Janssen Research & Development

Statistical Analysis Plan

A Phase 1b-2, Open-Label Study of JNJ-68284528, a Chimeric Antigen Receptor T-cell (CAR-T) Therapy Directed Against BCMA in Subjects with Relapsed or Refractory Multiple Myeloma

CARTITUDE-1

Protocol 68284528MMY2001; Phase 1b-2
AMENDMENT 1

JNJ-68284528 (ciltacabtagene autoleucel)

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Compliance: The study described in this report was performed according to the principles of Good Clinical Practice (GCP).

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AMENDMENT HISTORY

SAP Version	Date
Original SAP	8 August 2019
Amendment 1	23 September 2020

Amendment 1 (23 September 2020)

The overall reason for the amendment: The overall reason for the amendment is to update the SAP in accordance with the latest protocol amendment 4 (20 March 2020), add analyses according to health authority feedback, add or update analyses as deemed clinically relevant and/or statistically appropriate based on emerging data, and update analysis terminology according to Estimand framework in ICH E9(R1).

Applicable Section(s)	Description of Change(s)
Rationale: Updates made according to latest protocol amendment 4 and analyses added accordingly	
1.1, 1.2, 5.1, 7.1.1, 10	Updated texts according to latest protocol amendment and introduced corresponding analyses as applicable
Rationale: Analyses added according to health authority feedback	
3.1, 4.3.2.2, 4.3.3.2, 4.3.5.2, 4.3.6.2, 4.3.7.2	Added analyses based on all enrolled analysis set
Rationale: Updates in analysis made as deemed clinically relevant and/or statistically appropriate based on emerging data	
2.6, 3.1	Subgroup categorization updated for age, race, refractory status, ECOG performance score subgroups; categories for frequency summary updated for age, ECOG performance score
3.5, 3.6	Updated presentation for prior and concomitant therapy summaries, and refractory status summary
4.2.3, 4.3.4.2, References	Updated to use prevalence-adjusted-bias-adjusted kappa (PABAK) statistics to evaluate agreement; removed supplementary analysis based on mITT analysis set who had measurable disease at baseline and had one post-baseline disease assessment
4.3.4.1	Updated definition of duration of response, replacing “death due to PD” with “death due to any cause”, which will be counted as event
4.3.6.2, 7.3, 7.4, 7.5	Added additional exploratory analyses
5.3.1, 5.3.2	Updated analyses for neurologic adverse events; added clarification for grading system for cytokine release syndrome and immune effector cell-associated neurotoxicity
5.6	Updated clinically important abnormality threshold for oxygen saturation
4.3.2.1, 7.1.2	Updated to group subject with missing or unevaluable MRD status separately from MRD-positive subjects; removed timepoint analysis of MRD negativity rate
Rationale: Updates made according to Estimand framework in ICH E9(R1).	
4.2.2, 4.2.3, 4.3.1.2, 4.3.2.2, 4.3.3.2, 4.3.4.2, 4.3.5.2, 4.3.6.2, 4.3.7.2	Added the treatment attribute of the Estimand Updated terminology differentiating sensitivity and supplementary analyses

Applicable Section(s)	Description of Change(s)
Rationale: analyses added related to COVID-19	
11	Documented analysis for COVID-19
Rationale: Minor errors were noted	
Throughout the document	Minor grammatical, formatting, or spelling changes were made

ABBREVIATIONS

AE	adverse event
ALT/SGPT	alanine aminotransferase
AST/SGOT	aspartate aminotransferase
AUC	area under the curve
BCMA	B cell maturation antigen
BSA	body surface area
CAR-T	Chimeric antigen receptor T (cells)
CI	confidence interval
Cmax	maximum concentration
CBR	clinical benefit rate
COVID-19	Coronavirus Disease 2019
CR	complete response
CRS	cytokine release syndrome
CSR	Clinical Study Report
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organization for Research and Treatment of Cancer
EQ-5D-5L	EuroQol Five Dimension Questionnaire
eCRF	electronic case report form
FDA	Food and Drug Administration
FISH	fluorescence in situ hybridization
FLC	free light chain
GHS	global health status
HLGT	high level group term
HLT	high level term
ICANS	Immune effector cell-associated neurotoxicity
ICE	Immune-effector cell-associated encephalopathy
IMiD	Immunomodulatory drug
IMWG	International Myeloma Working Group
IRC	independent review committee
LVEF	left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
MID	minimum importance difference
mITT	modified intent-to-treat
MR	minimal response
MRD	minimal residual disease
MRU	medical resource utilization
MUGA	multiple-gated acquisition
NCI	National Cancer Institute
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NGS	next generation sequencing
ORR	overall response rate
OS	overall survival
PBMC	peripheral blood mononuclear cells
PD	progressive disease
PFS	progression-free survival
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PI	proteasome inhibitor
PK	pharmacokinetic(s)
PP	per protocol
PR	partial response
PRO	patient-reported outcome
PT	preferred term

