, and washout of prior therapy before initiation of lymphodepleting chemotherapy. If JCARH125 cannot be made from the first leukapheresis product, additional leukapheresis may be allowed after consultation with the Sponsor.

Following successful JCARH125 product generation, subjects will enter the treatment phase and will receive one cycle of JCARH125 treatment. A treatment cycle will include lymphodepleting chemotherapy with fludarabine (30 mg/m^2/day) and cyclophosphamide (300 mg/m^2/day) for 3 days followed by a single dose of JCARH125 administered intravenously (IV) on Day 1. JCARH125 will be administered 2 to 7 days after completion of lymphodepleting chemotherapy unless clinical or logistical circumstances require modification of this timing. Dose adjustments or changes to the lymphodepleting chemotherapy regimen may be indicated due to the subject's creatinine clearance.

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Follow-Up Period

Subjects will be followed under this protocol for 2 years after JCARH125 administration for safety, disease status, additional anticancer therapies, and survival. If disease progression occurs during this 2-year timeframe, subjects should still be followed per the Schedule of Evaluations outlined in Appendix A. The number of JCARH125 cells in peripheral blood and bone marrow will be assessed by quantitative polymerase chain reaction (qPCR) from the time of JCARH125 administration until the end of the study. Disease assessments will be performed approximately every 4 weeks following JCARH125 administration for the first 6 months, and then every 3 months until 2 years after JCARH125 administration or until disease progression, whichever comes first. Bone marrow biopsy, bone marrow aspirate and plasmacytoma biopsy if applicable will be performed for all subjects for disease response evaluations, PK, and/or research assessments at Day 15, Day 29, Month 3, Month 6, Month 12, Month 18, Month 24, for confirmation of CR, and in the event of disease progression. Response to JCARH125 will be assessed according to IMWG criteria. All subjects will have their response to JCARH125 assessed by the Investigator. In addition, all subjects treated at the RP2D, will have their responses assessed by the Investigator and by an Independent Review Committee (IRC). Evaluation of the primary efficacy endpoint of ORR in Phase 2 will be based on IRC assessment.

All subjects who receive JCARH125 will be asked to enroll in a separate Celgene-sponsored long-term follow-up (LTFU) study at the time of completion or discontinuation from this study. Subjects who enroll in the LTFU protocol will sign a separate informed consent form and may be followed per current FDA guidelines for up to 15 years after JCARH125 administration for long-term JCAR-related safety and efficacy.

Oversight Committees:

Data Safety Monitoring Board

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. In addition, in the event of a toxicity that meets the protocol-defined criteria for pausing the study, the DSMB will be convened to evaluate the comprehensive safety data and to make a recommendation for study continuation, modification, or termination. The DSMB has been assembled under a dedicated charter specifically developed for safety oversight of Juno-sponsored studies.

Independent Review Committee

An IRC will determine response and progression status for all subjects treated in the Phase 2 expansion portion of the study, as well as subjects in the Phase 1 dose escalation portion of the study, the Phase 1 anakinra cohort, and the Phase 2a prior BCMA-directed anti-myeloma therapy cohort who were treated with JCARH125 at the RP2D(s), for the purpose of the primary efficacy analysis.

Study Population:

The target study population consists of subjects with R/R MM who meet all of the following inclusion criteria and none of the exclusion criteria:

Inclusion Criteria:

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

1. Age ≥ 18 years at the time of consent.
2. Signed informed consent form.
3. Diagnosis of multiple myeloma (MM) with relapsed and/or refractory disease. Subjects must have received at least 3 prior anti-myeloma treatment regimens (note: induction with or without bone marrow transplant and with or without maintenance therapy is considered one regimen). Subjects must be refractory to the last anti-myeloma treatment regimen prior to entering the study. Refractory myeloma is defined as non-responsiveness (best response of ≤ stable disease) to last anti-myeloma treatment regimen or documented progressive disease during or within 60 days (measured from the last dose) of completing treatment with the last anti-myeloma treatment regimen before study entry. Subjects must have previously received all of the following therapies:
   a. Autologous stem cell transplant.

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b. A regimen that included an immunomodulatory agent (eg, thalidomide, lenalidomide, pomalidomide) and a proteasome inhibitor (eg, bortezomib, carfilzomib, ixazomib), either alone or in combination. Subjects must have undergone at least 2 consecutive cycles of treatment for each regimen unless progressive disease was the best response to the regimen.

c. Anti-CD38 (eg, daratumumab) as part of a combination regimen or as a monotherapy.

Subjects who have received prior allogeneic stem cell transplant or donor lymphocyte infusion (DLI) at least 100 days before enrollment with no signs of acute or chronic graft-versus-host disease (GVHD) will be considered eligible.

Subjects who were not candidates to receive one or more of the above treatments (ie, contraindicated) are eligible; the reason for not receiving treatment must be clearly documented in the case report form.

4. Subjects must have measurable disease as determined by the central laboratory defined as meeting at least one of the criteria below:
   a. Serum M-protein ≥ 1 g/dL.
   b. Urine M-protein ≥ 200 mg/24 hour.
   c. Involved serum free light chain (sFLC) level ≥ 10 mg/dL with abnormal κ/λ ratio (light chain disease is acceptable only for subjects without measurable disease in the serum or urine).
5. Subject must be willing to provide a fresh bone marrow biopsy sample during Screening (and at Pre-treatment Screening, if required).
6. Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1
7. Adequate organ function, defined as:
   a. Adequate renal function, defined as calculated creatinine clearance (Cockcroft-Gault) ≥ 60 mL/min without the assistance of hydration.
      i. Subjects must not have received IV rehydration within 3 days of renal function assessment.
   b. Adequate bone marrow function, defined as absolute neutrophil count (ANC) ≥ 1000 cells/mm^3, hemoglobin (Hb) ≥ 8 g/dL, and platelet count ≥ 50,000/mm^3. Transfusions and growth factors must not be used to meet these requirements at initial Screening.
      i. Subjects must not have received growth factors within 14 days of initial Screening.
      ii. Subjects must not have received red blood cell (RBC) transfusions within 21 days of initial Screening.
      iii. Subjects must not have received platelet transfusions within 7 days of initial Screening.
   c. Adequate hepatic function, defined as:
      i. Alanine aminotransferase (ALT) ≤ 3×ULN.
      ii. Aspartate aminotransferase (AST) ≤ 3×ULN.
      iii. Total bilirubin < 2.0 mg/dL (or < 3.0 mg/dL for subjects with documented Gilbert's syndrome).
      iv. International ratio (INR) or partial thromboplastin time (PTT) ≤ 1.5×ULN.
   d. Adequate pulmonary function, defined as saturated oxygen (SaO_2) ≥ 92% on room air.
   e. Adequate cardiac function, defined as left ventricular ejection fraction (LVEF) ≥ 40% as assessed by echocardiogram (ECHO) or multiple uptake gated acquisition (MUGA) scan performed within 8 weeks prior to initial Screening.
8. Subject either currently has central vascular access or is a candidate to receive central vascular access or peripheral vascular access for leukapheresis procedure.
9. Subjects must be at least 100 days since autologous stem cell transplant (ie, Day 0, receipt of hematopoietic stem cells) at the time of initial Screening, if performed.
10. Recovery to ≤ Grade 1 or baseline of any non-hematological toxicities due to previous therapy, except alopecia and peripheral neuropathy.
11. Females of reproductive potential (defined as all females physiologically capable of becoming pregnant) must agree to use one highly effective method of contraception from screening until at least 12 months

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following lymphodepleting chemotherapy. There are insufficient exposure data to provide any recommendation concerning the duration of contraception following treatment with JCARH125. Any decision regarding contraception after JCARH125 infusion should be discussed with the treating physician.

12. Females of reproductive potential must have 2 negative pregnancy tests as verified by the Investigator (one negative serum beta-human chorionic gonadotropin [ß-hCG] pregnancy test result at screening, and within 7 days prior to the first dose of lymphodepleting chemotherapy). This applies even if the subject practices true abstinence* from heterosexual contact.

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

13. Males who have partners of childbearing potential must agree to use an effective barrier contraceptive method from initiation of lymphodepleting chemotherapy and for at least 12 months after and should not donate semen or sperm during the entire study period and for at least 12 months following lymphodepleting chemotherapy.
14. Phase 2a prior BCMA-directed anti-myeloma therapy cohort only – Subjects with R/R MM who have been previously treated with prior BCMA-directed anti-myeloma therapy, achieved at least a partial response (PR) per IMWG response criteria and subsequently progressed on the following treatment:
    a. Subjects who have received prior BCMA-directed CAR T-cell therapy. The last CAR T-cell therapy must have been received at least 6 months prior to JCARH125 study enrollment (screening).
    b. Subjects who have received prior BCMA-directed TCE therapy.
    c. Subjects who have received prior BCMA-directed ADC therapy.

    Subjects with prior BCMA-directed anti-myeloma therapy are not required to have received at least 3 prior anti-myeloma treatment regimens and do not have to be refractory to the last anti-myeloma regimen to be eligible for this trial.

Exclusion Criteria:

Subjects who meet any of the following criteria will be excluded from participation in this study:

1. Subjects with known active or history of central nervous system (CNS) involvement by malignancy.
2. Subjects with solitary plasmacytoma; active or history of plasma cell leukemia (PCL); Waldenstrom's macroglobulinemia; POEMS syndrome (Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal plasmaproliferative disorder, Skin changes); or symptomatic amyloidosis.
3. Subjects who are considered eligible to receive and have refused an autologous stem cell transplant.
4. History of another primary malignancy that has not been in remission for at least 3 years. The following are exempt from the 3-year limit: non-melanoma skin cancer, curatively treated localized prostate cancer, cervical carcinoma in situ on biopsy or a squamous intraepithelial lesion on Pap smear, and in situ breast cancer that has been completely resected.
5. Require systemic immunosuppressive therapies (eg, calcineurin inhibitors, methotrexate, mycophenolate, rapamycin, thalidomide, immunosuppressive antibodies such as anti-interleukin 6 [IL-6] or anti-interleukin 6 receptor [IL-6R]).
6. Prior CAR T-cell or other genetically-modified T-cell therapy (not applicable to Phase 2a cohorts).
7. Prior treatment with a BCMA-directed therapy (not applicable to Phase 2a cohorts).
8. Human immunodeficiency virus (HIV) infection positive subjects
9. Hepatitis B virus (HBV) or hepatitis C virus (HCV) infection as indicated by positive serology or nucleic acid testing. Subjects who are solely hepatitis B surface antibody (HBsAb)-positive are eligible.
10. Untreated or active infection at the time of initial Screening, at the time of leukapheresis, within 72 hours before lymphodepletion, or 5 days before JCARH125 infusion. Subjects with ongoing use of prophylactic antibiotics, antifungals, or antivirals are eligible if no evidence of active infection.
11. History of any one of the following cardiovascular conditions within the 6 months prior to initial Screening: Class III or IV heart failure as defined by the New York Heart Association (NYHA),

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myocardial infarction, unstable angina, uncontrolled or symptomatic atrial arrhythmias, any ventricular arrhythmias, or other clinically significant cardiac disease.

12. History or presence of clinically relevant CNS pathology such as epilepsy, seizure, aphasia, stroke, severe brain injuries, dementia, Parkinson's disease, cerebellar disease, organic brain syndrome, or psychosis.
13. History of ≥ Grade 2 hemorrhage within 30 days or requirement for ongoing treatment with chronic, therapeutic doses of anticoagulants (eg, warfarin, low molecular weight heparin, or Factor Xa inhibitors).
14. Pregnant or nursing (lactating) women.
15. Treatment with the following therapies within the specified time period:
    a. Monoclonal antibodies (anti-CD38 and anti-SLAMF7 antibody) within 4 weeks prior to leukapheresis.
    b. Any other systemic therapy approved for the treatment of MM within 14 days before leukapheresis or within 14 days before lymphodepleting chemotherapy.
    c. Any experimental therapy within 8 weeks (for biologics) or 5 half-lives (for small molecules) before leukapheresis.
    d. Therapeutic doses of corticosteroids (defined as > 20 mg/day prednisone or equivalent) within 14 days before leukapheresis. Physiologic replacement, topical, and inhaled steroids are permitted.
    e. Radiation to a single lesion within 14 days before leukapheresis.
    f. Radiation that includes a large bone marrow field such as the pelvis or sternum within 6 weeks before leukapheresis.
16. Plasmapheresis within 14 days before leukapheresis.
17. Any medical, psychological, familial, sociological, or geographical conditions that do not permit compliance with the protocol, as judged by the Investigator; medical or psychiatric conditions or laboratory abnormalities that could jeopardize subject safety, as judged by the Investigator or Sponsor Medical Monitor; or unwillingness or inability to follow the procedures required in the protocol.
18. Use of any live vaccines against infectious diseases within 8 weeks before JCARH125 infusion.
19. Subjects with known hypersensitivity to Escherichia coli (*E. coli)*-derived proteins (only applicable for subjects getting prophylactic anakinra).
20. History of severe immediate hypersensitivity reaction to any of the protocol-mandated and recommended agents used in this study.

Investigational Product, Dose, and Mode of Administration:

The JCARH125 investigational drug product is composed of autologous CD4+ and CD8+ T cells that express a BCMA-specific CAR. The drug product is provided as a combined CD8+ and CD4+ frozen T-cell suspension in a medium containing dimethyl sulfoxide (DMSO) for IV administration.

JCARH125 will be administered as a single IV dose on Day 1 (between 2 to 7 days after completion of lymphodepleting chemotherapy).

Rationale for Starting Dose of JCARH125 in Phase 1 dose escalation:

The starting dose level for JCARH125 in Phase 1 is 50×10^6 CD3+ CAR+ T cells. The starting dose for this first-in-human Phase 1 trial with the JCARH125 investigational agent was selected based upon the clinical experience of other investigational CAR T cell agents in hematological malignancies of the B-cell lineage, including MM, including CAR T cells targeting BCMA. Subjects with chronic lymphocytic leukemia (CLL), non-Hodgkin lymphoma (NHL), acute lymphoblastic leukemia (ALL), and MM have been treated with doses ranging from 10^7 to 10^9 CAR+ T cells. As of May 2017, in a clinical trial testing BCMA-specific CAR T cells in a population similar to those to be enrolled in this trial, subjects had been treated with up to 800×10^6 CAR+ T cells with no DLTs, and there had been no reports of Grade 3 or 4 neurotoxicity.

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Study Duration:

The enrollment period is expected to take approximately 36 months and the follow-up period for each subject is approximately 24 months after JCARH125 administration. Thus, the total duration of the study is expected to be approximately 60 months.

Duration of Subject Participation:

The expected duration of participation for each subject in this treatment protocol will be approximately 26 months.

Study Sites:

It is planned to enroll subjects at approximately 20 sites in the United States.

Efficacy Assessments:

Disease response will be assessed according to the IMWG Uniform Response Criteria. The following assessments are used to assess disease status: measurement of M protein in blood and urine by electrophoresis and immunofixation, quantification of sFLC (κ and λ) in blood, skeletal survey, and imaging by positron emission tomography (PET)/computed tomography (CT) or diffusion-weighted magnetic resonance imaging (DW-MRI) in subjects with extramedullary disease. In addition, all subjects who achieve a CR must have a bone marrow evaluation, radiological assessment (for subjects with a history of extramedullary disease) for confirmation of CR per the IMWG criteria and must have a sample evaluated for MRD status if applicable.

Safety Assessments:

Adverse events (AEs), serious adverse events (SAEs), and laboratory abnormalities (type, frequency, and severity) will be collected. Adverse events of special interest (AESIs) will include infusion reactions, cytokine release syndrome (CRS), neurologic toxicity, macrophage activation syndrome (MAS), tumor lysis syndrome (TLS), severe infections, and severe prolonged cytopenias; the list of AESIs may be updated during the course of the study based on observed safety signals.

Replication-competent lentivirus (RCL) and viral vector sequence testing will be performed at specified time points during the study using polymerase chain reaction (PCR)-based assays.

DLT Definition:

DLTs are AEs that occur within 21 days following JCARH125 infusion and meet any of the following criteria:

- Treatment-emergent ≥ Grade 3 allergic reactions related to JCARH125
- Treatment-emergent Grade 3 seizures, regardless of attribution, that do not resolve to ≤ Grade 2 within 3 days in subjects who have no evidence of CNS involvement of MM or other CNS pathology
- Treatment-emergent autoimmune toxicity ≥ Grade 3, regardless of attribution (excluding B-cell aplasia)
- Treatment-emergent Grade 3 CRS that does not resolve to ≤ Grade 2 within 72 hours
- Any other treatment-emergent Grade 3 AE related to JCARH125 that does not resolve to ≤ Grade 2 within 7 days (see exceptions listed below)
- Any treatment-emergent Grade 4 AE related to JCARH125 that does not resolve to ≤ Grade 2 within 7 days (see exceptions listed below)
- Treatment-emergent Grade 4 CRS of any duration
- Any treatment-emergent Grade 5 toxicity not due to the underlying malignancy

The following will **not** be considered DLTs:

- Non-hematologic AEs:
  - Grade 4 infusional toxicities that are reversible to Grade ≤ 2 within 8 hours
  - Grade 3 fatigue lasting ≤ 7 days
  - Fever of any grade, including febrile neutropenia
  - Grade 4 increase in transaminases for ≤ 7 days

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- Grade 3 TLS for ≤ 2 weeks or Grade 4 TLS for ≤ 7 days
- Grade 4 hypotension (without other CRS symptoms) requiring a single vasopressor for support that resolves to Grade < 3 in ≤ 72 hours
- Grade 3 or 4 CRS with hypotension alone requiring a low dose of a single vasopressor (as defined by Lee et al (Lee, 2014)) for support (not requiring intubation) that resolves to Grade < 3 in ≤ 72 hours
- Grade 3 chills
- Grade 3 or 4 asymptomatic, non-hematological clinical laboratory abnormalities that return to Grade ≤ 2 within 7 days or electrolyte abnormalities that resolve with replacement
- Grade 3 diarrhea lasting ≤ 72 hours
- Grade 3 nausea/vomiting lasting ≤ 72 hours

- Hematologic AEs:
  - Grade 3 neutropenia of any duration or Grade 4 neutropenia lasting ≤ 28 days
  - Grade 3 or 4 lymphopenia of any duration
  - Grade 3 or 4 leukopenia of any duration
  - Grade 3 thrombocytopenia of any duration or Grade 4 thrombocytopenia lasting ≤ 28 days
  - Grade 3 anemia of any duration or Grade 4 anemia lasting ≤ 28 days

The timing and severity of AEs will be reviewed continuously with study Investigators and on a regular basis with the DSMB. In the event that AEs meeting DLT criteria occur beyond the DLT evaluation period, the DLT window may be extended following discussion with the Investigators.

Criteria for Pausing the Study during Phase 1 Dose Escalation, Phase 1 Anakinra Cohort, or Phase 2a:

Further enrollment or treatment of subjects in any or all appropriate cohorts will be paused pending notification of the DSMB and appropriate regulatory authorities if any subject experiences any of the following events within 30 days of a JCARH125 infusion:

- Life-threatening (Grade 4) toxicity attributable to JCARH125 that is unexpected and unrelated to chemotherapy

  Expected toxicities that would not lead to study interruption include Grade 4 CRS, neurotoxicity (eg, confusion, aphasia, seizures, convulsions, lethargy, and/or altered mental status), fever, hypotension, hypoxia, TLS, and disseminated intravascular coagulation. In addition, intensive care unit (ICU) admission, the need for dialysis, and/or the need for mechanical ventilation are also expected. These expected toxicities may also result in secondary toxicities of Grade 4 renal toxicity, hepatic toxicity, or other organ involvement. Any Grade 4 toxicity that is not considered to be a DLT (refer to listed exceptions) will not lead to study interruption.
- An unacceptably high incidence, across multiple dose levels or after at least 10 subjects have been treated at the RP2D, of expected Grade 4 toxicities, including Grade 4 CRS (> 40%), Grade 4 neurotoxicity (> 30%), Grade 4 renal toxicity not associated with disease progression (> 30%), and Grade 4 hepatotoxicity (> 30%), attributable to JCARH125 or chemotherapy
- Death related to JCARH125 therapy

Criteria for Terminating the Study (or Cohort) Prematurely:

Further enrollment or treatment of subjects in any or all appropriate cohorts will be terminated for the following reasons:

- Any subject develops confirmed RCL during the study
- The Sponsor, Institutional Review Board/Independent Ethics Committee, or DSMB decides that subject safety may be compromised by continuing the study (or cohort)
- The Sponsor decides to discontinue the development of JCARH125 entirely (or for the indications under evaluation in a given cohort)

Protocol Number: H125001	Product Name: JCARH125

Other Assessments:

The following assessments will be performed at specified time points:

PK assessments: Assessment of JCARH125 expansion and persistence will be determined by qPCR to detect the JCARH125 transgene. JCARH125 PK will be assessed from the time of the JCARH125 infusion until the end of study.

[redacted]

Health-related quality of life (HRQoL) assessments: HRQoL will be assessed using the EORTC QLQ-C30 questionnaire including the QLQ-MY20 MM module, as well as the EuroQol instrument EQ-5D-5L.

Statistical Methods:

Phase 1 Dose-Escalation Cohorts

Statistical analyses of the primary, secondary, and exploratory endpoints will be primarily descriptive for the Phase 1 dose-escalation portion of the trial; summaries will be provided by dose level and overall. The incidence of DLTs, the incidence and severity of AEs, and the incidence and severity of laboratory abnormalities will be described and summarized.

Phase 1 Anakinra Cohort - Prophylactic Treatment with Anakinra

Data from the Phase 1 anakinra cohort will be summarized separately but subjects treated in this cohort at the RP2D(s) will also be pooled with subjects treated at the RP2D(s) in Phase 1 dose escalation and Phase 2 expansion for the primary analyses. Statistical analyses of the primary, secondary, and exploratory endpoints will be primarily descriptive for this cohort. The incidence and severity of AEs and the incidence and severity of laboratory abnormalities will be described and summarized. The number and percentage of subjects developing Grade $\geq$ 2 CRS, as well as an upper 1-sided 80% confidence interval (CI) will be provided and benchmarked against the observed rate from dose levels 3 and/or 3a from the dose escalation portion of the trial. A similar analysis will be provided for the number and percentage of subjects with no CRS occurring on study days 1, 2, or 3. The onset of Grade $\geq$ 2 CRS will be summarized descriptively and will be referenced to onset of Grade $\geq$ 2 CRS in subjects treated at the RP2D(s) in the Phase 1 dose escalation portion of the trial.

Phase 2 Expansion Cohort

The efficacy analysis set for formal statistical hypothesis testing consists of all subjects across Phase 1 dose escalation, the Phase 1 anakinra cohort, and Phase 2 expansion who have measurable disease at the last disease assessment prior to JCARH125 infusion and who receive conforming product at the RP2D(s).

The primary endpoint for Phase 2 is ORR, defined as the rate of sCR + CR + very good partial response (VGPR) + partial response (PR), as assessed by the IRC. A key secondary endpoint for Phase 2 is CR rate, defined as the rate of sCR + CR as assessed by the IRC. Disease response will be assessed until disease progression, end of study, death, or the start of another anticancer therapy or hematopoietic stem cell transplant (HSCT). Subjects without any reported disease response assessments will be considered non-responders. Formal statistical hypothesis testing of ORR and CR will be based on the IRC.

Exact binomial tests at the 1-sided 0.025 significance level will be used to evaluate the statistical hypotheses to be formally tested and an exact 2-sided 95% confidence interval for ORR and CR will be provided for each analysis set using the Clopper-Pearson procedure.

A gatekeeping approach will be used to control the overall type 1 error rate for the analyses of the primary endpoint and the CR endpoint. The CR endpoint will only be tested for statistical significance if the primary endpoint is significant at the 1-sided 0.025 significance level.

Protocol Number: H125001	Product Name: JCARH125

Phase 2a Prior BCMA-directed Anti-Myeloma Therapy Cohort

Each Phase 2a cohort will be analyzed separately from the Phase 1 dose-escalation cohorts and the Phase 2 expansion cohort. Statistical analyses of the primary, secondary, and exploratory endpoints will be primarily descriptive for the Phase 2a portion of the trial. The ORR and CR will be summarized. The incidence and severity of adverse events (AEs) and the incidence and severity of laboratory abnormalities will be described and summarized.

Timing of Analyses

The primary analysis for ORR is planned after at least 75 subjects in the efficacy analysis set have been evaluated for response. The exact timing of the analysis will be determined after discussions with regulatory agencies.

An interim analysis may be performed after at least 20 subjects have been treated at the RP2D(s) pooled across Phase 1 dose escalation, the Phase 1 anakinra cohort, and Phase 2 expansion and are evaluable for response (ie, have had at least 1 post-treatment disease assessment and all objective responses confirmed). The purpose of the interim analysis is to inform the development program for JCARH125. There are no intentions to stop the trial early for positive efficacy; therefore, no adjustment to the alpha level will be made for the final analysis.

Sample Size

A sample size of approximately 75 treated subjects at the RP2D(s) is planned for the primary efficacy evaluation. A sample size of up to 120 subjects is planned for Phase 1 dose escalation with up to approximately 106 subjects potentially evaluated in Phase 1 dose escalation at dose levels not at the RP2D(s). The Phase 1 anakinra cohort will be comprised of up to 14 subjects and is planned to be included in the primary efficacy evaluation for subjects treated at the RP2D(s). Phase 2a will be comprised of up to 42 subjects (up to 14 subjects per cohort). Assuming approximately 5% to 10% of subjects may not be evaluable for the primary endpoint due to reasons such as not being evaluable for DLT assessment, receiving non-conforming product, or not having measurable disease after receiving bridging chemotherapy, a total sample size of 245 subjects is planned for this Phase 1/2 study.

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Abbreviation or Term	Definition/Explanation
ADC	antibody-drug conjugate
ADCC	antibody-dependent cell-mediated cytotoxicity
AE	adverse event
AESI	adverse event of special interest
ALC	absolute lymphocyte count
ALL	acute lymphoblastic leukemia
ALT	alanine aminotransferase
ANC	absolute neutrophil count
APRIL	a proliferation-inducing ligand
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
ASTCT	American Society for Transplantation and Cellular Therapy
[redacted]	[redacted]
AUC	area under the curve
ß-hCG	beta human chorionic gonadotropin
BAFF	B-cell activation factor
BBB	blood-brain barrier
BCMA	B-cell maturation antigen
BiTE	bispecific T-cell engager
BUN	blood urea nitrogen
CAR	chimeric antigen receptor
CBC	complete blood count
CFR	Code of Federal Regulations
CI	confidence interval
CLL	chronic lymphocytic leukemia
C_{max}	maximum concentration
CMV	cytomegalovirus
CNS	central nervous system
CONSORT	Consolidated Standards of Reporting Trials
CR	complete response
CRA	Clinical Research Associate
CrCl	creatinine clearance
CRF	case report form
CRP	C-reactive protein
CRS	cytokine release syndrome

Abbreviation or Term	Definition/Explanation
CSF	cerebrospinal fluid
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLI	donor lymphocyte infusion
DLT	dose-limiting toxicity
DMSO	dimethyl sulfoxide
DOCR	duration of complete response
DOR	duration of response
DSMB	Data Safety Monitoring Board
DW-MRI	diffusion-weighted magnetic resonance imaging
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EEG	electroencephalogram
EGFR	epidermal growth factor receptor
EGFRt	truncated epidermal growth factor receptor
EORTC	European Organization for Research and Treatment of Cancer
EOS	end of study
FDA	Food and Drug Administration
FFPE	formalin-fixed, paraffin-embedded
FHCRC	Fred Hutchinson Cancer Research Center
G-CSF	granulocyte colony-stimulating factor
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GM-CSF	granulocyte macrophage colony-stimulating factor
GVHD	graft-versus-host disease
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HEOR	health economics and outcomes research
HIPAA	Health Information Portability and Accountability Act of 1996
HIV	human immunodeficiency virus
HRQoL	health-related quality of life

Abbreviation or Term	Definition/Explanation
HSCT	hematopoietic stem cell transplant
IB	Investigator's Brochure
IBC	Institutional Biosafety Committee
ICF	informed consent form
ICH	International Conference on Harmonisation
ICU	intensive care unit
IEC	Independent Ethics Committee
IFN	interferon
IFN-g	interferon-gamma
IHC	Immunohistochemistry
IL-6	interleukin 6
IL-6R	interleukin 6 receptor
IMiD	immunomodulatory drug
IMWG	International Myeloma Working Group
IND	Investigational New Drug Application
INR	international normalized ratio
IRB	Institutional Review Board
IRC	Independent Review Committee
IUD	intrauterine device
IV	intravenous(ly)
IVIG	intravenous immunoglobulin
LDH	lactate dehydrogenase
LTFU	long-term follow-up
LVEF	left ventricular ejection fraction
mAb	monoclonal antibody
MAS	macrophage activation syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MM	multiple myeloma
MMSE	Mini Mental State Examination
MR	minimal response
MRD	minimal residual disease
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
mTPI	modified toxicity probability interval
MUGA	multiple uptake gated acquisition
NCI	National Cancer Institute

Abbreviation or Term	Definition/Explanation
NDA	no data available
NGS	next-generation sequencing
NHL	non-Hodgkin lymphoma
NK	natural killer
NT	neurologic toxicity
NYHA	New York Heart Association
ORR	overall response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
PCL	plasma cell leukemia
PCP	pneumocystis pneumonia
PCR	polymerase chain reaction
PD	progressive disease
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetic(s)
PN	polyneuropathy
PO	per oral
POEMS	Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal plasmaproliferative disorder, Skin changes
PR	partial response
PRES	posterior reversible encephalopathy syndrome
qPCR	quantitative polymerase chain reaction
RA	rheumatoid arthritis
RCL	replication-competent lentivirus
RP2D	recommended Phase 2 dose
R/R	relapsed and/or refractory
SAE	serious adverse event
SaO_2	saturated oxygen
SAP	statistical analysis plan
SC	subcutaneous(ly)
scFv	single chain variable fragment
SCID	severe combined immunodeficiency
sCR	stringent complete response
sCRS	severe cytokine release syndrome
SCT	stem cell transplant

Abbreviation or Term	Definition/Explanation
SD	stable disease
sFLC	serum free light chain
SNP	single nucleotide polymorphism
SOC	system organ class
SPEP	serum protein electrophoresis
SPM	second primary malignancy
TCE	T-cell engager
TEAE	treatment-emergent adverse event
TLS	tumor lysis syndrome
T_{max}	time to maximum concentration
TMG	toxicity management guidelines
TNF	tumor necrosis factor
TNF-α	tumor necrosis factor-alpha
TTCR	time to complete response
TTR	time to response
ULN	upper limit of normal
UPenn	University of Pennsylvania
UPEP	urine protein electrophoresis
US	United States
VGPR	very good partial response

1. INTRODUCTION

1.1. Multiple Myeloma

Multiple myeloma (MM) is a hematologic malignancy characterized by the clonal proliferation of plasma cells in the bone marrow. Clinical features of symptomatic disease are summarized by the so-called "CRAB criteria," which consist of hypercalcemia, renal impairment, anemia, and bone lesions (Palumbo, 2011; Gerecke, 2016; Naymagon, 2016).

It is estimated that there will be approximately 32,110 new cases diagnosed and 12,960 deaths from MM in the United States (US) in 2019 (Siegel, 2019). Myeloma primarily affects older individuals; the median age at diagnosis is 69 and less than 15% of those newly diagnosed are under the age of 55 (Howlader, 2016).

Although MM remains incurable, significant progress has been made over the past 20 years with the development of proteasome inhibitors (eg, bortezomib and carfilzomib), immunomodulators (IMiDs) (eg, lenalidomide, pomalidomide), and monoclonal antibodies (elotuzumab and daratumumab). Newly diagnosed patients who are medically fit commonly receive induction therapy prior to autologous stem cell transplant (SCT) with a triplet combination regimen consisting of a proteasome inhibitor and dexamethasone, together with lenalidomide, cyclophosphamide, or thalidomide (Raza, 2017). For older or medically unfit patients, first-line treatment may consist of lenalidomide with low-dose dexamethasone, a melphalan-containing regimen, or a dose-adjusted triplet regimen without SCT. The availability of these newer agents has extended median survival from 3 to 4 years to more than 7 years after initial diagnosis (Anderson, 2011).

Depth of response has been shown to correlate with improved overall survival in multiple myeloma. Multiple studies have shown that patients with MM who achieve a complete response (CR) following therapy with or without transplant had prolonged overall survival compared with patients achieving less than CR (van de Velde, 2007; Lahuerta, 2008; Gay, 2011). Assessment for minimal residual disease (MRD) by both flow cytometry and deep sequencing demonstrates a correlation between achieving an MRD-negative status and increased overall survival (Martinez-Lopez, 2014; Rawstron, 2015).

Despite improvements in the treatment of newly diagnosed MM, nearly all patients relapse and become increasingly resistant to treatment which may be attributed, at least in part, to genetic heterogeneity of myeloma cells and clonal evolution during treatment (Cornell, 2016; Chung, 2017). Treatment of R/R disease remains challenging. Patients refractory to both IMiDs and proteasome inhibitors have a median overall survival of only 9 months (Kumar, 2012). The development of the monoclonal antibodies elotuzumab and daratumumab has expanded treatment options for patients with relapsed disease; however, agents with a novel mechanism of action are still urgently needed to combat development of resistance to existing therapies.

1.2. BCMA as a Therapeutic Target

B-cell maturation antigen (BCMA), a member of the tumor necrosis factor (TNF) receptor superfamily, is a cell surface protein expressed on normal and malignant plasma cells that is involved in regulating the maturation of B cells and differentiation into plasma cells. It is induced during differentiation of plasma cells in parallel with the loss of expression of a related

receptor for B-cell activation factor (BAFF-R). Binding of BCMA to its ligands, B-cell activation factor (BAFF) and a proliferation-inducing ligand (APRIL), leads to survival of plasma cells, resulting in enhanced humoral immunity. BCMA is highly expressed on MM cell lines and on cells from patients with MM, and expression appears to increase with progression of the disease (Tai, 2015). Importantly, BCMA protein is not expressed by hematopoietic stem cells, naïve B cells, or normal non-hematopoietic cells (Carpenter, 2013; Tai, 2015). Thus, with the exception of possible B-cell aplasia, which is easily managed, toxicity associated with on-target/off-tumor interactions is not expected to be a concern with agents targeting BCMA.

1.3. BCMA-targeted Therapies

Three therapeutic modalities to target BCMA expressing myeloma cells have entered clinical trials: CAR T cells, antibody drug conjugates, and T cell engagers. The reasons for lack of response or relapse following these therapies is not well understood. Cross resistance across modalities has not been rigorously tested. Differences in mechanism of action or the design of CAR T constructs suggest that these agents may be potentially active when administered in sequence.

1.3.1. BCMA-targeted CAR T Cells

One therapeutic strategy that has demonstrated particular promise in hematologic cancers has been the development of chimeric antigen receptors (CARs) targeting the CD19 antigen for the treatment of CD19-positive B-cell malignancies. CARs are artificial single-transmembrane domain receptors typically composed of an extracellular antigen-specific binding domain linked to native T-cell receptor signaling domains, typically CD3ζ in tandem with either the CD28 or 4-1BB costimulatory domain. The antigen-binding domain may be generated using a single-chain variable fragment (scFv) from an antibody with appropriate antigen specificity. Antitumor activity against malignant B cells expressing the CD19 antigen is achieved via transduction of a patient's T cells with a retroviral or lentiviral vector containing the CD19-specific CAR and re-infusion into the patient. Engagement of the CAR T cells with CD19-expressing B cells elicits an immune response resulting in the targeted killing of the malignant cells. CR rates as high as approximately 90% have been reported in patients with acute lymphoblastic leukemia (ALL), and overall response rates (ORRs) of approximately 80% and approximately 90% have been reported in patients with non-Hodgkin lymphoma (NHL) and chronic lymphocytic leukemia (CLL), respectively (Park, 2016a; Turtle, 2016a; Abramson, 2017).

Based on the encouraging activity of CD19-targeted CAR T cells in B-cell malignancies, BCMA-directed CAR T cells are being evaluated for treatment of MM. In preclinical studies, T cells transduced with anti-BCMA CAR produced cytokines (eg, interferon gamma [IFN-γ]) and proliferated upon stimulation with BCMA-expressing target cells (Carpenter, 2013). In addition, anti-BCMA CAR T cells killed BCMA-expressing multiple myeloma cells and eradicated BCMA-expressing tumors in mouse xenograft models (Carpenter, 2013).

Several Phase 1 clinical trials evaluating different anti-BCMA CAR T cell-products are ongoing. Early results from a Phase 1 clinical trial (NCT02215967) by the National Cancer Institute (NCI) evaluating anti-BCMA CAR T cells in patients with MM appear promising:
2 treatment-refractory patients treated at the highest dose level (9×10^6 CAR T cells/kg) were

reported to achieve a response (one with a complete remission of 17 weeks before relapse and the second with a partial remission that was ongoing at the time of publication) (Ali, 2016). Toxicity reported for both patients treated at this dose level included symptoms associated with cytokine release syndrome (CRS) (fever, hypotension, dyspnea) and prolonged cytopenias.

In a Phase 1 CRB-401 study (NCT02658929), as of 29 March 2018, 43 subjects with R/R MM in dose-escalation (n = 21) and dose-expansion (n = 22) cohorts were treated at 4 dose levels of idecabtagene autoleucel (an investigational BCMA-targeted CAR T cell product). No dose-limiting toxicities (DLTs) were observed at any dose level studied. Subjects enrolled in the optimal dose levels (>150 × 10^6 CAR+ T cells) had received a median of 8 prior regimens (range 3 to 23). Cytokine release syndrome (CRS) occurred in 63% of subjects, mostly Grade 1 or 2 in severity and manageable. Responses were achieved by 95.5% of subjects at the optimal dose levels. The percentage of subjects with complete response (CR) or better (CR and stringent CR) was 50%, and 36.4% of subjects had a very good partial response (VGPR). Median progression-free survival (PFS) was 11.8 months in all subjects and 17.7 months in subjects who were MRD-negative (Raje, 2018). The pivotal Phase 2 KarMMa study of bb2121 further confirmed an overall response of 73% with a 31% CR rate. Safety results were consistent with the CRB-401 study data. Cytokine release syndrome occurred in 84% of subjects and neurotoxicity of any grade occurred in 15% of subjects. Grade 3 or higher CRS and neurologic toxicity (NT) were only observed in <6% of subjects (BMS, 2019).

One CAR construct employing a human BCMA-binding domain is currently undergoing evaluation by the University of Pennsylvania (UPenn) (NCT02546167). A total of 25 subjects with R/R MM received treatment with the UPenn CAR T cell product in one of 3 dose cohorts (9 subjects in cohort 1, 1 × 10^8 to 5 × 10^8 CART-BCMA cells alone; 5 subjects in cohort 2, cyclophosphamide [Cy] 1.5 g/m^2 plus 1 × 10^7 to 5 × 10^7 CART-BCMA cells; 11 subjects in cohort 3, Cy 1.5 g/m^2 plus 1 × 10^8 to 5 × 10^8 CART-BCMA cells). Clinical activity was reported for 17 subjects, including 1 stringent complete response (sCR), 1 complete response (CR), 5 VGPR, 5 partial response (PR), and 5 minimal response (MR). Overall response rate was 48% (12 out of 25). CRS was reported for 22 of the 25 subjects (88%), with Grade 3 CRS in 8 subjects and Grade 4 CRS in 3 subjects. A DLT of Grade 4 posterior reversible encephalopathy syndrome (PRES) was reported for 1 subject and Grade 3 cardiomyopathy and Grade 4 spontaneous hemothorax for 1 subject (Cohen, 2019).

Data from a fourth Phase 1 study conducted in China (sponsored by Nanjing Legend) with a data cutoff date of 31 Dec 2018, revealed an ORR of 88% among 57 subjects with R/R MM who received treatment with the BCMA-targeted CAR T cell product LCAR-B38M. Forty-two of the 57 subjects (74%) were reported to experience a CR, 2 subjects (4%) had VGPR, and 6 subjects (11%) had PR. Cytokine release syndrome was reported in 90% of subjects; only 4 subjects (7%) were reported to have Grade 3 CRS. Neurotoxicity was reported in 1 subject (Wang, 2019).