RCL	replication competent lentivirus
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SAP	Statistical Analysis Plan
sBCMA	soluble BCMA
sCR	stringent complete response
SD	standard deviation
SET	safety evaluation team
SOC	system organ class
TEAE	treatment-emergent adverse event
TLS	tumor lysis syndrome
Tmax	time to maximum concentration
TTR	time to response
VGPR	very good partial response
WHO	World Health Organization
WHO-DD	World Health Organization Drug Dictionary

1. INTRODUCTION

This statistical analysis plan (SAP) contains definitions of the analysis sets, derived variables and statistical methods for the planned analysis for the clinical study report (CSR) of the Phase 1b-2, open-label study of JNJ-68284528, a chimeric antigen receptor T cell (CAR-T) therapy directed against B cell maturation antigen (BCMA) in subjects with relapsed or refractory multiple myeloma.

Results will be presented separately for Phase 1b and Phase 2. In addition, subjects treated at the recommended Phase 2 dose (RP2D) dose level in Phase 1b and Phase 2 will be pooled for safety analysis. Pooled efficacy analysis may be performed if deemed appropriate.

1.1. Trial Objectives

Phase 1b

The primary objective is to evaluate the safety of JNJ-68284528 and establish the RP2D.

Phase 2

The primary objective is to evaluate the efficacy of JNJ-68284528, as measured by the overall response rate (ORR) (at least a partial response [PR] or better) as defined by the International Myeloma Working Group (IMWG) response criteria[5], as assessed by an Independent Review Committee (IRC), in subjects with relapsed or refractory multiple myeloma.

Secondary objectives include evaluating the safety, pharmacokinetics and pharmacodynamics, and immunogenicity, as well as additional efficacy of JNJ-68284528 including very good partial response (VGPR) or better rate, minimal residual disease (MRD) negativity rate as defined by the IMWG response criteria[5], clinical benefit rate (CBR; CBR = ORR + minimal response [MR]), duration of and time to response (DOR and TTR), progression-free survival (PFS), overall survival (OS), and health-related quality of life (HRQoL) using patient-reported outcome (PRO) measures including European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30, EuroQol Five Dimension Questionnaire (EQ-5D-5L), Patient Global Impression of Change (PGIC), Patient Global Impression of Severity (PGIS), and single items from EORTC QLQ-MY20.

The exploratory objectives are to explore:

- whether the infused CAR-positive T cell subsets impact pharmacodynamics, safety, and clinical activity of JNJ-68284528
- whether replication competent lentivirus may be present in subjects that receive JNJ-68284528
- whether there are predictive biomarkers of response or resistance to JNJ-68284528
- whether MRD negative rate correlates with DOR, PFS, OS
- the safety and efficacy of retreatment with JNJ-68284528

- pre-trial goals and expectations as well as post-treatment experience of JNJ-68284528 using semi-structured qualitative interviews
- the impact of JNJ-68284528 CAR-T process on medical resource utilization
- potential early clinical, translational, and imaging markers for neurotoxicity (predictive markers)

1.2. Trial Design

This is a Phase 1b-2, open-label, multicenter study of JNJ-68284528 administered to adult subjects with relapsed or refractory multiple myeloma. The aim of the study is to evaluate the safety and efficacy of JNJ-68284528. At least 24 and up to approximately 50 subjects will be enrolled in the Phase 1b dose period in which a RP2D of JNJ-68284528 will be established. Confirmation of the RP2D will be based on review of data from at least 24 subjects who were administered JNJ-68284528. Additional subjects (up to approximately 50) will be enrolled in the Phase 1b portion of the study to generate supplemental safety and efficacy data at the RP2D.