Another BCMA CAR T cell therapy with the same construct as BMCA CAR T cells investigated in China by Nanjing Legend Pharmaceutical is JNJ-68284528 (JNJ-4528). This BCMA CAR T cell construct contains two BCMA-targeting single-domain antibodies designed to confer avidity. As of the June 24, 2019 data cut, 21 patients that were evaluable for response had an overall response of 91% with a median follow up of 3 months. Four patients achieved sCR, 2 achieved CR, 7 achieved VGPR, and 6 achieved PR. Patients were treated with a single dose of JNJ-4528 at a targeted dose of 0.75 x 10^6 CAR+ cells/kg (target range 0.5-1.0 x 10^6). The

median age was 61 years (range 50–75). Patients had received a median of 5 (range 3–16) prior lines of treatment. A total of 88% were triple refractory to a PI, IMiD, and anti-CD38 antibody, 72% were penta-exposed, and 36% were penta-refractory. The median administered dose was $0.73x10^6$ CAR+ cells/kg (range $0.5–0.9x10^6$). Additionally, 80% (20/25) of subjects treated with JNJ-4528 suffered from Grade 1 or Grade 2 CRS. One subject had a Grade 3 CRS event, while another had a Grade 5 event. Three subjects also had CAR-T neurotoxicity of Grade 1 (2 subjects) and Grade 3 (1 subject) (Madduri, 2019).

bb21217 is an investigational BCMA-targeted CAR T cell therapy that uses the bb2121 construct with a modified manufacturing process designed to improve CAR T cell functional persistence. The phosphoinositide 3-kinase inhibitor bb007 is used during ex vivo culture to enrich the drug product for T cells with a memory-like phenotype. As of 20 April 2019, 22 subjects (median age 63 years old) have received bb21217 (12 at 150, 6 at 300 and 4 at 450 $\times 10^6$ CAR T cells). Eleven had high tumor burden, defined as ≥ 50% bone marrow plasma cells pre-infusion. Subjects had a median of 7 prior lines of therapy and 18 of 22 had prior autologous stem cell transplant; 7 of 22 had high-risk cytogenetics. Of the 22 subjects, 19 received prior daratumumab and 13 received prior bortezomib/lenalidomide/carfilzomib/pomalidomide/daratumumab. Median follow-up after bb21217 infusion was 23 weeks. As of the data cutoff, 13 of the 22 (59%) subjects had developed CRS (5 with maximum CRS severity of Grade 1, 7 with maximum severity of Grade 2, and 1 with maximum severity of Grade 3) and responded to supportive care, tocilizumab, and/or corticosteroids. Five (23%) subjects developed neurotoxicity [1 Grade 1, 2 Grade 2, 1 Grade 3 (vertigo/dizziness), 1 Grade 4 (encephalopathy, previously reported)]. For the 1 patient with Grade 4 neurotoxicity, Grade 3 CRS was also reported; both events have resolved. A total of 18 subjects were evaluable for response with ≥ 2 months of follow-up or PD within 2 months. Fifteen (83%) subjects demonstrated clinical response per International Myeloma Working Group (IMWG) criteria. Six (27%) of these subjects subsequently progressed. Nine (41%) subjects remained in response, including 2 subjects with ongoing response at Months 15 and 18. MRD-negative results at 10^{-5} nucleated cells or better were obtained by next-generation sequencing (NGS) in 10 of 10 evaluable responders at Month 1. Overall, 6 of 8 subjects evaluable at 6 months and 2 of 2 subjects evaluable at 12 months had detectable CAR T cells in peripheral blood (Berdeja, 2019).

1.3.2. BCMA-targeted Antibody Drug Conjugate

Antibody–drug conjugates, composed of recombinant monoclonal antibodies (mAbs) covalently bound to cytotoxic chemicals via synthetic chemical linkers, represent the fast-growing class of cancer therapeutics (McCombs, 2015). The antibody-drug conjugate (ADC) first identifies and binds to the antigen on the surface of tumor cells via the mAb, and then is absorbed or internalized. After the ADC is internalized, the cytotoxic chemicals are released in the lysosomes and transported to cytosol to kill the tumor cells.

Belantamab mafodotin is a humanized, IgG1 mAb with high affinity to BCMA (Kd of ~0.5 nM) (Tai, 2014), synthesized with a non-cleavable linker, maleimidocaproyl, and a new class of antimitotic agents, monomethyl auristatin F. This structure is characterized by high stability and high antitumor potency.

Belantamab mafodotin binds to all CD138+ and BCMA+ MM cell lines and patient MM cells and inhibits proliferation of myeloma cells. Belantamab mafodotin also triggers antibody-

dependent cell-mediated cytotoxicity (ADCC) and antibody-dependent cellular-mediated phagocytosis against patient MM cells. (Tai, 2014).

Belantamab mafodotin was evaluated in DREAMM-2, an open-label, 2-arm trial that recruited patients with R/R MM who have received at least 3 lines of anti-myeloma therapy. Patients were randomized to receive 2 separate doses of the agent, either 2.5 mg/kg or 3.4 mg/kg, via intravenous infusion every 3 weeks on day 1 of each cycle until disease progression or unacceptable toxicity. The overall response rate in each group exceeded 30%, with 31% of patients receiving 2.5 mg/kg (n = 97) and 34% of patients receiving 3.4 mg/kg (n = 99) achieving a response. Corresponding rates of very good partial response or better were 19% and 20% (Trudel, 2019). Two additional anti-BCMA ADCs, MEDI2228 and AMG 224, are in ongoing Phase 1 trials for R/R MM—NCT03489525 and NCT02561962, respectively. In the former, BCMA is conjugated via a protease-cleavable pyrrolobenzodiazepine warhead linker, while AMG 224 is comprised of an antitumor maytansine derivative connected to antibody lysine residues via the non-cleavable 4-(N-maleimidomethyl) cyclohexane-1-carboxylate linker.

1.3.3. BCMA-targeted TCE

T-cell engagers (TCE) are antibodies which bind simultaneously to a surface tumor cell antigen and a component of the T-cell receptor (TCR) complex to induce T cell–mediated killing of tumor cells harboring the target surface antigen. After formation of a cytolytic synapse, the T cells release perforin and granzyme B, finally leading to apoptosis of the tumor cells (Brischwein, 2006). Activation of T cells leads to transient release of cytokines, which engages other immune cells and broadens the immune response against the tumor tissue and ultimately leads to proliferation of T cells and serial killing of tumor cells (Hoffmann, 2005; Gruen, 2004; Baeuerle, 2009). Bispecific T-cell engager (BiTE) antibody constructs are highly potent and efficacious molecules but have a short half-life due to their small size (55kDa). BLINCYTO is the first anti-CD19 BiTE approved by the FDA for the treatment of adults and children with relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL) and B-cell precursor acute lymphoblastic leukemia (ALL) in first or second complete remission with minimal residual disease (MRD) greater than or equal to 0.1%. (BLINCYTO prescribing information, 2019).

Two BiTEs directed against BCMA are currently in Phase 1 development, including AMG 420 and AMG 701, a bispecific TCE targeting BCMA and CD3. No clinical data have been published for AMG 701; however, the predecessor compound, AMG 420, demonstrated a response rate of 70% among 10 subjects with R/R MM who were treated at the highest dose level. From 42 patients who have received AMG 420, 2 patients died due to adverse events (AEs) (acute respiratory distress from flu / aspergillosis; fulminant hepatitis related to adenovirus infection); neither were treatment related. Serious adverse events occurring in >1 patient were infections (n=12) and polyneuropathy (PN, n=2). Treatment-related SAEs included 2 grade 3 PNs and 1 edema. Grade 2-3 CRS was seen in 3 patients (Topp, 2019).

CC-93269 is another BCMA TCE. Results from a phase 1 dose escalation trial with data cutoff of 24 May 2019 showed an ORR of 53% (10/19) subjects. Cytokine release syndrome occurred in 90% of subjects, with only 1 grade 3 CRS (6%) was reported (Costa, 2019).

1.4. JCARH125 Investigational Drug Product

The JCARH125 investigational drug product comprises autologous CD4+ and CD8+ T cells that have been transduced using a replication-incompetent, self-inactivating lentiviral vector encoding a CAR directed to BCMA. The drug product is provided as a combined CD8+ and CD4+ frozen T-cell suspension in a formulation containing dimethyl sulfoxide (DMSO). JCARH125 is administered by intravenous (IV) infusion.

The BCMA-specific CAR comprises a binding domain isolated from a human scFv phage display library, an [redacted] hinge region, [redacted] transmembrane domain, and 4-1BB and CD3ζ signaling domains. [redacted]

In vitro pharmacology proof-of-concept studies have demonstrated the ability of JCARH125 to proliferate, secrete pro-inflammatory cytokines, and kill BCMA-expressing cells. This activity is minimally affected by the addition of increasing amounts of soluble BCMA. Studies conducted in tumor xenograft models in mice bearing BCMA-positive multiple myeloma tumor cells demonstrated tumor clearance and improved survival following JCARH125 administration.

Additional details are provided in the JCARH125 Investigator's Brochure.

1.5. Potential Risks of BCMA-Targeted CAR T Cells

The CAR T cell products furthest along in clinical development target the CD19 B-cell antigen that is expressed by most B-cell malignancies. Across CD19 CAR T cell programs, the most concerning safety issues have been CRS and neurotoxicity. CRS is a potentially life-threatening condition associated with the release of pro-inflammatory cytokines that occurs following activation of the CAR T cells upon antigen engagement. Symptoms may be evident as early as 1 day after CAR T cell infusion and can include high fever, fatigue, nausea, headache, dyspnea, tachycardia, rigors, hypotension, hypoxia, myalgia, arthralgia, and/or anorexia. The risk of severe CRS (sCRS) in patients with B-cell malignancies appears to be correlated with burden of disease at initiation of treatment (Geyer, 2016; Park, 2016b; Hay, 2017; Kymriah (tisagenlecleucel) prescribing information, 2018). Corticosteroids, interleukin-6 receptor inhibitor such as tocilizumab, or interleukin-6 inhibitor such as siltuximab are most commonly used to treat severe symptoms of CRS.

Neurotoxicity, which may manifest as altered mental status, aphasia, altered level of consciousness, encephalopathy, and/or seizures, can occur in the context of CRS symptoms, before or after onset of CRS, or in the absence of CRS. Several fatal cases of cerebral edema have been reported following administration of different CD19-directed CAR T cell products (Hu, 2016; Turtle, 2016b; Harris, 2017; Turtle, 2017). The pathogenesis of CAR T cell-induced neurotoxicity and optimal treatment regimens for reversing symptoms have yet to be determined.

Based on the data available from ongoing BCMA CAR T cell trials (see Section 1.3), CAR T cells targeted against the BCMA antigen appear to display some similar toxicities. CRS was commonly observed; symptoms of CRS were generally Grade 1 or 2 in severity. Grade 3 CRS was reported for 2 of 33 subjects (6%) treated with bb2121 (one each at dose levels of 450×10^6 and 800×10^6 CAR+ T cells) (Raje, 2019). The most common adverse events observed in subjects treated with LCAR-B38M CAR T cells was CRS (100%; Grade 1/2 [n=10]; Grade 3 [n=6]; Grade 5 [n=1]) (Chen, 2019). In the UPenn study, CRS Grade 3 and 4 on the Penn grading scale

was reported in 8 (32%) subjects, all of whom were treated at the 1×10^8 to 5×10^8 dose (Cohen, 2019). Severe neurotoxicity was less commonly observed with the BCMA CAR T cell products compared with CD19-directed CAR T cell therapies. In the UPenn study, neurotoxicity with transient confusion and/or aphasia was seen in 8 of 25 subjects (32%) and was mild (Grade 1–2) in 5 subjects. Three (12%) had Grade 3–4 encephalopathy including 1 subject with posterior reversible encephalopathy syndrome (PRES) with severe obtundation, recurrent seizures, and mild cerebral edema on MRI that fully resolved after treatment with high-dose methylprednisolone and cyclophosphamide. All 3 subjects with severe neurotoxicity had high tumor burden (2 with extramedullary disease), had received a dose of 5×10^8 CART-BCMA cells, and had Grade 3 or 4 CRS (Cohen, 2019). Neurotoxicity was reported for 14 of 33 subjects (42%) treated with bb2121 with Grade 1 or 2 reported in 13 subjects (39%). One subject (3%) with a high tumor burden had a Grade 4 neurotoxicity starting 11 days after the infusion; this effect resolved within 1 month. One subject reported a Grade 3 headache during CRS in the absence of other signs of neurotoxicity (Raje, 2019). No Grade 3 or 4 neurotoxicity has been reported with LCAR-B38M to date (Chen, 2019).

2. STUDY PURPOSE AND RATIONALE

The purpose of the study is to evaluate the safety, antitumor activity, and pharmacokinetics (PK) of JCARH125 in subjects with R/R MM.

2.1. JCARH125 Dose Rationale

The starting dose level for JCARH125 is 50×10^6 CD3+ CAR+ T cells with 4 additional dose levels of 150×10^6, 300×10^6, 450×10^6, and 600×10^6 CAR+ T cells being explored to date. The starting dose for this first-in-human Phase 1 trial with the JCARH125 investigational agent was selected based upon the clinical experience of other investigational CAR T cell agents in hematological malignancies of the B-cell lineage, including MM. Subjects with CLL, NHL, ALL, and MM have been treated with doses ranging from 10^7 to 10^9 CAR+ T cells (Maude, 2014b; Kochenderfer, 2015; Abramson, 2017; Berdeja, 2017). As of May 2017, subjects with MM had received doses of bb2121 up to 800×10^6 CAR+ T cells on the CRB-401 trial with no DLTs, and there had been no reports of Grade 3 or 4 neurotoxicity. As previously described in Section 1.3, Grade 3 CRS had been reported for 2 of 21 subjects (10%) in that study (1 each at dose levels of 450×10^6 and 800×10^6 CAR+ T cells) (Berdeja, 2017). At a dose of 150×10^6 CAR+ T cells, CRS had been reported for 2 subjects and were Grades 1 and 2 (Berdeja, 2017). At the starting dose in the CRB-401 trial (50×10^6 CAR+ T cells), 1 subject was reported to experience Grade 1 CRS and dramatically less antitumor activity was observed; only 1 subject out of 3 was reported to experience a PR, which lasted less than 8 weeks before the subject's disease progressed. In contrast, a response of PR or better was reported for all subjects who received doses of $\geq 150 \times 10^6$ CAR T cells and, as of May 2017, it was reported that none of these subjects had progression of their disease (Berdeja, 2017). Another BCMA-directed CAR T cell product, LCAR-B38M, has also reported only 2 events of Grade 3 CRS among 35 subjects treated (5.7%) (Fan, 2017). However, dose levels for LCAR-B38M have not been clearly described.

In general, the dose of CAR T cells varies by different products, indications and protocols; optimal cell doses, number of doses, and infusion timing that provide maximal efficacy with minimal toxicity are areas of active investigation. Two CAR T cell products have been approved so far, Kymriah and YESCARTA, both anti-CD19 CAR T cell products. Kymriah has a dose range for adult patients of 0.6 to 6×10^8 CAR + T cells. YESCARTA target dose is 2×10^6 CAR + T cells per kg body weight, with a maximum of 2×10^8 CAR + T cells. A different anti-BCMA CAR T cell product, bb2121 (Raje, 2019) explores a dose range from 50×10^6 to 800×10^6 BCMA CAR T cells, while at the University of Pennsylvania (Cohen, 2019), a dose range of 1×10^8 to 5×10^8 BCMA CAR T cells given over 3 days as split-dose intravenous infusions (10% of dose given on day 0, 30% on day 1, and 60% on day 2) has been explored. BCMA CAR T cells given over 3 days as split-dose intravenous infusions (10% of dose given on day 0, 30% on day 1, and 60% on day 2) has been explored.

In this study, more than one dose level of JCARH125 could be explored in the Phase 1 anakinra cohort, Phase 2 expansion and Phase 2a portions of study if there is consistent efficacy and acceptable tolerability at multiple dose levels.

2.2. Rationale for Lymphodepletion Chemotherapy

It is widely believed that lymphodepleting chemotherapy improves engraftment and activity of CAR T cells. However, the mechanism by which T-cell engraftment is facilitated by lymphodepleting chemotherapy is not fully understood. The rationale for combining adoptive T-cell immunotherapy with lymphodepleting therapy is multifold. First, lymphodepleting chemotherapy may enhance adoptively transferred tumor-specific T cells to proliferate in vivo through homeostatic proliferation (Grossman, 2004; Stachel, 2004). Second, chemotherapy may reduce or eliminate CD4+CD25+ regulatory T cells, which can suppress the function of tumor-targeted adoptively transferred T cells (Turk, 2004). Third, lymphodepleting chemotherapy prior to adoptive T-cell therapy may enhance the expression of stromal cell-derived factor 1 (SDF-1) in the bone marrow, enhancing the homing of modified T cells to the primary tumor site through binding of SDF-1 with CXCR-4 expressed on the T-cell surface (Pinthus, 2004). Finally, lymphodepleting chemotherapy may further reduce the subject's tumor burden and potentially lower the risk and severity of CRS.

In this study, lymphodepleting chemotherapy will consist of 30 mg/m^2 fludarabine and 300 mg/m^2 cyclophosphamide administered daily for 3 days with reduced dose for subjects with decreased renal function (Section 6.2). The combination of fludarabine and cyclophosphamide has been used for lymphodepletion in other CAR T cell trials with demonstrable CAR T cell expansion, persistence, and antitumor activity and acceptable safety (Kochenderfer, 2015; Turtle, 2016b; Abramson, 2017).

2.3. Rationale for Prophylactic Treatment with Anakinra

The toxicity caused by CAR T cells vary from fever as an only CRS symptom to neurotoxicity, macrophage activating syndrome (MAS) and other post-CAR T cells toxicities. The tocilizumab (Actemra) indication was expanded from its original designation of rheumatoid arthritis (RA) treatment to treating CRS in patients undergoing CAR T treatment. Tocilizumab works by blocking interleukin-6 (IL-6), an inflammatory cytokine. Even though this inhibitor has been quite effective in treatment of CRS in patients receiving CAR T treatment, it doesn't always provide relief from symptoms. CRS may respond to IL-6 receptor blockade but can require further treatment with high dose corticosteroids to curb potentially lethal severity (Maude, 2014a; Park, 2018; Barrett, 2014; Brudno, 2016; Neelapu, 2018).

The pathophysiology of CRS and neurotoxicity suggest that macrophage-produced IL-1 plays a major role in triggering CRS. CRS may also be associated with disseminated intravascular coagulation and it may cause a clinical and pathological picture that is similar to macrophage activating syndrome (MAS) (Hay, 2018; Wolf, 2019).

One of the selective interleukin-1 (IL-1) receptor antagonists (IL-1Ra) is anakinra. Anakinra was approved by the FDA for subjects with moderate to severe active rheumatoid arthritis (RA), in patients 18 years of age or older. IL-1 blockade through IL-1Ra can demonstrably prevent severe CRS while maintaining intact antitumor efficacy (Giavridis, 2018). The benefits of an IL-1 blockade through IL-1Ra are especially intriguing given the latter's ability to cross the blood–brain barrier and therefore reduce the severity of CAR T cell related neurotoxicity (Gutierrez, 1994), unlike tocilizumab (Neelapu, 2018). Anakinra has been proposed in a recent publication for treatment of refractory CRS and also in the setting of MAS/HLH (Shimabukuro-Vornhagen,

2018). As of now, subjects in this clinical trial treated with anakinra had no adverse events attributable to the use of anakinra in this setting.

The potential benefit of prophylactic treatment of anakinra on the onset, incidence and severity of CRS will be investigated.

2.4. Rationale for Study Design

The Phase 1 dose escalation part of this study will utilize a modified toxicity probability interval (mTPI) design (Ji, 2010; Guo, 2017) to determine the safety and tolerability of various JCARH125 dose levels in subjects with R/R MM. The mTPI design uses a Bayesian statistical framework and a beta/binomial hierarchic model to compute the posterior probabilities of three intervals that reflect the relative distance between the toxicity rate of each dose level to help identify an optimally safe dose range with the lowest number of treated subjects possible. The mTPI design has been demonstrated to more frequently select the true MTD for an investigational drug than the traditional 3+3 design (Ji, 2013).

2.5. Justification of Endpoints

The primary objective of the Phase 1 dose escalation portion of the study will be to establish the safety and tolerability of one or more dose levels for JCARH125 in subjects with R/R MM. This will be determined by the incidence and severity of all AEs, including DLTs.

The primary objective for the Phase 1 anakinra cohort will be to evaluate the safety and tolerability of JCARH125 at the at the dose level 3 and/or dose level 3a following prophylactic treatment with anakinra.

The primary endpoint of the Phase 2 portion of the study is ORR, defined as the rate of sCR + CR + VGPR + PR as assessed by an Independent Review Committee (IRC). A key secondary endpoint of Phase 2 is the CR rate, defined as the rate of sCR + CR as assessed by the IRC. Treatment response will be assessed according to the International Myeloma Working Group (IMWG) Uniform Response Criteria (Kumar, 2016). These response criteria are well accepted for use in assessing efficacy in this population.

The primary objective of the Phase 2a portion of the study will be to evaluate the efficacy of JCARH125 at the RP2D(s) in subjects with R/R MM who have relapsed following prior BCMA-directed therapy.

3. STUDY OBJECTIVES AND ENDPOINTS

The objectives and corresponding endpoints for the study are presented in Table 1.

Table 1: Study Objectives and Endpoints

Objective	Endpoints
Phase 1 Dose-Escalation	
Primary	
• To evaluate the safety and tolerability of JCARH125 in subjects with R/R MM • To determine the RP2D(s) of JCARH125 in subjects with R/R MM	• Incidence of DLTs • Incidence and severity of AEs • Incidence and severity of clinically significant laboratory abnormalities
Secondary	
• To evaluate the expansion and persistence (ie, PK) of JCARH125 in peripheral blood	• C_{max}, t_{max}, and AUC of JCARH125 CAR T cells in the blood • Duration of persistence of JCARH125 CAR T cells in the blood
• To assess preliminary antitumor activity of JCARH125	• Overall response rate (defined as sCR, CR, VGPR, or PR) assessed according to IMWG criteria • Complete response rate (defined as sCR or CR) assessed according to IMWG criteria
Phase 1 Anakinra Cohort	
Primary	
• To evaluate the safety and tolerability of JCARH125 at the dose level 3 and/or dose level 3a and to explore the incidence and onset of Grade ≥ 2 CRS in subjects with R/R MM who receive prophylactic treatment with anakinra	• Incidence and severity of AEs • Incidence of Grade ≥ 2 CRS in subjects receiving prophylactic anakinra relative to incidence of Grade ≥ 2 CRS in subjects treated at the RP2D(s) in the Phase 1 dose escalation portion of the trial • Onset of Grade ≥2 CRS in subjects receiving prophylactic anakinra relative to onset of Grade ≥ 2 CRS in subjects treated at the RP2D(s) in the Phase 1 dose escalation portion of the trial • The number and percentage of subjects with no CRS occurring on study days 1, 2, or 3 • Incidence and severity of clinically significant laboratory abnormalities
Secondary	
• To evaluate the expansion and persistence (ie, PK) of JCARH125 in subjects who receive prophylactic treatment with anakinra in peripheral blood	• C_{max}, t_{max}, and AUC of JCARH125 CAR T cells in the blood • Duration of persistence of JCARH125 CAR T cells in the blood

Table 1: Study Objectives and Endpoints (Continued)

Objective	Endpoints
• To assess preliminary antitumor activity of JCARH125 in subjects who receive prophylactic treatment with anakinra	• Overall response rate (defined as sCR, CR, VGPR, or PR) assessed according to IMWG criteria • Complete response rate (defined as sCR or CR) assessed according to IMWG criteria
Phase 2 Single-Agent Expansion	
Primary	
• To evaluate the antitumor activity of JCARH125 at the RP2D(s) in subjects with R/R MM	• Overall response rate (defined as sCR, CR, VGPR, or PR) assessed according to the IMWG criteria in the efficacy analysis set
Secondary	
• To evaluate the CR/sCR rate assessed according to IMWG criteria	• Complete response rate (defined as sCR or CR) as assessed according to IMWG criteria in the efficacy analysis set
• To assess DOR following treatment with JCARH125	• DOR, defined as the time from first response (sCR, CR, VGPR, or PR) to the earlier date of PD or death due to any cause • DOCR, defined as the time from first sCR or CR to the earlier date of PD or death due to any cause
• To evaluate the safety and tolerability of JCARH125 in subjects with R/R MM	• Incidence and severity of AEs • Incidence and severity of clinically significant laboratory abnormalities
• To evaluate OS and PFS	• OS, defined as the time from the JCARH125 infusion until death • PFS, as assessed by IMWG criteria, defined as the time from the JCARH125 infusion until the earliest of date of death or disease progression
• To assess time to response to JCARH125	• TTR, defined as the interval from JCARH125 infusion to the first documentation of sCR, CR, VGPR, or PR • TTCR, defined as the interval from JCARH125 treatment to the first documentation of sCR or CR
• To evaluate expansion and persistence (ie, PK) of JCARH125 in peripheral blood	• C_{max}, t_{max}, and AUC of JCARH125 CAR T cells in the blood • Duration of persistence of JCARH125 CAR T cells in the blood
• To assess HRQoL and HEOR	• Measurement of HRQoL changes as assessed using the EORTC QLQ-C30 and its MM-specific module QLQ-MY20, as well as the EuroQol instrument EQ-5D-5L • Numbers of ICU inpatient days and non-ICU inpatient days and reasons for hospitalization

Table 1: Study Objectives and Endpoints (Continued)

Objective	Endpoints
Phase 2a Prior BCMA-directed Anti-myeloma Therapy Cohort	
Primary	
• To evaluate the antitumor activity of JCARH125 at the RP2D(s) in subjects with R/R MM who had relapsed after prior BCMA-directed therapy	• Overall response rate (defined as sCR, CR, VGPR, or PR) assessed according to the IMWG criteria in the efficacy analysis set
Secondary	
• To evaluate the CR/sCR rate assessed according to IMWG criteria	• Complete response rate (defined as sCR or CR) as assessed according to IMWG criteria in the efficacy analysis set
• To assess DOR following treatment with JCARH125	• DOR, defined as the time from first response (sCR, CR, VGPR, or PR) to the earlier date of PD or death due to any cause • DOCR, defined as the time from first sCR or CR to the earlier date of PD or death due to any cause
• To evaluate the safety and tolerability of JCARH125 in subjects with R/R MM	• Incidence and severity of AEs • Incidence and severity of clinically significant laboratory abnormalities
• To evaluate OS and PFS	• OS, defined as the time from the JCARH125 infusion until death • PFS, as assessed by IMWG criteria, defined as the time from the JCARH125 infusion until the earliest of date of death or disease progression
• To assess time to response to JCARH125	• TTR, defined as the interval from JCARH125 infusion to the first documentation of sCR, CR, VGPR, or PR • TTCR, defined as the interval from JCARH125 treatment to the first documentation of sCR or CR
• To evaluate expansion and persistence (ie, PK) of JCARH125 in peripheral blood	• C_{max}, t_{max}, and AUC of JCARH125 CAR T cells in the blood • Duration of persistence of JCARH125 CAR T cells in the blood
Additional Exploratory Objectives in Phase 1, Phase 1 Anakinra Cohort, Phase 2, and Phase 2a	
[redacted]	

Table 1: Study Objectives and Endpoints (Continued)

Objective	Endpoints
[redacted]	

AE = adverse event; [redacted]; AUC = area under the curve; BCMA = B-cell maturation antigen; C_{max} = maximum concentration; CR = complete response; CRS = cytokine release syndrome; DLT = dose-limiting toxicity; DOCR = duration of complete response; DOR = duration of response; EORTC = European Organization for Research and Treatment of Cancer; HEOR = health economics and outcomes research; HRQoL = health-related quality of life; ICU = intensive care unit; IMWG = International Myeloma Working Group; MM = multiple myeloma; MRD = minimal residual disease; ORR = overall response rate; OS = overall survival; PD = progressive disease; PFS = progression-free survival; PK = pharmacokinetics; PR = partial response; RP2D = recommended Phase 2 dose; R/R = relapsed and/or refractory; sCR = stringent complete response; t_{max} = time to maximum concentration; TTR = time to response; VGPR = very good partial response.

4. STUDY DESIGN AND INVESTIGATIONAL PLAN

4.1. Overall Study Design

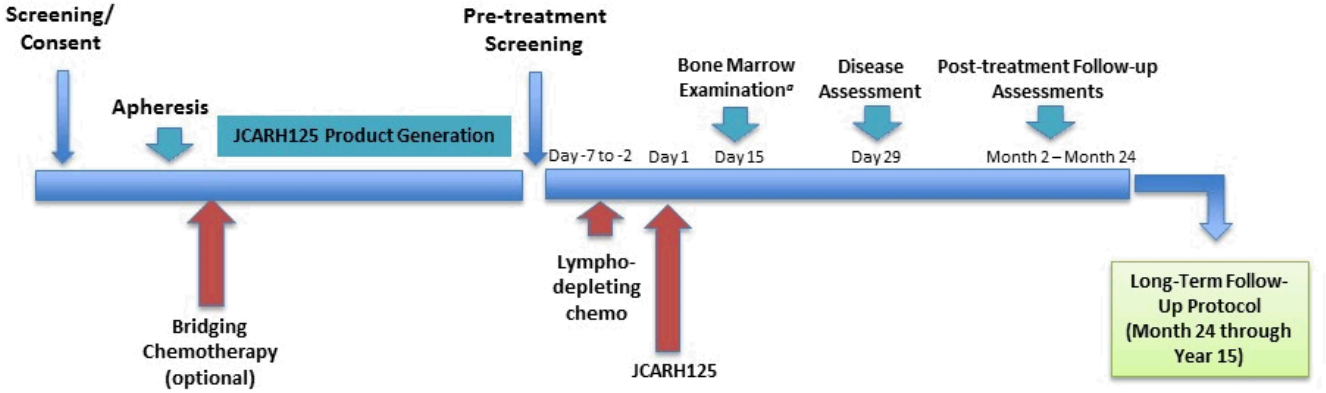
This is an open-label, multicenter, Phase 1/2 study to determine the safety, PK, and antitumor activity of JCARH125 in adult subjects with R/R MM. The Phase 1 dose-escalation portion of the study will evaluate the safety and tolerability of increasing dose levels of JCARH125 in order to identify RP2D(s). The Phase 2a portion of the study will evaluate the antitumor activity of JCARH125 at the RP2D(s) in subjects who have been previously treated with BCMA-directed therapy. The Phase 1 anakinra cohort will evaluate the safety and tolerability of JCARH125 at the dose level 3 and/or dose level 3a in subjects who receive prophylactic treatment with anakinra. The Phase 2 expansion portion of the study will further evaluate the safety, PK, and antitumor activity of JCARH125 at the RP2D(s).

A tumor biopsy sample (bone marrow biopsy, bone marrow aspirate) will be obtained from all subjects during initial screening. A plasmacytoma biopsy sample will also be obtained at screening if feasible (see the H125001 Central Laboratory Manual).

Subjects who meet all eligibility criteria will be enrolled and will undergo leukapheresis to enable JCARH125 product generation. Subjects may receive bridging therapy, excluding experimental and biological agents (eg, daratumumab), after leukapheresis and before lymphodepleting chemotherapy if deemed necessary by the treating physician for disease control during JCARH125 manufacturing (see Section 8.4 for allowed therapies). Bridging therapies must be discontinued at least 14 days prior to initiation of lymphodepletion and subjects must continue to meet eligibility criteria pertaining to adequate organ function, active infections, pregnancy, measurable disease, and washout of prior therapy before initiation of lymphodepleting chemotherapy. If JCARH125 cannot be made from the first leukapheresis product, additional leukapheresis may be allowed after consultation with the Sponsor.

Following successful JCARH125 product generation, subjects will enter the treatment phase and will receive lymphodepletion followed by JCARH125 infusion. Eligibility criteria and disease assessments will be confirmed prior to initiation of lymphodepletion and JCARH125 infusion (see Section 8.5.1). A treatment cycle will include lymphodepleting chemotherapy with fludarabine and cyclophosphamide (see Section 6.2 for regimen), followed by a single dose of JCARH125 administered IV on Day 1. JCARH125 will be administered 2 to 7 days after completion of lymphodepleting chemotherapy unless clinical or logistical circumstances require modification of this timing. Dose adjustments or changes to the lymphodepleting chemotherapy regimen may be indicated due to the subject's creatinine clearance (CrCl) as described in Section 6.2. The sequence of events is depicted in Figure 1.

Figure 1: H125001 Study Schema



[a] For research evaluations

Subjects will be followed under this protocol for 2 years after JCARH125 administration for safety, disease status, additional anticancer therapies, and survival. If disease progression occurs during this 2-year timeframe, subject should still be followed per the Schedule of Evaluations outlined in Appendix A. The number of JCARH125 cells in both peripheral blood and bone marrow samples will be assessed by quantitative polymerase chain reaction (qPCR) from the time of JCARH125 administration until the end of the study. Disease assessments will be performed prior to study treatment, approximately every 4 weeks following JCARH125 administration for the first 6 months, and then every 3 months until 2 years after JCARH125 administration or until disease progression has been confirmed, whichever comes first. Bone marrow biopsy and aspirate will be performed for all subjects for disease response evaluations, PK, and/or research assessments at Day 15, Day 29, Month 3, Month 6, Month 12, Month 18, and Month 24 for confirmation of CR, and in the event of disease progression. Response to JCARH125 will be assessed according to the 2016 IMWG criteria (Appendix B). In Phase 1 and Phase 2a, response to JCARH125 will be assessed by the Investigator. In Phase 2 and for subjects treated in Phase 1 and the Phase 1 anakinra cohort at the RP2D(s), response will be assessed by the Investigator and confirmed by an Independent Review Committee (IRC). Evaluation of the primary efficacy endpoint of ORR in Phase 2 will be based on IRC assessment.

All subjects who receive JCARH125 will be asked to enroll in a separate Celgene-sponsored long-term follow-up (LTFU) study at the time of completion or discontinuation from this study. Subjects who enroll in the LTFU protocol will sign a separate informed consent form and may be followed for up to 15 years after JCARH125 administration as per current FDA guidelines (Food and Drug Administration, 2006a) for long-term JCARH125-related safety and efficacy.

4.2. Phase 1 Dose-Escalation

The JCARH125 dose levels to be evaluated in Phase 1 are provided in Table 2. Dose-escalation/de-escalation will follow a modified toxicity probability interval (mTPI-2) algorithm (Guo, 2017) with a target DLT rate of 30% and an equivalence interval of 25% to 35%. The table in Appendix J provides the dose-escalation and de-escalation guidelines based on the number of subjects treated at a dose level who experience a DLT. Dose-escalation may be halted once one

or more dose levels with acceptable safety and satisfactory antitumor activity has been selected for evaluation in Phase 2 expansion and Phase 2a. A maximum tolerated dose (MTD) may not be defined in this study.

For a dose level to be considered safe, at least 3 DLT-evaluable subjects must have completed the 21-day DLT evaluation period and the level is estimated to be safe per the mTPI-2 algorithm. The decision to open a dose level for enrollment will be made by the Sponsor based on results from the mTPI-2 algorithm after consultations with the Principal Investigators at each site as appropriate.

Table 2: Planned JCARH125 Dose Levels

Dose Level	JCARH125 Dose (CD3+CAR+ cells)
-1	25×10^6
1	50×10^6
2	150×10^6
2a[a]	300×10^6
3	450×10^6
3a[b]	600×10^6
4	800×10^6

[a] Introduced with Protocol Amendment 4 (10 September 2018) as a part of safety measures.
[b] Introduced with Protocol Amendment 5 (31 May 2019) as a possible intermediate dose level.
Note: Intermediate dose levels may be evaluated based on ongoing safety and efficacy data.

The first 3 subjects treated in the Phase 1 dose escalation portion of the study will be treated with JCARH125 at Dose Level 1 (50×10^6 CD3+CAR+ cells). Within the first dose cohort, treatment of the first 3 subjects will be staggered by a minimum of 14 days. At each higher dose level, treatment of the first 3 subjects within the dose cohort will be staggered by a minimum of 7 days. Staggering of subjects in a dose cohort may be lifted after a minimum of 3 subjects have been treated in that dose cohort, have completed the 21-day DLT evaluation period, and the dose level is determined to be safe according to the mTPI-2 algorithm.

A maximum of 3 subjects will initially be treated at a dose level. If none of these 3 subjects experience a DLT, the dose may be escalated to the next higher dose level. If 1 of 3 subjects experiences a DLT at a dose level, then additional subjects will be enrolled at this dose level and dose-escalation/de-escalation decisions will be made per the mTPI-2 algorithm after the DLT data for these additional subjects are available. If 2 of 3 subjects experience a DLT at a dose level, then the dose will be de-escalated to the next lower dose level. If all 3 subjects experience a DLT at a dose level, the dose will be de-escalated and this dose and all higher doses will be removed from further evaluation in the trial. The mTPI-2 decision table is provided in Appendix J.

To be considered evaluable for DLT, a subject must have received the conforming JCARH125 cell product at the assigned dose of JCARH125 and completed the 21-day evaluation period or experienced a DLT prior to completing the 21-day evaluation. Subjects who are not evaluable for DLT will be replaced.

Based on the cumulative safety and antitumor activity data from subjects treated in Phase 1, one or more dose levels may be selected for further evaluation in the Phase 2 expansion and Phase 2a portions of the trial (the RP2D). The RP2D(s) will be selected by the Sponsor in collaboration with the Investigators. It is not necessary for the MTD to be determined per the mTPI algorithm to select the dose level(s) to be evaluated in Phase 2.

If a dose level is deemed to be safe (ie, 'S' to stay at the same dose or 'E' to escalate to the next higher dose level) per the mTPI-2 algorithm, the dose level can be expanded to treat a maximum number of 30 subjects. A sample size of 14 to 30 subjects at a dose level will provide a high probability of excluding an overly toxic dose level from RP2D consideration. Dose expansion at a dose level may also be stopped for lack of efficacy, defined as the lower 80% 1-sided confidence interval for ORR less than 30% based on a minimum of 10 efficacy-evaluable subjects.

4.3. Dose-Limiting Toxicities

Dose-limiting toxicities in this study are defined as AEs that occur within 21 days following JCARH125 infusion and meet any of the following criteria:

- Treatment-emergent Grade ≥ 3 allergic reactions related to JCARH125
- Treatment-emergent Grade 3 seizures, regardless of attribution, that do not resolve to Grade ≤ 2 within 3 days in subjects who have no evidence of central nervous system (CNS) involvement of MM or other CNS pathology
- Treatment-emergent autoimmune toxicity Grade ≥ 3, regardless of attribution (excluding B-cell aplasia)
- Treatment-emergent Grade 3 CRS that does not resolve to Grade ≤ 2 within 72 hours
- Any other treatment-emergent Grade 3 AE related to JCARH125 that does not resolve to Grade ≤ 2 within 7 days (see exceptions listed below)
- Any treatment-emergent Grade 4 AE related to JCARH125 that does not resolve to Grade ≤ 2 within 7 days (see exceptions listed below)
- Treatment-emergent Grade 4 CRS of any duration
- Any treatment-emergent Grade 5 toxicity not due to the underlying malignancy

The following will not be considered DLTs:

- Non-hematologic AEs:
  - Grade 4 infusional toxicities that are reversible to Grade ≤ 2 within 8 hours
  - Grade 3 fatigue lasting ≤ 7 days
  - Fever of any grade, including febrile neutropenia
  - Grade 4 increase in transaminases for ≤ 7 days
  - Grade 3 tumor lysis syndrome (TLS) for ≤ 2 weeks or Grade 4 TLS for ≤ 7 days

  - Grade 4 hypotension (without other CRS symptoms) requiring a single vasopressor for support that resolves to Grade < 3 in ≤ 72 hours
  - Grade 3 or 4 CRS with hypotension alone requiring a low dose of a single vasopressor (as defined by Lee et al [Lee, 2014]) for support (not requiring intubation) that resolves to Grade < 3 in ≤ 72 hours
  - Grade 3 chills
  - Grade 3 or 4 asymptomatic, non-hematological clinical laboratory abnormalities that return to Grade ≤ 2 within 7 days or electrolyte abnormalities that resolve with replacement
  - Grade 3 diarrhea lasting ≤ 72 hours
  - Grade 3 nausea/vomiting lasting ≤ 72 hours
- Hematologic AEs:
  - Grade 3 neutropenia of any duration or Grade 4 neutropenia lasting ≤ 28 days
  - Grade 3 or 4 lymphopenia of any duration
  - Grade 3 or 4 leukopenia of any duration
  - Grade 3 thrombocytopenia of any duration or Grade 4 thrombocytopenia lasting ≤ 28 days
  - Grade 3 anemia of any duration or Grade 4 anemia lasting ≤ 28 days

The timing and severity of AEs will be reviewed continuously with study Investigators and on a regular basis with the Data Safety Monitoring Board (DSMB). In the event that AEs meeting DLT criteria occur beyond the DLT evaluation period, the DLT window may be extended following discussion with the Investigators.

4.4. Phase 1 Anakinra Cohort

The primary objective of the Phase 1 anakinra cohort will evaluate the safety and tolerability of JCARH125 at the dose level 3 and/or dose level 3a in subjects with R/R MM who received a prophylactic treatment with anakinra. The potential benefit of prophylactic treatment with anakinra on the onset, incidence and severity of CRS will be investigated.

Subjects will receive 2 doses of 100 mg anakinra administered subcutaneously (SC), one the night before and one in the morning, 3 hours before JCARH125 infusion. Subjects will continue with anakinra treatment for 5 consecutive days at a dose of 100 mg SC. In the case of CRS (any grade) onset, 100 mg anakinra SC should be administered twice daily until CRS resolution. Anakinra should be administered at approximately the same time every day. In the case of CRS worsening and/or in case of onset of neurological toxicity, the toxicity management guidelines from the protocol should be followed (see Appendix D).

If prophylactic administration of anakinra shows a positive effect on the onset, incidence and severity of CRS, prophylactic treatment with anakinra may be subsequently implemented in the Phase 2 dose expansion portion of the trial.

4.5. Phase 2a – Subjects with Prior BCMA-directed Anti-myeloma Therapy Cohort

The Phase 2a cohorts will evaluate the safety and tolerability of JCARH125 administered at the RP2D(s) in subjects who have been previously treated with BCMA-directed anti-myeloma therapy. The primary objective of these cohorts is to determine the efficacy of JCARH125 at the RP2D(s) in this particular population of patients.

In the Phase 2a portion of the study, 3 separate cohorts of subjects with exposure to prior BCMA-directed anti-myeloma therapy including TCE, ADC, or CAR T-cell therapies will be treated at the RP2D(s) identified in Phase 1.

Cohort 1: 14 subjects who have been exposed to prior BCMA-directed CAR T-cell therapy

Cohort 2: 14 subjects who have been exposed to prior BCMA-directed TCE therapy

Cohort 3: 14 subjects who have been exposed to prior BCMA-directed ADC therapy

4.6. Phase 2 Expansion

Phase 2 is an expansion stage to further evaluate safety, PK, and antitumor activity of JCARH125 administered at the RP2D(s). The primary objective of this part of the study is to evaluate the efficacy of JCARH125 administered at the RP2D(s).

In the Phase 2 part of the study, subjects will be treated at the RP2D(s) identified in Phase 1. The primary analysis population for evaluation of JCARH125 efficacy (ie, the efficacy analysis set) will include all subjects treated at the RP2D(s) in Phase 2 expansion, as well as subjects treated at the RP2D(s) in Phase 1 dose escalation and in the Phase 1 anakinra cohort, who have measurable disease as determined by the central laboratory at the last disease assessment prior to JCARH125 infusion and receive conforming JCARH125 product. The efficacy analysis set will include at least 75 subjects who are evaluable for both safety and efficacy (as defined in Section 10.2.3.1).

4.7. Study Duration and Duration of Subject Participation

The enrollment period is expected to take approximately 36 months and the follow-up period for each subject is approximately 24 months after JCARH125 administration. Thus, the total duration of the study is expected to be approximately 60 months.

The expected duration of participation for subjects who complete the study will be approximately 26 months. All subjects who receive JCARH125 will be eligible to enroll in a separate Celgene-sponsored LTFU protocol after completion of this study or earlier discontinuation, per health authority regulatory guidelines, currently up to 15 years after JCARH125 administration.

4.8. Criteria for Pausing the Study During Phase 1 Dose Escalation, Phase 1 Anakinra Cohort, and Phase 2a prior BCMA-directed Anti-myeloma Therapy Cohort

Further enrollment or treatment of the subjects in any or all appropriate cohorts will be paused pending notification of the DSMB and appropriate regulatory authorities if any subject experiences any of the following events within 30 days of a JCARH125 infusion:

- Life-threatening (Grade 4) toxicity attributable to JCARH125 that is unexpected and unrelated to chemotherapy
- Expected toxicities that would not lead to study interruption include Grade 4 CRS, neurotoxicity (eg, confusion, aphasia, seizures, convulsions, lethargy, and/or altered mental status), fever, hypotension, hypoxia, TLS, and disseminated intravascular coagulation. In addition, ICU admission, the need for dialysis, and/or the need for mechanical ventilation are also expected. These expected toxicities may also result in secondary toxicities of Grade 4 renal toxicity, hepatic toxicity, or other organ involvement, each of which also would not lead to study interruption. A Grade 4 toxicity that is not considered to be a DLT (refer to listed exceptions in Section 4.3) will not lead to study interruption.
- An unacceptably high incidence, across multiple dose levels or after at least 10 subjects have been treated at the RP2D(s), of expected Grade 4 toxicities, including Grade 4 CRS (> 40%), Grade 4 neurotoxicity (> 30%), Grade 4 renal toxicity not associated with disease progression (> 30%), and Grade 4 hepatotoxicity (> 30%), attributable to JCARH125 or chemotherapy
- Death related to JCARH125 therapy

4.9. Criteria for Terminating the Study Prematurely

Further enrollment or treatment of subjects in any or all appropriate cohorts will be terminated for any of the following reasons:

- Any subject develops confirmed replication-competent lentivirus (RCL) during the study
- The Sponsor, Institutional Review Board (IRB)/Independent Ethics Committee (IEC), or DSMB decides that subject safety may be compromised by continuing the study
- The Sponsor decides to discontinue the development of JCARH125 entirely (or for the indications under evaluation in a given cohort)

4.10. Study Completion

A subject is considered to have completed the study if he/she has completed the last scheduled visit shown in the Schedule of Evaluations (Appendix A).

The end of the study is defined as the date of the last scheduled assessment shown in the Schedule of Evaluations for the last subject in the trial.

4.11. Study Oversight

4.11.1. Data Safety Monitoring Board

An independent 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. In addition, in the event of a toxicity that meets the criteria for pausing the study (see Section 4.8), the DSMB will be convened to evaluate the comprehensive safety data and to make a recommendation for study continuation, modification, or termination. The DSMB has been assembled under a dedicated charter specifically developed for safety oversight of Juno-sponsored studies.

Subject safety will be evaluated as specified in the DSMB charter. The DSMB will provide advice to the Sponsor and study investigators as outlined in the DSMB charter. Juno will provide a DSMB review summary to the study investigators for submission to the site's IRB/IEC within 10 working days of receipt of the statement.

4.11.2. Independent Review Committee

An IRC will determine response and progression status for all subjects treated in the Phase 2 expansion portion of the study, as well as subjects in the Phase 1 dose escalation, Phase 1 anakinra cohort and Phase 2a portion of the study who were treated with JCARH125 at the RP2D(s). The IRC will include qualified physicians; the details of the review processes and methods will be described in a charter developed by Juno.

Clinical management of study subjects will be based upon Investigator assessment. The findings of the IRC will serve as the basis for the primary analyses of ORR, CR, DOR, and other endpoints based on IMWG criteria in the Phase 2 portion of the study.

4.12. Suspension or Early Termination of the Study

The study can be suspended or terminated at any time by the Sponsor, the Food and Drug Administration (FDA), the DSMB, or an IRB/IEC for any reason. Circumstances that may warrant suspension or termination include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to subjects (see Section 4.8 and Section 4.9 for criteria for pausing and stopping the study, respectively)
- Determination of futility
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable

If the study is suspended or terminated for safety reasons, Juno will promptly inform the Investigator, and will also inform the regulatory authorities of the suspension or termination of the study and the reasons for the action. The Investigator may be informed of additional procedures to be followed to ensure adequate protection of subjects. The Investigator will be responsible for promptly informing IRBs/IECs, other applicable regulatory committees, and

study subjects of the suspension or early termination of the trial, including the reasons for suspension or termination and any other regulatory committee as applicable.

The study may resume once concerns about safety, protocol compliance, and data quality are addressed to the satisfaction of the Sponsor, IRB, and/or FDA.

5. STUDY POPULATION

5.1. Inclusion Criteria

Subjects must meet all of the following criteria to be enrolled into this study:

1. Age ≥ 18 years at the time of consent
2. Signed informed consent form
3. Diagnosis of multiple myeloma (MM) with relapsed and/or refractory disease. Subjects must have received at least 3 prior anti-myeloma treatment regimens (note: induction with or without bone marrow transplant and with or without maintenance therapy is considered one regimen). Subjects must be refractory to the last anti-myeloma treatment regimen prior to entering the study. Refractory myeloma is defined as non-responsiveness (best response of ≤ stable disease) to last anti-myeloma treatment regimen or documented progressive disease during or within 60 days (measured from the last dose) of completing treatment with the last anti-myeloma treatment regimen before study entry. Subjects must have previously received all of the following therapies:
    a. Autologous stem cell transplant.
    b. A regimen that included an immunomodulatory agent (eg, thalidomide, lenalidomide, pomalidomide) and a proteasome inhibitor (eg, bortezomib, carfilzomib, ixazomib), either alone or in combination. Subjects must have undergone at least 2 consecutive cycles of treatment for each regimen unless progressive disease was the best response to the regimen.
    c. Anti-CD38 (eg, daratumumab) as part of a combination regimen or as a monotherapy.

    Subjects who have received prior allogeneic stem cell transplant or donor lymphocyte infusion (DLI) at least 100 days before enrollment with no signs of acute or chronic graft-versus-host disease (GVHD) will be considered eligible.

    Subjects who were not candidates to receive one or more of the above treatments (ie, contraindicated) are eligible; the reason for not receiving treatment must be clearly documented in the case report form (CRF).
4. Subjects must have measurable disease as determined by the central laboratory defined as meeting at least one of the criteria below:
    a. Serum M-protein ≥ 1 g/dL
    b. Urine M-protein ≥ 200 mg/24 hour
    c. Involved serum free light chain (sFLC) level ≥ 10 mg/dL with abnormal κ/λ ratio (light chain disease is acceptable only for subjects without measurable disease in the serum or urine)

5. Subject must be willing to provide a fresh bone marrow biopsy sample during Screening (and at Pre-treatment Screening, if required).
6. Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1 (Appendix F).
7. Adequate organ function, defined as:
   a. Adequate renal function, defined as calculated creatinine clearance (Cockcroft-Gault) ≥ 60 mL/min without the assistance of hydration
      i. Subjects must not have received IV rehydration within 3 days of renal function assessment.
   b. Adequate bone marrow function, defined as absolute neutrophil count (ANC) ≥ 1000 cells/mm^3, hemoglobin (Hb) ≥ 8 g/dL, and platelet count ≥ 50,000/mm^3. Transfusions and growth factors must not be used to meet these requirements at initial Screening.
      i. Subjects must not have received growth factors within 14 days of initial Screening
      ii. Subjects must not have received red blood cell (RBC) transfusions within 21 days of initial Screening
      iii. Subjects must not have received platelet transfusions within 7 days of initial Screening
   c. Adequate hepatic function, defined as:
      i. Alanine aminotransferase (ALT) ≤ 3 × ULN
      ii. Aspartate aminotransferase (AST) ≤ 3 × ULN
      iii. Total bilirubin < 2.0 mg/dL (or < 3.0 mg/dL for subjects with documented Gilbert's syndrome)
      iv. International ratio (INR) or partial thromboplastin time (PTT) ≤ 1.5 × ULN
   d. Adequate pulmonary function, defined as saturated oxygen (SaO_2) ≥ 92% on room air
   e. Adequate cardiac function, defined as left ventricular ejection fraction (LVEF) ≥ 40% as assessed by echocardiogram (ECHO) or multiple uptake gated acquisition (MUGA) scan performed within 8 weeks prior to initial Screening
8. Subject either currently has central vascular access or is a candidate to receive central vascular access or peripheral vascular access for leukapheresis procedure
9. Subjects must be at least 100 days since autologous stem cell transplant (ie, Day 0, receipt of hematopoietic stem cells) at the time of initial Screening, if performed.
10. Recovery to Grade ≤ 1 or baseline of any non-hematological toxicities due to previous therapy, except alopecia and peripheral neuropathy
11. Females of reproductive potential (defined as all females physiologically capable of becoming pregnant) must agree to use one highly effective method of contraception from screening until at least 12 months following lymphodepleting chemotherapy. There are insufficient exposure data to provide any recommendation concerning the duration of contraception following treatment with JCARH125. Any decision regarding contraception after JCARH125 infusion should be discussed with the treating physician. (see Section 5.3)

12. Females of reproductive potential must have 2 negative pregnancy tests as verified by the Investigator (one negative serum beta-human chorionic gonadotropin [ß-hCG] pregnancy test result at screening, and within 7 days prior to the first dose of lymphodepleting chemotherapy). This applies even if the subject practices true abstinence* (see Section 5.3 for details) from heterosexual contact.

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

13. Males who have partners of childbearing potential must agree to use an effective barrier contraceptive method from initiation of lymphodepleting chemotherapy and for at least 12 months and should not donate semen or sperm during the entire study period and for at least 12 months following lymphodepleting chemotherapy (see Section 5.3).

14. Phase 2a prior BCMA-directed anti-myeloma therapy cohort only – Subjects with R/R MM who have been previously treated with prior BCMA-directed anti-myeloma therapy, achieved at least a partial response (PR) per IMWG response criteria and subsequently progressed on the following treatment:

    a. Subjects who have received prior BCMA-directed CAR T-cell therapy. The last CAR T-cell therapy must have been received at least 6 months prior to JCARH125 study enrollment (screening).
    b. Subjects who have received prior BCMA-directed TCE therapy.
    c. Subjects who have received prior BCMA-directed ADC therapy.
    Subjects with prior BCMA-directed anti-myeloma therapy are not required to have received at least 3 prior anti-myeloma treatment regimens and do not have to be refractory to the last anti-myeloma regimen to be eligible for this trial.

5.2. Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from participation in this study:

1. Subjects with known active or history of CNS involvement by malignancy
2. Subjects with solitary plasmacytoma; active or history of plasma cell leukemia (PCL); Waldenstrom's macroglobulinemia; POEMS syndrome (Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal plasmaproliferative disorder, Skin changes); or symptomatic amyloidosis
3. Subjects who are considered eligible to receive and have refused an autologous stem cell transplant
4. History of another primary malignancy that has not been in remission for at least 3 years. The following are exempt from the 3-year limit: non-melanoma skin cancer, curatively treated localized prostate cancer, cervical carcinoma in situ on biopsy or a squamous intraepithelial lesion on Pap smear, and in situ breast cancer that has been completely resected.
5. Require systemic immunosuppressive therapies (eg, calcineurin inhibitors, methotrexate, mycophenolate, rapamycin, thalidomide, immunosuppressive antibodies such as anti-IL-6 or anti-IL-6 receptor [IL-6R])

6. Prior CAR T cell or other genetically-modified T-cell therapy (not applicable to Phase 2a cohorts)
7. Prior treatment with a BCMA-directed agent (not applicable to Phase 2a cohorts)
8. Human immunodeficiency virus (HIV) infection positive subjects
9. Hepatitis B virus (HBV) or hepatitis C virus (HCV) infection as indicated by positive serology or nucleic acid testing. Subjects who are solely hepatitis B surface antibody (HBsAb)-positive are eligible.
10. Untreated or active infection at the time of initial Screening, at the time of leukapheresis, or within 72 hours before lymphodepletion, or 5 days before JCARH125 infusion. Subjects with ongoing use of prophylactic antibiotics, antifungals, or antivirals are eligible if no evidence of active infection.
11. History of any one of the following cardiovascular conditions within the 6 months prior to initial Screening: Class III or IV heart failure as defined by the New York Heart Association (NYHA), myocardial infarction, unstable angina, uncontrolled or symptomatic atrial arrhythmias, any ventricular arrhythmias, or other clinically significant cardiac disease
12. History or presence of clinically relevant CNS pathology such as epilepsy, seizure, aphasia, stroke, severe brain injuries, dementia, Parkinson's disease, cerebellar disease, organic brain syndrome, or psychosis.
13. History of Grade ≥ 2 hemorrhage within 30 days or requirement for treatment with chronic, therapeutic doses of anticoagulants (eg, warfarin, low molecular weight heparin, or Factor Xa inhibitors)
14. Pregnant or nursing (lactating) women
15. Treatment with the following therapies within the specified time period:
    a. Monoclonal antibodies (anti-CD38 and anti-SLAMF7 antibody) within 4 weeks prior to leukapheresis
    b. Any other systemic therapy approved for the treatment of MM within 14 days before leukapheresis or within 14 days before lymphodepleting chemotherapy
    c. Any experimental therapy within 8 weeks (for biologics) or 5 half-lives (for small molecules) before leukapheresis
    d. Therapeutic doses of corticosteroids (defined as > 20 mg/day prednisone or equivalent) within 14 days before leukapheresis. Physiologic replacement, topical, and inhaled steroids are permitted.
    e. Radiation to a single lesion within 14 days before leukapheresis.
    f. Radiation that includes a large bone marrow field such as the pelvis or sternum within 6 weeks before leukapheresis
16. Plasmapheresis within 14 days before leukapheresis
17. Any medical psychological, familial, sociological, or geographical conditions that do not permit compliance with the protocol, as judged by the Investigator; any medical or psychiatric conditions or laboratory abnormalities that could jeopardize subject safety, as

judged by the Investigator or Sponsor Medical Monitor; or unwillingness or inability to follow the procedures required in the protocol

18. Use of any live vaccines against infectious diseases within 8 weeks before JCARH125 infusion
19. Subjects with known hypersensitivity to *E. coli*-derived proteins (only applicable for subjects getting prophylactic anakinra)
20. History of severe immediate hypersensitivity reaction to any of the protocol-mandated and recommended agents used in this study

5.3. Childbearing Potential and Contraception Requirements

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

1. Achieved menarche at some point, or
2. Has not undergone a hysterectomy or bilateral oophorectomy, or
3. Has not been naturally post-menopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 12 consecutive months (ie, has had menses at any time in the preceding 12 consecutive months).

Female study participants of reproductive potential must have 2 negative pregnancy tests as verified by the Investigator (one negative serum beta-human chorionic gonadotropin [ß-hCG] pregnancy test result at screening, and within 7 days prior to the first dose of lymphodepleting chemotherapy). This applies even if the subject practices true abstinence* from heterosexual contact.

Female subjects with reproductive potential who are not sexually abstinent must agree to use one highly effective method of contraception from screening until at least 12 months following lymphodepleting chemotherapy. There are insufficient exposure data to provide any recommendation concerning the duration of contraception following treatment with JCARH125. Any decision regarding contraception after JCARH125 infusion should be discussed with the treating physician.

Male subjects who have partners of childbearing potential must agree to use an effective barrier contraceptive method from initiation of lymphodepleting chemotherapy and for at least 12 months after and should not donate semen or sperm during the entire study period and for at least 12 months after lymphodepleting chemotherapy.

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

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

5.4. Removal of Subjects from Treatment or Study

At the time of consent, subjects will be advised that they are free to withdraw from the study at any time for any reason; however, all subjects who have received treatment with JCARH125 will be encouraged to continue all study evaluations through the End-of-Study (EOS) visit and to participate in the LTFU study. The Sponsor must be notified if a subject is withdrawn from the study, and the reason(s) for withdrawal must be documented.

5.4.1. Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but are determined not to meet all eligibility criteria required to participate in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, reason for screen failure, and, if applicable, any serious AEs (SAEs). Biopsy samples obtained during Screening for subjects who are determined to be screen failures may be used by the Sponsor for exploratory research.

Individuals who do not meet the criteria for participation in this study (screen failures) may be rescreened.

5.4.2. Subject Withdrawal from Study

A subject may be withdrawn from the study for any of the following reasons:

- Subject did not receive JCARH125 due to disease-related complications
- Subject did not receive JCARH125 due to interim treatment-related toxicities
- Subject no longer meets eligibility criteria for other reasons (not related to disease or interim treatment)
- JCARH125 could not be manufactured
- Subject withdrawal of consent
- Study termination by Sponsor, an IRB/IEC, a regulatory authority or based on a determination by the DSMB
- Lost to follow up
- Death
- Other (specified on CRF)

If a subject is withdrawn prematurely from the study, the reason for study discontinuation must be recorded in the CRF and the Principal Investigator should ask the subject to participate in the Celgene-sponsored LTFU protocol. The discussion between the subject and the Investigator must be documented in the subject source documents.

5.4.3. Replacement of Study Subjects

Subjects in Phase 1 who sign the informed consent form but do not receive JCARH125 may be replaced. The reason(s) for not receiving JCARH125 must be recorded in the CRF. Subjects in Phase 1 who are not evaluable for DLT (see Section 10.2.1.4 for criteria for inclusion in the DLT-evaluable analysis set) may also be replaced. Subject numbers will not be re-used. Efficacy classification of subjects who undergo leukapheresis but do not receive JCARH125 is described in Section 10.3.6.

6. STUDY TREATMENTS

6.1. Therapy for Disease Control during JCARH125 Manufacturing

At the Investigator's discretion, subjects may receive bridging therapy for disease control while their JCARH125 product is being manufactured (see Section 8.4 for allowed therapies).

6.2. Lymphodepleting Chemotherapy

Lymphodepleting chemotherapy will consist of 3 days of fludarabine (30 mg/m^2) and cyclophosphamide (300 mg/m^2) and must be completed between 2 days (≥ 48 hours) and 7 days prior to the JCARH125 infusion. The recommended order and timing of administration is as follows:

1. The IV hydration is 1 L of 0.9% NaCl given at 500 mL/h starting 2 hours prior to cyclophosphamide
2. Fludarabine 30 mg/m^2 IV over 30 minutes or per institutional standard
3. Cyclophosphamide 300 mg/m^2 IV over 60 minutes
4. Additional 1 L of 0.9% NaCl given at 500 mL/h

Lymphodepleting chemotherapy should be withheld if the calculated CrCl (Cockcroft-Gault; Appendix D) is < 60 mL/min or radioisotope glomerular filtration rate (GFR) is <60 mL/min/1.73 m^2. Delay of lymphodepleting chemotherapy by more than 14 days from the Pre-treatment screening start date requires discussion with the Sponsor and may require rescreening. If lymphodepleting chemotherapy had to be delayed for reasons previously discussed with the Sponsor Medical Monitor, and if the delay was not longer than 14 days, please refer to Appendix A for which safety assessments have to be repeated. Disease assessments do not need to be repeated unless there is clinical evidence of progression. Safety assessments should be conducted per the Schedule of Evaluations in Appendix A.

Subjects who cannot receive lymphodepletion within 8 weeks after leukapheresis must be rescreened and safety and efficacy assessments must be repeated. Disease assessments as part of pre-treatment screening may be reduced for those subjects following discussion with the Sponsor Medical Monitor.

Subjects with CrCl between 60 and 70 mL/min should have a 20% reduction of fludarabine.

Antiemetic therapy, except dexamethasone or other steroids, may be given prior to lymphodepleting chemotherapy per institutional practice. Mesna may be used for subjects with a history of hemorrhagic cystitis per institutional practice.

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

6.3. Anakinra (for Subjects Treated with Prophylactic Anakinra)

Anakinra is an interleukin-1 receptor antagonist indicated for the reduction in signs and symptoms and slowing the progression of rheumatoid arthritis (RA) in patients 18 years of age or older at the recommended dose of 100 mg/day administered daily by SC injection. Anakinra is also indicated for cryopyrin-associated periodic syndromes (CAPS), with a phenotype of neonatal-onset multisystem inflammatory disease (NOMID).

The potential benefit of prophylactic treatment with anakinra on the onset, incidence and severity of CRS will be investigated.

Subjects will receive 2 doses of 100 mg anakinra SC, one the night before and one 3 hours before JCARH125 infusion. Subjects will continue with anakinra treatment for 5 consecutive days at a dose of 100 mg SC. In the event of CRS onset, 100 mg anakinra SC should be administered twice daily until CRS resolution. Anakinra should be administered at approximately the same time every day. In the event of worsening CRS and/or in case of onset of neurological toxicity, the toxicity management guidelines from the protocol should be followed (see Appendix D). If prophylactic treatment with anakinra shows a positive effect on the onset, incidence and severity of CRS, prophylactic anakinra may be implemented in the Phase 2 portion of the trial.

Anakinra has been associated with an increased incidence of serious infections (2%) vs. placebo (< 1%) in clinical trials in rheumatoid arthritis. Treatment with anakinra should not be initiated in patients with severe active infections. The safety and efficacy of anakinra in immunosuppressed patients or in patients with chronic infections have not been evaluated.

Drugs that affect the immune system by blocking tumor necrosis factor (TNF) have been associated with an increased risk of reactivation of latent tuberculosis (TB). It is possible that taking drugs such as anakinra that blocks IL-1 increases the risk of TB or other atypical or opportunistic infections. The most common side effects include mild to moderate swelling, redness, or pain at the injection site. Rare and/or serious side effects include allergic reaction, serious infections, and decrease in white blood cell counts. Refer to the package insert for further details on administration of this agent.

6.4. Investigational Product: JCARH125

JCARH125 is a CAR T cell product composed of autologous CD4+ and CD8+ T-cell populations that have been transduced with a genetically-engineered, replication-incompetent, self-inactivating lentiviral vector to express a BCMA-specific CAR comprising a human BCMA-specific scFv, an [redacted] hinge region, [redacted] transmembrane domain, a CD137 (4-1BB) costimulatory domain, and a CD3ζ signaling domain. [redacted]

The drug product is provided as a combined CD8+ and CD4+ frozen T-cell suspension in a formulation containing DMSO for IV administration. Additional details of product formulation, packaging, labeling, tracking, accountability, preparation, administration, disposal, and destruction are provided in the JCARH125 Product Administration Manual.

6.4.1. Dose and Schedule

JCARH125 will be administered as an IV infusion at the dose level to which the subject is assigned 2 to 7 days after completion of lymphodepleting chemotherapy. The list of planned JCARH125 dose levels to be investigated is provided in Section 4.2.

6.4.2. Pre-medication

All subjects will receive the following pre-medications approximately 30 to 60 minutes prior to JCARH125 infusion: acetaminophen (650 mg orally [PO]) or diphenhydramine (25 to 50 mg PO or IV), or both at the discretion of the Investigator. These medications may be repeated every 6 hours as needed based on the Investigator's assessment of symptoms. Pre-medication with steroids is not allowed (see Section 6.8).

6.4.3. JCARH125 Preparation and Administration

Each JCARH125 dose consists of CD3+ CAR+ T cells. The subject must be continuously monitored during IV administration of JCARH125. Assessments performed on the day of administration are described in Section 8.5.3 and Appendix A.

Additional information is provided in the JCARH125 Product Administration Manual.

6.4.4. Overdose

Overdose, as defined for this protocol, refers to lymphodepleting chemotherapy with fludarabine/cyclophosphamide (Flu/Cy), anakinra or JCARH125. On a per-dose basis, an overdose is defined as the following amount over the protocol-specified dose of these drug(s) assigned to a given subject, regardless of any associated AEs or sequelae:

- PO: any amount over the protocol-specified dose
- IV: 10% over the protocol-specified dose

On a schedule or frequency basis, an overdose is defined as anything more frequent than the protocol-required schedule or frequency. On an infusion rate basis, an overdose is defined as any rate faster than the protocol-specified rate.

Complete data about drug administration, including any overdose, regardless of whether the overdose was accidental or intentional, should be reported in the CRF. See Section 9 for the reporting of AEs associated with overdose.

6.5. Avoidance of Bias

This is an open-label study. Potential bias will be reduced by the use of an IRC (described in Section 4.11.2) for centralized review of efficacy assessments as per the IRC charter for all subjects in Phase 2 and for subjects treated in Phase 1 and in the Phase 1 anakinra cohort with JCARH125 at the RP2D(s).

6.6. Recommended Supportive Care, Additional Treatment, and Monitoring

Because of the risk of CRS, subjects treated on this protocol should initially remain within approximately 60 minutes of the participating institution for 21 days after infusion with JCARH125. The Sponsor may decide to remove the proximity restriction based upon cumulative safety data.

- **Acute infusion reactions** may occur with administration of JCARH125. Guidelines for the treatment of acute T-cell infusion reactions are provided in Section 7.7.
- **TLS treatment and TLS prophylaxis** are strongly recommended for subjects at risk for TLS, per institutional or clinical standards. Guidelines for the treatment of TLS are provided in Section 7.8.
- **CRS management** and supportive care are detailed in Appendix D
- **Infections** should be ruled out when a subject develops fever and/or if laboratory findings indicate possible ongoing infection. In those cases, the subject should be monitored as per institutional or standard clinical practice. The use of prophylactic or empiric anti-infective agents (eg, trimethoprim/sulfamethoxazole for pneumocystis pneumonia [PCP] prophylaxis, broad-spectrum antibiotics, antifungal agents, or antiviral agents for febrile neutropenia) is recommended per institutional or standard clinical practice. The use of prophylactic or empiric anti-infective agents is especially recommended in subjects presenting with prolonged and/or recurrent cytopenias, especially in conjunction with hypogammaglobulinemia, CD4 T-cell count of < 200/μL, and/or recent use of corticosteroids, and subjects with a history of repetitive and/or recent infections. Guidelines for fever and infection assessments, and infection prophylaxis are provided in Section 7.2 and Section 7.4, respectively.
- **Neurologic toxicities (NT)** – Levetiracetam or alternative anti-seizure medication should be considered for seizure prophylaxis. Management of neurologic events and prophylactic treatment measures are detailed in Appendix D and Section 7.5.
- **Macrophage activation syndrome (MAS)** may occur with clinical manifestations and laboratory findings that can considerably overlap with CRS. Subjects treated with JCARH125 should be monitored for MAS. More information including considerations for treatment are provided in Section 7.6.
- **Granulocyte colony-stimulating factor (G-CSF) and transfusions of blood and blood products** – The use of red blood cells and platelet transfusions, and/or colony-stimulating factors is permitted after determination of eligibility at initial Screening, per institutional or clinical standards. However, a short-acting G-CSF, eg, filgrastim, is prohibited starting 7 days prior to JCARH125 infusion to 7 days after the infusion. A long-acting G-CSF (eg, pegfilgrastim) is prohibited starting 11 days prior to JCARH125 infusion to 7 days after the infusion. Prophylaxis may be provided for lymphopenia and/or neutropenia.
- **IV rehydration** is prohibited within 3 days prior to renal function assessment at the time of eligibility determination at initial Screening.

Hospitalization is required for all subjects in Phase 1 and Phase 1 anakinra cohort after treatment with JCARH125 for monitoring or management of any treatment associated-toxicities. For subjects in Phase 2, and Phase 2a who do not have accommodation within an approximately 30-minute drive from the hospital or do not have reliable transportation to the clinic for scheduled evaluation or emergencies should be considered for hospitalization for the at least first 7 days after JCARH125 treatment.

6.7. Concomitant Medications

6.7.1. Reporting Periods

Reporting periods for concomitant medications are summarized in Table 3.

Table 3: Reporting Periods for Concomitant Medications

Reporting Period	What to Record/Report
Informed consent to leukapheresis	Any ongoing medications at the time of informed consent and any newly started concomitant medications or transfusions during this period
Leukapheresis to start of lymphodepleting chemotherapy	Any newly started medications or transfusions during this period
From start of lymphodepleting chemotherapy to 90 days following the dose of JCARH125, or to EOS visit, whichever is earlier	All medications must be recorded/reported
From 91 days following the dose of JCARH125 until EOS visit	The following medications must be recorded/reported: • G-CSF (until start of new MM therapy) • Transfusions (until start of new MM therapy) • IVIG (until start of new MM therapy) • Anticancer therapies • Medications used to treat Grade ≥ 3 AEs/SAEs related to JCARH125

AE = adverse event; EOS = end of study; G-CSF = granulocyte colony-stimulating factor; IVIG = intravenous immunoglobulin; MM = multiple myeloma; SAE = serious adverse event.

6.7.2. Concomitant Medications during Hospitalizations

Due to the large amount of data generated during hospitalizations, a reduced concomitant medication collection approach will be utilized for the CRF during hospital stays. Therefore, the following medications should **not** be entered on the Concomitant Medication CRF during inpatient and ICU stays:

- IV fluids (except boluses used to treat impaired renal function or CRS, and hydration of subjects prior to JCARH125 infusion, both of which should be recorded)
- Heparin flushes
- Stool softeners
- Vitamins, minerals, health supplements
- Saline

- Lotions

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

- Vasopressors
- Oxygen use
- Antibiotics/antifungals/antivirals
- Growth factors
- Transfusions
- Systemic anticoagulants

6.8. Prohibited Medications, Devices, and Procedures

The following medications are prohibited until disease progression, 1 year following JCARH125 treatment, or loss of detectable JCARH125 cells, whichever comes first:

- Steroids: Pre-medication with steroids for JCARH125 administration is not allowed. Therapeutic doses of corticosteroids (defined as > 20 mg/day prednisone or equivalent) must not be administered within 72 hours before JCARH125 administration. After JCARH125 infusion, administration of therapeutic doses of corticosteroids is not permitted unless used for treatment of Grade ≥ 2 CRS or any grade of neurotoxicity. Therapeutic doses may be used in life-threatening situations and for other medical conditions when indicated, or after loss of detectable JCARH125 cells. Pre-treatment containing steroids may be given for necessary medications (eg, IV immunoglobulin) after discussion with the Sponsor. Physiologic replacement dosing of steroids (≤ 12 mg/m^2/day hydrocortisone or equivalent [≤ 3 mg/m^2/day prednisone or ≤ 0.45 mg/m^2/day dexamethasone]) is allowed. Topical steroids and inhaled steroids are permitted.

As noted in Section 6.6, filgrastim (G-CSF) is prohibited starting 7 days and pegfilgrastim starting 11 days prior to JCARH125 infusion to 7 days after the infusion.

Use of any live vaccines is prohibited within 8 weeks before JCARH125 infusion.

Plasmapheresis is prohibited at any time between screening and JCARH125 infusion.

A re-infusion of autologous peripheral blood stem cells (stem cell boost) preceded by bridging chemotherapy is not permitted.

Inferior vena cava (IVC) filter utilization is prohibited for treatment of deep vein thrombosis at any time between screening and JCARH125 infusion.

The following medications are prohibited during the treatment and follow-up periods until disease progression or discontinuation from the study:

- Non-protocol-specified anticancer agents. Lympholytic cytotoxic chemotherapy may be administered as an extraordinary measure to treat AEs of uncontrolled JCARH125 proliferation or CRS or neurotoxicity unresponsive to other therapeutic interventions.
- Any anti-epidermal growth factor receptor (EGFR) treatments

- Experimental agents
- Curative radiation (palliative radiation for pain management is permitted)

7. MANAGEMENT OF TOXICITIES ASSOCIATED WITH JCARH125

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

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

A complete discussion of identified and potential risks associated with JCARH125 is available in the current version of the JCARH125 Investigator's Brochure (IB).

7.1. Cytokine Release Syndrome

Administration of CAR T cells, such as JCARH125, is associated with CRS. CRS is characterized by high fever, fatigue, nausea, headache, dyspnea, tachycardia, rigors, hypotension, hypoxia, myalgia/arthralgia, and/or anorexia. Clinical symptoms and severity of CRS are highly variable (Lee, 2014), and management can be complicated by concurrent conditions. CRS symptoms typically appear a few hours to a few days following administration of CAR T cells and may be severe and life-threatening. Refer to Appendix D for a detailed description of CRS and for grading and treatment recommendations. Fever ≥ 38.5°C or ≥ 101.3°F is a commonly observed hallmark of CRS, and many features of CRS mimic infection. Hence, infection must be considered in all subjects presenting with CRS symptoms, and appropriate cultures must be obtained and empiric antibiotic therapy initiated per institution standard of care.

Less common symptoms associated with CRS include cardiac dysfunction, adult respiratory distress syndrome, renal and/or hepatic failure, coagulopathies, disseminated intravascular coagulation, and capillary leak syndrome.

Neurologic toxicity has been observed concurrently with CRS.

With other CAR T cell products, CRS has been reported to be associated with findings of macrophage activation syndrome/hemophagocytic lympho-histiocytosis (MAS/HLH), and the physiology of the syndromes may overlap (Section 7.6).

7.2. Fever

Subjects who develop a fever (temperature ≥ 38.5ºC) should be evaluated for infection and treated with antibiotics, fluids, and other supportive care as per institutional or standard clinical

practice, and as determined by the Investigator or treating physician. Neutropenic fever should be evaluated promptly (eg, blood cultures obtained, imaging as clinically required for identification of potential source of infection) and managed medically per institutional or standard clinical practice.

The possibility of CRS should be considered for all subjects with fever following JCARH125 infusion. Any onset of fever (≥ 38.0°C/100.4°F) within the first 2 weeks after JCARH125 infusion should be further investigated and subjects admitted for observation. Febrile subjects should be monitored closely for hemodynamic instability and changing neurologic status.

7.3. Cytopenias

Severe (Grade ≥ 3) and prolonged cytopenias, including anemia, leukopenia, neutropenia, and thrombocytopenia, may occur with both lymphodepleting chemotherapy and JCARH125. Complete blood counts (CBCs) should be monitored both prior to and after JCARH125 infusions. Institutional guidelines should be followed in the event of Grade ≥ 3 cytopenias.

7.4. Infections

Life-threatening and fatal infections associated with CAR T cell therapy, including JCARH125 have been observed. Severe infections may include bacterial, fungal (including pneumocystis jirovecii), and viral infections (including cytomegalovirus (CMV), HBV, and other respiratory viruses). Subjects with prolonged and/or recurrent cytopenias, especially in conjunction with hypogammaglobulinemia, CD4 T-cell count of < 200 µL, and/or recent use of corticosteroids are at increased risk of viral reactivation and serious opportunistic infections. In these settings, prophylactic, pre-emptive, or symptomatic treatment with antimicrobial, antifungal, anti-pneumocystic, and/or antiviral therapies is recommended per local institutional guidelines or standard clinical practice.

Antiviral therapy with appropriate antiviral agent for HBV is recommended for subjects with positive hepatitis B surface antigen, HBcAb, and/or measurable viral load.

Subjects with a CD4 T-cell count of < 200 µL should be maintained on pneumocystis prophylaxis with trimethoprim-sulfamethoxazole. If subjects cannot tolerate trimethoprim/sulfamethoxazole, an alternative pneumocystis prophylaxis should be used.

7.5. Neurologic Toxicities

CAR T cell therapy is associated with unique neurologic toxicities. Neurologic symptoms may include altered mental status, aphasia, altered level of consciousness, and seizures or seizure-like activity. Neurologic symptoms may begin 2 to 14 days after CAR T cell infusion and in severe cases may require admission to the ICU for frequent monitoring, respiratory support, or intubation for airway protection (Davila, 2014; Maude, 2014a; Kochenderfer, 2015; Gardner, 2016; Turtle, 2016a). The symptoms are variable and generally occur as CRS is resolving or after CRS resolution.

Refer to Appendix D for a detailed description of neurologic toxicities and for grading and treatment recommendations.

7.6. Macrophage Activation Syndrome (MAS) / Hemophagocytic Lympho-histiocytosis (HLH)

Macrophage activation syndrome (MAS) is a serious disorder potentially associated with uncontrolled activation and proliferation of CAR T cells and subsequent activation of macrophages. Macrophage activation syndrome 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 natural killer (NK) cells. Other findings may include elevated levels of transaminases, signs of acute liver failure, coagulopathy, and disseminated intravascular coagulopathy. There are no definitive diagnostic criteria for MAS; it is typically diagnosed using published criteria for hemophagocytic lympho-histiocytosis (Schulert, 2015). While there is considerable overlap in clinical manifestations and laboratory findings between MAS and CRS, other distinguishing MAS physical findings such as hepatosplenomegaly and lymphadenopathy are not common in adult subjects treated with activated T-cell therapies. Subjects treated with JCARH125 should be monitored for MAS, and in case of MAS occurrence, cytokine-directed therapy with an IL-1 receptor antagonist therapy anakinra, eg, should be considered as clinically indicated. Refer to Appendix D for a detailed description of MAS and treatment recommendations.

7.7. Infusion Reactions

Administration of JCARH125 may cause infusion reactions, including fever, rigors, rash, urticaria, dyspnea, hypotension, and/or nausea. To minimize the risk of infusion reactions, all subjects should be pre-medicated with acetaminophen and/or diphenhydramine (see Section 6.4.2). Mild infusion reactions should be managed expectantly with antipyretics, antihistamines, and anti-emetics. Corticosteroids should be avoided because of the potential impact on efficacy of infused JCARH125 cells. Rigors may be treated with meperidine.

The following guidelines should be followed for infusion reactions:

- Grade 1: administer symptomatic treatment, continue JCARH125 administration at the same dose and rate
- Grade 2: stop administration of JCARH125, administer symptomatic treatment, resume JCARH125 administration at a reduced rate only after symptoms resolve
- Grade 3: stop administration of JCARH125, administer symptomatic treatment, and resume JCARH125 administration at a reduced rate of administration only after symptoms resolve. If Grade 3 reaction recurs, discontinue JCARH125; no further JCARH125 should be administered
- Grade 4: discontinue administration of JCARH125 and administer symptomatic treatment as necessary; no further JCARH125 should be administered

7.8. Tumor Lysis Syndrome

Both the lymphodepleting chemotherapy employed in this protocol and JCARH125 therapy may cause TLS in subjects with high disease burden. Subjects should be closely monitored for laboratory evidence of TLS (hyperuricemia, hyperkalemia, hyperphosphatemia, and

hypocalcemia) and subjects at high risk for developing TLS, such as those with high disease burden and high cell turnover, should receive prophylactic treatment, including administration of allopurinol and hydration, as per standard clinical practice.

7.9. B-cell Aplasia

This toxicity may be managed by monitoring serum immunoglobulin levels, and infusion of intravenous immunoglobulin (IVIG) for hypogammaglobulinemic subjects (serum IgG < 400 mg/dL) should be considered.

7.10. Uncontrolled T-cell Proliferation

CAR T cells, including JCARH125, could theoretically proliferate out of control. If uncontrolled JCARH125 T-cell proliferation occurs, subjects may be treated with high-dose steroids (eg, methylprednisolone 1 to 3 mg/kg/day, tapered over 7 days) or lymphodepleting doses of cyclophosphamide (1-3 g/m^2 IV). If an Investigator suspects uncontrolled JCARH125 proliferation, the Sponsor should be contacted immediately.

7.11. Replication-Competent Lentivirus, Clonality, and Insertional Oncogenesis

Lentiviral vectors used in gene transfer are engineered to be replication-defective; however, generation of replication-competent lentiviruses (RCL) during manufacturing is still a possibility. Modern vector production systems have been improved to reduce the risk of RCL generation. To date, there have been no reports of RCL generated during lentiviral vector manufacturing, which may be due, at least in part, to the use of self-inactivating vectors such as the lentiviral vector used in the production of JCARH125 (Rothe, 2013).

Concerns for possible vector integration into the host genome have arisen due to preclinical studies that have shown retrovirus-mediated malignant transformation in mice (Li, 2002; Modlich, 2005) and monkeys (Donahue, 1992), and a single clinical study reporting development of leukemia in subjects with X-linked severe combined immunodeficiency (SCID) who received retroviral-modified CD34+ hematopoietic stem cells (Hacein-Bey-Abina, 2003), including 1 subject who died (Couzin, 2005). Of note, no instances of RCL generation during production or lentivirus-mediated malignant transformation in animals or subjects have been reported to date.

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

Per the FDA Recombinant DNA Advisory Committee guidelines (Food and Drug Administration, 2006b; Food and Drug Administration, 2006a), all subjects treated with JCARH125 will be followed for RCL and vector sequences for up to 15 years following JCARH125 administration as part of a LTFU protocol. All subjects will be monitored for evidence of unexpected JCARH125 expansion and the emergence of a new malignancy, particularly one of T-cell origin. Investigators should contact the Sponsor immediately if a new malignancy arises.