Safety evaluation team (SET) meetings will be convened: 1) during the Phase 1b study to evaluate for escalation and de-escalation of dose level after completion of the DLT evaluation period of every 6 subjects through 24 subjects and every 12 subjects thereafter, and 2) after SET evaluation of at least 24 subjects evaluated, administration of JNJ-68284528 to subjects in the Phase 2 portion of the study may begin concurrently with ongoing administration of JNJ-68284528 to subjects in the Phase 1b portion of the study. All available data including safety, pharmacodynamic, pharmacokinetic, and efficacy data from subjects enrolled in Phase 1b study will be considered. The SET or sponsor may also determine whether additional subjects are required to further evaluate safety and dose prior to proceeding to the Phase 2 portion of the study. The planned sample size for the Phase 2 portion will be approximately 60 subjects.

Eligible subjects will undergo apheresis for collection of peripheral blood mononuclear cells (PBMC). Study enrollment is defined at the day of initial apheresis. JNJ-68284528 will be generated from T cells selected from the apheresis. Subjects for whom apheresis or manufacturing fails will be allowed a second attempt at apheresis. Bridging therapy will be allowed when clinically indicated, with the permission of the sponsor.

After meeting safety criteria for lymphodepletion treatment, subjects will be administered a conditioning regimen of IV cyclophosphamide 300 mg/m^2 and fludarabine 30 mg/m^2 daily for 3 days. After meeting safety criteria for CAR-T cell therapy, JNJ-68284528 will be administered at a total targeted dose of 0.75 x 10^6 CAR-positive viable T cells/kg (range: 0.5-1.0 x 10^6 CAR-positive viable T cells/kg) 5 to 7 days after start of the conditioning regimen. In the event of excess toxicity, a dose de-escalation to dose level -1 (0.3 x 10^6 CAR-positive viable T cells/kg [range: 0.1-0.5 x 10^6 cells/kg]) for new subjects will occur (Section 3.3 of Protocol). Additionally, a dose escalation to dose level 2 (target dose not to exceed a 3-fold dose escalation [2.25 x 10^6 CAR-positive viable T cells/kg, range: ±30%, depending on target dose chosen for dose level 2]) will be considered if specified safety criteria are met (Section 3.4 of Protocol).

Disease status will be evaluated by an IRC according to clinical judgement guided by the IMWG consensus recommendations[5] for multiple myeloma treatment response criteria (Attachment 1 of Protocol). The process and convention of the IRC will be detailed in a separate charter.

Safety evaluations will include a review of adverse events (AEs), laboratory test results, electrocardiogram (ECG), echocardiogram or multiple-gated acquisition (MUGA) scan, vital sign measurements, physical examination findings, handwriting assessments, and assessment of Eastern Cooperative Oncology Group (ECOG) performance status grade. The safety profile will be evaluated at SET meetings during the Phase 1b portion of the study. Follow up of subjects for disease progression and survival will continue during the Posttreatment Phase. All study evaluations will be conducted according to the Time and Events Schedules (Table 1 and Table 2 of Protocol).

Subjects may be considered for retreatment with JNJ-68284528 within the same dose range to which they were initially assigned, or the de-escalated dose if de-escalation is mandated. A maximum of 1 retreatment may occur per subject. Bridging therapy prior to retreatment may be considered based on subject's clinical status and timing of availability of CAR-T product. Investigator must contact the sponsor for approval. Subjects who received treatment with JNJ-68284528 and are in follow-up at the end of the study (2 years after the last subject receives the initial dose of JNJ-68284528) will be monitored in the long-term follow-up study for 15 years from the time of last treatment.

The first analysis will be conducted approximately 6 months after the last subject receives their initial dose of JNJ-68284528. An update of the analysis will be provided at approximately 9 – 12 months after last subject receives their initial dose of JNJ-68284528 and at the end of the study, which is defined as 2 years after the last subject has received their initial dose of JNJ-68284528. The data cutoff will be communicated to the sites. The sponsor will monitor subjects treated with JNJ-68284528 for 15 years for complications of lentiviral integration, including second primary malignancies on a separate long-term follow-up study.

1.3. Statistical Hypotheses for Trial Objectives

Treatment with JNJ-68284528 will demonstrate acceptable safety and will have significant anti-myeloma activity (i.e., the lower limit of two-sided 95% confidence interval [CI] for ORR, as assessed by the IRC, is greater than 30%) at the targeted RP2D dose level in subjects with advanced relapsed or refractory multiple myeloma.

1.4. Sample Size Justification

Approximately 24 subjects will be treated in Phase 1b part to confirm the RP2D and assess safety. With 24 treated subjects, if the true incidence rate of certain AEs (refer to Table 3 of the protocol) is 10%, the probability of observing at least one subject experiencing event is more than 90%.

The sample size for the Phase 2 portion of the study assumes that the ORR will be at least 50%. With 60 subjects treated with JNJ-68284528 in the Phase 2 portion of the study, there will be

approximately 90% power to declare the ORR is higher than 30% at the 1-sided significance level of 0.025.

1.5. Randomization and Blinding

Randomization and blinding are not used in this study.

2. GENERAL ANALYSIS DEFINITIONS

2.1. Visit Windows

Unless otherwise specified, data to be analyzed or listed over time will be presented by day and time point (as appropriate) that are recorded in the electronic case report form (eCRF).

2.2. Pooling Algorithm for Analysis Centers

Data from all study centers will be pooled for analyses.

2.3. Study Treatment and Study Drug

Study treatment refers to cyclophosphamide, fludarabine, and JNJ-68284528. Study drug refers to JNJ-68284528.

2.4. Dose Level

Subjects who receive JNJ-68284528 infusion will undergo one of the following three dose levels:

- Dose Level 1: 0.75×10^6 CAR-positive viable T-cells/kg (range: $0.5\text{-}1.0\times10^6$)
- Dose Level -1: 0.3×10^6 CAR-positive viable T-cells/kg (range: $0.1\text{-}<0.5\times10^6$)
- Dose Level 2: not to exceed 2.25×10^6 CAR-positive viable T-cells/kg (range: ±30%)

2.5. Analysis Sets

2.5.1. All Enrolled Set

This set consists of all subjects who underwent apheresis and will be used for the summary of subject disposition and protocol deviation, as well as selected listings for adverse events.

2.5.2. Modified Intent-To-Treat (mITT) Analysis Set

This set consists of subjects who received a JNJ-68284528 infusion at the targeted RP2D dose level (i.e., within the RP2D dose range) and will be considered as the primary analysis set for all efficacy summaries.

2.5.3. All Treated Analysis Set

This set consists of subjects who received JNJ-68284528 infusion and will be considered as the primary analysis set for safety summaries.

2.5.4. Pharmacokinetic Analysis Set

This set consists of all subjects who received JNJ-68284528 infusion and have at least 1 post-dose pharmacokinetic sample.

2.5.5. Immunogenicity Analysis Set

This set consists of all subjects who received JNJ-68284528 infusion and have at least 1 post-dose immunogenicity sample.

2.6. Definition of Subgroups

The subgroups are summarized in Table 1. Additional exploratory subgroup analyses may be performed.

Table 1: Subgroups

Subgroup	Definition of Group	Analysis Type
Sex	• Male • Female	S, E
Age	• <65 years • 65 – 75 years • >75 years	S, E
Race	• White • African American • Other	S, E
Total CAR-positive viable T cells infused (x10E6 cells)	• < median value • ≥ median value	S, E
ECOG performance score prior to JNJ-68284528 infusion	• 0 • 1 • 2	E
Number of lines of prior therapy	• <= 4 • > 4	E
Baseline International Staging System (ISS)[a]	• I • II • III	E
Prior autologous stem cell transplant	• Yes • No	E
Prior allogenic stem cell transplant	• Yes • No	E
Type of myeloma	• IgG • Non-IgG	E
Refractory to [b]	• Yes • No	E
cytogenetic risk groups [c]	• High-risk • Standard-risk	E
Bone marrow % plasma cells	• <= 30 • > 30 to < 60 • >= 60	S, E
Baseline tumor BCMA expression	• ≥ median value • < median value	E
Study site	• each individual site	E

E= efficacy (ORR, VGPR or better rate, DOR, MRD negativity rate); ECOG= Eastern Cooperative Oncology Group; S= safety

[a] Baseline ISS will be derived based on serum β2-microglobulin and albumin

[b] Including last line of prior therapy, PI+IMiD, PI+IMiD+anti-CD38 antibody, at least 2 PIs + at least 2 IMiDs + 1 anti-CD38 antibody, pomalidomide (POM), carfilzomib (CARF), daratumumab (DARA)

[c] High-risk is defined as having t(4:14), t(14;16), or del17p by FISH or karyotype testing

2.7. Study Day and Relative Day

Study Day 1 refers to the start of the initial administration of JNJ-68284528. All efficacy and safety assessments at all visits will be assigned a day relative to this date.