7.12. Adverse Reactions to Excipients

Because JCARH125 is a cryopreserved autologous cell product containing DMSO, subjects may notice a garlic-like taste and odor and/or experience other side effects associated with DMSO, including tachycardia, bradycardia, hypertension, hypotension, chest tightness, dyspnea, pulmonary edema, abdominal cramping, diarrhea, shivering, and restlessness.

7.13. Autoimmune Reactions

Because JCARH125 cells are activated immune cells, it is theoretically possible that the JCARH125 cells could attack normal cells in the skin, liver, kidney, bone marrow, and joints. Additionally, cytokines released from genetically modified T cells could trigger other T cells in the body to attack normal tissue, resulting in an autoimmune reaction.

7.14. Risks Associated with Anakinra treatment

For subjects who receive prophylactic treatment with anakinra, refer to the local package insert for specific details regarding the risks of anakinra.

7.15. Risks Associated with Lymphodepleting Chemotherapy

Subjects will receive fludarabine and cyclophosphamide prior to treatment with JCARH125 to facilitate lymphodepletion and CAR T cell engraftment. Refer to the local package inserts for specific details surrounding the risks of fludarabine and cyclophosphamide.

8. STUDY ASSESSMENTS AND PROCEDURES

A schedule of evaluations is provided in Appendix A. Specific visits are described in Section 8.2 through Section 8.5 and descriptions of study assessments are presented in Section 8.12.

All procedures and clinical laboratory assessments on days that lymphodepleting chemotherapy or JCARH125 is administered must be performed pre-dose unless otherwise specified. With the exception of CrCl, which must be measured on the first day of lymphodepleting chemotherapy (see Section 6.2), clinical laboratory assessments may be performed within 1 day prior to start of lymphodepleting chemotherapy or JCARH125 administration. Results from the clinical laboratory assessments must be reviewed prior to initiation of lymphodepleting chemotherapy or JCARH125 administration.

8.1. Schedule of Evaluations

The study schedule is divided into 3 parts: Pre-treatment, Treatment, and Post-treatment periods.

The Pre-treatment period includes:

1. **Screening**, to determine initial eligibility for study participation
2. **Apheresis**, for all subjects who meet all initial eligibility criteria at Screening
3. **Pre-treatment Screening**, to confirm that subjects meet eligibility criteria at the time of study treatment initiation (both prior to lymphodepleting chemotherapy and prior to JCARH125 infusion)

Eligibility will be assessed by the Sponsor at the following time points:

1. Prior to leukapheresis following site's completion of all screening assessments
2. Prior to lymphodepleting chemotherapy
3. Prior to JCARH125 infusion

The treatment period includes lymphodepleting chemotherapy (Section 6.2) and JCARH125 administration (Section 6.4), as well as follow-up through Day 29. The Post-treatment period continues through Month 24 unless the subject discontinues early or is lost to follow-up. All subjects will be assessed for response in accordance with the IMWG criteria at the times noted in Appendix A.

The Post-treatment period includes follow-up visits for evaluation of safety and disease status at indicated times. The 24-month visit will be the EOS visit, unless a subject discontinues early. Subjects who experience disease progression or relapse should complete the PD visit and will be encouraged to continue all study evaluations through the EOS visit, as well as participate in the LTFU study (Section 8.11). For subjects who withdraw from the study before the 24-month visit, the EOS visit should be completed at the time of study withdrawal.

8.2. Screening

The standard screening process begins when the subject signs the IRB/IEC-approved informed consent form for participation in the study and continues until the subject is determined to be eligible and is enrolled or is determined to be a screen failure.

The following assessments will be performed during Screening (may be performed up to 4 weeks following informed consent):

- Assess eligibility per inclusion/exclusion criteria. All eligibility criteria must be met for subjects to continue in the study.
- Obtain clinically significant medical history, including disease diagnosis and history, HSCT history, and chemotherapy, radiation, and surgical history. May include history of toxicities related to prior treatments and allergies
- ECOG performance status assessment (see Appendix F)
- Physical examination, including routine neurologic examination, vital signs, height, and weight
- Brain magnetic resonance imaging (MRI) (may be performed within 8 weeks prior to Screening)
- 12-Lead electrocardiogram (ECG) (may be performed up to 8 weeks prior to Screening)
- Cardiac ECHO or MUGA scan (may be performed up to 8 weeks prior to Screening)
- Collection of peripheral blood samples for local clinical laboratory evaluations (hematology, coagulation, chemistry, viral serology) and serum pregnancy test (see Section 8.12.6). Hematology, chemistry, coagulation, and inflammatory markers results should not be older than 5 days.

- Lumbar puncture (only required in subjects with signs/symptoms of potential CNS involvement)
- Bone marrow aspirate, bone marrow biopsy, and plasmacytoma biopsy (if accessible) sampling for morphology, MRD-clonotype analysis, PK, analysis of BCMA expression, and research evaluations
- Serum and urine M-protein (serum protein electrophoresis [SPEP] and 24-hour urine protein electrophoresis [UPEP])
- Serum and urine immunofixation
- sFLC
- Quantitative immunoglobulins
- Positron emission tomography (PET)/computed tomography (CT) or diffusion-weighted magnetic resonance imaging (DW-MRI) (Note: the same imaging modality should be used for all assessments of extramedullary disease during the study follow-up period).
- Skeletal survey; PET/CT or DW-MRI may be used in place of standard X-ray skeletal survey if the same imaging modality is used to evaluate for bone lesions for all assessments
- β_2-microglobulin
- Record all AEs/SAEs related to protocol-mandated procedures and concomitant medications taken at that time

8.3. Leukapheresis

Following enrollment on the study, a leukapheresis collection will be performed on each subject to obtain a sufficient quantity of peripheral blood mononuclear cells (PBMCs) for the production of the JCARH125 investigational product (see exclusion criteria in Section 5.2 for timing of leukapheresis in relationship to previous therapies). If a technical issue arises during the procedure or in the immediate processing of the product such that it cannot be used for JCARH125 production, the subject may have additional leukapheresis procedures performed.

Leukapheresis should be scheduled as soon as possible after the subject meets eligibility requirements, in coordination with the Sponsor. Venous access is required for leukapheresis and should be determined according to institutional practice.

The following assessments will be conducted on the day of leukapheresis:

- Collection of peripheral blood samples for local clinical laboratory evaluations, including:
  - Hematology (complete blood count [CBC] with differential)

Note: Hematology results must be evaluated prior to leukapheresis; in order to ensure results are available, sample may be collected up to 24 hours prior to leukapheresis.

- Vital signs (before leukapheresis)

- Record all AEs related to protocol-mandated procedures, all SAEs, and concomitant medications taken at that time

8.4. Anticancer Treatments between Leukapheresis and JCARH125 Production

The manufacturing and quality testing of JCARH125 may take several weeks following leukapheresis. During this time, subjects may receive short term (≤ 4 weeks) bridging therapy with one of the following recommended regimens:

- Dexamethasone, cyclophosphamide, etoposide, and cisplatin (DCEP)
- Bortezomib, dexamethasone, cisplatin, doxorubicin, cyclophosphamide, and etoposide (VD-PACE)
- Cyclophosphamide, vincristine, doxorubicin, and dexamethasone (CVAD)
- Pulsed dexamethasone

An alternate bridging therapy regimen that is institutional standard may be used, following discussion with the Sponsor's Medical Monitor. Anti-CD38 agents such as daratumumab, or other monoclonal antibodies (eg, elotuzumab) are not permitted as bridging therapy. A re-infusion of autologous peripheral blood stem cells (stem cell boost) preceded by bridging chemotherapy is not permitted. Experimental agents are not permitted. Duration of bridging therapy is limited to a maximum of 4 weeks. All therapies (including steroids) must be discontinued at least 14 days prior to initiation of lymphodepletion and the time period from leukapheresis to lymphodepletion cannot exceed 8 weeks. Subjects must have recovered from bridging therapy-related toxicities to Grade ≤ 2 (except for alopecia) prior to initiation of lymphodepletion. Subjects who cannot receive lymphodepletion within 8 weeks after leukapheresis must be rescreened and must complete all screening assessments.

Palliative radiation is permitted but must be discussed with the Sponsor's Medical Monitor in advance.

If bridging anticancer therapy is necessary, appropriate disease measurements (eg, bone marrow evaluation, serum and urine M-protein, serum and urine immunofixation, sFLC, quantitative immunoglobulins, and a PET/CT or DW-MRI) **must** be repeated prior to lymphodepletion and all subjects **must** have measurable disease prior to initiating lymphodepletion. Subjects who did not have extramedullary disease at screening and who do not have evidence of disease progression do not have to repeat a PET/CT or DW-MRI after bridging therapy. Subjects who respond to bridging chemotherapy and who no longer have measurable disease must wait until their disease becomes measurable to be considered for JCARH125 treatment.

8.5. Study Visits

8.5.1. Pre-treatment Screening and Baseline Evaluations

The subject must continue to meet eligibility criteria pertaining to adequate organ function, active infections, pregnancy, measurable disease, and washout of prior therapy before initiation of lymphodepleting chemotherapy (see Section 5.1 and Section 5.2). Growth factors and

transfusions may be administered for subjects who do not meet the minimum ANC, hemoglobin, and platelet count requirements at the Pre-treatment Screening evaluation.

Subjects whose disease becomes non-measurable following bridging chemotherapy will not receive lymphodepleting chemotherapy or JCARH125. These subjects may be treated with the study regimen when their disease becomes measurable; rescreening is required.

Pre-treatment Screening evaluations must occur within 14 days (+3 days) prior to initiation of lymphodepleting chemotherapy and must occur after the completion of any bridging chemotherapy. For subjects who receive bridging chemotherapy with potentially cardiotoxic drugs, a repeat MUGA/ECHO must be performed within 7 days prior to initiation of lymphodepleting chemotherapy. Evaluations will be performed as indicated in the Schedule of Evaluations (see Appendix A).

Subjects should have a hemoglobin level of ≥ 8 g/dL and a platelet count of ≥ 50,000/mm^3 prior to lymphodepletion; RBC transfusions and other supportive measures may be used. If lymphodepleting chemotherapy had to be delayed for reasons previously discussed with the Sponsor Medical Monitor, and if the delay was not longer than 14 days, only safety assessments have to be repeated. Disease assessments do not need to be repeated unless there is clinical evidence of disease progression.

8.5.2. Lymphodepleting Chemotherapy

Upon notification from the Sponsor that JCARH125 will be available, lymphodepleting chemotherapy should be initiated (see Section 6.2 for details and timing of the lymphodepleting regimen and criteria for withholding or adjusting treatment based on reduced CrCl; see Section 8.5.3 for criteria for initiating treatment).

The following assessments will be performed on each day of lymphodepleting chemotherapy, prior to administration of lymphodepleting chemotherapy:

- Physical examination, including routine neurologic examination, vital signs, and weight
- ECOG performance status assessment (first day of lymphodepleting chemotherapy only) (see Appendix F)
- Local laboratory assessments, including hematology, coagulation, and chemistries
- Record all AEs and concomitant medications

8.5.3. Criteria for JCARH125 Infusion (Day -1)

Subjects should not experience a significant worsening in clinical status compared to initial eligibility criteria that would, in the opinion of the treating physician, increase the risk of adverse events associated with JCARH125 infusion. Subjects who meet at least one of the following criteria within 24 hours prior to the scheduled JCARH125 infusion should have JCARH125 administration delayed:

- Suspected or active systemic infection 5 days before JCARH125 infusion
  - All cultures must be negative if subject had a recent infection

- Onset of fever ≥ 38.0°C/100.4°F, not related to underlying disease
- Platelet count < 50,000/mm^3
- Calculated creatinine clearance (Cockcroft Gault) < 60 mL/min
- Presence of progressive radiographic abnormalities on chest x-ray, or requirement for supplemental oxygen to keep saturation greater than 91%
- Cardiac arrhythmia not controlled with medical management
- Hypotension requiring vasopressor support
- New-onset or worsening of other non-hematologic organ dysfunction Grade ≥ 3
- Taking any of the prohibited medications as described in Section 6.8

In the event that a subject experiences any of the above, the Sponsor must be contacted and discussion regarding delay of treatment must occur. Subjects with active infection must have JCARH125 infusion postponed until the active infection has resolved (subjects with suspected/active infection must have negative culture for at least 24 hours on appropriate antibiotics or negative rapid viral panel). Subjects with organ toxicities may not receive JCARH125 until the organ toxicities have recovered to Grade ≤ 2. In case of delayed infusion, lymphodepleting chemotherapy may need to be repeated after discussion with the Sponsor (see Section 6.2).

8.5.3.1. Phase 1 Anakinra Cohort (JCARH125 Infusion [Day -1])

Subjects receiving prophylactic treatment with anakinra and who do not meet any of criteria listed above will receive 1 dose of 100 mg anakinra SC the night before JCARH125 infusion.

8.5.4. JCARH125 Administration (Day 1)

JCARH125 will be administered as described in Section 6.4. Evaluations will be performed as indicated in the Schedule of Evaluations (see Appendix A). Additionally, vital signs (see Section 8.12.3) will be measured within approximately 15 minutes (±5 min) before and 15 minutes (±5 min) after infusion, then approximately every 15 minutes thereafter for the first hour and hourly (±15 min) for the next 3 hours. Thereafter, vital signs should continue to be monitored until stable and as clinically indicated.

8.5.5. Day 2 through Day 29

Evaluations will be performed as indicated in the Schedule of Evaluations (see Appendix A).

Subjects in the Phase 1 anakinra cohort will continue with anakinra treatment for 5 consecutive days at a dose of 100 mg SC. In the event of CRS onset, 100 mg anakinra SC should be administered twice daily until CRS resolution. Anakinra should be administered at approximately the same time every day.

8.5.6. Follow-up Period: Month 2 through Month 24

All subjects, including subjects with PD, will be asked to complete the Post-treatment follow-up visits at Months 2, 3, 4, 5, 6, 9, 12, 15, 18, 21, and 24 after administration of JCARH125 for

disease status and survival. Evaluations will be performed as indicated in the Schedule of Evaluations (see Appendix A).

8.6. Unscheduled Evaluations

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

- Physical examination
- Vital signs
- ECOG performance status assessment
- Clinical laboratory evaluations (eg, hematology, coagulation, chemistries)
- Note: If peripheral blood samples are obtained for clinical laboratory evaluations, samples should also be collected and submitted to the Sponsor for exploratory research.
- Bone marrow or plasmacytoma biopsy
- Note: If bone marrow or plasmacytoma samples are obtained, samples should also be collected and submitted to the Sponsor for exploratory research.
- Other tissue assessments (eg, CSF, SPM)
- Note: If tissue or fluid samples are obtained, samples should also be collected and submitted to the Sponsor for exploratory research.
- CNS imaging (CT and/or MRI)
- Note: If scans are obtained as part of a neurologic examination, results should be reported.
- Disease assessments as needed to confirm a response (eg, SPEP, 24-hour UPEP, serum and urine immunofixation, sFLC, quantitative immunoglobulins, PET/CT, DW-MRI scan or skeletal survey)
- If collected, samples for SPEP, 24-hour UPEP, serum and urine immunofixation, and sFLC must be submitted to the central laboratory.
- MMSE (see Appendix E)
- Subjects who develop neurologic symptoms suspicious of and/or diagnosed as neurologic toxicity will have daily MMSEs until resolution of symptoms, unless the subject is medically incapacitated and/or medically unable to complete the MMSE.

8.7. Assessments to be Performed in the Event of Death

In the event of a subject's death, autopsy may be requested. If an autopsy is performed, tissue samples may be requested and sent to the Sponsor for evaluation of the presence of JCARH125 cells in brain, liver, kidney, lungs, bone marrow, blood, heart, reproductive organs, and any sites

of disease (see the H125001 Central Laboratory Manual). Every effort will be made to assay for RCL in a sample of the pertinent autopsy tissue.

8.8. Assessments to be Performed upon Disease Progression or Relapse

The assessments listed in the Schedule of Evaluations for PD or relapse (Appendix A) will be performed as soon as possible after disease progression/relapse is suspected. These subjects should be encouraged to continue to be followed as per the Schedule of Evaluations Table A-4 through Month 24.

8.9. Assessments to be Performed in the Event of a new Second Primary Malignancy

Second primary malignancies (SPMs) will be monitored as events of interest and must be reported as SAEs regardless of treatment subject is receiving (see Section 9.1.2). Events of SPM are to be reported using the SAE Report Form and must be considered "Important Medical Events" if no other serious criteria apply; these events must also be documented in the appropriate page(s) of the eCRF and subject's source documents. Documentation on the diagnosis of SPM must be provided at the time of SAE reporting (eg, any confirmatory histology or cytology results, x-rays, CT scans).

If subject develops a new malignancy, the sponsor will request a tumor sample (refer to laboratory manual) and blood samples (Section 8.12.9.1 and Section 8.12.10).

8.10. Early Withdrawal

If a subject withdraws prematurely from the study, an EOS visit will be scheduled as soon as possible and all of the assessments listed for the EOS visit will be performed. The reason for early withdrawal will be captured in the CRF.

8.11. Long-Term Follow-Up

Because this protocol involves gene transfer, follow up for lentiviral vector safety, disease status, and long-term survival will continue on this protocol until 24 months after JCARH125 administration, regardless of disease status, and under a separate Celgene-sponsored LTFU protocol for up to 15 years after JCARH125 administration.

All subjects treated with JCARH125 who either complete the primary follow-up period specified in this protocol or who prematurely withdraw after at least one dose of JCARH125 will be asked to enroll in the Celgene-sponsored LTFU protocol at the EOS visit or at the time of withdrawal, respectively. A separate informed consent form will be provided for the Celgene-sponsored LTFU protocol. Subjects who do not consent to participate in the Celgene-sponsored LTFU protocol or who are lost to follow-up will be followed for survival through public record.

8.12. Study Assessments

All study assessments should be performed at the times indicated in the Schedule of Evaluations in Appendix A.

8.12.1. Disease Assessments

Response to JCARH125 will be assessed according to the IMWG criteria (Kumar, 2016) (see Appendix B). In Phase 2, and for subjects in Phase 1 and the Phase 1 anakinra cohort who receive JCARH125 at the RP2D(s), response will be assessed by an IRC in addition to the Investigator assessment, as described in Section 4.11.2.

Some or all of the following are required for the assessment of disease status:

- SPEP and 24-hour UPEP (central laboratory)
- For subjects with disease that is only detectable in the serum, a 24-hour UPEP is only required at Screening, for confirmation of CR, as clinically indicated, and at EOS.
- Serum/urine immunofixation (central laboratory)
- Quantitative sFLC (central laboratory)
- Quantitative immunoglobulins (central laboratory)
- Bone marrow assessment for plasma cell percentage (central pathology review)
- Bone marrow evaluations are required for all subjects at Screening, Day 15, Day 29, Month 3, Month 6, Month 12, Month 18, Month 24/EOS, for confirmation of CR, and in the event of PD. In addition, subjects for whom inadequate or insufficient samples were available at Screening and subjects who receive bridging chemotherapy will also have bone marrow evaluations at Pre-treatment Screening.
- Skeletal survey
- The skeletal survey is required at Screening and will only be performed as clinically indicated thereafter. At the Investigator's discretion, a PET/CT or DW-MRI may be performed in lieu of the skeletal survey to evaluate for bone lesions at Screening, provided that the same imaging modality is used for all future assessments.
- Imaging by PET/CT or DW-MRI in subjects with extramedullary disease or if a new extramedullary lesion is suspected.
- MRD assessment by next-generation sequencing and/or flow cytometry evaluation of bone marrow aspirate samples collected at Screening (clone identification), Day 29, Month 3, Month 6, Month 12, Month 18, Month 24/EOS, and if otherwise collected to confirm CR.

8.12.2. Physical Examination, Neurologic Examination, and MMSE

Physical examinations must include, at a minimum, neurologic, cardiovascular, pulmonary, abdominal, and extremity examinations. In addition, symptom-directed exams should be performed as appropriate. Height and weight will be measured at visits specified in Appendix A.

The neurologic examination should include, at minimum, a physical examination to assess cranial nerves, motor and sensory skills, coordination, and balance, as well as an MMSE.

The MMSE (see Appendix E) may be administered by an appropriately trained provider (eg, physician, nurse); a neurologist is not required. Efforts should be made to have the same provider perform the MMSE on a given subject to maintain consistency of these assessments.

Subjects who develop neurologic symptoms suspicious of and/or diagnosed as neurologic toxicity will have daily MMSEs performed per Appendix E until resolution of symptoms, unless the subject is medically incapacitated and/or medically unable to complete the MMSE.

8.12.3. Vital Signs

Vital signs include temperature, respiratory rate, heart rate, blood pressure, and SaO_2 by pulse oximetry.

8.12.4. Electrocardiogram

An ECG will be performed at Screening to assess eligibility to participate in the study. Additional ECGs may be required as clinically indicated by the Investigator in order to support diagnosis and monitoring of any cardiac-associated adverse events.

8.12.5. Echocardiogram and Multigated Acquisition

A cardiac ECHO or MUGA scan will be performed at Screening to assess eligibility to participate in the study. Subjects who receive bridging chemotherapy with potentially cardiotoxic drugs must have a repeat ECHO or MUGA within 7 days prior to initiation of lymphodepleting chemotherapy.

8.12.6. Local Laboratory Evaluations

Screening and other laboratory evaluations (see Table 4) will be performed at study visits indicated in Appendix A. Additional assessments should be performed between scheduled study visits as clinically required in order to diagnose and monitor AEs or expected events. Requirements for reporting laboratory abnormalities are provided in Section 9.4.2.

Table 4: Analytes for Local Laboratory Evaluations

Laboratory Panel	Analytes
Hematology	CBC with differential; absolute lymphocyte count (ALC) required within 24 hours prior to leukapheresis, CD4 T-cell count (or ALC if CD4 T-cell count is not available) is required at Pre-treatment Screening and as clinically indicated
Chemistry	Glucose, BUN, serum creatinine[a], sodium, potassium, chloride, calcium, total protein, albumin, total and direct bilirubin, alkaline phosphatase, ALT, AST, magnesium, phosphate, bicarbonate, LDH, uric acid, triglycerides, beta-2-microglobulin[b]
Coagulation	Prothrombin time/ aPTT, INR, fibrinogen, and D-dimer
Viral serology	HIV-1 and HIV-2 Hepatitis B (HBsAb, HBsAg, and HBcAb) Hepatitis C (Hep C Ab and HCV RNA)
Serum pregnancy	Serum ß-hCG pregnancy test
Inflammatory markers	CRP, ferritin
CSF (if clinically indicated)	Protein, cell counts
Bone marrow	Cytogenetics (at screening visit if recent analysis not available)

ALC = absolute lymphocyte count; ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; ß-hCG = beta human chorionic gonadotropin; BUN = blood urea nitrogen; CBC = complete blood count; CRP = C-reactive protein; HBcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; Hep C Ab = hepatitis C antibody; HIV = human immunodeficiency virus; INR = international normalized ratio; LDH = lactate dehydrogenase.

[a] Serum creatinine, used to calculate creatinine clearance prior to initiation of lymphodepleting chemotherapy (see Section 6.2 and Appendix C).

[b] Beta-2-microglobulin is only required at the time points indicated in Appendix A.

8.12.7. CSF Examination and CNS Symptom Assessment

CSF assessments and CNS imaging should be performed after JCARH125 administration as clinically indicated (eg, if new CNS symptoms occur, or if clinical signs or suspicion of CNS involvement by MM). If CT and/or MRI scans are obtained as part of a neurologic examination, results should be reported. If CSF fluid is collected, a sample should be submitted to the central laboratory to evaluate for the presence of JCARH125 (see the H125001 Central Laboratory Manual for instructions on sending a sample for JCARH125 testing).

8.12.8. Pharmacokinetics, Vector Sequence Testing, and Exploratory Research Evaluations

Testing and analysis of samples will generally follow the Schedule of Evaluations in Appendix A. Allocation of samples to specific testing may be modified where sample material is limited; however, the total volume and type of material collected will not be modified beyond what is described in the H125001 Central Laboratory Manual. Instances where specimens are not collected at the required study visit due to insufficient sample volume or subject refusal will not be reported as a protocol deviation.

Detailed information regarding the collection, handling, and shipment of samples for PK, [redacted] and exploratory research assessments is provided in the H125001 Central Laboratory Manual.

8.12.9. Pharmacokinetic Assessments

Assessment of JCARH125 expansion and persistence (PK) in blood [redacted] will be determined by qPCR to detect the JCARH125 transgene.

8.12.9.1. Viral Vector Sequence Testing

In accordance with the FDA guideline for evaluating delayed adverse events (Food and Drug Administration, 2006a), if more than 1% of cells in test samples collected at the Month 12 visit or later test positive for the JCARH125 transgene (as determined using the qPCR PK assay), the pattern of vector integration sites will be analyzed. If a predominant integration site is detected, then the subject will be asked to provide another blood draw 3 months later for follow-up testing.

If a subject develops disease recurrence or a new malignancy, the Sponsor will request a tumor sample and blood sample at time of new malignancy for assessment of viral vector sequence testing.

8.12.10. RCL Testing

Details regarding sample collection and processing are provided in the H125001 Central Laboratory Manual. RCL testing will be performed using an analytically validated polymerase chain reaction (PCR)-based assay to detect viral envelope sequence in peripheral blood. If all samples collected within the first year after the final dose of JCARH125 are negative, subsequent samples will be archived at a central laboratory. However, if any of the samples are positive, additional testing will be performed on PBMCs to confirm the result. If the repeat test is also positive, further analysis of the RCL will be undertaken to ascertain the nature of the RCL and potential effects. Any confirmed positive result from RCL testing will be reported as an adverse experience in the form of an Investigational New Drug (IND) safety report.

If a subject develops a new or recurrent neoplasm, the Sponsor will request a blood sample for assessment of RCL.

8.12.11. Health-Related Quality of Life

Health-related quality of life outcomes will be assessed using the EORTC QLQ-C30 and its MM-specific module QLQ-MY20, as well as the EuroQol instrument EQ-5D-5L.

The EORTC QLQ-C30 is a 30-item scale composed of both multi-item scales and single-item measures. All of the scales and single-item measures range in score from 0 to 100. A higher scale score represents a higher level of well-being and better ability of daily functioning. A 10-point change in the scoring is considered to be a meaningful change in HRQoL. Thus, a high score for a functional scale represents a high/healthy level of functioning; a high score for the global health status/HRQoL represents a high HRQoL, but a high score for a symptom scale/item represents a high level of symptomatic problem. A copy of a sample QLQ-C30 questionnaire is presented in Appendix G.

QLQ-MY20 is composed of questions that address various domains of HRQoL important in MM. It was developed using the EORTC recommended guidelines, with additional patient

interviews based on a grounded theory approach. A copy of a sample QLQ-MY20 questionnaire is presented in Appendix H.

Subjects should complete the questionnaires at the study visit, prior to any procedure or clinical evaluation. For subjects who do not complete the questionnaire, the reason for not completing the questionnaires(s) will be recorded (eg, too sick/unable to complete, administration error, subject refusal). If the subject withdraws from the study prematurely, all attempts should be made to obtain final quality-of-life questionnaires prior to subject discontinuation.

8.12.12. Health Economics and Outcomes Research

Health utility scores will be measured by the EuroQol instrument EQ-5D-5L. EQ-5D is a standardized measure of health status developed by the EuroQol Group in order to provide a simple, generic measure of health for clinical and economic appraisal. The EQ-5D-5L consists of the EQ-5D-5L descriptive system and the EQ visual analogue scale (EQ VAS). The descriptive system comprises dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression). Each dimension has 5 levels. A copy of a sample EQ-5D-5L questionnaire is presented in Appendix I.

Subjects should complete the questionnaires at the study visit, prior to any procedure or clinical evaluation. For subjects that do not complete the questionnaire, the reason for not completing the questionnaires(s) will be recorded (eg, too sick/unable to complete, administration error, subject refusal). If the subject withdraws from the study prematurely, all attempts should be made to obtain final quality-of-life questionnaires prior to subject discontinuation.

Hospital resource utilization will be assessed based on the numbers of ICU inpatient days and non-ICU inpatient days. Dates of admission and discharge to the hospital and to the ICU will be collected on the appropriate CRF.

9. ASSESSMENT OF SAFETY

9.1. Definitions

9.1.1. Adverse Event

In accordance with the International Conference on Harmonisation (ICH) E2A guideline and 21 CFR §312.32, an AE is defined as any untoward medical occurrence in a clinical study subject administered a pharmaceutical product which does not necessarily have a causal relationship with this treatment.

Abuse, withdrawal, sensitivity, or toxicity to an investigational product should be reported as an AE. Overdose, accidental or intentional, whether or not it is associated with an AE should be reported on the Study Drug Administration CRF (see Section 6.4.4 for the definition of overdose). Any sequela of an accidental or intentional overdose of an investigational product should be reported as an AE on the AE CRF. If the sequela of an overdose is an SAE, then the sequela must be reported on an SAE report form and on the AE CRF. The overdose resulting in the SAE should be identified as the cause of the event on the SAE report form and CRF but should not be reported as an SAE itself.

In the event of overdose, the subject should be monitored as appropriate and should receive supportive measures as necessary. There is no known specific antidote for JCARH125 or fludarabine/cyclophosphamide overdose. Actual treatment should depend on the severity of the clinical situation and the judgment and experience of the treating physician.

9.1.2. Serious Adverse Event

A serious adverse event (SAE) is defined as an event that, at any dose, meets any of the criteria in Table 5. Special considerations for SAE reporting, including events that should always be reported as SAEs in this study, are presented in Table 6.

Table 5: Definitions of Serious Adverse Events

Criteria	Description
Fatal	The AE resulted in death.
Life-threatening	The AE placed the subject at immediate risk of death. (This classification does not apply to an AE that hypothetically might have caused death if it had been more severe).
Hospitalization/prolongation of hospitalization	The AE resulted in hospitalization or prolongation of hospitalization (see Table 6).
Disability/incapacity	The AE resulted in a disability, significant incapacity, or substantial disruption of the subject's ability to conduct normal life functions
Congenital anomaly/birth defect	The AE was an adverse outcome in a child or fetus of a subject exposed to the study treatment regimen before conception or during pregnancy
Medically important	The AE was a medically important event that did not meet any of the above criteria, but may have jeopardized the subject and may have required medical or surgical intervention to prevent one of the outcomes listed above (examples include allergic bronchospasm that required treatment in an emergency room, seizures that do not result in hospitalization, or blood dyscrasias)

Table 6: Special Considerations for SAE Reporting

Criteria	Description
Other events that should always be reported as SAEs through the EOS visit (per the FDA's Guidance for Industry; Gene Therapy Clinical Trials – Observing Subjects for Delayed Adverse Events)	New/secondary malignancies New onset or exacerbation of a pre-existing neurologic disorder New onset or exacerbation of rheumatologic or other autoimmune disorder New onset hematologic disorder Rare and unexpected disorders with and unknown etiology (eg, Guillain-Barre, Stevens-Johnson's syndrome)

Table 6: Special Considerations for SAE Reporting (Continued)

Criteria	Description
Hospitalization/ prolongation of hospitalization Note: Complications and/or prolonged admissions for routine treatment or procedure do require SAE reporting.	This classification does not apply for the following hospitalizations: • Admissions for social or situational reasons (eg, no place to stay, live too far away to come for hospital visits) in the absence of any clinical AE • Admissions at the discretion of the Investigator for administration of lymphodepleting chemotherapy or JCARH125 • Admissions for elective or pre-planned treatment or procedure for a pre-existing condition that is unrelated to the condition under study and has not worsened since providing informed consent • Admissions for routine treatment (eg, platelet transfusion) or monitoring of the condition under study that is not associated with any deterioration in condition. • Admissions for routine procedures (eg, bone marrow aspiration) associated with the disease under study • Emergency outpatient treatment or observation that does not result in admission, unless fulfilling other seriousness criteria above

9.2. Grading and Intensity of Adverse Events

Adverse events, with the exception of CRS, will be graded using the NCI Common Terminology Criteria for Adverse Events (CTCAE), version 4.03.

CRS will be graded according to the grading scale adapted from Lee et al (Lee, 2014), which is provided in Table 8 in Appendix D.

The reported verbatim term should be the most descriptive medical diagnosis and does not have to be found in CTCAE.

AE severity and seriousness will be assessed independently. 'Severity' refers to the intensity of an AE, while 'serious' is a regulatory definition and serves as a guide to the Sponsor for defining regulatory reporting obligations.

9.3. Relationship to Study Drug

The assessment of the relationship (related or not related) of an AE to lymphodepleting chemotherapy or JCARH125 is a clinical decision based on all available information and the following considerations:

Related: There is a reasonable possibility and/or evidence to suggest a causal relationship between study drug and the AE and no other more likely alternative cause (concomitant drugs, therapies, disease complications, etc.) is suspected.

Not related: There is no reasonable possibility and/or evidence to suggest a causal relationship between study drug and the AE and another more likely alternative cause (concomitant drugs or therapies, disease complications, etc.) is suspected.

9.4. Recording Adverse Events

AEs/SAEs are recorded on the CRF in accordance with the reporting criteria for different time periods as defined in Section 9.5. Each AE/SAE is to be evaluated for:

- Duration (onset and resolution dates)
- Severity, including Grade changes as per the CRF completion guidelines (see Section 9.2)
- Outcome
- Seriousness (see Section 9.1.2)
- Causal relationship with protocol-mandated procedures, lymphodepleting chemotherapy, or JCARH125 (see Section 9.3)

9.4.1. Recording a Diagnosis versus Signs and Symptoms

Whenever possible, a unifying diagnosis should be reported as opposed to a listing of individual symptoms. However, symptoms should be grouped into a diagnosis only if each sign or symptom is a medically confirmed component of that diagnosis as evidenced by current standard medical textbooks. If any aspect of a sign or symptom does not fit into a classic pattern of the diagnosis, the individual symptom should be reported as a separate AE.

One exception to reporting a diagnosis as opposed to symptoms is the event of CRS. If a subject experiences an event of CRS, a diagnosis of CRS and any Grade changes for the event of CRS should be reported as an AE. Individual signs and symptoms of CRS, and maximum Grade for those signs and symptoms, should be entered as CRS symptoms on a separate CRF.

When manifestations of neurologic toxicities appear in the presence of CRS, those manifestations should be reported as separate AEs.

9.4.2. Clinical Laboratory Abnormalities and Other Abnormal Assessments

Any laboratory abnormality (eg, clinical chemistry or hematology) or other abnormal assessment findings (eg, ECG or vital signs) that meets any of the following criteria should be recorded as an AE or SAE:

- Requires medical or surgical intervention
- Leads to product discontinuation, delay, or interruption
- Associated with clinical signs and/or symptoms
- Otherwise clinically significant as determined by the Investigator

Whenever possible, the clinical diagnosis, rather than the laboratory result, should be reported by the Investigator (eg, 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.

9.4.3. Recording Serious Adverse Events

The following should be considered when recording SAEs:

- Death is an outcome of an event. The event that resulted in death should be recorded in the CRF and reported on the SAE report form.
- For hospitalizations or surgical or diagnostic procedures, the illness leading to the surgical or diagnostic procedure should be recorded as the SAE, not the procedure itself. The procedure should be captured in the narrative as part of the action taken in response to the illness.
- Events related to disease progression must be reported as SAEs if they meet serious criteria. When reporting an SAE of progression of the disease under investigation, specific manifestations of the progression (eg, "new bone pain," "worsening anemia and renal failure") should be reported, rather than the general term "disease progression."

9.4.4. Death Reports

Deaths must be reported as an SAE on the Death CRF per the reporting periods described in Table 7.

Progressive disease is considered a study endpoint; however, death due to disease progression must be reported as an SAE if it occurs from the start of leukapheresis to within 90 days of JCARH125 administration. Deaths that occur more than 90 days after JCARH125 infusion will be captured on the Death CRF and reported as an SAE only if considered related to any protocol-mandated procedure or JCARH125.

9.4.5. Pregnancy

To ensure subject safety, each pregnancy occurring in a female subject or in the female partner of a male subject from the time of informed consent until the end of study must be reported to the Sponsor within 24 hours of learning of its occurrence. If the pregnancy is discovered following initiation of lymphodepleting chemotherapy treatment, the pregnancy should be followed to determine outcome. All pregnancies or suspected pregnancies occurring at any time after receipt of JCARH125, in either a female subject of childbearing potential or partner of childbearing potential of a male subject, are immediately reportable events.

Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the Investigator to the Sponsor. Pregnancy follow-up should be recorded on the same form and should be submitted to the Sponsor within 24 hours of awareness. Any SAE experienced during pregnancy must be reported on the SAE Report Form. Abortion, whether accidental, therapeutic, or spontaneous, should be reported as an SAE. Congenital anomalies or birth defects, as defined by the "seriousness criteria" in Section 9.1.2, should be reported as SAEs.

All pregnancies should be monitored for the full duration, and all perinatal and neonatal outcomes should be reported.

9.5. Reporting Adverse Events to the Sponsor

9.5.1. Reporting Periods for AEs and SAEs

Reporting periods for AEs and SAEs are summarized in Table 7.

Table 7: Reporting Periods for AEs and SAEs

Time Period	Events to Record
Informed consent to leukapheresis	Only AEs/SAEs related to protocol-mandated procedures
Leukapheresis to start of lymphodepleting chemotherapy	• AEs related to protocol-mandated procedures • All SAEs • AEs associated with any signs/symptoms/diagnosis of opportunistic infections
From start of lymphodepleting chemotherapy to 90 days following the dose of JCARH125 (or to 30 days after the last dose of Flu/Cy for subjects who are discontinued from the study prior to JCARH125 administration)	All AEs/SAEs (note that this includes complications that arise from any procedure, whether or not the procedure was considered protocol-mandated) must be recorded/reported
For subjects starting a subsequent non-chemotherapy-containing anticancer therapy (eg, checkpoint inhibitors, IMiDs) prior to 90 days following the dose of JCARH125	All AE/SAEs will be collected after initiation of the subsequent therapy for 90 days following final JCARH125 infusion or 30 days following subsequent therapy, whichever is longer.
For subjects starting a subsequent chemotherapy-containing anticancer therapy prior to 90 days following the dose of JCARH125	Only AEs and SAEs related to JCARH125 or a protocol-mandated procedure must be recorded/reported after initiation of subsequent therapy
From 91 days following the dose of JCARH125 to end of study	Only AEs and SAEs related to JCARH125 or a protocol-mandated procedure must be recorded/reported
Other events that should always be reported as SAEs through the EOS visit (per the FDA's Guidance for Industry; Gene Therapy Clinical Trials – Observing Subjects for Delayed Adverse Events)	• New/second primary malignancies • New onset or exacerbation of a pre-existing neurologic disorder • New onset or exacerbation of rheumatologic or other autoimmune disorder • New onset hematologic disorder • Rare and unexpected disorders with and unknown etiology (eg, Guillain-Barre, Stevens-Johnson's syndrome)

SAEs will be followed until they resolve or return to baseline, the event stabilizes or is no longer considered clinically significant by the Investigator, the subject dies or withdraws consent, or the study is closed. All non-serious AEs will be followed through the safety reporting period

described in Table 7. Certain non-serious AEs, as requested by the Sponsor, may be followed until resolution, return to baseline, or study closure.

9.5.2. Reporting Timelines for SAEs

All SAEs must be reported within 24 hours of awareness. An SAE Report Form may be submitted and should also include supporting documentation (eg, hospital admission notes, test results).

For initial SAE reports, the following minimum criteria must be reported on the SAE form:

- Subject number
- Date of event onset
- Description of event
- Study treatment
- Relationship to study treatment

The completed SAE Report Form and supporting documentation should be sent according to the instructions on the SAE Report Form.

Relevant follow-up information is to be submitted to the Sponsor as soon as it becomes available.

10. STATISTICAL METHODS

10.1. General Considerations

All analyses will be separated by dose level unless otherwise specified. In the Phase 1 dose escalation portion of the trial, summaries will be prepared by dose level and overall. Data from Phase 1 dose escalation at the RP2D(s), data from the Phase 1 anakinra cohort at the RP2D(s), and data from Phase 2 expansion will be pooled for analysis. If more than 1 dose level is selected as the RP2D, then analyses pooled across the RP2D levels in Phase 1 dose escalation, the Phase 1 anakinra cohort, and Phase 2 expansion will be considered as the primary analyses, with analyses by dose level being considered as supplementary. The Phase 2 efficacy analysis may be refined in a detailed statistical analysis plan (SAP), following further discussion with regulatory authorities. Data from the Phase 1 anakinra cohort will be summarized separately but subjects treated in this cohort at the RP2D(s) will also be pooled with subjects treated at the RP2D(s) in Phase 1 dose escalation and Phase 2 expansion for the primary analyses. Data from the Phase 2a prior BCMA-directed anti-myeloma therapy cohorts will be analyzed separately from Phase 1 and Phase 2 expansion. Supplementary analyses pooling across all subjects treated at the RP2D(s) across all cohorts may be performed if deemed warranted.

By-subject listings will be provided. Summary tables for continuous variables will contain the following statistics: N (number in population), n (number with data), mean, standard deviation, 95% confidence intervals (CIs) on the mean as appropriate, median, minimum, and maximum. Summary tables for categorical variables will include: N, n, percentage, and 95% CIs on the

percentage as appropriate. Unless otherwise indicated, 95% CIs for binary variables will be calculated using the binomial distribution (exact method) and will be 2-sided.

Unless otherwise specified, all statistical hypothesis testing will be 2-sided at the 0.05 level of significance.

Subjects who do not receive JCARH125 will be included in by-subject listings but will not be included in data summaries unless otherwise specified.