Study day or relative day for a visit is defined as:

- Visit date - (Date of Study Day 1) +1, if visit date is ≥ date of Study Day 1
- Visit date - Date of Study Day 1, if visit date < date of Study Day 1

2.8. Baseline

The baseline value is defined as the closest non-missing value before the initial dose of JNJ-68284528 (including time if time is available), with exception of parameters associated with disease-related efficacy assessment for which the baseline value is defined as the non-missing value closest to the start of conditioning regimen and before JNJ-68284528 infusion.

The baseline value for the retreatment phase is defined similarly.

2.9. Imputation Rules for Missing Date/Time of Onset/Resolution

Unless specified otherwise, no data imputation will be applied for missing safety and efficacy evaluations. For analysis and reporting purposes, missing or partial dates in AE (AE onset date/time; AE end date/time), concomitant therapies (start date; end date), multiple myeloma diagnosis date, prior multiple myeloma therapies (start date; end date), progressive disease date on prior multiple myeloma therapy, and start date of subsequent antimyeloma therapy will be imputed.

2.9.1. Adverse Event Start/End Date/Time

If the start date of an AE is missing completely or partially, the following imputation rules will be used:

- When month and year are present and the day is missing: if the onset month and year are the same as the month and year of initial dosing date of study drug, the day of initial dosing or the day-component of the AE end date (possibly imputed) is imputed, whichever is earlier; if the onset month and year are not the same as the month and year of the initial dose of study drug, the first day of the month is imputed.
- When only a year is present or no components of the onset date are present: if the onset year is the same as the year of first dosing of study drug, or if AE end date is available and is prior to initial dosing date, the day and month of AE end date are imputed. Otherwise, the day and month of the initial dosing date are imputed. If the onset year is different from the year of first dosing of study drug, the 1st of January is imputed.
- If the onset date is completely missing, the earlier one of the initial dosing date and the AE end date is imputed as the onset date.

If the end date of an AE is missing completely or partially, the following imputation rules will be used:

- If month and year are present and the day of the month is missing, the last day of the month is imputed.
- If only a year is present, the 31st of December is used.
- If the imputed date is later than the date of death (if available) after imputation, the date of death will be used as the imputed date.
- If the year of end date is missing, no imputation will be applied.

AE start/end dates with missing times will be imputed as follows:

- A missing time of onset of an AE will be set to the earlier of:
    - 00:01 as long as the onset date is after the initial dosing date
    - The time of the initial dosing if this is on the same day of the AE occurred.
- The missing time of the end of an AE will be set to 23:59.
- If a missing time is associated with a partial or missing date, the date will be imputed first prior to imputing the time. If a missing time is associated with a completely missing date, the missing time will not be imputed.

2.9.2. Concomitant Medication Start/End Date

In case of partially missing dates, the imputation will be done as follows:

- If the date is completely missing, no imputation will be performed.
- Otherwise, the following rules will be applied to impute partially missing dates (start date, end date). If only the day is missing, the 15th day of the month will be used. If both the day and month are missing, the 30th of June will be used.

If the medication was taken prior to study start, and the imputed start date is after initial dosing date of study drug, further adjust the imputed start date as the day prior to initial dosing date; if the medication was taken after study start, and the imputed start date is prior to initial dosing date, further adjust the imputed start date as initial dosing date. Also adjust the imputed medication end date so that it is on or after initial dosing date.