Subjects who receive non-conforming product of JCARH125 will be analyzed separately.

10.2. Analysis Sets

10.2.1. Analysis Sets for Phase 1 Dose Escalation

10.2.1.1. Screened Analysis Set

The Screened Analysis Set includes all subjects who have signed informed consent.

10.2.1.2. Leukapheresed Analysis Set

The Leukapheresed Analysis Set includes all subjects who have signed informed consent and who undergo leukapheresis.

10.2.1.3. Safety Analysis Set

The Safety Analysis Set includes all subjects who receive JCARH125.

10.2.1.4. DLT-evaluable Analysis Set

The DLT-evaluable Analysis Set includes all subjects who have received the conforming JCARH125 cell product at the assigned dose level, and who have either experienced a DLT or were followed for the full DLT evaluation period. This analysis set will be used for the determination of the MTD. The DLT-evaluable period is defined as Days 1 to 22, for a total evaluation period of 21 days following JCARH125 infusion.

10.2.1.5. Efficacy Analysis Set

The Efficacy Analysis Set in Phase 1 includes all subjects who have received conforming JCARH125 cell product, have measurable disease at the last disease assessment prior to receiving JCARH125 infusion, and who have at least 1 post-infusion disease response assessment.

10.2.1.6. Pharmacokinetic Analysis Set

The Pharmacokinetic Analysis Set includes subjects in the safety analysis set who have the necessary PK measurements to provide interpretable results for the specific parameters of interest.

10.2.2. Analysis Sets for the Phase 1 Anakinra Cohort

10.2.2.1. Safety Analysis Set

The Safety Analysis Set for the Phase 1 anakinra cohort includes all subjects who receive JCARH125 and at least one dose of anakinra as prophylactic intervention.

10.2.2.2. Efficacy Analysis Set

The Efficacy Analysis Set for the Phase 1 anakinra cohort includes all subjects who have received conforming JCARH125 cell product at the dose level 3 and/or dose level 3a, received at least one dose of anakinra as prophylactic intervention, have measurable disease at the last disease assessment prior to receiving JCARH125 infusion, and who have at least 1 post-infusion disease response assessment. All efficacy endpoints will be analyzed using this analysis set.

10.2.2.3. Additional Analysis Sets

The Screened Set, Leukapheresed Analysis Set, and PK Analysis Set for the Phase 1 anakinra cohort will follow the same definition as in Phase 1 dose escalation.

10.2.3. Primary Analysis Sets

Data from Phase 1 dose escalation at the RP2D(s), data from the Phase 1 anakinra cohort at the RP2D(s), and data from Phase 2 expansion will be pooled for the primary analyses of the study.

10.2.3.1. Efficacy Analysis Set

The Efficacy Analysis Set includes all subjects across Phase 1 dose escalation, the Phase 1 anakinra cohort, and Phase 2 expansion of the trial who have measurable disease at the last disease assessment prior to JCARH125 infusion and who receive conforming product at the RP2D(s). All efficacy endpoints will be analyzed using this analysis set.

10.2.3.2. Safety Analysis Set

The Safety Analysis Set includes all subjects who receive JCARH125. This analysis set will be used in the analyses of safety endpoints.

10.2.3.3. Additional Analysis Sets

The Screened Set, Leukapheresed Analysis Set, and PK Analysis Set for the primary analyses will follow the same definition as in Phase 1 dose escalation. Additional analysis sets may be defined in the SAP.

10.2.4. Analysis Sets for the Phase 2a Prior BCMA-Directed Anti-Myeloma Therapy Cohorts

Each prior BCMA-directed anti-myeloma therapy cohort will have separate analysis datasets.

10.2.4.1. Safety Analysis Set

The Safety Analysis Set for each prior BCMA-directed anti-myeloma therapy cohort includes all subjects who receive JCARH125.

10.2.4.2. Efficacy Analysis Set

The Efficacy Analysis Set for each prior BCMA-directed anti-myeloma therapy cohort includes all subjects who have received conforming JCARH125 cell product at the RP2D(s) and have measurable disease at the last disease assessment prior to receiving JCARH125 infusion. All efficacy endpoints will be analyzed using this analysis set.

10.2.4.3. Additional Analysis Sets

The Screened Set, Leukapheresed Analysis Set, and PK Analysis Set for each prior BCMA-directed anti-myeloma therapy cohort will follow the same definition as in Phase 1 dose escalation.

10.3. Planned Analyses

10.3.1. Subject Disposition and Baseline Characteristics

Descriptive summaries of demographics, baseline characteristics, and subject disposition will be provided for each analysis set.

10.3.2. Primary Endpoints in Phase 1 Dose Escalation

The following are primary endpoints in Phase 1 dose escalation:

- Incidence of DLTs

  The type and incidence of DLTs will be summarized by dose level and total. The rates of DLT at each dose level and the MTD will be estimated using isotonic regression as described in (Ji, 2010)

- Type, frequency, and severity of AEs
- Incidence and severity of clinically significant laboratory abnormalities

All AEs will be listed and summarized (see Section 10.3.11.110.3.11.1 for details).

10.3.3. Secondary Endpoints in Phase 1 Dose Escalation

Secondary endpoints in Phase 1 dose escalation are:

- C_{max}, t_{max}, and AUC of JCARH125 CAR T cells in the blood

  Determination of these parameters will be based on data obtained after the JCARH125 infusion through the Day 29 visit. C_{max} is the maximal concentration after infusion; t_{max} is the first study day the C_{max} is reached. AUC will be calculated using the trapezoid rule.

- Duration of persistence of JCARH125 CAR T cells in the blood

  Persistence will be defined as the time between the first measurement above the limit of detection until the last measurement above the limit of detection.

- Overall response rate (defined as sCR, CR, VGPR, or PR) assessed according to IMWG criteria

- Complete response rate (defined as sCR or CR) assessed according to IMWG criteria

Analysis of PK endpoints is discussed in Section 10.3.13.

10.3.4. Primary Endpoints for the Phase 1 Anakinra Cohort

The following are primary endpoints in the Phase 1 anakinra cohort:

- Incidence and severity of AEs
- Incidence of Grade ≥ 2 CRS in subjects receiving prophylactic anakinra relative to incidence of Grade ≥ 2 CRS in subjects treated at the RP2D(s) in the Phase 1 dose escalation portion of the trial
- Onset of Grade ≥2 CRS in subjects receiving prophylactic anakinra relative to onset of Grade ≥ 2 CRS in subjects treated at the RP2D(s) in the Phase 1 dose escalation portion of the trial
- The number and percentage of subjects with no CRS occurring on study days 1, 2, or 3
- Incidence and severity of clinically significant laboratory abnormalities

All AEs will be listed and summarized (see Section 10.3.11.1 for details).

The number and percentage of subjects developing Grade ≥ 2 CRS, as well as an upper 1-sided 80% CI will be provided and benchmarked against the observed rate from dose levels 3 and/or 3a from the dose escalation portion of the trial. A similar analysis will be provided for the number and percentage of subjects with no CRS occurring on study days 1, 2, or 3. The onset of Grade ≥ 2 CRS will be summarized descriptively and will be referenced to onset of Grade ≥ 2 CRS in subjects treated at the RP2D(s) in the Phase 1 dose escalation portion of the trial.

10.3.5. Secondary Endpoints for the Phase 1 Anakinra Cohort

The following are secondary endpoints in the Phase 1 anakinra cohort:

- C_{max}, t_{max}, and AUC of JCARH125 CAR T cells in the blood
- Duration of persistence of JCARH125 CAR T cells in the blood
- Overall response rate (defined as sCR, CR, VGPR, or PR) assessed according to IMWG criteria
- Complete response rate (defined as sCR or CR) assessed according to IMWG criteria

Analysis of PK endpoints is discussed in Section 10.3.13.

10.3.6. Primary Endpoint for Phase 2

ORR (defined as sCR, CR, VGPR, or PR), as assessed by the IRC according to IMWG criteria, is the primary endpoint for Phase 2.

The ORR is the best overall response recorded from the time of the JCARH125 infusion until disease progression, end of study, or the start of another anticancer therapy or stem cell transplant. Subjects without any reported disease response assessments will be considered non-responders.

The primary analysis of the primary endpoint will be conducted in the Efficacy Analysis Set as defined in Section 10.2.3.1. The primary efficacy analysis in Phase 2 will test the null hypothesis of ORR ≤ 30% against the alternative hypothesis that the ORR > 30% at a 1-sided 0.025 level of significance based on the exact binomial test, ie,

H_0: ORR ≤ 30% vs H_a: ORR > 30%

In addition, an exact 2-sided 95% CI for ORR will be provided for the primary analysis.

Data will be presented for both Investigators' assessments and IRC assessments. The findings of the IRC will be considered primary for analysis of ORR. Concordance between IRC and Investigator assessments will be summarized by the percent agreement for ORR.

A sensitivity analysis including all subjects in the leukapheresed analysis set will be conducted for the primary endpoint based on IRC assessment. Subjects who underwent leukapheresis but did not have any reported disease assessments by the IRC will be considered as non-responders for the sensitivity analysis.

10.3.7. Secondary Endpoints for Phase 2

Secondary efficacy endpoints in Phase 2 include the following:

1. CR rate, defined as CR or sCR, as assessed by the IRC according to IMWG criteria. Subjects without any reported disease response assessments will be considered non-responders.
2. Duration of response, defined as the time from first objective response (sCR, CR, VGPR, or PR) as assessed by the IRC until the earliest date of PD or death from any cause
3. Duration of complete response, defined as the time from first complete response (sCR, CR) as assessed by the IRC according to IMWG criteria until the earliest date of PD or death from any cause
4. Incidence and severity of AEs
5. Incidence and severity of clinically significant laboratory abnormalities
6. Time to response, defined as the time from JCARH125 infusion until first objective response (sCR, CR, VGPR, or PR) as assessed by the IRC according to IMWG criteria
7. Time to complete response, defined as the time from JCARH125 infusion until first complete response (sCR, CR) as assessed by the IRC according to IMWG criteria
8. OS, defined as the time from JCARH125 infusion until death from any cause
9. PFS, as assessed by the IRC according to IMWG criteria, defined as the time from the JCARH125 infusion until the earliest date of disease progression or death from any cause
10. C_{max}, T_{max}, and AUC of JCARH125 CAR T cells in the blood
11. Duration of persistence of JCARH125 CAR T cells in the blood
12. Measurement of HRQoL changes as assessed using the EORTC QLQ-C30 and its MM-specific module QLQ-MY20, as well as the EuroQol instrument EQ-5D-5L

13. Numbers of ICU inpatient days and nonICU inpatient days and reasons for hospitalization

A key secondary efficacy analysis in Phase 2 will test the null hypothesis of CR ≤ 5% against the alternative hypothesis that the CR > 5% at a 1-sided 0.025 level of significance using the exact binomial test based on the Efficacy Analysis Set. In addition, an exact 2-sided 95% CI for CR will be provided. To preserve the type I error rate, a gatekeeping approach will be used as discussed in Section 10.4.

The Kaplan-Meier method will be used to summarize time-to-event endpoints, and the median time to event and associated 95% CI will be provided.

Duration of response will be summarized using the Kaplan-Meier method on the set of subjects that achieved sCR, CR, VGPR, or PR as assessed by the IRC according to IMWG criteria. Subjects that do not progress or die will be censored at the last disease response assessment. Subjects will also be censored at the last disease response assessment prior to receiving a new anticancer agent. Duration of CR will be summarized in a similar manner on the set of subjects that achieved sCR or CR as assessed by the IRC according to IMWG criteria.

Time to response and time to complete response will be summarized using descriptive statistics.

OS will be summarized using the Kaplan-Meier method. Subjects that do not die will be censored at the last known date alive.

PFS will be summarized using the Kaplan-Meier method. Subjects that do not progress or die will be censored at the last disease response assessment. Subjects will also be censored at the last disease response assessment prior to receiving a new anticancer agent.

10.3.7.1. Efficacy Subgroup Analyses

Efficacy subgroup analysis will be performed on the following variables:

- Age: < 65 versus ≥ 65 years at the time of the JCARH125 infusion
- Sex: male versus female
- Ethnicity: Hispanic or Latino versus not Hispanic or Latino
- Race: White versus other races
- Prior autologous stem cell transplant status: yes versus no
- Prophylactic anakinra usage: yes versus no

Subgroup analyses will be performed for the primary and secondary efficacy endpoints and will only be performed if there are at least 5 subjects in each subgroup. Other subgroup analyses will also be performed if deemed appropriate.

10.3.8. Other Secondary Endpoints for Phase 2

Other secondary endpoints for Phase 2 are:

- Type, frequency, and severity of AEs

- Type, frequency, and severity of clinically significant laboratory abnormalities as recorded on the adverse event page
- C_{max}, t_{max}, and AUC of JCARH125 CAR T cells in the blood
- Duration of persistence of JCARH125 CAR T cells in the blood
- HRQoL change from baseline
- Days hospitalized in ICU and days hospitalized in non-ICU

All AEs will be listed and summarized (see Section 10.3.11.1 for details).

Details regarding analysis of pharmacokinetic data are provided in Section 10.3.13.

10.3.9. Primary Endpoint for the Phase 2a Prior-BCMA Directed Anti-Myeloma Therapy Cohort

ORR (defined as sCR, CR, VGPR, or PR) as assessed by the IRC according to IMWG criteria, is the primary endpoint for the Prior-BCMA Directed Anti-Myeloma cohorts.

The ORR is the best overall response recorded from the time of the JCARH125 infusion until disease progression, end of study, or the start of another anticancer therapy or stem cell transplant.

The primary efficacy analysis in Phase 2a will test for each cohort separately the null hypothesis of ORR $\leq$ 10% against the alternative hypothesis that the ORR > 10% at a 1-sided 0.20 level of significance based on the exact binomial test, ie,

H_0: ORR $\leq$ 10% vs H_a: ORR > 10%

In addition, exact lower 1-sided 80% and exact 2-sided 95% CI for ORR will be provided for the primary analysis. If the lower 1-sided confidence limit for ORR exceeds the 10% null hypothesis threshold (for example, 3 or more responders out of 14 subjects), then this would be considered a preliminary positive signal.

A 2-stage approach is planned for each cohort in the Phase 2a portion of the study with a futility analysis for each cohort planned after 6 subjects have been evaluated for response and stopping for futility if no responses have been observed.

Analyses pooling across all cohorts in Phase 2a will also be provided.

10.3.10. Secondary Endpoints the Phase 2a Prior-BCMA Directed Anti-Myeloma Therapy Cohorts

The following are secondary endpoints in Phase 2a:

- Complete response rate as assessed by the IRC according to IMWG criteria
- Incidence and severity of AEs
- Incidence and severity of clinically significant laboratory abnormalities
- C_{max}, t_{max}, and AUC of JCARH125 CAR T cells in the blood
- Duration of persistence of JCARH125 CAR T cells in the blood

- Duration of response as assessed by the IRC according to IMWG criteria
- Duration of CR as assessed by the IRC according to IMWG criteria
- Time to response as assessed by the IRC according to IMWG criteria
- Time to complete response as assessed by the IRC according to IMWG criteria
- OS
- PFS as assessed by the IRC according to IMWG criteria

Analysis of secondary efficacy endpoints in Phase 2a will be produced separately for each cohort and will be based on the methods outlined in Section 10.3.6. No formal statistical hypothesis testing is planned for the complete response endpoint in Phase 2a, however exact 80% and 95% CIs will be generated for the complete response rate for each cohort in Phase 2a.

Details regarding analysis of pharmacokinetic data are provided in Section 10.3.13.

10.3.11. Safety Analyses

Safety analyses will be based on the Safety Analysis Set.

10.3.11.1. 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 starts any time from initiation of JCARH125 administration through and including 90 days following the JCARH125 infusion. 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 subject who reports multiple occurrence of TEAEs within the same SOC and Preferred Term is counted only once using the maximum severity grade for summaries.

10.3.11.2. Laboratory Data

All laboratory data will be listed. The focus of laboratory data summarization (including hematology, chemistry) will be on treatment-emergent laboratory abnormalities. A treatment-emergent laboratory abnormality is defined as an abnormality that, compared with baseline, worsens by at least one grade within 90 days following the JCARH125 infusion. The baseline value is defined as the last available recorded value on or prior to the date of the JCARH125 infusion.

If baseline data are missing, then any graded abnormality (ie, an abnormality that is Grade ≥ 1 in severity) will be considered treatment-emergent. Hematological and chemistry 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 (ie, increased, decreased) will be presented separately.

The following summaries will be presented for selected analytes:

- Raw values and changes from baseline will be summarized by visit for numerical lab results in conventional units
- Number of subjects by CTCAE severity grade, with corresponding percentages at each visit, and maximum post-baseline severity grade
- Number and percentage of subjects with a treatment-emergent CTCAE Grade 3 or 4 laboratory abnormality

Shift tables showing the change in CTCAE severity grade from baseline to the maximum severity grade post baseline; for laboratory tests where CTCAE grade does not exist, the shift table will present the low/normal/high shift.

[redacted]

10.3.11.4. Other Safety Analyses

Vital signs and the MMSEs will be summarized using descriptive statistics and listed. All other safety data will be listed.

10.3.11.5. Safety Subgroup Analyses

In the safety analysis set, safety subgroup analyses will be performed for key safety summaries and will only be performed if there are at least 5 subjects in each subgroup. Other subgroup analyses will also be performed if deemed appropriate.

Subgroup analysis will be performed for key safety summaries based on the following variables:

- Age: < 65 versus ≥ 65 years at the time of the JCARH125 infusion
- Sex: male versus female
- Ethnicity: Hispanic or Latino versus not Hispanic or Latino
- Race: White versus other races
- Prophylactic anakinra usage: yes versus no

10.3.12. Concomitant Medications

Prior and concomitant medications will be coded with the World Health Organization Drug Dictionary (WHO-DD) and listed. All concomitant medications and blood product transfusions administered after the JCARH125 infusion will be summarized.

Specific treatments for CRS (eg, corticosteroids, tocilizumab) will be summarized, as will specific treatments for neurotoxicity.

Anticancer interventions will be summarized.

10.3.13. Pharmacokinetic Analyses

Assessment of JCARH125 expansion and persistence (PK) in blood [redacted] will be determined by qPCR to detect the JCARH125 transgene.

For all subjects in the PK analysis set, the in vivo PK profile of JCARH125 cells in target tissues (blood, [redacted] and CSF if collected) will be characterized, including C_{max}, t_{max}, AUC, and other relevant PK parameters. The maximum extent of expansion of JCARH125 in the blood will be determined by C_{max}, along with the persistence of JCARH125 in the blood [redacted] based on the qPCR assay (time above lower limit of detection).

The following PK parameters will be displayed graphically where possible: qPCR-based JCARH125 concentration versus time in peripheral blood [redacted]

The following PK parameters, along with other relevant PK parameters, will be estimated from the individual concentration-time profiles using a non-compartmental analysis approach: AUC, C_{max}, t_{max}, and time above lower limit of detection. C_{max} is the maximal concentration after infusion. t_{max} is the first study day the C_{max} is reached. AUC will be calculated using the trapezoid rule. Determination of AUC, C_{max}, and t_{max} will be based on data obtained after the JCARH125 infusion through the Study Day 29 visit. All concentrations below the limit of detection or quantitation, or missing data, will be labeled as such in the concentration data listings.

Persistence will be defined as the time between the first measurement above the limit of detection until the last measurement above the limit of detection.

Descriptive statistics for PK parameters will be categorized by key efficacy and safety measures and will include mean, standard deviation, coefficient of variation, minimum, and maximum.

[redacted]

10.3.13.1. Pharmacokinetic Subgroup Analyses

Subgroup analyses will be based on the PK analysis set and performed for key PK summaries based on the following variables:

- Age: < 65 versus ≥ 65 years at the time of the JCARH125 infusion
- Sex: male versus female
- Cellular and/or humoral immunogenicity: present (positive) or absent (negative)
- Ethnicity: Hispanic or Latino versus not Hispanic or Latino
- Race: White versus other races
- Prophylactic anakinra usage: yes versus no

10.3.14. Health-Related Quality of Life

In the absence of a more specific hypothesis, the global score will be used as the primary HRQoL outcome and the physical functional score and fatigue item will be used as secondary outcomes.

The EORTC QLQ-C30 and QLQ-MY20 will be analyzed according to the functional scores and the recommendations in the scoring manual. Scores will be descriptively tabulated (number, mean, standard deviation, median, 95% CI) at each time point with change from baseline and summarized over time with graphical displays by cohort and for all subjects. Single items will be also described in terms of number and frequency. Details will be given in the HRQoL SAP.

10.3.15. Health Economics and Outcomes Research

The EQ-5D-5L will be analyzed according to the recommendations in the scoring manual. Hospital resource utilization will be assessed based on the numbers of ICU inpatient days and non-ICU inpatient days. Descriptive statistics of ICU inpatient days and non-ICU inpatient days will be provided.

Details will be given in a separate HEOR SAP.

10.3.16. Exploratory Endpoints

The exploratory endpoints for the study are listed in Section 3. Details of the exploratory analyses are provided in the SAP.

10.4. Multiplicity

The overall type 1 error rate will be strongly controlled at the 1-sided 2.5% level.

The statistical hypotheses planned to be tested are:

1. H_0 ORR $\leq$ 30%, H_a ORR > 30% in the Efficacy Analysis Set
2. H_0 CR $\leq$ 5%, H_a CR > 5% in the Efficacy Analysis Set

A gatekeeping approach will be used to control the type 1 error rate at the 1-sided 2.5% significance level for evaluations of the primary endpoint and the CR endpoint. Hypothesis 2) will only be tested at the 1-sided 0.025 significance level if hypothesis 1) is rejected at the 1-sided 0.025 significance level.

10.5. Sample Size Considerations

Subjects in Phase 1 who are not evaluable for DLT will be replaced. A sample size of approximately 75 treated subjects at the RP2D(s) is planned for the primary efficacy evaluation. A sample size of up to 120 subjects is planned for Phase 1 dose escalation with up to approximately 106 subjects potentially evaluated in Phase 1 dose escalation at dose levels not at the RP2D(s). The Phase 1 anakinra cohort will be comprised of up to 14 subjects and is planned to be included in the primary efficacy evaluation. Phase 2a will be comprised of up to 42 subjects (up to 14 subjects per cohort). Assuming approximately 5% to 10% of subjects may not be evaluable for the primary endpoint due to reasons such as not being evaluable for DLT assessment, receiving non-conforming product, or not having measurable disease after receiving bridging chemotherapy, a total sample size of 245 subjects is planned for this Phase 1/2 study.

Upon completion of the Phase 1 dose-escalation portion of the study, additional subjects will be enrolled such that at least 75 subjects will be included in the Efficacy Analysis Set. The appropriate sample size per dose level will be based on discussions with regulatory agencies if more than 1 dose level is selected as the RP2D(s).

Based on the cumulative safety and antitumor activity data from subjects treated in Phase 1 dose escalation, one or more dose levels will be selected for further evaluation in the Phase 2 expansion and Phase 2a portions of the trial (the RP2D(s)). It is anticipated that 14-30 subjects will be treated at a dose level in Phase 1 dose escalation prior to determination of a RP2D(s). A sample size of 14-30 subjects at a dose level will provide a high probability of excluding an overly toxic dose level from RP2D(s) consideration. For example, if the true DLT rate for a dose level is 45%, then the probability of excluding this dose level from RP2D(s) consideration per the mTPI-2 table is ≥ 74% for all sample sizes in the range of 14-30 subjects. The standard error of the ORR point estimate based on 14 or 30 subjects will be <13.4% or 9.2%, respectively, providing reasonable precision for decision making regarding the determination of the RP2D(s).

For the primary efficacy endpoint of ORR in the Efficacy Analysis Set, a sample size of 75 subjects will allow for approximately 90% power or higher based on the null hypothesis of ORR ≤ 30% assuming an effect size of ORR ≥ 49% using a 1-sided exact test at the 0.025 level. For the key secondary endpoint of CR in the Efficacy Analysis Set, a sample size of 75 subjects will allow for approximately 80% power or higher based on the null hypothesis of CR ≤ 5% assuming an effect size of CR ≥ 15%.

The reference ORR of 30% is based on results from a daratumumab monotherapy study (Lonial, 2016) evaluated in 106 subjects with R/R MM who had received at least 3 prior lines of therapy including a proteasome inhibitor and an immunomodulatory agent or who were double-refractory to a proteasome inhibitor and an immunomodulatory agent. The ORR and CR rate were 29.2% (95% CI: 20.8, 38.9) and 2.8% (95% CI: 0.6, 8.0), respectively, in the daratumumab monotherapy study.

A sample size of up to 14 subjects per cohort as a proof of concept in the Phase 2a prior-BCMA directed anti-myeloma therapy portion of the study allows for approximately 80% power or greater using a 1-sided exact test at the 0.20 level based on the null hypothesis of ORR ≤ 10% assuming an effect size of ORR ≥ 30%. A 2-stage approach is planned for each cohort in the Phase 2a portion of the study with a futility analysis for each cohort planned after 6 subjects have been evaluated for response and stopping for futility if no responses have been observed.

A sample size of 14 subjects is planned for the Phase 1 anakinra cohort. An objective of this cohort is to investigate if prophylactic use of anakinra in subjects treated at the RP2D(s) with JCARH125 will reduce the onset, incidence and severity of CRS relative to subjects treated with JCARH125 at the RP2D(s) in Phase 1. The following hypothesis will be tested in this cohort as an evaluation of the potential merits of prophylactic intervention with anakinra:

H_0 $P \geq P_0$, H_a $P < P_0$ where P denotes the true Grade 2 or higher CRS TEAE incidence rate when JCARH125 is administered at the dose level 3 and/or dose level 3a with prophylactic use of anakinra and P_0 denotes the observed Grade 2 or higher TEAE CRS incidence rate for the subjects in Phase 1 of this trial treated at the dose level 3 and/or dose level 3a. A 1-sided test at the 0.20 significance level using a normal approximation to the binomial distribution will be used for this hypothesis test. A sample size of 14 subjects will provide at least 80% power for this hypothesis test assuming P_0 is at least 40% and assuming an effect size of at least a 50% or more reduction in P_0 if subjects are treated with JCARH125 at the dose level 3 and/or dose level 3a with prophylactic anakinra.

10.6. Timing of Analyses

10.6.1. Interim Analyses

An interim analysis may be performed after at least 20 subjects have been treated at the RP2D(s) pooled across Phase 1 dose escalation, the Phase 1 anakinra cohort and Phase 2 expansion and are evaluable for response (ie, have had at least 1 post-treatment disease assessment and all objective responses confirmed). The purpose of the interim analysis is to inform the development program for JCARH125. There are no intentions to stop the trial early for positive efficacy; therefore, no adjustment to the alpha level will be made for the final analysis.

10.6.2. Primary Analyses

The primary analysis for ORR is planned after at least 75 subjects in the Efficacy Analysis Set have been evaluated for response. The exact timing of the analysis will be determined after discussions with regulatory agencies.

10.6.3. Final Analysis

The final analyses will be carried out after all subjects have completed or discontinued the study for any reason. No formal hypothesis testing will be performed at the final analysis.

11. DATA MANAGEMENT

11.1. Data Collection System

An electronic data capture (EDC) system provided by Juno will be used for data collection. The EDC system is 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. A Juno Clinical Research Associate (CRA) or designee will verify data 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 Juno 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.

The Principal Investigator is responsible for ensuring that the data entered into the CRFs are complete and accurate and will electronically sign the CRFs for each subject prior to database lock.

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

12. STUDY ADMINISTRATION

12.1. Regulatory and Ethical Considerations

12.1.1. Regulatory Authority Review

The study will be conducted in accordance with Good Clinical Practice (GCP), the protocol, and any other applicable Federal, state, and/or local regulatory requirements.

12.1.2. Institutional Review Board/Independent Ethics Committee Approval

It is the responsibility of the Investigator to ensure that the appropriate IRB or IEC has reviewed and approved this protocol prior to initiating the study. The IRB/IEC must also review and approve the investigative site's Informed Consent Form (ICF), other written information provided to the subject, and all subject materials that may be used.

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

12.1.3. Institutional Biosafety Committee Approvals

JCARH125 is composed of autologous T cells that have been manipulated via genetic modification in vitro to express a CAR directed against BCMA. Since neither the subject 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 JCARH125 investigational drug product should be handled according to institutional procedures for materials that may contain infectious materials (eg, 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, protocol amendments, and any other required materials prior to initiating the study if required per institutional policy.

Each site will be approved by the IBC in accordance with local procedures and country-specific regulatory requirements. Documentation of IBC approval must be in place prior to JCARH125 shipment to the site.

12.1.4. Subject Informed Consent

Prior to study entry, the Investigator, or a qualified person designated by the Investigator, will be responsible for explaining the nature, purpose, benefits, and risks of participation in the study to each subject, subject's legally acceptable representative, or impartial witness. Written informed consent must be obtained prior to the subject entering the study (before initiation of any study related procedure). Sufficient time will be allowed to discuss any questions raised by the subject. The Investigator or designated staff will document this process in the study records. The Investigator must use the current IRB/IEC-approved consent form for documenting written informed consent. Each informed consent form will be appropriately signed and dated by the subject or the subject's legally authorized representative and the person conducting the consent

discussion, and also by an impartial witness if required by IRB or IEC or local requirements. The process of obtaining the informed consent will be in compliance with all federal regulations, 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/IEC. The investigative site must use the amended ICF for all new subjects and, if required per institutional policy, repeat the consent process with the amended ICF for any ongoing subjects.

12.2. Investigator Obligations

12.2.1. Investigator Responsibilities

The Investigator is responsible for ensuring that all study site personnel, including sub-investigators 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 GCP, as outlined in 21 CFR 312, Subpart D, "Responsibilities of Sponsors and Investigators," 21 CFR, Part 50 and 21 CFR, Part 56.

The Investigator, sub-investigators, and key study staff as listed on FDA Form 1572 will comply with 21 CFR, Part 54, providing documentation of any financial conflict of interest. This documentation must be provided prior to the Investigator's (and any sub-investigators') participation in the study. The Investigator and sub-investigator(s) agree to notify Juno of any change in reportable interests during the study and for 1 year following study close-out at the Investigator's site.

If necessary to amend either the protocol or the study ICF, the Investigator will be responsible for ensuring that the IRB/ IEC reviews and approves the amended documents, and that subjects are informed of applicable changes, and updates.

The Investigator will sign and return to Juno the "Protocol Signature Page" of the original protocol and any protocol amendment, provide current medical licenses, curriculum vitae, and FDA Form 1572 "Statement of Investigator." All forms must be updated as applicable throughout the study.

12.2.2. Investigator Reporting Requirements

In accordance with applicable regulatory requirements, the Investigator is solely obligated to inform the IRB/IEC of progress of the study and notify the IRB/IEC of study closure. The Investigator must also provide Juno with copies of all IRB/IEC correspondence that relate to study approvals, updates, or changes. The Investigator must also forward all IRB/IEC renewals to Juno.

12.2.3. Product Quality Complaint

A Product Quality Complaint (PQC) is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, purity, or performance of any drug product manufactured by or on behalf of Celgene Corporation

after it is released for distribution. PQCs may reduce the usability of the product for its intended function or affect performance of the product and therefore pose a significant risk to the subject. Examples of PQCs include (but are not limited to): mixed product, mislabeling, lack of effect, seal/packaging breach, product missing/short/overage, contamination, suspected falsified, tampered, diverted or stolen material, and general product/packaging damage. If you become aware of a suspected PQC, you are obligated to report the issue immediately. You can do so by emailing [redacted] or by contacting the Celgene Customer Care Center [redacted]

12.3. Access to Information for Monitoring

Site monitoring is necessary to ensure that the rights and well-being of study subjects are protected; that the reported trial data are accurate, complete, and verifiable; and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with ICH GCP, and with applicable regulatory requirement(s). In accordance with regulations and guidelines, the designated Juno CRA must have direct access to the Investigator's source documentation (including medical records, test and procedure results, investigator and study staff notes, etc.) in order to verify the accuracy of the data recorded in the CRF.

The CRA is responsible for routine review of the CRFs at regular intervals throughout the study to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them. The CRA should have access to any subject records needed to verify the entries on the CRFs. The Investigator agrees to cooperate with the CRA to ensure that any problems detected through any type of monitoring (central, on site) are resolved.

Details regarding site monitoring are provided in the H125001 Study Monitoring Plan.

12.4. Site Audits and Regulatory Inspections

Representatives of regulatory authorities, Juno, or IRB/IEC may conduct inspections or audits of the clinical study. If the Investigator is notified of an inspection by a regulatory authority, the Investigator will notify the Juno Study Manager immediately. The Investigator will provide to representatives of a regulatory agency or Juno access to records, facilities, and personnel for the effective conduct of any inspection or audit.

12.5. Protocol Deviations

Protocol deviations must be sent to the site's IRB per their policies. The Investigator is responsible for knowing and adhering to the institution's IRB requirements.

12.6. Quality Assurance and Quality Control

Juno or its designee will perform quality control and quality assurance checks of all clinical studies that it sponsors. Before the enrollment of any subject in this study, Juno personnel will review and provide training as needed to the Investigator, sub-investigators, and study site personnel regarding the following: protocol, IB, CRFs and procedures for their completion, informed consent process, and procedures for reporting SAEs. Site visits will be performed by Juno CRAs or designees periodically throughout the study. During these visits, information recorded on the CRFs will be verified against source documents, and requests for clarification or

correction may be made. The CRFs will be reviewed by the CRA for safety information, completeness, accuracy, and logical consistency. Computer programs that identify data inconsistencies may be used to help monitor the clinical study. Requests for clarification or correction will be sent to Investigators via data queries.

12.7. 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, Juno will be responsible for ensuring that this protocol is listed at the ClinicalTrials.gov website per the US FDA requirement and that information at the website relating to study design and conduct is appropriately updated during the course of the study.

12.8. Study Completion

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

- Return of all electronic and any non-electronic study data to Juno, if requested
- Data clarifications and/or resolutions
- Accounting, reconciliation, and final disposition of used and unused study drug
- Review of site study records for completeness

In addition, Juno reserves the right to temporarily suspend or prematurely terminate this study for any reason (see Section 4.12).

12.9. Site Termination

Juno has the right to terminate a study site at any time for various reasons. Study termination and follow-up will be performed in compliance with the conditions set forth in 21 CFR Parts 312.50 and 312.56 and local regulation.

12.10. Records Retention

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. Records of subjects, source documents, monitoring visit logs, inventory logs of study investigational product, regulatory documents, and other Juno correspondence pertaining to the study must be kept in the appropriate study files at the site. Source documents include all recordings and observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical study. This includes any electronic records. These records will be retained in a secure file for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study intervention. These documents should be retained for a longer period, however, if required by local regulations. Prior to the transfer or

destruction of these records, Juno must be notified in writing and be given the opportunity to further store such records.

12.11. Confidentiality of Information

Individual subjects and their research data will be identified by a unique study identification number. Subjects' names will remain confidential and will not be included in the database. This confidentiality extends to testing of biological samples and genetic tests in addition to the clinical information relating to subjects. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the Sponsor. All study findings will be stored in electronic databases. The Investigator will maintain a personal subject identification list (subject numbers with the corresponding subject names) to enable records to be identified.

For tracking purposes and product chain of custody, subjects' name and date of birth will be communicated to the study sponsor's scheduling and manufacturing staff. This information will also be listed on the leukapheresis cell collection bag, and other containers throughout the JCARH125 manufacturing process. This information will be maintained in a separate limited-access database and not together with any other clinical information. Only staff who need to use this information will have access to it.

12.12. Future Use of Stored Specimens and Data

Samples of blood and/or tissue collected during this study may be stored for future research at Juno in subjects who provide consent.

12.13. Publication Plan

Interim data from this study may be presented at scientific meetings. Juno is responsible for the H125001 final clinical study report (CSR) prepared according to ICH guidelines. A final CSR will be prepared and will include any subject who has signed informed consent, regardless of whether the study is completed or prematurely terminated. If appropriate, an abbreviated report may be prepared. The CSR will be in compliance with any applicable regulatory requirements and national laws and will be written in English.

12.14. Conflict of Interest

Any potential conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed in accordance with 21 CFR Part 54.

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14. APPENDICES

APPENDIX A. SCHEDULES OF EVALUATIONS

Table A-1: Pre-treatment Period

Procedure (protocol section reference)	Study period			Notes
	Screening	Apheresis	Pre-treatment Screening (≤ 14 [+3] days prior to lymphodepletion)	
Informed consent/HIPAA	X			
Eligibility criteria (5.1, 5.2)	X		X	
Medical history	X			
ECOG (Appendix F)	X		X	
Height/weight	X			
Physical examination (8.12.2)	X		X	Should include a routine neurologic examination with evaluation of the cranial nerves, motor and sensory skills, coordination, and balance, as well as a mental status examination
Vital signs (8.12.3)	X	X	X	
12-lead ECG (8.12.4)	X			May be performed up to 8 weeks before Screening
MUGA/ECHO	X[a]		X[b]	[a] May be performed up to 8 weeks before Screening [b] Only required for subjects who receive bridging chemotherapy with potentially cardiotoxic drugs; must be conducted within 7 days prior to lymphodepletion
Viral serology (8.12.6)	X			
Brain MRI	X			May be performed up to 8 weeks before Screening
CSF assessment (8.12.7)	X			Only required in subjects with signs/symptoms of potential CNS involvement
Serum pregnancy test	X		X[c]	Only in females of childbearing potential [c] Must be done within 7 days prior to initiation of lymphodepleting chemotherapy

Table A-1: Pre-treatment Period

Procedure (protocol section reference)	Study period			Notes
	Screening	Apheresis	Pre-treatment Screening (≤ 14 [+3] days prior to lymphodepletion)	
Pregnancy prevention counseling	X		X	To be documented in patient source at site.
Hematology (8.12.6)	X	X[d]	X	[d] May be done up to 24 hours prior to leukapheresis Hematology should be performed within 5 days prior to eligibility verification and subject enrollment
Coagulation (8.12.6)	X		X	Coagulation tests should be performed prior to any biopsy procedures Coagulation tests should be performed within 5 days prior to eligibility verification and subject enrollment
Chemistry (8.12.6)	X		X	Chemistry should be performed within 5 days prior to eligibility verification and subject enrollment
Inflammatory markers	X		X	Includes CRP and ferritin Inflammatory markers should be performed within 5 days prior to eligibility verification and subject enrollment
β_2-microglobulin	X		X	β_2-microglobulin must be performed within 5 days prior to eligibility verification and subject enrollment and within 3 days prior to initiation of lymphodepleting chemotherapy
MM serum tests	X		X	Includes SPEP, immunofixation, sFLC, quantitative immunoglobulins
MM 24-hour urine tests (UPEP and immunofixation)	X		X	Pre-treatment Screening sample is not required for subjects with negative M-protein in their urine (by both UPEP and immunofixation) at Screening
Cytogenetics	X			A cytogenetics report is requested if available; a new test is not required
PET/CT or DW-MRI	X[e]		X[f]	[e] All subjects **must** have either a PET/CT or DW-MRI at Screening to evaluate for extramedullary plasmacytomas. At the Investigator's discretion, PET/CT or DW-MRI may be used in lieu of the skeletal survey to evaluate for bone lesions provided the same imaging modality is used for all future assessments

Table A-1: Pre-treatment Period

Procedure (protocol section reference)	Study period			Notes
	Screening	Apheresis	Pre-treatment Screening (≤ 14 [+3] days prior to lymphodepletion)	
				[f] A PET/CT or DW-MRI is required for subjects who had extramedullary lesions at Screening, received subsequent bridging therapy after leukapheresis, or who have suspicion of a new extramedullary lesion. The same imaging modality should be used for all assessments. Subjects who did not have extramedullary disease at screening and who do not have an evident proof of disease progression, do not have to repeat a PET/CT or DW MRI after bridging therapy.
Skeletal survey	X			At the Investigator's discretion, PET/CT or DW-MRI may be performed in lieu of the skeletal survey to evaluate for bone lesions provided the same imaging modality is used for all future assessments
Bone marrow biopsy/aspirate, plasmacytoma biopsy for disease assessments (8.12.1) and PK [redacted] 8.12.9.3)	X[g]		X[h]	[g] Bone marrow samples required for all subjects. [h] Bone marrow samples required only for subjects who had inadequate or insufficient bone marrow samples at Screening and for subjects who received bridging chemotherapy. Plasmacytoma biopsy samples are also requested for subjects with accessible lesions.
Blood sample for PK, [redacted] (8.12.8)			X	
Blood sample for RCL (8.12.10)			X	
HRQoL questionnaires (8.12.11)			X	
Leukapheresis (8.3)		X		
Adverse events (9.5.1)	X[i]	X[j]	X[j]	[i] Record AEs/SAEs related to protocol-mandated procedures until leukapheresis [j] Record AEs related to protocol-mandated procedures and all SAEs

Table A-1: Pre-treatment Period

Procedure (protocol section reference)	Study period			Notes
	Screening	Apheresis	Pre-treatment Screening (≤ 14 [+3] days prior to lymphodepletion)	
Concomitant medications (6.7)	X[k]	X[l]	X[l]	[k] Record all medications taken at the time of AEs/SAEs related to protocol-mandated procedures until leukapheresis [l] Record all medications taken at the time of AEs related to protocol-mandated procedures and at the time of an SAE
MMSE			X	If subjects develop neurologic symptoms suspicious of and/or diagnosed as neurologic toxicity, subjects will have daily MMSE exams (see Appendix E) until resolution of symptoms, unless the subject is medically incapacitated and/or medically unable to complete the MMSE

AE, adverse event; BCMA, B-cell maturation antigen; CNS, central nervous system; CRP, C-reactive protein; CSF, cerebrospinal fluid; DW-MRI, diffusion-weighted magnetic resonance imaging; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; HIPAA, Health Insurance Portability and Accountability Act; HRQoL, health-related quality of life; MM, multiple myeloma; MMSE, Mini Mental State Examination; MRI, magnetic resonance imaging; PET/CT, positron emission tomography/computed tomography; PK, pharmacokinetics; RCL, replication-competent lentivirus; SAE, serious adverse event; sFLC, serum free light chain; SPEP, serum protein electrophoresis; UPEP, urine protein electrophoresis.