2.9.3. Multiple Myeloma Diagnosis Date

For partial date of original multiple myeloma diagnosis, the following imputation rules will be applied:

- If only day is missing,
    - if month and year of start of 1st line of prior multiple myeloma therapy are the same year and month of diagnosis, and day of start of 1st line of prior multiple myeloma therapy is available, impute day with day of start of 1st line of prior multiple myeloma therapy
    - otherwise, impute day with 15
- If both month and day are missing,

  - if year of diagnosis is the same as year of start of 1st line of prior multiple myeloma therapy, and month info is available for start of the 1st line of prior multiple myeloma therapy
    - impute month with month of start of 1st line of prior multiple myeloma therapy
    - if day of start of 1st line of prior multiple myeloma therapy is available, impute diagnosis day with day of start of 1st line of prior multiple myeloma therapy; otherwise, impute diagnosis day with 15
  - otherwise, impute with June 30

- If year is missing, no imputation will be applied.

2.9.4. Prior Multiple Myeloma Therapy Start/End Date

For partially missing prior multiple myeloma therapy start/end dates, the following imputation rules will be applied. If the date is completely missing, no imputation will be performed.

- If only the day is missing, the 15th day of the month will be used.
- If both the day and month are missing, the 30th of June will be used.

If the imputed start/end date is after initial dosing date, further adjust the imputed start/end date as the day prior to initial dosing date.

2.9.5. Progressive Disease Date on Prior Multiple Myeloma Therapy

For partially missing progressive disease date on prior multiple myeloma therapy, the following imputation rules will be applied. If the date is completely missing, no imputation will be performed. Partially missing prior multiple myeloma therapy start/end dates will be imputed before imputing partially missing progressive disease date.

- If only the day is missing,
  - if the month and the year are the same as the month and the year of prior multiple myeloma therapy start date, then the day of prior multiple myeloma therapy start date will be used.
  - otherwise, 15th day of the month will be used
- If both the day and month are missing,
  - if the year is the same as the year of prior multiple myeloma therapy start date, then the month and day of prior multiple myeloma therapy start date will be used
  - otherwise, the 30th of June will be used

If the imputed progressive disease date is before the prior multiple myeloma therapy start date, further adjust the imputed progressive disease date as the prior multiple myeloma therapy start date.

2.9.6. Subsequent Antimyeloma Therapy Start Date

If no components of the start date are present, no imputation will be performed.

If both the month and day components are missing, the following steps apply:

- If the year is the same as the year of last study treatment end date or the year of the first post-baseline progressive disease as assessed by the investigator, then the month and day of last study treatment end date + 1 day or the month and day of the first post-baseline progressive disease date + 1 day will be used, whichever is later.
- Otherwise, the 30th of June or the stop date of subsequent antimyeloma therapy, whichever is earlier will be used.

If only the day-component is missing, the following steps apply:

- If the month and year of the start date are the same as the month and year of the last study treatment end date or the month and year of the first post-baseline progressive disease as assessed by the investigator, then the day of last study treatment end date + 1 day or the day of the first post-baseline progressive disease date + 1 day will be used, whichever is later.
- Otherwise, the first day of the month is imputed.
- If the imputed start date of subsequent antimyeloma therapy is after the stop date of subsequent therapy, further adjust the imputed start date of subsequent antimyeloma therapy as the stop date of subsequent therapy.

No imputation will be applied for missing or partial subsequent antimyeloma therapy end date.

3. SUBJECT INFORMATION

3.1. Demographics and Baseline Characteristics

Table 2 presents a list of the demographic variables that will be summarized by dose level and overall for all treated analysis set.

Table 2: Demographic Variables

Continuous Variables	**Summary Type**
Age (years)	Descriptive statistics (N, mean, standard deviation [SD], median and range [minimum and maximum]).
Weight (kg)	
Height (cm)	
Body Surface Area (BSA) (m^2)	
Categorical Variables	
Age (<65 years, 65-75 years, >75 years)	Frequency distribution with the number and percentage of subjects in each category.
Sex (male, female, undifferentiated, unknown)	
Race[a] (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander, White, Not reported)	
Ethnicity (Hispanic or Latino, not Hispanic or Latino, not reported)	
ECOG performance status (0, 1, 2)	

[a] If multiple race categories are indicated, the Race is recorded as 'Multiple'

Table 3 presents a list of the baseline characteristics variables that will be summarized by dose level and overall for all treated analysis set.

Table 3: Baseline Characteristics Variables

Continuous Variables	**Summary Type**
Time since initial multiple myeloma diagnosis (years)	Descriptive statistics (N, mean, standard deviation [SD], median and range [minimum and maximum]).
Selected hematology laboratory analytes (hemoglobin, platelets, absolute lymphocyte count, white blood cell count, absolute neutrophil count)	
Selected chemistry laboratory analytes (AST, ALT, Alkaline phosphatase, creatinine clearance, total bilirubin, corrected serum calcium, ferritin, c-reactive protein)	
Coagulation laboratory analytes (Prothrombin time/INR, activated partial thromboplastin time, fibrinogen, D-dimer)	
Vital sign parameters (pulse, systolic blood pressure, diastolic blood pressure, temperature, respiratory rate, oxygen saturation)	
Echocardiogram/MUGA results at baseline (LVEF %)	
Categorical Variables	
Type of multiple myeloma (IgG, IgA, IgM, IgD, IgE, free light chain only, biclonal, or negative immunofixation)	Frequency distribution with the number and percentage of subjects in each category.
Type of measurable disease (Serum only, Serum and urine, Urine only, or Serum FLC)	
ISS staging by central laboratory assessment (I, II, III)	
Number of lytic bone lesions (None, 1-3, 4-10, more than 10)	
Presence of extramedullary plasmacytomas (Yes, No)	
Bone marrow % plasma cells (<10, 10-30, >30-<60, ≥60)	
Bone marrow cellularity (hypercellular, normocellular, hypocellular, indeterminate) by biopsy or aspirate	
Standard-risk and high-risk cytogenetic abnormalities (del17p, t(4;14), t(14;16))	
Baseline toxicity grade (1, 2, 3, 4) of selected hematology laboratory analytes	
Baseline toxicity grade (1, 2, 3, 4) of selected chemistry laboratory analytes	
Baseline toxicity grade (1, 2, 3, 4) of selected coagulation laboratory analytes	
Medical history collected at screening visit (by system organ class, preferred term)	
Neurologic history collected at screening visit and the toxicity grade	
ECG overall interpretation at baseline (normal, abnormal and clinically significant, abnormal and not clinically significant, not evaluable)	
Echocardiogram/MUGA scan overall interpretation at baseline (normal, abnormal and clinically significant, abnormal and not clinically significant, not evaluable)	
Transfusion during screening until JNJ-68284528 infusion	
Immune-effector cell-associated encephalopathy (ICE) scores at baseline	

Note: Applicable laboratory results will be graded according to NCI-CTCAE version 5.0

In addition, selected key demographic variables and baseline disease characteristics variables at enrollment (ie, prior to apheresis) will be summarized for all enrolled analysis set.

Subject who received apheresis (ie, subjects enrolled) will be presented according to region and country.

In addition, listings for the following subsets will be provided.

- Subjects who did not meet study eligibility criteria
- Subjects had apheresis but did not receive conditioning regimen
- Subjects had conditioning regimen but did not receive JNJ-68284528 infusion

3.2. Disposition Information

Number of subjects who completed or discontinued from treatment will be summarized for the all enrolled analysis set, together with the reason for discontinuation of treatment reported on the

eCRF. Number of subjects who discontinued from study and the reported reason on the eCRF will be presented similarly. A listing for subject disposition will also be provided.

3.3. Extent of Exposure

Extent of exposure to the initial dose of study treatment will be summarized and presented based on the all treated analysis set.

Descriptive statistics (N, mean, SD, median, and range) for JNJ-68284528 infusion duration, total volume of the JNJ-68284528 infusion bag, and time from apheresis to JNJ-68284528 infusion will be presented by dose level and overall.

The total CAR-positive viable T cells infused (x10E6 cells), weight-adjusted CAR-positive viable T cells infused (x10E6 cells/kg) will be summarized by dose level and overall.

Similarly, the total dose of the cyclophosphamide and fludarabine infusion (mg/m^2) will be respectively summarized overall.

The number (%) of subjects with a dose adjustment (infusion aborted or interrupted for JNJ-68284528 infusion, cyclophosphamide and fludarabine infusions) will be summarized by dose level (for JNJ-68284528 infusion) and overall. The reasons (adverse events, other) for dose adjustments will also be summarized.

The number (%) of subjects with delay of conditioning regimen and the reasons (AE or other) for delay will be summarized overall. Similar summaries will be provided for subjects with delay of JNJ-68284528 infusion.