Table A-2: Treatment Period

	Lymphodepletion	JCARH125									Notes
Study day	**-7 to -2[a]**	**1[b]**	**2**	**3**	**4-5**	**8**	**11**	**15**	**22**	**29**	[a] All evaluations should be performed daily prior to administration of Flu/Cy unless otherwise indicated [b] All evaluations should be performed prior to JCARH125 administration unless otherwise indicated
Month											
Visit window (days)						±1	±1	±2	±2	±2	
Procedure (protocol section reference)											
ECOG (Appendix F)	X									X	First day of lymphodepletion only
Weight	X										First day of lymphodepletion only (may be obtained within the previous 48 hours)
Physical examination (8.12.2)	X	X	X	X	X	X	X	X	X	X	Should include a routine neurologic examination with evaluation of the cranial nerves, motor and sensory skills, coordination, and balance, as well as a mental status examination
Vital signs (8.12.3)	X	X	X	X	X	X	X	X	X	X	
ECG		X									
Brain MRI		As clinically indicated to assess signs and symptoms of neurotoxicity									If CT and/or MRI scans are obtained as part of a neurologic examination, results should be reported
CSF assessment (8.12.7)		As clinically indicated to assess signs and symptoms of neurotoxicity									If a lumbar puncture is performed, samples should be submitted to the central laboratory for evaluation of JCARH125 cells and inflammatory markers
Hematology (8.12.6)	X[c]	X	X	X	X	X	X	X	X	X	[c] Hematology should be performed within 48 hours prior to the start of lymphodepleting chemotherapy
Coagulation (8.12.6)	X	X	X	X	X	X	X	X	X	X	Coagulation tests should be performed within 7 days prior to any biopsy procedures

Table A-2: Treatment Period

	Lymphodepletion	JCARH125									Notes
Study day	**-7 to -2[a]**	**1[b]**	**2**	**3**	**4-5**	**8**	**11**	**15**	**22**	**29**	[a] All evaluations should be performed daily prior to administration of Flu/Cy unless otherwise indicated [b] All evaluations should be performed prior to JCARH125 administration unless otherwise indicated
Month											
Visit window (days)						±1	±1	±2	±2	±2	
Chemistry (8.12.6)	X[d]	X	X	X	X	X	X	X	X	X	[d] Chemistry should be performed within 48 hours prior to the start of lymphodepleting chemotherapy, serum creatinine is used to calculate the creatinine clearance using the Cockcroft-Gault equation (Appendix D)
Inflammatory markers		X	X	X	X	X	X	X	X	X	Includes CRP and ferritin. Inflammatory markers should be performed within 48 hours prior to the start of lymphodepleting chemotherapy.
β_2-microglobulin										X	
MM serum tests										X	Includes SPEP, immunofixation, sFLC, quantitative immunoglobulins
MM 24-hour urine tests										X	Day 29 sample is not required for subjects with negative M-protein in their urine (by both UPEP and immunofixation) at Screening
PET/CT or DW-MRI										X[e]	[e] Day 29 is only required if clinically indicated to assess rapidly progressing MM disease. The same imaging modality should be used for all assessments.
Skeletal survey		As clinically indicated for signs/symptoms of new bone lesions									At the Investigator's discretion, PET/CT or DW-MRI may be performed in lieu of the skeletal survey to evaluate for bone lesions provided the same imaging modality is used for all assessments
Bone marrow biopsy/aspirate (8.12.1), plasmacytoma biopsy for disease assessments and PK								X[f]		X	Required for all subjects. [f] Plasmacytoma biopsy at Day 15 is not required.

Table A-2: Treatment Period

	Lymphodepletion	JCARH125									Notes
Study day	**-7 to -2[a]**	**1[b]**	**2**	**3**	**4-5**	**8**	**11**	**15**	**22**	**29**	[a] All evaluations should be performed daily prior to administration of Flu/Cy unless otherwise indicated [b] All evaluations should be performed prior to JCARH125 administration unless otherwise indicated
Month											
Visit window (days)						±1	±1	±2	±2	±2	
and biomarker evaluations (8.12.9.3)											
Disease response assessment by Investigator (8.12.1)										X	
Blood sample for PK, [redacted] (8.12.8)		X	X		X	X	X	X	X	X	
HRQoL questionnaires (8.12.11)										X	
Lymphodepleting chemotherapy (6.2)	X										Lymphodepleting chemotherapy should be withheld if the calculated CrCl is ≤ 60 mL/min or radioisotope GFR is ≤ 60 mL/min/1.73 m^2. Subjects with CrCl between 60 and 70 mL/min should have a 20% reduction of fludarabine.

Table A-2: Treatment Period

	Lymphodepletion	JCARH125									Notes
Study day	**-7 to -2[a]**	**1[b]**	**2**	**3**	**4-5**	**8**	**11**	**15**	**22**	**29**	[a] All evaluations should be performed daily prior to administration of Flu/Cy unless otherwise indicated [b] All evaluations should be performed prior to JCARH125 administration unless otherwise indicated
Month											
Visit window (days)						±1	±1	±2	±2	±2	
Anakinra prophylaxis* (6.3)	X	X	X	X	X						*For subjects receiving prophylactic intervention of anakinra. 1 dose of 100 mg SC the night before and in the morning, 3 hours before JCARH125 infusion. Continue for d1, d2, d3, d4, d5 at a dose of 100 mg SC. In the case of CRS onset, anakinra 100 mg SC should be administered twice daily until CRS resolution. The anakinra dose should be administered at approximately the same time every day.
JCARH125 administration (6.3)		X									
AEs (9.5.1)	X	X	X	X	X	X	X	X	X	X	Collect all AEs/SAEs from start of lymphodepleting chemotherapy to 90 days after the dose of JCARH125 (or to 30 days after the last dose of Flu/Cy for subjects who are discontinued from the study prior to JCARH125 administration)
Concomitant medications (6.7)	X	X	X	X	X	X	X	X	X	X	Record all concomitant medications from start of lymphodepleting chemotherapy to 90 days after the dose of JCARH125 (or to 30 days after the last dose of Flu/Cy for subjects who are discontinued from the study prior to JCARH125 administration)

Table A-2: Treatment Period

	Lymphodepletion	JCARH125									Notes
Study day	**-7 to -2[a]**	**1[b]**	**2**	**3**	**4-5**	**8**	**11**	**15**	**22**	**29**	[a] All evaluations should be performed daily prior to administration of Flu/Cy unless otherwise indicated [b] All evaluations should be performed prior to JCARH125 administration unless otherwise indicated
Month											
Visit window (days)						±1	±1	±2	±2	±2	
MMSE		X			X	X		X		X	Subjects who develop neurologic symptoms suspicious of and/or diagnosed as neurologic toxicity will have daily MMSE exams (see Appendix E) until resolution of symptoms, unless the subject is medically incapacitated and/or medically unable to complete the MMSE.

AE, adverse event; CR, complete response; CrCl, creatinine clearance; CRP, C-reactive protein; CSF, cerebrospinal fluid; Cy, cyclophosphamide; ECOG, Eastern Cooperative Oncology Group; Flu, fludarabine; GFR, glomerular filtration rate; HRQoL, health-related quality of life; MM, multiple myeloma; MMSE, Mini Mental State Examination; MRI, magnetic resonance imaging; PET/CT, positron emission tomography/computed tomography; PK, pharmacokinetics; sFLC, serum free light chain; SC = subcutaneous; SPEP, serum protein electrophoresis; UPEP, urine protein electrophoresis.

Table A-3: Post-treatment Period

	Post-treatment										PD or relapse	EOS	
Study day	**60**	**90**	**120**	**150**	**180**	**270**	**365**						
Month	**2**	**3**	**4**	**5**	**6**	**9**	**12**	**15**	**18**	**21**		**24**	
Visit window (days)	±14	±14	±14	±14	±14	±14	±14	±14	±14	±14	±14	±14	**Notes**
Procedure (protocol section reference)													
ECOG (Appendix F)	X	X	X	X	X	X	X	X	X	X	X	X	
Weight and vital signs											X	X	
Physical examination (8.12.2)	X	X	X	X	X	X	X	X	X	X	X	X	Should include a routine neurological examination with evaluation of the cranial nerves, motor and sensory skills, coordination, and balance, as well as a mental status examination
Brain MRI	As clinically indicated to assess signs and symptoms of neurotoxicity												If CT and/or MRI scans are obtained as part of a neurological examination, results should be reported
CSF assessment (8.12.7)	As clinically indicated to assess signs and symptoms of neurotoxicity												If a lumbar puncture is performed, samples should be submitted to the central laboratory for evaluation of JCARH125 cells and inflammatory markers
Serum pregnancy test		X			X	X	X						Only in females of childbearing potential
Pregnancy prevention counseling		X			X	X	X						
Hematology (8.12.6)	X	X	X	X	X	X	X	X	X	X	X	X	
Coagulation (8.12.6)	X	Coagulation tests should be performed prior to any biopsy procedures											
Chemistry (8.12.6)	X	X	X	X	X	X	X	X	X	X	X	X	
Inflammatory markers	X	X	X	X	X	X	X	X	X	X	X	X	Includes CRP and ferritin
β_2-microglobulin	X	X	X	X	X	X	X	X	X	X	X	X	

Table A-3: Post-treatment Period

	Post-treatment										PD or relapse	EOS	
Study day	**60**	**90**	**120**	**150**	**180**	**270**	**365**						
Month	**2**	**3**	**4**	**5**	**6**	**9**	**12**	**15**	**18**	**21**		**24**	
Visit window (days)	±14	±14	±14	±14	±14	±14	±14	±14	±14	±14	±14	±14	**Notes**
MM serum tests	X	X	X	X	X	X	X	X	X	X	X	X	Includes SPEP, immunofixation, sFLC, quantitative immunoglobulins
MM 24-hour urine test	X	X	X	X	X	X	X	X	X	X	X	X	Subjects who are negative for M-protein in their urine (by both UPEP and immunofixation) at Screening are only required to provide a 24-hour urine sample to confirm a CR and at EOS, or as clinically indicated
PET/CT or DW-MRI		X			X	X	X	X	X	X	X	X	Required at all disease measurement time points for all subjects with extramedullary disease at Screening or Pre-treatment Screening or if a new extramedullary lesion is suspected. Unscheduled assessment is required if clinically indicated to assess rapidly progressing MM disease.
Skeletal survey	As clinically indicated for signs/symptoms of new bone lesions												At the Investigator's discretion, PET/CT or DW-MRI may be performed in lieu of the skeletal survey (x-ray) to evaluate for bone lesions provided the same imaging modality is used for all assessments
Bone marrow biopsy/aspirate (8.12.1), plasmacytoma biopsy for disease assessments and PK [redacted] (8.12.9.3)		X			X		X		X		X	X	• Bone marrow samples required at indicated time points for all subjects. • Bone marrow samples are also required at any time when necessary to confirm a CR/sCR response. • When accessible, plasmacytoma biopsy samples are also requested for subjects who

Table A-3: Post-treatment Period

	Post-treatment										PD or relapse	EOS	
Study day	**60**	**90**	**120**	**150**	**180**	**270**	**365**						
Month	**2**	**3**	**4**	**5**	**6**	**9**	**12**	**15**	**18**	**21**		**24**	
Visit window (days)	±14	±14	±14	±14	±14	±14	±14	±14	±14	±14	±14	±14	**Notes**
													are suspected of achieving responses of sCR/CR/VGPR, or in case of disease progression and occurrence of new plasmacytomas.
Disease response assessment by Investigator (8.12.1)	X	X	X	X	X	X	X	X	X	X	X	X	
Blood sample for PK, [redacted] (8.12.8)	X	X			X	X	X		X		X	X	
Blood sample for RCL (8.12.10)		X			X		X				X	X	
HRQoL questionnaires (8.12.11)		X			X		X		X		X	X	
MMSE		X											Subjects who develop neurologic symptoms suspicious of and/or diagnosed as neurologic toxicity will have daily MMSE exams (see Appendix E) until resolution of symptoms, unless the subject is medically incapacitated and/or medically unable to complete the MMSE.
Adverse events (9.5.1)	Collect all AEs/SAEs[d]	Collect AEs/SAEs related to JCARH125											[d] Collect all AEs/SAEs to 90 days after the dose of JCARH125 (or to 30 days after the last dose of Flu/Cy for subjects who are discontinued from the study prior to JCARH125 administration)
Concomitant medications (6.7)	Record all con meds[e]	Record the following medications:											

Table A-3: Post-treatment Period

	Post-treatment										PD or relapse	EOS	
Study day	**60**	**90**	**120**	**150**	**180**	**270**	**365**						
Month	**2**	**3**	**4**	**5**	**6**	**9**	**12**	**15**	**18**	**21**		**24**	
Visit window (days)	±14	±14	±14	±14	±14	±14	±14	±14	±14	±14	±14	±14	**Notes**
			• G-CSF (until start of new MM therapy) • Transfusions (until start of new MM therapy) • IVIG (until start of new MM therapy) • Anticancer therapies • Medications used to treat Grade ≥3 AEs/SAEs related to JCARH125										[c] Record all con meds to 90 days after the dose of JCARH125 (or to 30 days after the last dose of Flu/Cy for subjects who are discontinued from the study prior to JCARH125 administration)

AE, adverse event; CR, complete response; CRP, C-reactive protein; CSF, cerebrospinal fluid; Cy, cyclophosphamide; ECOG, Eastern Cooperative Oncology Group; EOS, End of Study; Flu, fludarabine; GVHD, graft-versus-host disease; HRQoL, health-related quality of life; IVIG, intravenous immunoglobulin; MM, multiple myeloma; MMSE, Mini Mental State Examination; MRI, magnetic resonance imaging; PD, progressive disease; PET/CT, positron emission tomography/computed tomography; PK, pharmacokinetics; SAE, serious adverse event; sFLC, serum free light chain; SPEP, serum protein electrophoresis; UPEP, urine protein electrophoresis.

Table A-4: Post-PD Period

	Post-treatment										EOS	
Study day	**60**	**90**	**120**	**150**	**180**	**270**	**365**					
Month	**2**	**3**	**4**	**5**	**6**	**9**	**12**	**15**	**18**	**21**	**24**	
Visit window (days)	±14	±14	±14	±14	±14	±14	±14	±14	±14	±14	±14	**Notes**
Procedure (protocol section reference)												
Blood sample for PK, [redacted] (8.12.8)	X	X			X	X	X		X		X	
Blood sample for RCL (8.12.10)		X			X		X				X	
Serum pregnancy test		X			X	X	X					
Pregnancy prevention counseling		X			X	X	X					
Adverse events (9.5.1)	Collect all AEs/SAEs[d]		Collect AEs/SAEs related to JCARH125									[d] Collect all AEs/SAEs to 90 days after the dose of JCARH125 (or to 30 days after the last dose of Flu/Cy for subjects who are discontinued from the study prior to JCARH125 administration)
Concomitant medications (6.7)	Record all con meds[e]		Record the following medications: • Anticancer therapies • Medications used to treat Grade ≥3 AEs/SAEs related to JCARH125									[e] Record all con meds to 90 days after the dose of JCARH125 (or to 30 days after the last dose of Flu/Cy for subjects who are discontinued from the study prior to JCARH125 administration)

AE, adverse event; Cy, cyclophosphamide; EOS, End of Study; Flu, fludarabine; PD, progressive disease; PK, pharmacokinetics; RCL, replication-competent lentivirus; SAE, serious adverse event.

APPENDIX B. IMWG UNIFORM RESPONSE CRITERIA FOR MULTIPLE MYELOMA

Response[a]	Criteria
Sustained MRD-negative[b]	• MRD negativity in the marrow (NGF or NGS, or both) and by imaging as defined below, confirmed minimum of 1 year apart. Subsequent evaluations can be used to further specify the duration of negativity (eg, MRD-negative at 5 years)
Flow MRD-negative[b]	• Absence of phenotypically aberrant clonal plasma cells by NGF on bone marrow aspirates using the EuroFlow standard operation procedure for MRD detection in multiple myeloma (or validated equivalent method) with a minimum sensitivity of 1 in 10^5 nucleated cells or higher
Sequencing MRD-negative[b]	• Absence of clonal plasma cells by NGS on bone marrow aspirate in which presence of a clone is defined as less than two identical sequencing reads obtained after DNA sequencing of bone marrow aspirates using the LymphoSIGHT platform (or validated equivalent method) with a minimum sensitivity of 1 in 10^5 nucleated cells or higher
Imaging-positive MRD-negative[b]	• MRD negativity as defined by NGF or NGS plus disappearance of every area of increased tracer uptake found at baseline or a preceding PET/CT or decrease to less mediastinal blood pool SUV or decrease to less than that of surrounding normal tissue
Stringent complete response (sCR)	• CR as defined below plus normal FLC ratio and absence of clonal cells in bone marrow biopsy by immunohistochemistry • (κ/λ ratio ≤4:1 or ≥1:2 for κ and λ patients, respectively, after counting ≥ 100 plasma cells)c
Complete response (CR)	• Negative immunofixation of serum and urine and disappearance of any soft tissue plasmacytomas and < 5% plasma cells in bone marrow aspirates • When the only method to measure disease is by serum FLC levels, CR can be defined as a normal FLC ratio of 0.26 to 1.65, in addition to the CR criteria listed previously.
Very good partial response (VGPR)	• Serum and urine M-protein detectable by immunofixation but not on electrophoresis or ≥ 90% reduction in serum M-protein level plus urine M-protein level < 100 mg/24 h • When the only method to measure disease is by serum FLC levels, VGPR requires a ≥ 90% decrease in the difference between involved and uninvolved FLC levels.
Partial response (PR)	• ≥ 50% reduction of serum M-protein plus reduction in 24-hour urinary M-protein by ≥ 90% or to < 200 mg/24 h • If the serum and urine M-protein are unmeasurable, a ≥ 50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria. • If serum and urine M-protein are unmeasurable, and serum-free light assay is also unmeasurable, ≥ 50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma-cell percentage was ≥ 30%. • In addition to these criteria, if present at baseline, a ≥ 50% reduction in the size (SPD)d of soft tissue plasmacytomas is also required
Minimal response (MR)	• ≥ 25% but ≤ 49% reduction of serum M-protein and reduction in 24-h urine M-protein by 50%–89%. In addition, if present at baseline, a ≥ 50% reduction in the size (SPD)d of soft tissue plasmacytomas is also required
Stable disease (SD)	• Not meeting criteria for CR, VGPR, PR, MR, or PD • Not recommended for use as an indicator of response; stability of disease is best described by providing the time-to-progression estimates.
Progressive disease (PD)[e,f,g]	Any one or more of the following criteria:

Response[a]	Criteria
	• Increase of ≥ 25% from lowest confirmed response value in one or more of the following criteria: – Serum M-protein (absolute increase must be ≥ 0.5 g/dL) – Serum M-protein increase ≥1 g/dL, if the lowest M component was ≥ 5 g/dL – Urine M-protein (absolute increase must be ≥ 200 mg/24 h) – In subjects without measurable serum and urine M-protein levels at baseline, the difference between involved and uninvolved FLC levels (absolute increase must be > 10 mg/dL) – In subjects without measurable serum and urine M-protein levels and without measurable involved FLC levels at baseline, bone marrow plasma-cell percentage irrespective of baseline status (absolute increase must be ≥ 10%) • Appearance of a new lesion(s), ≥ 50% increase from nadir in SPDd of > 1 lesion, or ≥ 50% increase in the longest diameter of a previous lesion >1 cm in short axis • ≥ 50% increase in circulating plasma cells (minimum of 200 cells/μL) if this is the only measure of disease
Relapse *(not applicable for this study)*	Clinical relapse requires one or more of the following criteria: • Direct indicators of increasing disease and/or end organ dysfunction (CRAB features) related to the underlying clonal plasma-cell proliferative disorder. It is not used in calculation of time to progression or progression-free survival but is listed as something that can be reported optionally or for use in clinical practice • Development of new soft tissue plasmacytomas or bone lesions (osteoporotic fractures do not constitute progression) • Definite increase in the size of existing plasmacytomas or bone lesions. A definite increase is defined as a 50% (and ≥ 1 cm) increase as measured serially by the SPDd of the measurable lesion • Hypercalcaemia (> 11 mg/dL) • Decrease in hemoglobin of ≥ 2 g/dL not related to therapy or other non-myeloma-related conditions; • Rise in serum creatinine by 2 mg/dL or more from the start of the therapy and attributable to myeloma • Hyperviscosity related to serum paraprotein

FLC = free light chain; MRD = minimal residual disease; NGF = next-generation flow; NGS = next-generation sequencing; SPD = sum of the products of the maximal perpendicular diameters of measured lesions; SUV = standardized uptake value.

[a] All categories of response and MRD require no known evidence of progressive or new bone lesions if radiographic studies were performed. All response categories require two consecutive assessments (confirmatory measurement); however, consecutive assessments of bone marrow for CR and MRD is not required. Confirmatory evaluations can be carried out at any time following the initial test provided it is before any new/non-protocol therapy.

[b] IMWG MRD criteria requires a CR

[c] Presence/absence of clonal cells on immunohistochemistry is based upon the κ/λ/L ratio. An abnormal κ/λ ratio by immunohistochemistry requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is κ/λ of > 4:1 or < 1:2.

[d] Plasmacytoma measurements should be taken from the CT portion of the PET/CT, or MRI scans, or dedicated CT scans where applicable. For subjects with only skin involvement, skin lesions should be measured with a ruler. Measurement of tumor size will be determined by the SPD.

[e] Positive immunofixation alone in a subject previously classified as achieving a complete response will not be considered progression. For purposes of calculating time to progression and progression-free survival, subjects who have achieved a CR and are MRD-negative should be evaluated using criteria listed for progressive disease. Criteria for relapse from a CR or relapse from MRD should be used only when calculating disease-free survival.

[f] In the case where a value is felt to be a spurious result per physician discretion (eg, a possible laboratory error), that value will not be considered when determining the lowest value.

[g] All relapse categories require two consecutive assessments made at any time before classification as disease progression and/or institution of any new therapy.

Source: (Kumar, 2016).

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

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

APPENDIX D. MANAGEMENT OF TOXICITIES ASSOCIATED WITH JCARH125

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

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

1. CYTOKINE RELEASE SYNDROME

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

1.1 Pathophysiology of Cytokine Release Syndrome

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

1.2 Clinical Presentation of Cytokine Release Syndrome

Cytokine release syndrome is characterized by high fever, fatigue, nausea, headache, dyspnea, tachycardia, rigors, hypotension, hypoxia, myalgia/arthralgia, and/or anorexia. Clinical symptoms and severity of CRS are highly variable (Lee, 2014), and management can be complicated by concurrent conditions. In multiple myeloma (MM) subjects treated with JCARH125, CRS usually occurs within 10 days after infusion (Mailankody, 2018).

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

1.3 Clinical Management of Cytokine Release Syndrome

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

CRS has been described to be more severe in subjects with multiple myeloma with higher disease burden and is associated with increased serum cytokines including IL-6, IFN-γ, and other cytokines together with elevation of inflammatory markers C-reactive protein (CRP) and ferritin (Cohen, 2019; Brudno, 2016; Lee, 2015; Davila, 2014).

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

A modification of the CTCAE CRS grading scale has been established to better reflect CAR T cell-associated CRS, as detailed in Table 8 (Lee, 2014).

Table 8: Grading Criteria for Cytokine Release Syndrome

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

CRS = cytokine release syndrome; FiO_2 = fraction of inspired oxygen; IV = intravenous; N/A = not applicable; SaO_2 = oxygen saturation; SBP = systolic blood pressure
[a] Definition of high-dose vasopressors in Table 9.

Table 9: High-dose Vasopressors (all doses required for ≥ 3 hours)

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

[a] VASST Trial Vasopressor Equivalent Equation: Norepinephrine equivalent dose = [norepinephrine (µg/min)] + [dopamine (µg/kg/min) ÷ 2] + [epinephrine (µg/min)] + [phenylephrine (µg/min) ÷ 10].
Source: Adapted from (Lee, 2014).

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

Tocilizumab, an anti-IL-6R (interleukin 6 receptor)-antibody, may be required in some cases to treat toxicities such as severe CRS. Please refer to the currently approved Actemra® prescribing information (United States) or RoActemra® Summary of Product Characteristics (Europe). Actemra has been approved by the Food and Drug Administration (FDA) for the treatment of CAR T cell-induced severe or life-threatening CRS in adults. RoAcetmra has been approved by the European Medicines Agency (EMA) for the treatment of CAR T cell-induced severe or life-threatening CRS in adults. The preferred dose to intervene in adult subjects with CRS is 8 mg/kg (maximum 800 mg) intravenously (IV). In the absence of clinical improvement within 24 hours

after the first dose or if rapid deterioration should occur, a second dose of tocilizumab should be administered and a second-line agent, such as a corticosteroid, should also be introduced simultaneously.

Corticosteroids have been successfully used in the treatment of CRS, as both first- and second-line treatment. Many times, only short courses of corticosteroids are required (Turtle, 2016; Lee, 2015; Maude, 2014a; Schuster, 2017; Park, 2018). In case of rapid onset of CRS Grade 1 in severity or slow onset of CRS starting as Grade 2 in severity following tocilizumab, initiation of therapy with dexamethasone should be considered (Figure 2).

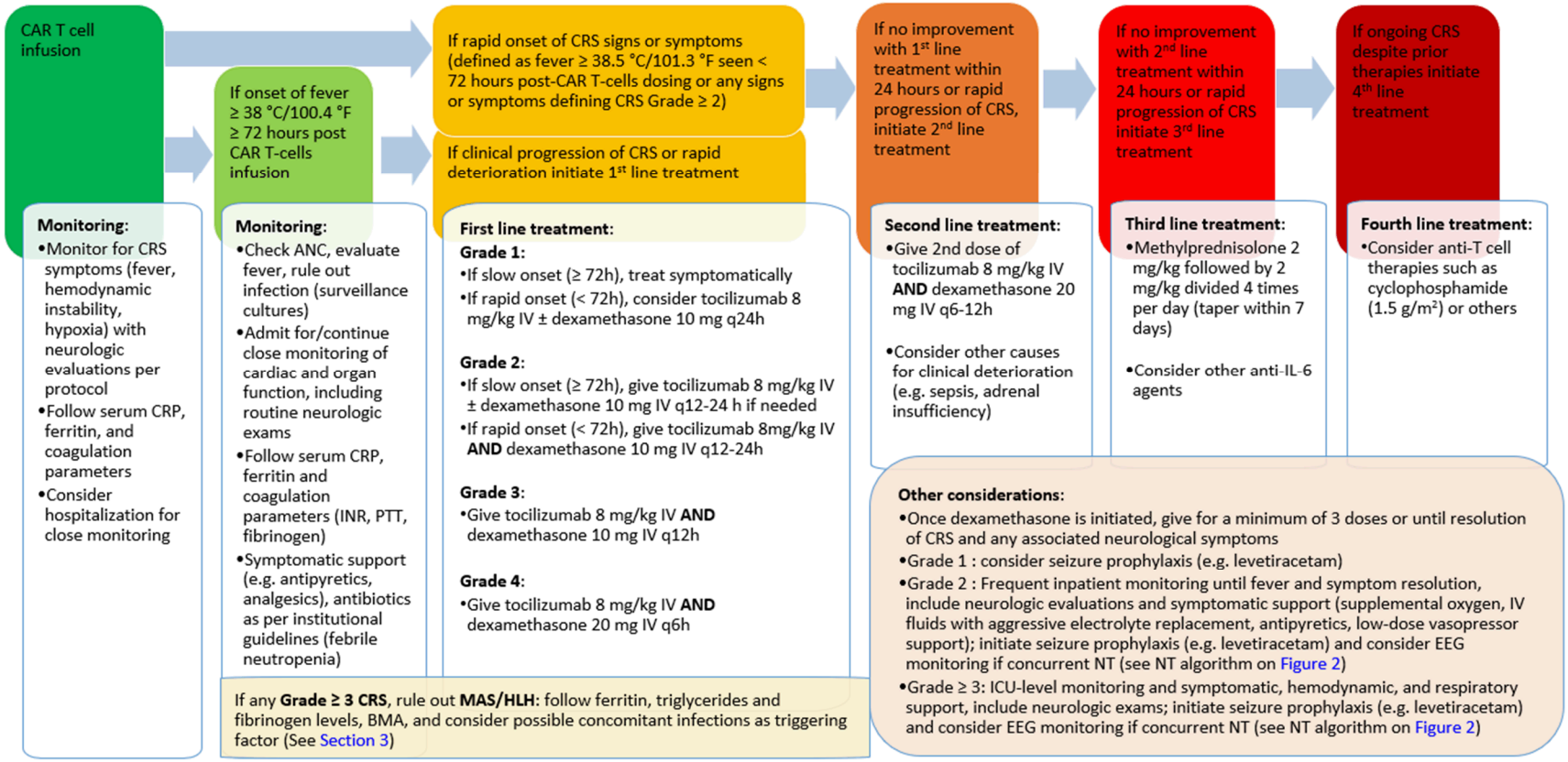
Other anti-IL-6 agents such as **siltuximab**, if available, should be considered in the event that severe CRS is not responding to tocilizumab and corticosteroids. Siltuximab is another monoclonal antibody that blocks IL-6 signaling by binding IL-6 itself and preventing it from activating immune effector cells. Siltuximab has a higher affinity for IL-6 than tocilizumab has for the IL-6R, making it a very effective tool in managing CRS. If a patient does not respond to tocilizumab and corticosteroids, then the use of siltuximab is encouraged. Dosing of any other anti-IL-6 agent should be per prescribing information.

Interleukin 1 blockade through IL-1 receptor antagonist (IL-1Ra) could demonstrably prevent severe CRS while maintaining intact antitumor efficacy (Giavridis, 2018). The benefits of an IL-1 blockade through IL-1Ra are especially intriguing given the latter's ability to cross the blood–brain barrier (BBB) (Gutierrez, 1994), unlike tocilizumab (Neelapu 2018). Human microglia activated by IL-1 may produce inducible nitric oxide synthase and proinflammatory cytokines (Liu, 1996; Tarassishin, 2014); therefore, blocking IL-1 could potentially not only protect from severe CRS but also could reduce the severity of CAR T cell–related neurotoxicity. One of the selective IL-1Ra is anakinra. **Anakinra** should be considered in the event that severe CRS is not responding to tocilizumab and corticosteroids. Anakinra should be given until resolution of CRS with a daily dose of 100 mg subcutaneously (SC). In more severe CRS cases, especially if combined with MAS/HLH and/or neurotoxicity, anakinra 100 mg twice daily (every 12 hours) SC should be given until resolution of CRS and other concurrent CAR T cell toxicities, like neurotoxicity and/or MAS/HLH which could benefit from anakinra treatment.

In the most unresponsive severe cases, additional treatments should be considered. Recent data suggest that monocytes and macrophages contribute to the development of CRS and neurotoxicity after CAR T cell therapy. Therefore, neutralization of GM-CSF has been investigated as a potential strategy to manage CAR T cell–associated toxicities. **Lenzilumab** is a humanized monoclonal antibody that neutralizes GM-CSF. Pre-clinical and clinical data demonstrate that lenzilumab can prevent CRS and significantly reduce serious neurological toxicities (Sterner, 2018; Sterner, 2019).

Other possible treatments for persistent or worsening CRS include etanercept and infliximab (TNF-α inhibitors), T cell depleting alemtuzumab, anti-thymocyte globulin (ATG), cyclophosphamide, ruxolitinib, or ibrutinib (Borrega, 2019). However, if subject is still receiving anakinra for management of CAR T cells toxicity, the use of anakinra in combination with TNF blocking agents is not recommended.

Figure 2: Cytokine Release Syndrome Treatment Algorithm



ANC = absolute neutrophil count; BMA = bone marrow aspirate; CAR = chimeric antigen receptor; CRP = C-reactive protein; CRS = cytokine release syndrome; EEG = electroencephalogram; HLH = hemophagocytic lympho-histiocytosis; ICU = intensive care unit; IL-6 = interleukin 6; IL-1Ra = interleukin 1 receptor antagonist; INR = international normalized ratio; IV = intravenous; MAS = macrophage activation syndrome; NT = neurologic toxicity; PTT = partial thromboplastin time; q = every.

2. Macrophage Activation Syndrome /Hemophagocytic Lympho-histiocytosis

Macrophage activation syndrome or HLH is a rare, potentially fatal immune-mediated disease, which is caused by impaired NK and cytotoxic T cell function. This syndrome has a wide range of causes, symptoms, and outcomes, but all lead to a hyperinflammatory response with some characteristics that overlap with CRS and organ damage (Ramos-Casals, 2014). Pathophysiology of MAS/HLH is divided into primary (genetic) and secondary (reactive) forms. Secondary MAS/HLH is subclassified as viral, autoimmune, or tumor related. Macrophage activation syndrome/HLH has both infectious and non-infectious triggers (Ramos-Casals, 2014). Viral infection is the most frequent trigger, either due to primary infection or after reactivation in immunosuppressed patients. Hemophagocytic lympho-histiocytosis can be triggered by viral infections, malignancy, autoimmune disease, and acquired immune deficiencies (Usmani, 2013), whereas MAS is most often associated with autoimmune and autoinflammatory diseases (Ravelli, 2016). Bacterial and fungal infections can also trigger MAS/HLH. Both conditions are characterized by a dysregulated immune response resulting in a cytokine storm. Available data suggests MAS/HLH emergence as a possible consequence of CRS with CAR T cells being a trigger of MAS/HLH (Neelapu, 2017; Borrega, 2019). In many aspects, severe CRS resembles MAS/HLH (Borrega, 2019). In clinical and laboratory findings, the cytokine profile and myeloid-driven inflammatory responses are closely related between MAS/HLH and severe CRS. In patients with CRS-related MAS/HLH-like syndrome (MALS), additional cytokines such as IL-18, IL8, IP10, MCP1, MIG, and MIP1β are also elevated (Teachey, 2016). These cytokines also have been reported to be elevated in classical MAS/HLH. In addition, IL-6 may also promote the development of MAS/HLH in the setting of CRS by inducing dysfunction of cytotoxic activity in T and NK cells, which is a hallmark of MAS/HLH (Cifaldi, 2015). Consequently, CRS-related MAS/HLH is difficult to distinguish from primary MAS/HLH or other conditions that can mimic MAS/HLH such as sepsis. Table 10 summarizes some of the factors that help to distinguish CRS-related MAS/HLH from other conditions that present similarly.

Table 10: Differential Diagnoses of CRS-related MAS/HLH

	Familial HLH	Secondary HLH/MAS	CRS-related HLH/MAS	Sepsis
Genetic Predisposition	Homozygous mutations	Heterozygous mutations in some patients	unknown	unknown
Age group	Young children	All ages	All ages	All ages
Biomarkers				
IL-10	↑↑↑	↑↑↑	↑	↑
IFN-γ	↑↑↑	↑↑↑	↑↑↑	←→
IL-6	↑	↑	↑↑↑	↑↑↑
Ferritin	↑↑↑	↑↑↑	↑↑↑	↑
CD163	↑↑↑	↑↑↑	NDA	↑

HLH = hemophagocytic lympho-histiocytosis; IFN-γ = interferon gamma; IL = interleukin; MAS = macrophage activation syndrome; NDA = no data available.
Source: Shimabukuro-Vornhagen, 2018.

Although in most cases MAS/HLH that develops concurrently with CRS is triggered by CRS, other causes of MAS/HLH, such as genetic defects (in pediatric patients), autoimmune disease,

infection, or the underlying malignancy itself should be considered. Patients with hematological malignancies have a higher risk of developing MAS/HLH. Macrophage activation-like syndrome is a distinct entity that leads to early death in septic patients and must be carefully ruled out in patients who are prone to develop severe infections, including patients following CAR T cell therapy (Karakike, 2019).

2.1 Clinical Presentation and Diagnosis of Macrophage Activation Syndrome/Hemophagocytic Lympho-histiocytosis

The presentation of secondary MAS/HLH is heterogeneous and characterized by a panoply of clinical signs and symptoms. Cytokine release syndrome shares many pathogenetic and clinical similarities with MAS/HLH such as high fever, very high ferritin levels, cytokine profiles, and the importance of macrophages in the pathogenesis (Ravelli, 2016). The clinical syndrome can be acute or subacute with non-specific symptoms appearing over a few days to 4 weeks (Ramos-Casals, 2014). The cardinal features are continuous high fever (≥ 38.5°C) and enlarged lymphohematopoietic organs (spleno/hepatomegaly), occasionally accompanied by adenopathy. Pulmonary, neurologic, cutaneous, and gastrointestinal involvement may also be present.

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

Detection of any ongoing infection acting as a trigger for MAS/HLH is critical (Figure 2). Standard tests should be used to screen for infections caused by the most common viruses such as herpes, cytomegalovirus (CMV), and Epstein-Barr virus (EBV). Other infectious agents (eg, mycobacteria, parasites, and fungi, particularly Candida and Mucor) should be ruled out according to specific clinical or epidemiological features (Ramos-Casals, 2014; Lehmberg, 2015).

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

The diagnosis of MAS/HLH (according to HLH-2004 consensus criteria, further revised in 2014 for HLH associated with malignancies) (Lehmberg, 2015) can be established if either of the 2 criteria below is fulfilled:

1. A molecular diagnosis consistent with MAS/HLH
2. Diagnostic criteria for MAS/HLH fulfilled (5 out of the 8 criteria below):
    a. high persistent fever (≥ 38.5°C)
    b. splenomegaly
    c. cytopenias (affecting 2 of 3 lineages in the peripheral blood): Hemoglobin < 90 g/L, platelets < 100 x 10^9/L, and neutrophils < 1.0 x 10^9/L
    d. triglycerides ≥ 3.0 mmol/L (ie, 265 mg/dL) or fibrinogen ≤ 1.5 g/L
    e. hemophagocytosis in bone marrow, spleen, and/or lymph nodes
    f. low or absent NK-cell activity (according to local laboratory reference range)
    g. ferritin ≥ 500 ng/mL
    h. soluble CD25 (ie, soluble IL-2 receptor) ≥ 2,400 U/mL

2.2 Clinical Management of Macrophage Activation Syndrome/Hemophagocytic Lympho-histiocytosis

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

1. **Supportive care** is essential because of frequent life-threatening, severe manifestations at presentation.
2. **Appropriate broad-spectrum antiviral, antibacterial, antifungal prophylaxis, and treatment** must be initiated. The elimination of triggers (particularly infection) is crucial to remove the stimuli that initiate the abnormal immune system activation.
3. Suppression of the inflammatory response and cell proliferation by immunosuppressive and cytotoxic drugs, respectively, is necessary.
    a. **First-line treatment** includes IL-6-blockade with tocilizumab unless tocilizumab was already administered for the management of CRS. Glucocorticoids are also indicated for the initial treatment of MAS/HLH, irrespective of the cause (CRS Grade 4 treatment recommendations should be followed).
    b. **Second-line treatment** includes interleukin 1 blockade with anakinra. Anakinra should be given until resolution of MAS/HLH as a daily dose of 100 mg SC.
    c. **In case of rapidly progressing clinical course** with ongoing CRS, anakinra should be administered as first-line treatment. In more severe MAS/HLH cases, especially if combined with CRS and/or neurotoxicity, anakinra 100 mg SC twice daily should be given until resolution of MAS/HLH and other concurrent CAR T cell toxicities, which could benefit from anakinra treatment.
    d. Anti-IL-6 antibody, siltuximab, might be considered as second-line therapy. The use of cyclosporin, cyclophosphamide, etoposide, and/or intrathecal methotrexate is not generally indicated in patients who develop MAS/HLH after CAR T cell therapy but may have to be employed in refractory cases.
    e. Newer emerging treatments include emapalumab (anti-IFN-γ antibody), which has been approved by the FDA for the treatment of primary refractory or recurrent MAS/HLH (Benedetti, 2019).

3. Neurologic Toxicities

CAR T cell therapy is associated with unique neurologic toxicities. Neurologic symptoms may include altered mental status, aphasia, altered level of consciousness, and seizures or seizure-like activity. The start of neurologic symptoms has been noted with JCARH125 between 3 to 12 days with median time to onset of 3 days after CAR T cell infusion (Mailankody, 2018). With another B-cell maturation antigen (BCMA) CAR T cell therapy, bb2121, the start of neurologic symptoms has been noted between 3 to 11 days (median 5 days) after CAR T cell infusion (Raje, 2019). Severe neurological toxicity cases may require admission to the intensive care unit (ICU) for frequent monitoring, respiratory support, or intubation for airway protection. The symptoms are variable and generally occur as CRS is resolving or after CRS resolution.

3.1. Pathophysiology of Neurologic Toxicities

The pathogenesis of neurotoxicity is poorly defined. The pathophysiology of neurologic symptoms in CAR T cell therapy is poorly understood, but the lack of a strict temporal

association with CRS indicates that it might be independent from CRS. In addition, IL-6 pathway blockade does not seem to be beneficial in the treatment of neurologic symptoms, unlike in CRS, indicating a different pathomechanism. The evaluation of larger patient collectives showed that a high tumor burden and a more severe CRS lead to a more severe neurotoxicity (Gust, 2017; Santomasso, 2018). Neurotoxicity has been associated with early onset of CRS and rapid elevation of inflammatory cytokines both within the serum and central nervous system (CNS), perhaps leading to BBB disruption (Gust, 2017). Analysis of subjects with R/R MM treated with CAR T BCMA cells at the University of Pennsylvania, a peak in serum increases of IL-6, IFN-γ, and MIP-1α was identified as most associated with neurotoxicity in this study. Interestingly, neurotoxicity was also associated with peak fold-increases in IL-1Ra, an endogenous inhibitor of the proinflammatory effects of IL-1 alpha (IL-1α) and IL-1 beta (IL-1β), which have been implicated in post-CAR T cell neurotoxicity (Giavridis, 2018; Norelli, 2018). This potentially suggests that augmenting IL-1 blockade with the recombinant IL-1Ra anakinra in myeloma patients with CAR T cell–associated neurotoxicity may have therapeutic benefit, as demonstrated in preclinical models (Giavridis, 2018; Norelli 2018).

An analysis showed higher levels for cytokines which are usually associated with a systemic inflammation (ie, IL-6, IL-10, and interferon-gamma (IFN-g)) in patients who develop severe neurotoxicity indicating a correlation between systemic inflammation and neurologic events (Gust, 2017; Turtle, 2017; Santomasso, 2018).Peak levels in CRP are also significantly higher in subjects who develop any Grade or Grade 3 or higher neurotoxicity (Turtle, 2016; Heipel, 2017). Other organ dysfunction (hepatic and renal), as well as hypoxemia and infection, might also contribute to encephalopathy (Neelapu, 2018). In another study, it has been reported that evidence for cytokine-mediated endothelial activation causes coagulopathy, capillary leak, and BBB disruption, allowing transit of high concentrations of systemic cytokines into the cerebrospinal fluid. (Gust, 2017).

3.2 Clinical Management of Neurologic Toxicities

Levetiracetam or alternative anti-seizure medication should be considered for seizure prophylaxis. The optimal management of CAR T cell-induced neurotoxicity is unknown at this time. These management guidelines below represent the current state of knowledge and additional information will be provided to Investigators as it becomes available. A thorough neurologic evaluation, including electroencephalogram (EEG), magnetic resonance imaging (MRI), or computer tomography (CT) scan of the brain, and diagnostic lumbar puncture and frequent monitoring of cognitive function (eg, mini mental status examinations or handwriting tests) should be considered.

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

Magnetic resonance imaging and CT scans of the brain are usually negative for any anatomical pathology that would account for the neurotoxicity symptoms observed in subjects treated with CAR T cell therapy, although rare cases of reversible T2/fluid attenuated inversion recovery (FLAIR) MRI hyperintensity involving the thalami, dorsal pons, and medulla, and cerebral edema have been reported (Neelapu, 2018).

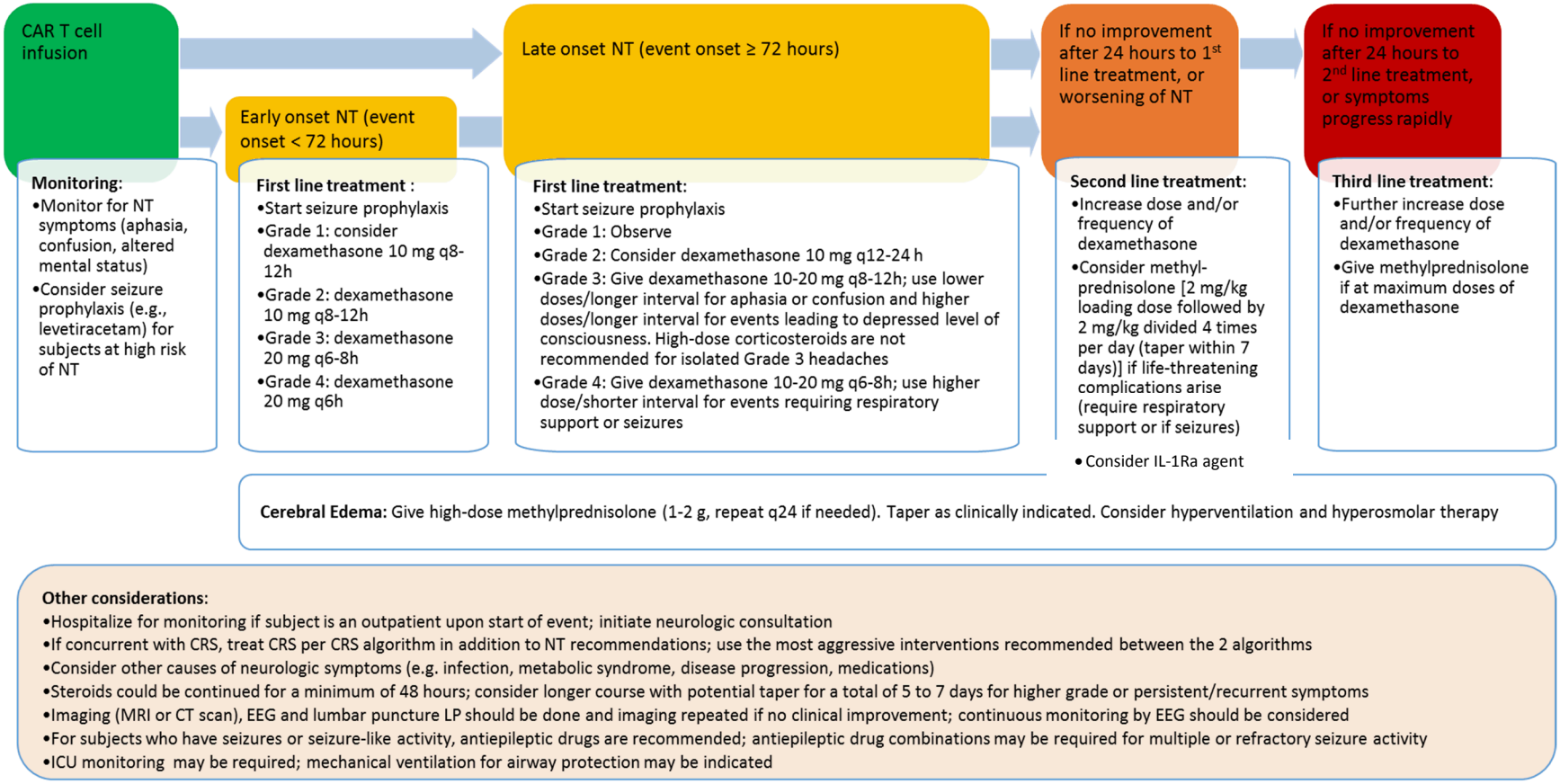
For subjects who have neurologic toxicity in the presence of CRS, the CRS should be managed following the guidelines provided in Figure 3.

Neurotoxicity management guidelines are provided in Figure 3.

First-line treatment includes corticosteroids to be used for severe neurotoxicity, especially in the absence of the classic hemodynamic perturbations of CRS. Tocilizumab does not cross the BBB and results in transient elevated IL-6 levels in the serum, which is implicated in the pathogenesis of neurotoxicity (Nellan, 2018). Thus, **tocilizumab is not recommended for the primary management of isolated neurotoxicity.** For the corticosteroids dosing regimen, please refer to Figure 3.

Second-line treatment includes siltuximab which effectively removes active IL-6 from circulation and since the siltuximab IL-6 complex is unlikely to cross the BBB, siltuximab should have a role in the management of CAR T cell-induced neurotoxicity (Riegler, 2019). Anakinra should be considered in the event of neurotoxicity onset with ongoing CRS as well as neurotoxicity. It should be given as a daily dose of 100 mg SC or 200 mg SC (100 mg every 12 hours) depending on the severity of neurotoxicity and other concurrent CAR T cell-related toxicities. Anakinra should be given until resolution of neurotoxicity and other concurrent CAR T cell toxicities which could benefit from anakinra treatment.

Figure 3: Neurotoxicity Treatment Algorithm



CAR = chimeric antigen receptor; CRS = cytokine release syndrome; CT = computed tomography; EEG = electroencephalogram; ICU = intensive care unit; IL = interleukin 1 receptor antagonist; LP = lumbar puncture; MRI = magnetic resonance imaging; NT = neurologic toxicity; q = every.

APPENDIX E. 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)

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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.**]

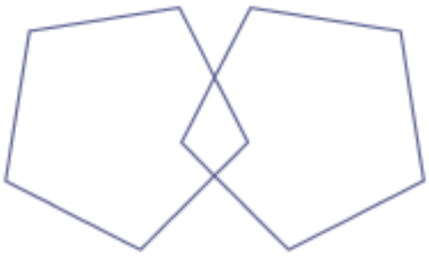
Score 1 point if the sentence is comprehensible and contains a subject and a verb. Ignore errors in grammar or spelling.

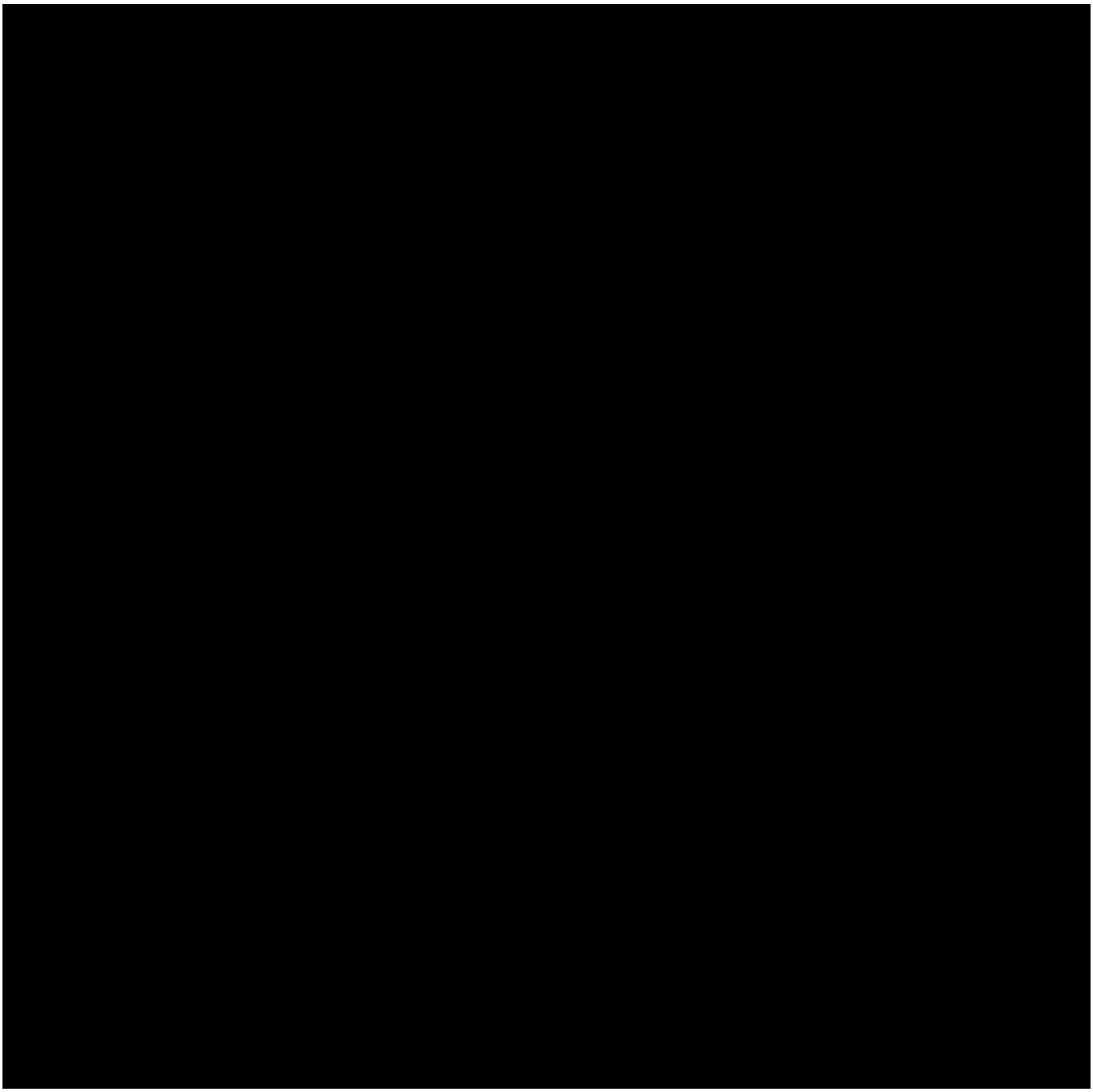
DRAWING

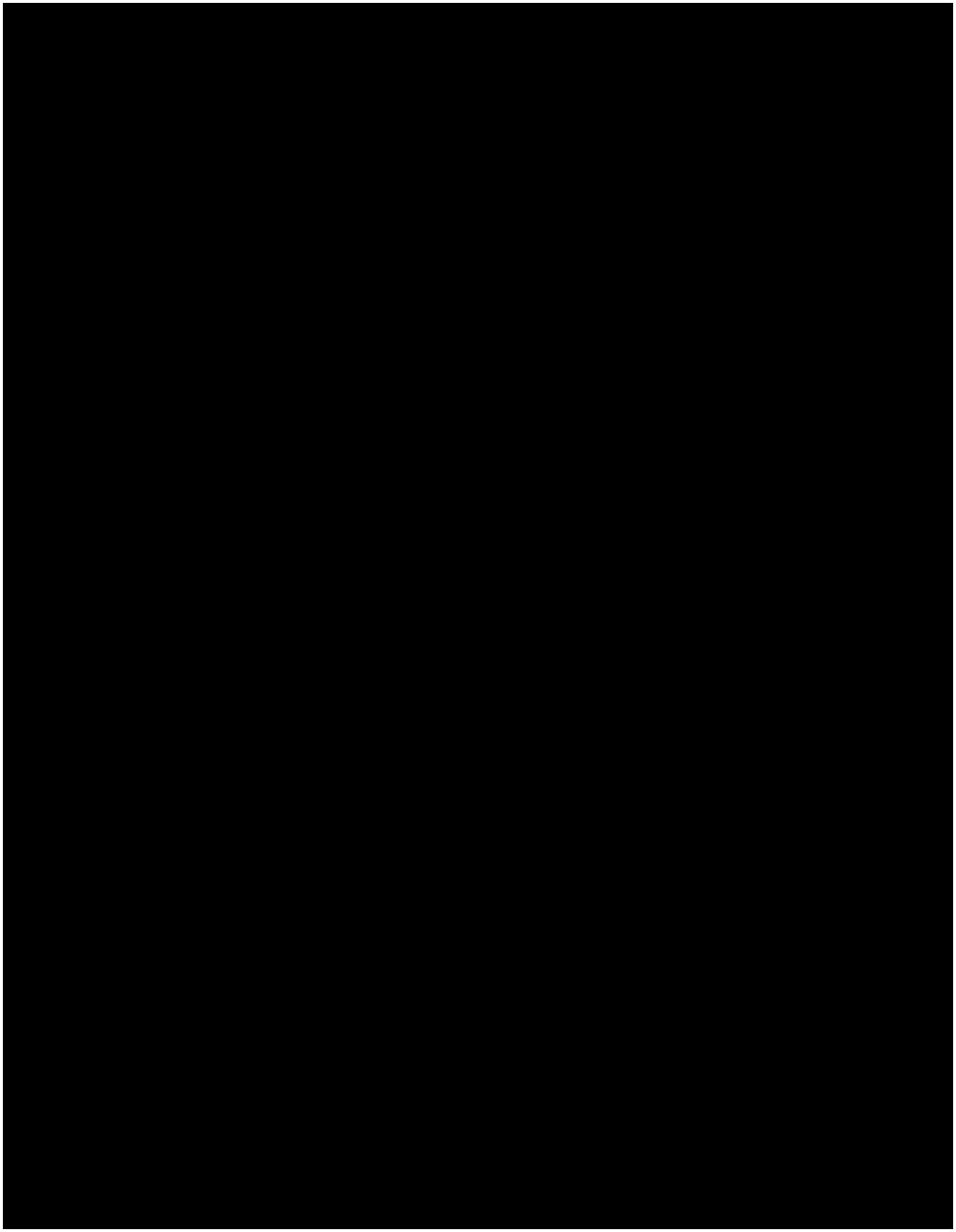
[*Display the intersecting pentagons on the stimulus form and provide a pen or pencil.*] **Please copy this design.** Score 1 point if the drawing consists of two 5-sided figures that intersect to form a 4-sided figure. 0 1

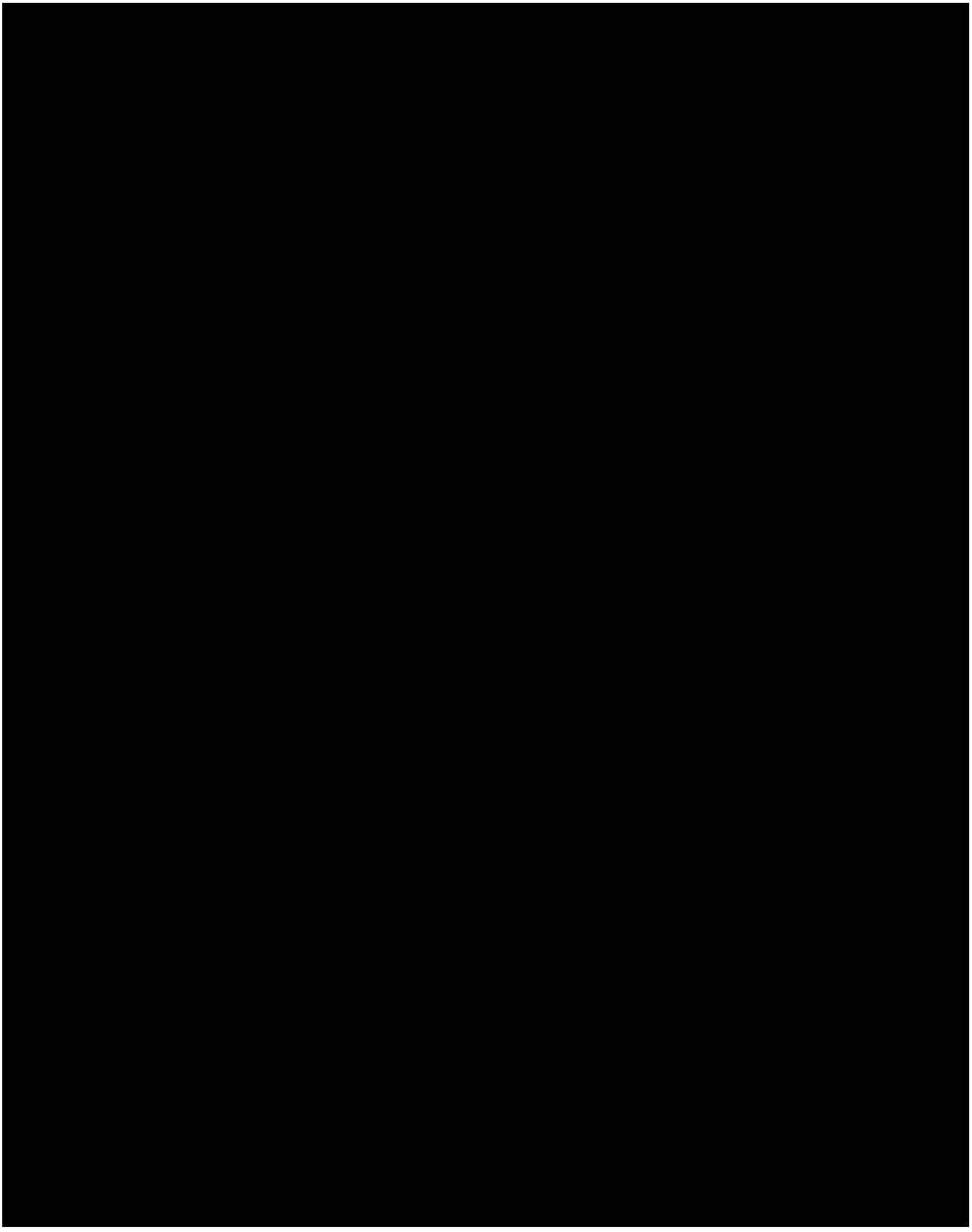
MMSE-2:SV total raw score ☐ (30 max. points)

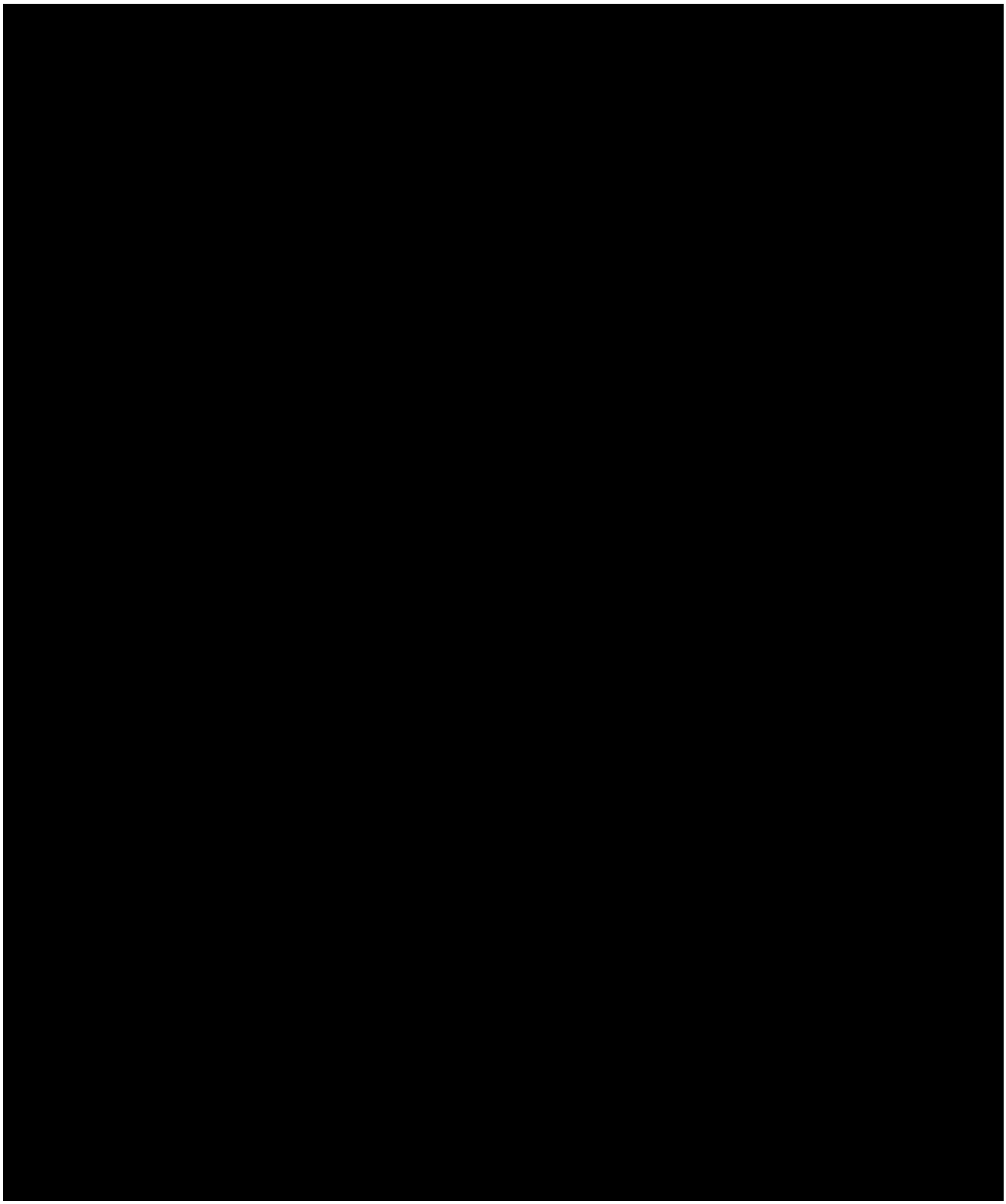
CLOSE YOUR EYES

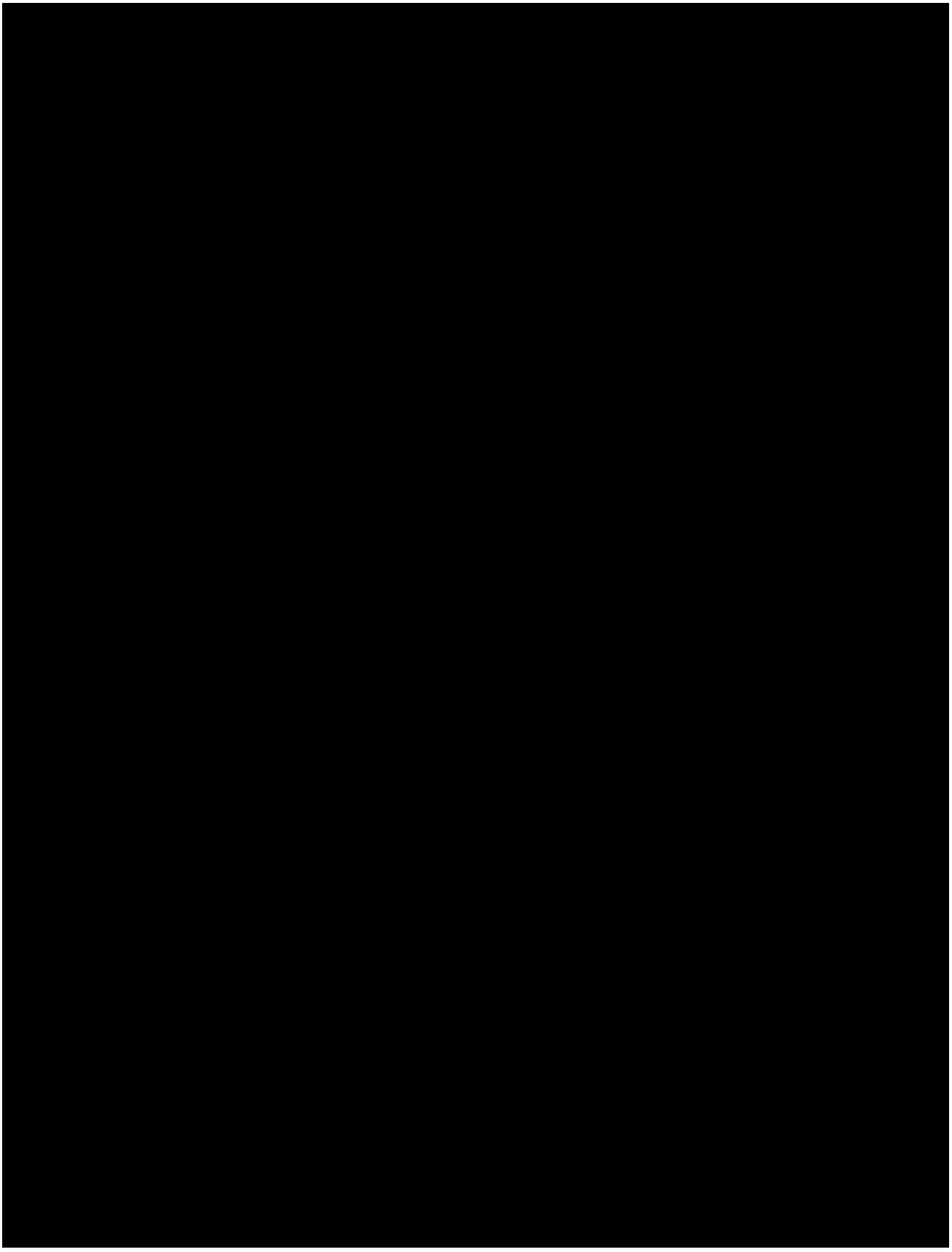


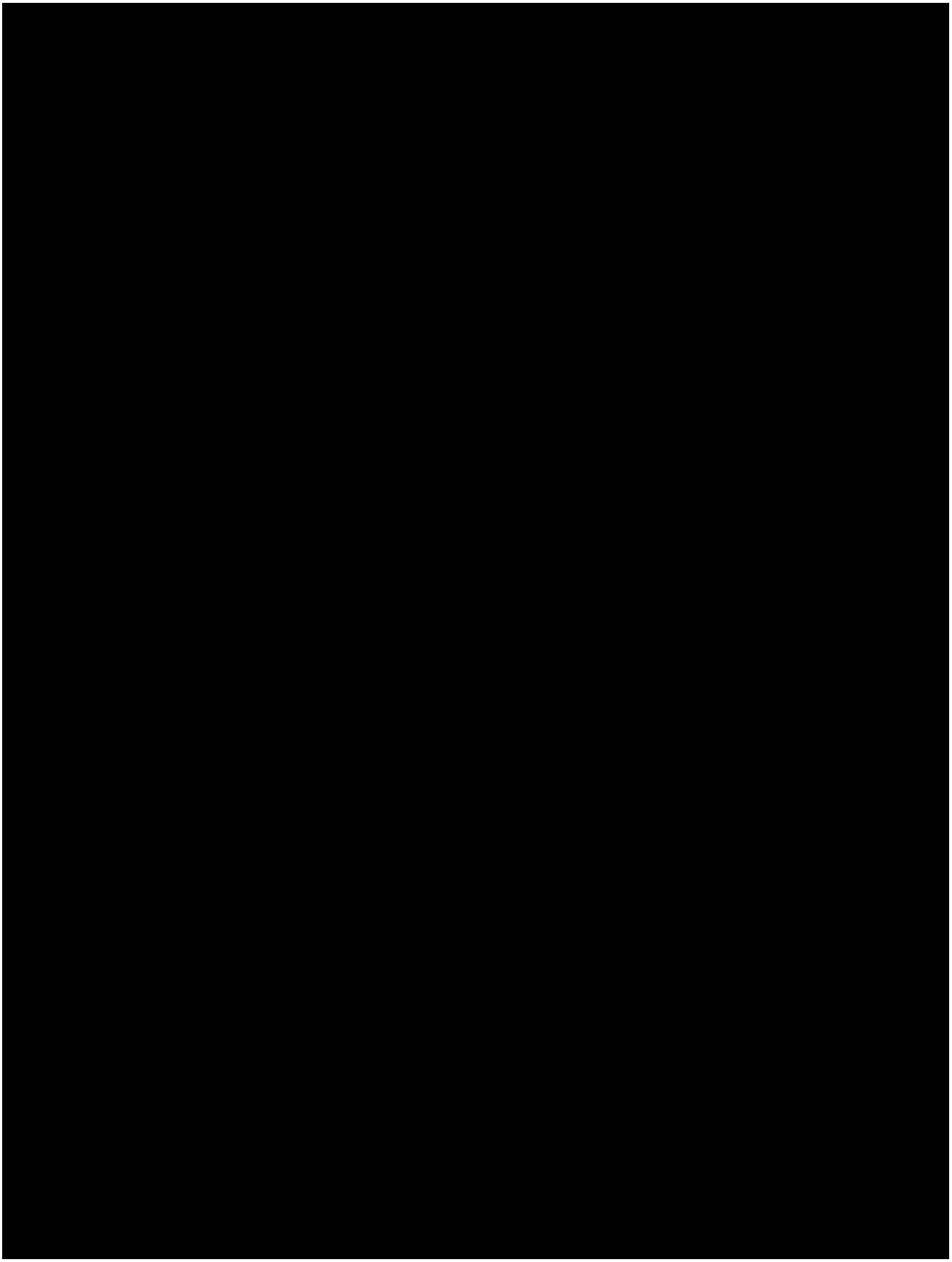


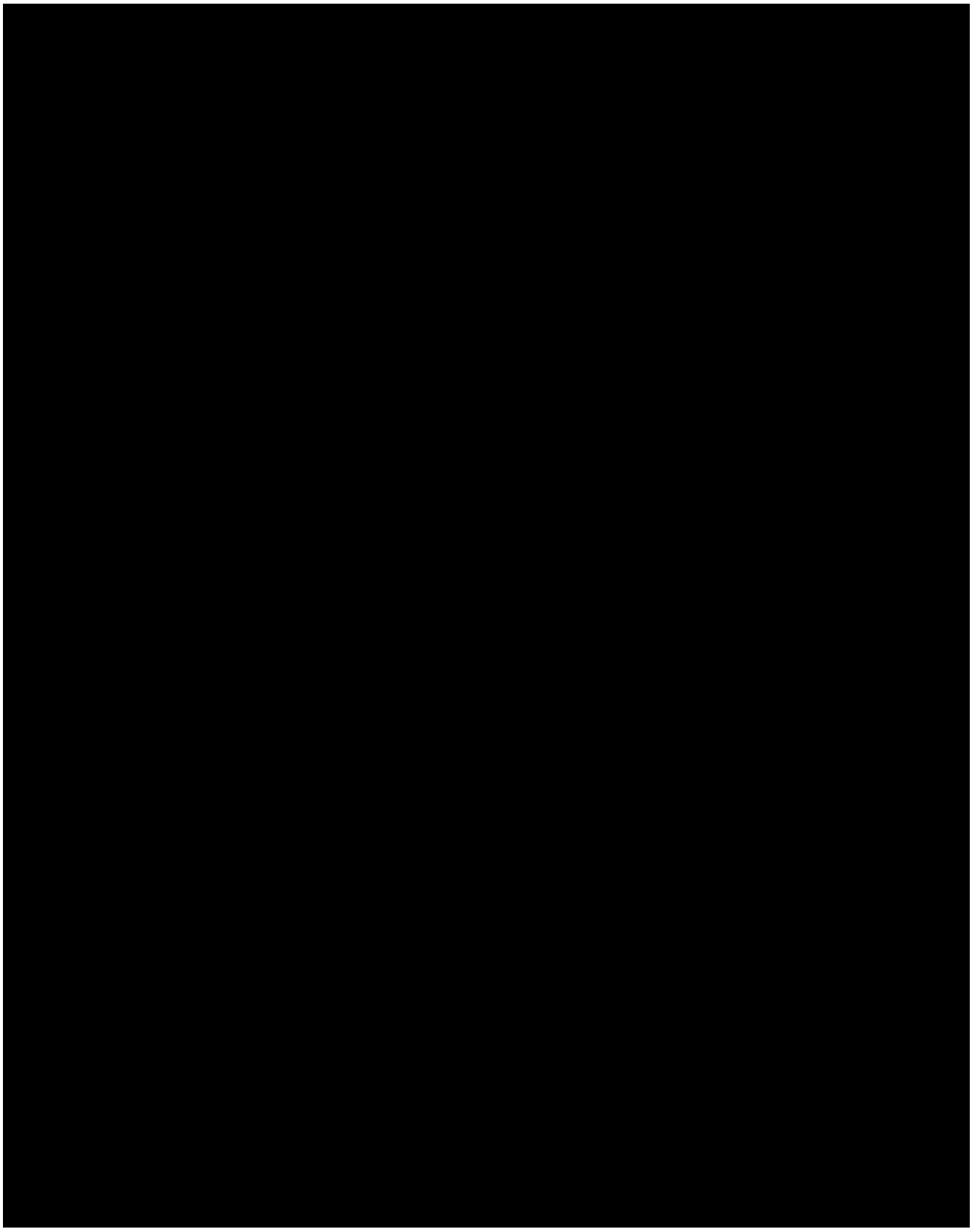












APPENDIX J. MODIFIED TOXICITY PROBABILITY INTERVAL DECISION TABLE (PHASE 1)

Number of Subjects																																			
Number of DLTs	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	31	32	33	34	35	36
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	E	E	E	E
1			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	E	E	E	E	E	E	E
2		D	D	D	D	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	E	E
3			X	X	D	D	D	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
4				X	X	X	D	D	D	D	D	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
5					X	X	X	X	X	D	D	D	D	D	S	S	S	S	S	S	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E
6						X	X	X	X	X	X	D	D	D	D	D	D	S	S	S	S	S	S	S	E	E	E	E	E	E	E	E	E	E	E	E
7							X	X	X	X	X	X	X	D	D	D	D	D	D	D	S	S	S	S	S	S	S	S	E	E	E	E	E	E	E	E
8								X	X	X	X	X	X	X	X	X	D	D	D	D	D	D	S	S	S	S	S	S	S	S	E	E	E	E
9									X	X	X	X	X	X	X	X	X	X	X	D	D	D	D	D	D	S	S	S	S	S	S	S	S	S	S	S
10										X	X	X	X	X	X	X	X	X	X	X	X	D	D	D	D	D	D	D	S	S	S	S	S	S	S	S
11											X	X	X	X	X	X	X	X	X	X	X	X	X	X	D	D	D	D	D	D	D	S	S	S	S	S
12												X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	D	D	D	D	D	D	D	S	S
13													X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	D	D	D	D	D	D	D
14														X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	D	D	D	D
15															X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	D
16																X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Note: Table will be applied separately for each dose level. Column indicates number of subjects treated within a given dose level; row indicates number of subjects with DLTs at that dose level.
E = Escalate to the next higher dose.
S = Stay at the same dose.
D = De-escalate to the previous lower dose.
X = De-escalate to the previous lower dose and the current dose will never be used again in the trial.

Celgene Signing Page

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

UserName: [redacted]
Title: [redacted]
Date: Monday, 10 February 2020, 07:01 PM Eastern Daylight Time
Meaning: Approved, no changes necessary.
==========

1. JUSTIFICATION FOR AMENDMENT

Significant changes included in this amendment are to explore anakinra as a toxicity mitigation agent and to evaluate the safety and efficacy in subjects who have had prior exposure to other therapeutic agents directed against BCMA, and they are summarized below:

Updated Introduction

The introduction was updated to include literature references of recent clinical data with B-cell maturation antigen (BCMA)-targeted chimeric antigen receptor (CAR T) cell therapies and BCMA directed T cell engager (TCE) and antibody-drug conjugate (ADC) therapies that have shown promising activity in multiple myeloma. The potential risks associated with these therapies were updated to align with recent published data. These references provide rationale for exploration of the prior BCMA directed therapies cohorts.

Ongoing study data to support BCMA-targeted CAR T cells cohort was updated with data from current literature or press releases.

Revised Sections: Section 1.3.1, Section 1.3.2, Section 1.3.3, Section 1.5, Section 2.1

JCARH125 Dose Rationale

Removed clinical data that was used for justifying the addition of the 300M dose level from this ongoing trial as it is not in accordance with Celgene standards.

Revised Section: Section 2.1

Addition of Phase 1 Anakinra Cohort

Interleukin 1 (IL-1) blockade through IL-1 receptor antagonist (IL-1Ra) can demonstrably prevent severe cytokine release syndrome (CRS) while maintaining intact antitumor efficacy. The benefits of an IL-1 blockade through IL-1Ra are especially intriguing given the latter's ability to cross the blood-brain barrier, unlike tocilizumab. Human microglia activated by IL-1 may produce inducible nitric oxide synthase and proinflammatory cytokines; therefore blocking IL-1 could potentially not only protect from severe CRS but also could reduce the severity of CAR T cell–related neurotoxicity. Therefore, anakinra has been included in this trial. Furthermore, anakinra has been proposed in recent publication for treatment of refractory CRS and in the setting of macrophage activation syndrome (MAS)/ hemophagocytic lympho-histiocytosis (HLH).

Added the primary, secondary and exploratory objectives and endpoints of the Phase 1 anakinra cohort.

Added study design for the Phase 1 anakinra cohort.

Added the rationale for prophylactic treatment with anakinra to align with current literature.

Added Section 6.3 for information and risks about anakinra.

Added the dosing schedule to follow for the Phase 1 anakinra cohort.

Defined the safety analysis set and the efficacy analysis set for the Phase 1 anakinra cohort.

Revised Sections: Protocol synopsis, Section 2.1, Section 2.3, Section 2.5, Section 3, Table 1, Section 4.1, Section 4.4, Section 4.6, Section 4.8, Section 4.11.2, Section 6.3, Section 6.4.4, Section 6.5, Section 6.6, Section 7.14, Section 8.5.3.1, Section 8.5.5, Section 8.12.1, Section

8.12.9.3, Section 10.1, Section 10.2.2.1, Section 10.2.2.2, Section 10.2.2.3, Section 10.2.3, Section 10.2.3.1, Section 10.3.4, Section 10.3.5, Section 10.3.7.1, Section 10.3.11.5, Section 10.3.13.1, Section 10.5, Section 10.6.1, Table A-2, Appendix D

Addition of Phase 2a prior BCMA-directed Anti-myeloma Therapy Cohort

Although BCMA-directed CAR T cell therapies have been demonstrated to induce rapid and deep responses in almost all subjects, the durability of response remains an issue. Relapse post-CAR T therapy may be mediated by multiple mechanisms: CAR-intrinsic (loss of functional CAR T persistence) or tumor intrinsic (antigen loss), or other mechanisms yet to be determined (such as lack of CAR infiltration into suppressive TME in plasmacytomas). Given the potential for multiple mechanisms, it may be possible to treat subjects who have relapsed after prior BCMA CAR T therapy with JCARH125.

Published data of 4 subjects with relapsed and/or refractory multiple myeloma (R/R MM) treated with CT103A, BCMA CAR T cells with human binder, were very encouraging. Patients who were previously treated with murine BCMA CAR T cells, after CT103A infusion achieved excellent responses of complete response (CR) (3 patients) and very good partial response (VGPR) (1 patient).

Cohen et al. described 2 patients who progressed after 1 BCMA-targeted therapy and then responded to a subsequent BCMA-targeted therapy.

A recent publication describes twenty subjects who were evaluable for BCMA surface expression on MM cells by flow cytometry performed on fresh marrow aspirates prior to treatment. BCMA intensity was lowest on residual MM cells 1 month after BCMA CAR T cell infusion and increased back toward baseline in most. Neither progression-free nor overall survival was significantly associated with baseline BCMA expression in this trial.

These cases demonstrate that BCMA targeted therapies may be beneficial in patients previously exposed to other BCMA-targeted agents and, therefore, this population has been added to explore safety and efficacy in a separate cohort of this trial. BCMA expression will be evaluated using the same exploratory methodologies currently in use for the H125001 Phase 1 and pivotal cohorts. These assessments will be performed on samples collected at screening to address baseline BCMA expression prior to JCARH125 infusion and also on samples collected after infusion. IHC will be utilized to measure BCMA expression on CD138+ plasma cells in bone marrow biopsies. Flow cytometry will also be used to measure BCMA expression on plasma cells in bone marrow aspirates. Results from both assays will be used to evaluate the relationship between baseline BCMA expression and JCARH125 activity (safety, efficacy, PK and PD). These results will also allow us to address whether subjects who have received prior BCMA-directed therapies have differential expression of BCMA relative to subjects in the Phase 1 cohort.

Added the primary, secondary and exploratory objectives and endpoints for the Phase 2a portion.

Added study design for the Phase 2a portion.

Defined the safety analysis set and the efficacy analysis set for the Phase 2a portion.

Revised Sections: Protocol synopsis, Section 1.3, Section 1.3.1, Section 1.3.2, Section 1.3.3, Section 2.1, Section 2.5, Section 3, Table 1, Section 4.1, Section 4.2, Section 4.5, Section 4.6, Section 4.8, Section 4.11.2, Section 5.1, Section 5.2, Section 6.6, Section 8.12.9.3, Section 10.1,

Section 10.2.4, Section 10.2.4.1, Section 10.2.4.2, Section 10.2.4.3, Section 10.3.9, Section 10.3.10, Section 10.5, Table A-2.

Updated Study Objectives and Endpoints

- From the secondary objective in Phase 1 "Duration of persistence of JCARH125 CAR T cells in the blood and bone marrow" bone marrow was removed and added as part of the exploratory objective and endpoint.

Revised sections: Protocol synopsis, Section 2.5, Section 3, Table 1

Overall Study Design

Added language to the overall study design which now includes the addition of the Phase 1 anakinra cohort and the Phase 2a portion for patient with prior BCMA targeted therapy.

Changed the primary analysis population for evaluation of JCARH125 efficacy (ie, the efficacy analysis set) to include all subjects treated at the RP2D(s) in Phase 2, as well as subjects treated at the RP2D(s) in Phase 1 and in the Phase 1 anakinra cohort.

Clarified that a bone marrow biopsy and a plasmacytoma biopsy (if feasible) will also be required at screening in order to align with the schedule of events.

Revised Section: 4.1, Section 4.6

Updated Eligibility Criteria

- Clarified inclusion criterion number 3

  Refractory myeloma is defined as non-responsiveness (best response of ≤ stable disease) to last anti-myeloma treatment regimen or documented progressive disease during or within 60 days (measured from the last dose) of completing treatment with the last anti-myeloma treatment regimen before study entry.

  Clarified that subjects who received prior allogeneic stem cell transplants or donor lymphocyte infusion (DLI) at least 100 days before enrollment will be considered eligible.

  This additional editorial change was made to provide further clarification for sites and to provide consistency across MM and CAR T-cell programs.

  Revised Sections: Protocol Synopsis, Section 5.1

- **Clarified inclusion criterion number 11**

  Females of reproductive potential (defined as all females physiologically capable of becoming pregnant) must agree to use one highly effective method of contraception from screening until at least 12 months following lymphodepleting chemotherapy. There are insufficient exposure data to provide any recommendation concerning the duration of contraception following treatment with JCARH125. Any decision regarding contraception after JCARH125 infusion should be discussed with the treating physician.

  Revised Sections: Protocol Synopsis, Section 5.1, Section 5.3

- **Clarified inclusion criterion number 12**

Females of reproductive potential must have 2 negative pregnancy tests as verified by the Investigator (one negative serum beta-human chorionic gonadotropin [β-hCG] pregnancy test result at screening, and within 7 days prior to the first dose of lymphodepleting chemotherapy). This applies even if the subject practices true abstinence from heterosexual contact. True abstinence was defined and added.

Revised Sections: Protocol Synopsis, Section 5.1

- **Clarified inclusion criterion number 13**

Males who have partners of childbearing potential must agree to use an effective barrier contraceptive method from initiation of lymphodepleting chemotherapy and for at least 12 months and should not donate semen or sperm during the entire study period and for at least 12 months following lymphodepleting chemotherapy.

Revised Sections: Protocol Synopsis, Section 5.1, Section 5.3

- **Inclusion criterion number 14 was added**

Phase 2a prior BCMA-directed anti-myeloma therapy cohort only – Subjects with R/R MM who have been previously treated with prior BCMA-directed anti-myeloma therapy, achieved at least a partial response (PR) per IMWG response criteria and subsequently progressed on the following treatment:

a. Subjects who have received prior BCMA-directed CAR T-cell therapy. The last CAR T-cell therapy must have been received at least 6 months prior to JCARH125 study enrollment (screening).

b. Subjects who have received prior BCMA-directed TCE therapy.

c. Subjects who have received prior BCMA-directed ADC therapy.

Subjects with prior BCMA-directed anti-myeloma therapy are not required to have received at least 3 prior anti-myeloma treatment regimens and do not have to be refractory to the last anti-myeloma regimen to be eligible for this trial.

This additional inclusion criterion was added for subjects enrolled in the Phase 2a cohort (prior BCMA-directed anti-myeloma therapy cohort).

Revised Section: Protocol Synopsis, Section 5.1

- **Exclusion criterion number 19 was added**

Subjects with known hypersensitivity to *Escherichia coli* (*E. coli*)-derived proteins (only applicable for subjects in the Phase 1 anakinra cohort).

Anakinra is produced by recombinant DNA technology using an *E. coli* bacterial expression system and is not recommended for subjects that have a hypersensitivity to *E. coli*-derived proteins. This additional exclusion criterion was added to promote subject safety in the Phase 1 anakinra cohort.

Revised Sections: Protocol Synopsis, Section 5.2

- **Exclusion criterion number 20 was added**

  History of severe immediate hypersensitivity reaction to any of the protocol mandated and recommended agents used in this study.

  Anakinra, tocilizumab, dexamethasone, fludarabine, and cyclophosphamide are amongst some of the mandated or recommended agents used in this trial. Therefore, this additional exclusion criterion was added to promote subject safety.

  Revised Sections: Protocol Synopsis, Section 5.2

Updated Pregnancy and Contraception Language

There are insufficient exposure data to provide any recommendation concerning the duration of contraception following treatment with JCARH125. Clarification was added to the contraception language to better define effective contraception barrier methods and ensure pregnancy testing is consistent across the CAR T program.

Added the following language: All pregnancies or suspected pregnancies occurring at any time after receipt of JCARH125, in either a female subject of childbearing potential or partner of childbearing potential of a male subject, are immediately reportable events.

Revised Sections: Protocol synopsis, Section 5.1, Section 5.3, Section 9.4.5, Table A-1, Table A-3, Table A-4

Prohibited Medications

Re-infusion of autologous peripheral blood stem cells (stem cell boost) preceded by bridging chemotherapy is not permitted. Inferior vena cava (IVC) filter utilization is prohibited for treatment of deep vein thrombosis at any time between screening and JCARH125 infusion.

Revised Sections: Section 6.8, Section 8.4

Toxicity Management – Cytokine Release Syndrome, Lee Criteria 2014

- Added clarification to Table 8 that temperature of 38.5˚C or higher is required per Lee criteria
- Updated Figure 2 to include laboratory monitoring for grade ≥3 CRS to rule out MAS/HLH
- Added more detailed information about treatment options to consider for rapid onset CRS, including tocilizumab and corticosteroids
- Addition of treatment options to consider for CRS: siltuximab, anakinra, lenzilumab
- Cytokine release syndrome and NT language, table, and figures were updated to align with recent literature (Appendix D, Section 1.3, Table 8, and Figure 2, and Appendix D, Section 3 and Figure 3, respectively)
- Added information about CRS management, tocilizumab, lenzilumab, and corticosteroids as treatment for CRS to align with recent literature (Appendix D, Section 1.3 and Table 8)

Revised sections: Section 7, Appendix D, Appendix D Section 1, Section 1.2, Section 1.3, Table 8

Toxicity Management - Macrophage Activation Syndrome/Hemophagocytic Lympho-histiocytosis (MAS/HLH)

In Appendix D, Section 2, MAS/HLH was added to include more detailed information about MAS diagnosis and treatment from recent clinical data. This additional change was made to provide further clarification for sites and to provide consistency across MM and CAR T cell programs.

- Added information about what MAS/HLH is and how it is differentiated from CRS
- Added Table 10: Differential diagnosis of CRS-related MAS/HLH
- Added detailed information about MAS/HLH diagnosis, occurrence and treatment recommendations, including how to establish a diagnosis
- **Clinical presentation**:
  - Added information about what MAS/HLH is and how it resembles CRS
  - Updated to include literature references of recent clinical data on MAS/HLH
  - Added information about associated laboratory markers
  - Added Table 10 to define MAS/HLH
- **Addition of detailed treatment management of MAS/HLH**: supportive care, elimination of infection (i.e. administer antiviral, antibacterial, antifungal prophylaxis and treatment), suppression of the inflammatory response and cell proliferation by immunosuppressive and cytotoxic drugs. Details were added for first line and second line treatment suggestions. Additional treatment suggestions were added for use in refractory cases.

Revised Section: Appendix D, Section 2, Table 10, Section 2.1, Section 2.2

Toxicity Management – Neurotoxicity

- Changed the start of neurologic symptoms from 2 to 14 day to between 3 to 12 days with median time to onset of 3 days after CAR T cell infusion.
- Added information that with another BCMA CAR T cell therapy bb2121, the start of neurologic symptoms has been noted between 3 to 11 days (median 5 days) after CAR T cell infusion.
- Added additional data based on published information about neurologic toxicities (NTs)
- Updated Figure 3 to consider adding an interleukin-1 (IL-1) receptor antagonists (IL-1Ra) agent as part of second line treatment.
- Added additional information about pathophysiology of neurologic toxicities to align with current literature.
- Updated clinical management of neurologic toxicities
  - Added the following treatment options to consider for NT: Levetiracetam or alternative anti-seizure medication, corticosteroids for severe neurotoxicity, siltuximab, and anakinra.

  - Tocilizumab is not recommended for the primary management of isolated neurotoxicity as it does not cross the blood brain barrier (BBB)

- Removed: management of NT should be guided per institutional guidelines

Revised Sections: Section 7.5, Appendix D, Section 3, Section 3.1, Section 3.2

The amendment also includes several other minor updates, clarifications and corrections:

- Updated the List of Abbreviations to align with updates made throughout the protocol
- Provided updated information on other CAR-T cell therapy options including safety and efficacy data (Section 1.3)
- Updated sample size by dose level to range from 14 to 30. (Section 4.2, Section 10.5)
- Updated dose-limiting toxicities (DLT): Rolled Grade 5 CRS into the next bullet defined as "any treatment emergent Grade 5 toxicity not due to the underlying malignancy" (Protocol synopsis, Section 4.3)
- Updated the enrollment period of the study from 12 to 36 months and the overall duration from 36 to 60 months (Protocol synopsis, Section 4.7)
- Added Phase 1, Phase 2a, and Phase 1 anakinra cohort to the title of Section 4.8 and made editorial updates to this section (Section 4.8)
- Added Phase 1 anakinra cohort and Phase 2a cohort to the Independent Review Committee (IRC) review (Section 4.11.2)
- Clarified that a fresh biopsy in inclusion criterion 5 is a bone marrow biopsy (Protocol synopsis, Section 5.1)
- Removed the word 'not' from inclusion #3 so it is no longer a double negative. Subjects who are considered eligible to receive and have 'not' refused an ASCT.
- Exclusion criterion number 2 was modified to correctly define the M in POEMS syndrome (Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal plasmaproliferative disorder, Skin changes) by changing 'monoclonal proteins' to 'monoclonal plasmaproliferative disorder (Protocol synopsis, Section 5.2)
- Exclusion criterion number 6 clarifies that it is not applicable to Phase 2a. (Protocol Synopsis, Section 5.2)
- Exclusion criteria number 7 clarifies that it is not applicable to Phase 2a. (Protocol Synopsis, Section 5.2)
- Exclusion criteria number 15a was modified to include all monoclonal antibodies (anti-CD38 and anti-SLAMF7) as part of the 4-week washout period. (Protocol synopsis, Section 5.2)
- Exclusion criteria number 17 was modified to exclude subjects with any condition that permits compliance with the protocol and exclude any psychiatric condition that could jeopardize subject safety. (Protocol synopsis, Section 5.2)

- Modified text for withholding lymphodepleting (LD) chemotherapy when calculated creatinine clearance (CrCl) or glomerular filtration rate (GFR) from ≤50 to <60mL/min and modified text that CrCl between 60 and 70 mL/min would have a 20% reduction in fludarabine (Section 6.2, Table A-2)
- Updated the avoidance of bias to include Phase 1 and the Phase 1 anakinra cohort (Section 6.5)
- Updated hospitalization requirements for the Phase 1 anakinra cohort and the driving distance for the Phase 2 and 2a cohorts from approximately a 60 minute drive to approximately a 30 minute drive (Section 6.6)
- Updated recommendations and monitoring for infections (Section 6.6)
- Updated the hospitalization requirements to include the Phase 2a cohort, the Phase 1 anakinra cohort, and that subjects should be within approximately 30-minute drive from the hospital (Section 6.6)
- Additional concomitant medication reporting suggestions are provided in Table 3 of Section 6.7.1
- Addition of antifungals and antivirals to the concomitant medication reporting suggestions during intensive care unit (ICU) stay (Section 6.7.2)
- Added devices and new medications to the prohibited medication section (Section 6.8)
- Section 7 was updated with current data for management of toxicities (Section 7)
- Added the option of collecting American Society for Transplantation and Cellular Therapy (ASTCT) score for neurologic toxicities (Section 7, Appendix D)
- Clarified that treatment with antivirals is 'recommended' rather than 'should be considered' (Section 7.4)
- Moved information about MAS to Appendix D (Section 7.6, Appendix D)
- Added associated risks for anakinra (Section 7.14)
- Removed collection of archival bone marrow or plasmacytoma from screening procedures (Section 8.2)
- Clarified that all safety labs should not be older than 5 days at the time of screening assessment. (Section 8.2, Table A-1)
- Clarified that subjects who did not have extra-medullary plasmacytomas (EMPs) at screening would not have to repeat the assessment for positron emission tomography (PET)/ computed tomography (CT) or diffusion-weighted magnetic resonance imaging (DW-MRI) after bridging therapy (Section 8.4, Table A-1)
- Added information about anakinra dosing on Day -1 (Section 8.5.3.1)
- Moved the PET/CT, DW-MRI and skeletal survey assessments to part of the unscheduled disease assessments (Section 8.6)

- Removed the clarification that during the treatment period, Day 29 PET/CT or DW/MRI is only required if clinically indicated or to assess rapidly progressing MM (Section 8.12.1)
- Clarified that bone marrow exams and MRD assessments are required at Month 24/ EOS (Section 8.12.1)
- Added CD4 T-Cell count under the hematology lab evaluations and clarified that bone marrow for cytogenetics is required at screening if recent analysis is not available (Section 6.6, Section 8.12.6, Table 4)
- Added adverse events (AEs) associated with any signs/symptoms/diagnosis of opportunistic infections to the reporting periods for AEs (Section 9.5.1, Table 7)
- Updated the general considerations for statistical methods and the analysis sets to include the data from Phase 1 anakinra cohort, Phase 1 and Phase 2a portions (Section 10.1, Section 10.2.2, Section 10.2.2.1, Section 10.2.2.2, Section 10.2.2.3)
- Defined the safety and efficacy analysis sets for all subjects n Phase 1 anakinra cohort and Phase 2a cohort (Section 10.2.2, Section 10.2.2.1, Section 10.2.2.2, Section 10.2.2.3, Section 10.2.3, Section 10.2.3.1, 10.2.3.3, Section 10.2.4, Section 10.2.4.1, Section 10.2.4.2, Section 10.2.4.3)
- Added all primary and secondary endpoints from Section 3, Table 1 to ensure Section 10.3.4, 10.3.5 were aligned (Section 10.3.4, Section 10.3.5, Section 10.3.9, Section 10.3.10)
- Added prophylactic anakinra usage (yes vs no) as subgroup analyses for efficacy, safety, and pharmacokinetics (Section 10.3.7.1, Section 10.3.11.5, Section 10.3.13.1)
- Updated the sample size consideration to align with the new Phase 2a portion and Phase 1 anakinra cohort (Protocol Synopsis, Section 10.5)
- Updated the interim analysis definitions to include the Phase 1 anakinra cohort (Section 10.6.1)
- Updated References (Section 13)
- Added clarification to the Schedule of Evaluations that inflammatory markers should be performed within 48 hours prior to the start of lymphodepleting chemotherapy and schedule of assessments was updated to add this assessment to the regular visit schedule (Table A-2, Table A-3)

1. JUSTIFICATION FOR AMENDMENT

Significant changes included in this amendment are summarized below:

- **Non-Dose Limiting Toxicities (DLT) adverse events were clarified**

– **The following are updated non-hematologic adverse events:**

  - Fever of any grade, including febrile neutropenia
  - Grade 4 increase in transaminases for ≤ 7 days
  - Grade 4 hypotension (without other CRS symptoms) requiring vasopressor for support that resolves to <Grade 3 in ≤ 72 hours

– **The following was removed from the non-hematologic adverse events list:**

  - Grade 3 bone pain due to T cell expansion in marrow compartments for ≤ 2 weeks

– **The following are updated hematologic adverse events:**

  - Grade 3 neutropenia of any duration or Grade 4 neutropenia lasting ≤ 28 days
  - Grade 3 or 4 leukopenia of any duration
  - Grade 3 thrombocytopenia of any duration or Grade 4 thrombocytopenia lasting ≤ 28 days
  - Grade 3 anemia of any duration or Grade 4 anemia lasting ≤ 28 days

– **The following was removed from the hematologic adverse events list:**

  - Grade 3 or 4 B-cell aplasia and hypogammaglobulinemia

These clarifications made to the hematologic and non-hematologic adverse events were created to promote consistency across CAR T cell programs.

Revised Sections: Protocol Synopsis, Section 4.3

- **PK assessment alterations**

JCARH125 expansion and persistence will be determined by only qPCR to detect the JCARH125 transgene, flow cytometry will no longer be utilized.

This editorial change was made to provide consistency across MM and CAR T-cell programs.

Revised Sections: Protocol Synopsis, Section 8.12.8.1, Section 10.3.9

- **Evaluation of the depth of response using MRD assessment was removed as a secondary objective in Phase 1 and 2 and was added as an exploratory objective in Phase 1 and Phase 2**

  This modification was incorporated to promote consistency across CAR T cell programs.

  Revised Sections: Protocol Synopsis, Table 1, Section 10.3.5, Appendix B

- **Planned JCARH125 dose levels were modified as follows:**

Dose Level	JCARH125 Dose (CD3+CAR+ cells)
-1	25×10^6
1	50×10^6
2	150×10^6
2a[a]	300×10^6
3	450×10^6
3a[b]	600×10^6
4	800×10^6

The new dose escalation scheme used in conjunction with the mTPI-2 dosing algorithm will help yield a both safe and effective recommended phase 2 dose (RP2D).

Revised Sections: Protocol Synopsis, Table 2

- **JCARH125 sample size**

Clarified that 20-30 subjects per dose may be treated.

Based on the cumulative safety and antitumor activity data from subjects treated in Phase 1, one or more dose levels will be selected for further evaluation in the Phase 2 portion of the trial (the RP2D). A sample size of 20-30 subjects at a dose level is used to minimize the probability of selecting an overly toxic dose as an RP2D.

Revised Sections: Section 2.1, Section 4.2, Section 10.5

- **Eligibility Criteria**

– **Clarified inclusion criterion number 3**

Subjects who received prior allogeneic stem cell transplants at least 100 days before enrollment with no signs of acute or chronic graft-versus-host disease (GVHD) are now eligible in the study.

This additional editorial change was made to provide further clarification for sites and to provide consistency across MM and CAR T-cell programs.

Revised Section: Protocol Synopsis, Section 5.1

– **Clarified inclusion criterion number 7a**

Adequate renal function, defined as calculated creatinine clearance (Cockcroft Gault) ≥ 60 mL/min without the assistance of hydration. Subjects must not have received IV rehydration within 3 days of renal function assessment

An increased incidence of neurotoxicity was noticed in subjects treated with JCARH125 who met inclusion criteria with a serum creatinine of ≤ 1.5 x upper limit of normal who also had creatinine clearance of less than 60 mL/min.

Revised Section: Protocol Synopsis, Section 5.1

- **Removed the previously reported exclusion criterion number 8**

  Prior allogeneic stem cell transplant performed was removed. See Inclusion criterion 3.

  This additional editorial change was made to provide further clarification for sites and to provide consistency across MM and CAR T-cell programs.

  Revised Section: Protocol Synopsis, Section 5.2

- **Newly reported exclusion criterion number 8**

  Human immunodeficiency virus (HIV) infection positive subjects.

  Editorial change to highlight HIV as an exclusion criterion.

  Revised Section: Protocol Synopsis, Section 5.2

- **Exclusion criterion number 9 was updated**

  Hepatitis B virus (HBV) or hepatitis C virus (HCV) infection as indicated by positive serology or nucleic acid testing. Subjects who are solely hepatitis B surface antibody (HBsAb)-positive are eligible.

  This additional editorial change was made to provide further clarification for sites and to provide consistency across MM and CAR T-cell programs.

  Revised Section: Protocol Synopsis, Section 5.2

- **Exclusion criterion number 18 was added**

  Use of any live vaccines against infectious diseases within 8 weeks before JCARH125 infusion.

  Due to the increased risk of cytopenias and infection caused by CAR T cell products, this additional exclusion criterion was added to promote subject safety. Additionally, editorial changes were made to provide consistency across MM programs.

  Revised Sections: Protocol Synopsis, Section 5.2

- **Modified the lymphodepleting (LD) chemotherapy creatinine clearance exclusion to ≤ 50 mL/min. Language was also added explaining that if LD chemotherapy is delayed for reasons previously discussed with Sponsor's Medical Monitor, and if the delay was not longer than 14 days, safety assessments have to be repeated per Appendix A. Lastly, subjects who cannot receive lymphodepletion within 8 weeks after leukapheresis must be rescreened and safety and efficacy assessments must be repeated. Modified that the reduction of fludarabine/cyclophosphamide (Flu/Cy) will now be when CrCl is between 50 and 70 rather than 30 and 49 mL/min.**

  Subjects with a creatinine clearance of < 60 mL/min are excluded from receiving JCARH125 treatment. This additional exclusion will ensure subjects with sufficient renal function receive study therapy. Additionally, testing for safety and/or efficacy in the event of LD chemotherapy treatment delay was added to ensure subjects continue to meet the inclusion and exclusion criteria at the time of LD chemotherapy.

  Revised Sections: Section 6.2, Section 8.5.1, Section 8.5.2, Table 4, Table A-2

- **Updated prophylaxis recommendations and supportive care monitoring and treatment suggestions for tumor lysis syndrome, cytokine release syndrome, infections, neurological toxicity, macrophage activation syndrome, granulocyte colony-stimulating factors, transfusions, and IV rehydration.**

  This additional editorial change was made to provide further clarification on the recognition and treatment of a variety of conditions subjects could experience while be treated with study medications. It also provides consistency across MM and CAR T-cell programs.

  Revised Sections: Section 6.6, Section 7.1, Section 7.3, Section 7.4, Section 7.5, Section 7.6, Section 7.7, Section 7.8

- **Additional JCARH125 infusion criteria for Day -1**

  The additional and/or modified criteria state that JCARH125 infusion should be delayed if any of the following are met:

  - Suspected or active systemic infection 5 days before JCARH125 infusion
    - All cultures must be negative if subject had a recent infection
  - Platelet count < 50,000/mm^3
  - Calculated creatinine clearance (Cockcroft Gault) < 60 mL/min

  These eligibility criteria on the day prior to treatment were added to ensure subject safety and eligibility prior to infusion.

  Revised Sections: Protocol synopsis, Section 5.2, Section 8.5.3

- **Added the Mini-Mental State Examination (MMSE) to assess memory and other cognitive functions as part of the routine neurological exams done at study visits as well as daily during any neurological adverse event that is suspected to be CAR T cell associated neurological toxicity**

  Revised Sections: Section 8.6, Section 8.12.2, Section 10.3.7.4, Table A-1, Table A-2, Table A-3, Appendix E

- **Added assessments for Second Primary Malignancy (SPM) to monitor for and identify the potential cause of an SPM**

  Revised Sections: Section 8.6, Section 8.9, Section 8.12.8.2, Section 8.12.9

- **Added new Table A-4 to the Schedule of Evaluations to clarify the assessments required after a subject has disease progression**

  Added Table A-4

The amendment also includes several other minor updates, clarifications and corrections:

- Added nominal study name to the protocol title
- Changed sponsor contact for safety reporting and updated H125001 study team contact information.
- Updated the Sponsor signature page study team contact information.

- Modified the sponsor name in the protocol synopsis to "Juno Therapeutics, Inc., a wholly owned subsidiary of Celgene Corporation."
- Updated the study rationale in the protocol synopsis to include more current data on multiple myeloma treatment and BCMA CAR T cell therapy.
- Updated the multiple myeloma epidemiology information (Section 1.1)
- Provided updated information on other CAR T cell therapy options including safety and efficacy data (Section 1.3)
- Clarified that when disease progression occurs during the 2-year follow-up timeframe, subjects are still followed according to the Schedule of Evaluations. (Protocol Synopsis, Section 4.1)
- Lines of therapy was replaced with anti-myeloma treatment regimens in inclusion criterion number 3 (Protocol Synopsis, Section 5.1)
- Added verbiage to inclusion criterion number 4 that clarified subjects must have measurable disease as determined by a central laboratory. (Protocol Synopsis, Section 5.1)
- Clarification added to inclusion criterion number 13 that states males who have partners of childbearing potential must agree to use an effective barrier contraceptive method from initiation of lymphodepleting chemotherapy and for 1 year after the last dose of study therapy and should not donate semen or sperm during the entire study period. (Section 5.1, Section 5.3).
- Exclusion criterion number 3 clarifies that subjects who have refused autologous stem cell transplant are not eligible for the study. (Protocol Synopsis, Section 5.2)
- Exclusion criterion number 4 was modified to exclude subjects with another primary malignancy that has not been in remission for at least 3 years. Additionally, subjects with completely resected Stage 1 solid tumor with low risk for recurrence was removed from the exceptions list. (Protocol Synopsis, Section 5.2)
- Verbiage was included that states the Principal Investigator should ask subjects who withdraw prematurely from the study to participate in the Celgene sponsored long term follow up protocol. (Section 5.4.2)
- The statement suggesting bridging therapy must be discontinued at least 14 days prior to initiation of lymphodepleting chemotherapy was removed. (Section 6.1)
- Added verbiage explaining that administration of JCARH125 may occur 2 to 7 days after completion of lymphodepleting chemotherapy. (Protocol Synopsis, Section 4.1, Section 6.2, Section 6.3.1)
- Corrected text in Section 6.3.3 to state that each JCARH125 dose consists of CD3+ CAR+ T cells.
- Additional concomitant medication reporting suggestions are provided in Table 3 of Section 6.7.1. (Table A-4)

- Plasmapheresis was added as a prohibited procedure between screening and JCARH125 infusion (Section 6.6, Section 6.8)
- The use of live vaccines was added as a prohibited medication within 8 weeks before JCARH125 infusion (Section 6.8)
- Pegfilgrastim ≤ 11 days prior to JCARH125 infusion or ≤ 7 days after infusion was added to the prohibited medications list. (Section 6.8)
- Removed the following text: B-cell aplasia is an expected potential off-tumor, on-target toxicity, arising from targeted elimination of non-malignant BCMA-positive B cells. The main risk of B-cell aplasia is hypogammaglobulinemia, which may increase the risk of infection. (Section 7.9)
- Revisions to methylprednisolone dose from 2 mg/kg/day to 1 to 3 mg/kg/day and timing of taper from 2-3 weeks to 7 days was updated. (Section 7.10)
- Verbiage was added to state that eligibility will be assessed by the sponsor prior to leukapheresis, prior to lymphodepleting chemotherapy, and prior to JCARH125 infusion. (Section 8.1)
- The option for additional electrocardiograms (ECGs) as clinically indicated was added. (Section 8.12.4)
- Assessment of health-related quality of life (HRQoL) and health economics and outcomes research (HEOR) in subjects were clarified in Phase 2 (Section 8.12.10, Section 8.2.11).
- Added all primary and secondary endpoints from Table 1 to ensure Section 10.3.2 and 10.3.5 were aligned (Section 10.3.2, Section 10.3.5)
- Clarified that the EQ-5D-5L and will be analyzed according to the recommendations in the scoring manual. (Section 10.3.11)
- Increased the overall study sample size up to 200 subjects in Phase 1/2 and up to 120 in Phase 1 (Protocol Synopsis, Section 10.5).
- Added protocol Section 12.2.3 Product Quality Complaint, to align with the Celgene protocol template language (Section 12.2.3)
- Clarified that unscheduled assessment for PET/CT or DW/MRI is required if clinically indicated to assess rapidly progressing MM disease (Table A-3)

1. OVERALL SUMMARY OF CHANGES

Amendment 4 of Protocol H125001 was prepared to add an intermediate dose level of 300×10^6 CD3+CAR+ T cells to the dose levels selected for evaluation. The rationale for investigating this intermediate dose level is based on adverse events that occurred in the first 2 subjects treated at Dose Level 3 (450×10^6 CD3+CAR+ T cells). Both subjects treated at this dose level experienced rapid onset of cytokine release syndrome (CRS) within 8 hours after JCARH125 infusion and received treatment with tocilizumab. The first subject experienced Grade 2 neurotoxicity, which completely resolved after treatment with tocilizumab and corticosteroids. The second subject developed Grade 4 CRS and Grade 4 neurotoxicity unresponsive to corticosteroid therapy, Grade 4 aspartate aminotransferase (AST) increased, Grade 4 acute kidney injury, and Grade 5 septic shock. The events experienced by the second subject met dose-limiting toxicity (DLT) criteria. Based on the safety results in subjects treated at the 300×10^6 CD3+CAR+ cell dose level, the Sponsor, in collaboration with study investigators, will make an assessment as to whether it is appropriate to evaluate additional subjects at the 450×10^6 CD3+CAR+ cell dose level.

Accordingly, the following major changes were made to the protocol in this amendment:

- A dose level of 300×10^6 CD3+CAR+ T cells was added as Dose Level 2a.
- The rationale for evaluating the intermediate dose level was provided in Section 2.1.

The following changes were also made:

- The requirement to treat only one subject per day after staggering of the first 3 subjects by 7 days was removed.
- The recommendation to hospitalize subjects in Phase 1 starting at the time of lymphodepleting chemotherapy was removed.
- The following treatments were added as treatments that should be recorded during hospitalizations: antibiotics, growth factors, transfusions, and systemic anticoagulants.
- The temperature threshold above which subjects should have JCARH125 administration delayed and be hospitalized following JCARH125 infusion was lowered from 38.5°C to 38.0°C.
- The requirement to notify the Sponsor and to collect tissue samples for analysis by the central laboratory was removed from the instructions to be followed for unscheduled evaluations.
- A mental status evaluation was added to the list of assessments required to be performed as part of the neurological examination.
- The email address for safety reporting was updated to direct reports to Celgene Drug Safety rather than Juno Pharmacovigilance.

In addition, other minor administrative clarifications and typographical corrections were made.

1. OVERALL SUMMARY OF CHANGES

Amendment 3 of Protocol H125001 was prepared primarily to further refine the study population in order to collect and analyze data on a more homogeneous study population.

The following major changes were made to the protocol in this amendment:

- The inclusion criterion regarding required prior treatments was revised to clarify that subjects must have had an immunomodulatory agent and a proteasome inhibitor, either in the same combination regimen or as separate regimens.
- The requirement for subjects to be relapsed or refractory was modified to require that subjects be refractory to their last prior regimen, defined as disease that is nonresponsive or progresses on treatment, or that shows progression within 60 days after the last prior line of therapy.
- Grade 4 lymphopenia lasting more than 14 days will not be considered a dose-limiting toxicity (DLT).
- Separate analyses in the BCMA-high population were removed.
- Reference to the use of the truncated epidermal growth factor (EGFRt) portion of the lentiviral vector encoding the BCMA CAR for the purpose of analytical detection of transduced T cells and ablation of CAR T cells in the event of CAR T-cell-related toxicity was removed.
- Language in the management of cytokine release syndrome (CRS) and neurotoxicity sections was updated to align with language in the Celgene-approved guidance document; an appendix containing an updated algorithm for CRS management and a new algorithm for management of neurotoxicity was added.
- Bone marrow evaluations at Pre-treatment Screening will only be performed in subjects with inadequate or insufficient samples at Screening and in subjects who receive bridging chemotherapy.
- Bone marrow evaluations were added at Month 12, Month 18, and Month 24 (end of study [EOS]).
- Minimum renal function (creatinine clearance [CrCl] or glomerular filtration rate [GFR]) required for initiating lymphodepleting chemotherapy was decreased from 60 mL/min to 30 mL/min; instruction to reduce the dose of fludarabine by 40% was added for subjects with CrCl between 30 and 49 mL/min.
- Language in the Safety section (Section 9) was updated to reflect requirements by the European Medicines Agency, including defining and requirements for reporting instances of overdose, and guidance by the Food and Drug Administration (FDA) for reporting delayed adverse events.

The following additional changes were also made in this amendment:

- The normal range for serum creatinine for determination of eligibility will not be adjusted by age.
- Requirements for clotting time were added to inclusion criteria, and an exclusion criterion was added for subjects with a history of ≥ Grade 2 hemorrhage or requirement for ongoing treatment with chronic, therapeutic doses of anticoagulants.
- Clarification was made that subjects are required to have recovered from *non-hematological* toxicities due to prior therapy (hematologic requirements are listed in definition of adequate bone marrow function in Inclusion Criterion 7b).
- Subjects with non-secretory disease (ie, those with disease only in the bone marrow and those with solitary plasmacytoma) will be excluded.
- Subjects with a history of central nervous system (CNS) malignancies will be excluded in addition to those with active CNS malignancy.
- Subjects with Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal protein, Skin changes (POEMS) syndrome and Waldenstrom's macroglobulinemia will be excluded.
- The exclusion criterion prohibiting untreated or active infection at the time of Screening and before leukapheresis was modified to also exclude infection at the time of leukapheresis.
- An exclusion criterion was added for plasmapheresis within 14 days before leukapheresis.
- Medical conditions or laboratory abnormalities that, in the judgment of the Investigator, could jeopardize subject safety were added to the exclusion criteria.
- Guidance for recording intravenous (IV) fluids administered during hospitalization for treatment of CRS was added.
- Evaluations of serum chemistry, coagulation parameters, and lymphocyte enumeration on the day of apheresis were removed.
- Clarification was made that only subjects who receive bridging chemotherapy with potentially cardiotoxic drugs are required to have a repeat echocardiogram or multiple uptake gated acquisition (MUGA) at Pre-Treatment Screening.
- Language regarding criteria for JCARH125 infusion was modified to align with language in other Juno/Celgene protocols.
- Instruction was added to perform biopsies of any new plasmacytomas when feasible.
- Guidance to submit samples from serum protein electrophoresis (SPEP), 24-hour urine protein electrophoresis (UPEP), serum and urine immunofixation, and/or serum free light chain (sFLC) evaluations collected at unscheduled visits was added.
- An appendix defining a line of therapy was added.

Other minor clarifications and administrative changes were also made.

1. OVERALL SUMMARY OF CHANGES

Amendment 2 of Protocol H125001 was prepared to address FDA feedback following their review of Amendment 1 of the protocol

The following changes were made to the protocol as a result of FDA feedback:

- Details were added regarding dose escalation/de-escalation decisions based on the first 3 subjects treated at a dose level.
- The inclusion criteria pertaining to relapsed or refractory disease were further clarified.
- Changes were made to the DLT criteria.
- Replacement of subjects was changed to be limited to Phase 1.
- Details regarding the recommended management and hospitalization of subjects prior to and after JCARH125 administration, including subjects who develop fever following the JCARH125 infusion, were added.
- Guidance for prohibiting filgrastim during the immediate pre-infusion and post-infusion periods was added.
- Changes were made to safety reporting to start collecting all SAEs from the time of leukapheresis.
- The CRS treatment algorithm was updated to reference the Actemra label as indicated for managing severe or life-threatening CRS.
- Details regarding recommended regimens for bridging therapy and maximum allowed duration between leukapheresis and initiation of study treatment were added.
- A repeat MUGA/ECHO scan was added prior to initiation of lymphodepleting chemotherapy for subjects that receive bridging therapy during JCARH125 manufacturing.
- Criteria for receiving JCARH125 infusion were added.
- Details regarding the specific cytokines to be evaluated in research samples were added.
- Details regarding reporting of disease progression as SAEs were added.
- A statement was added indicating the Phase 2 efficacy analysis may be refined in a detailed statistical analysis plan (SAP), following further discussion with regulatory authorities.
- Details regarding the endpoints to be evaluated at the interim analysis were added.
- Details regarding the timing of the primary analysis were added.
- Details regarding a sensitivity analysis to be performed in all subjects who undergo leukapheresis but who may not receive treatment on study were added.
- Clarification was made throughout the protocol that only a single dose of JCARH125 will be administered in this study, ie, retreatment with a second dose is not an option in this first-in-human trial.

The following additional changes were also made in this amendment:

- Cytogenetics was removed from research evaluations; information will be obtained through a previous report if available.
- HLA typing and donor chimerism were removed from laboratory evaluations since subjects with prior allogeneic transplant are excluded.

Other minor clarifications and administrative changes were also made.

1. OVERALL SUMMARY OF CHANGES

Amendment 1 of Protocol H125001 was prepared to remove patient selection in Phase 1 based on expression of B-cell maturation antigen (BCMA) in tumor biopsy samples. Data generated at Juno Therapeutics from a recent evaluation of BCMA expression in tumor samples from patients with multiple myeloma (MM) suggest that more than 90% of MM patients express some level of BCMA. Based on the biological dynamics of BCMA, the heterogeneity of MM, and the potential for epitope spreading, there is reason to believe that patients with low BCMA expression in a single biopsy sample may benefit from BCMA-directed CAR T-cell therapy. This modification allows patients to enroll in Phase 1 at any time, regardless of level of BCMA expression; clinical benefit relative to BCMA expression will be explored during the study.

In addition, the analysis for the primary endpoint of overall response rate (ORR), as well as the secondary endpoint of complete response (CR) rate, was redefined to include two analysis populations: (1) all subjects in Phase 1 and Phase 2 who receive treatment with JCARH125 at the recommended Phase 2 dose (RP2D) regardless of level of BCMA expression and (2) subjects with BCMA expression on > 90% of plasma cells (ie, the BCMA-high population).

Accordingly, the following changes were made to the protocol:

- The Pre-Screening visit in Phase 1 for evaluation of BCMA expression in archival samples was removed. Biopsy samples will be collected from all subjects in Phase 1 and Phase 2 during Screening and Pre-treatment Screening and analyzed for BCMA expression, but BCMA expression level will not be used to determine eligibility in either Phase 1 or Phase 2 of the study. Archival samples obtained within 1 year prior to Screening will be requested from all subjects for whom such samples are available and analyzed for BCMA expression.
- The statistical method for control of the overall type 1 error rate was updated to reflect that analysis of the primary endpoint will be performed in two separate populations, and that these analyses are both considered primary.
- The primary analysis population for efficacy endpoints other than ORR and CR rate, which were previously based on subjects expressing BCMA above the pre-defined threshold, will now include all evaluable subjects treated at the RP2D in either Phase 1 or Phase 2 of the study. The name of this analysis population was changed from the "primary analysis set" to the "efficacy analysis set."
- The effect size detectable with 90% power in the BCMA-high population was changed to reflect an expectation that 45 subjects determined to be BCMA-high will be included in the analyses for this population.
- The timing of the primary analysis was changed to occur after all subjects in the efficacy analysis set have been evaluated for response.

The following additional changes were also made in this amendment:

- The inclusion criterion for prior autologous stem cell transplant was deleted and replaced with an exclusion criterion excluding subjects eligible for an autologous stem cell transplant.
- Minimum hemoglobin at Screening was reduced from 9 g/dL to 8 g/dL.
- Exceptions to exclusion criterion related to toxicities due to previous therapy were modified (skin-limited graft-vs-host disease removed as an exception; anemia, thrombocytoypenia, and neutropenia added as exceptions).
- Infection within 72 hours prior to JCARH125 infusion was removed as an exclusion criterion.
- A statement was added indicating that the DLT evaluation period may be extended beyond 21 days in the event that adverse events meeting DLT criteria are found to occur beyond the DLT window.
- The sample size was increased from approximately 112 subjects to approximately 118 subjects.
- Pre-treatment disease assessments and biopsies, previously required only for subjects who received bridging chemotherapy during JCARH125 production, will be required for all subjects.
- PET/CT scans at Pre-treatment Screening, previously required for all subjects, will only be performed on subjects with extramedullary lesions identified on scans at Screening and on subjects with clinical suspicion of new extramedullary lesions.
- Clarification was made that growth factors and transfusions will be allowed for subjects who do not meet the minimum requirements for absolute neutrophil count (ANC), hemoglobin, and platelet count requirements at Pre-treatment Screening.
- Criteria for hemoglobin $\geq$ 8 g/dL and platelet count $\geq$ 30,000/mm^3 were added prior to JCARH125 administration; red blood cell transfusions and other supportive measures may be used.

Other minor clarifications and administrative changes were also made.