A listing of exposure information might be provided for each subject, including the start date/time, end date/time, total dose received, dose adjustments (infusion aborted or interrupted) and adjustment reasons of JNJ-68284528, cyclophosphamide, and fludarabine infusions. A listing will be provided for subjects who received the JNJ-68284528 product that did not meet all the pre-specified release criteria including the criterion not met.

Similar summaries will be provided for subjects who received the retreatment of JNJ-68284528.

3.4. Protocol Deviations

In general, the following list of major protocol deviations may have the potential to impact subjects' rights, safety or well-being, or the integrity and/or result of the clinical study. Subjects with major protocol deviations will be identified prior to database lock and the subjects with major protocol deviations will be summarized by category for all enrolled analysis set.

- Entered but did not satisfy criteria
- Developed withdrawal criteria but not withdrawn
- Received wrong treatment or incorrect dose
- Received a disallowed concomitant treatment

- Other

A listing of all major protocol deviations including subject ID, type of deviation, and reasons for deviation will be provided.

3.5. Prior Therapies for Multiple Myeloma

3.5.1. Prior Exposure to Multiple Myeloma Therapies

A summary of prior exposure to multiple myeloma therapies (systemic therapy, stem cell transplant, radiotherapy, or cancer-related surgery/procedure) will be provided by dose level and overall. Specifically, the number of prior lines of therapy will be calculated and summarized by the following categories: <3, 3, 4, 5, >5 through frequency and descriptive statistics.

Additionally, the summary of prior systemic therapies will be presented by therapeutic class, pharmacologic class, and drug name, coded using the latest version of World Health Organization (WHO) Drug Dictionary.

The therapy classes include proteasome inhibitors (PI), immunomodulatory drugs (IMiD), anti-CD38 antibody, steroids, alkylating agents and anthracyclines. Therapies included in the PI class are: bortezomib, carfilzomib, oprozomib and ixazomib; IMiD class: lenalidomide, pomalidomide, and thalidomide; anti-CD38 antibody class: daratumumab, isatuximab, TAK-079, and MOR202, and steroids class: dexamethasone and prednisone, among others. Other therapies or therapy classes may be summarized as deemed clinically relevant.

The number of subjects who had prior exposure to multiple therapy classes (e.g., PI + IMiD) or multiple therapies (e.g., bortezomib + lenalidomide) may be provided, if the number of subjects who exposed to those therapy classes or therapies is sufficient.

3.5.2. Refractory Disease

Refractory is defined as being nonresponsive while on therapy or progressed within 60 days of last therapy[6].

Refractory status (yes, no) to a particular prior multiple myeloma therapy class (i.e., PI/IMiD) or prior multiple myeloma therapy (e.g., bortezomib or thalidomide) refers to refractory to any prior therapy-containing line for this subject.

The number and percentage of subjects' refractory status to PI, IMiD, or anti-CD38 antibody therapy class will be summarized by the following categories including, but not limited to, PI+IMiD+anti-CD38 antibody, at least 2 PIs + at least 2 IMiDs +1 anti-CD38 antibody. Refractory to specific prior MM therapy, such as bortezomib, carfilzomib, ixazomib, lenalidomide, pomalidomide, thalidomide, daratumumab, isatuximab, TAK-079, MOR202, and the relevant combinations of the aforementioned therapies will be provided separately.

The incidence of subjects who are refractory to their last line of therapy will be reported.

3.6. Concomitant Medications

Concomitant medications collected in the eCRF page during the study will be summarized by therapy class and therapy, coded using the latest version of WHO Drug Dictionary.

A similar summary will be provided for growth factor use and pre-infusion medication, as well as for bridging therapy, respectively.

Therapeutic/surgical procedures collected in the eCRF page during the study will also be provided. In addition, anti-IL6 receptor tocilizumab, IL-1 receptor antagonist anakinra, vasopressors, systemic steroids and levetiracetam as concomitant medication use for CRS and CAR-T cell neurotoxicity will be summarized. Additionally, prophylactic antimicrobial medication use will be tabulated.

Transfusions and oxygen supplementation will be summarized respectively as well.

3.7. Subsequent Antimyeloma Therapy

The total number of subjects who received subsequent antimyeloma therapy will be reported for each dose level. A summary of subsequent antimyeloma therapy will be presented by therapeutic class, pharmacologic class and drug name, coded using the latest version of WHO Drug Dictionary.

In addition, for subjects who received subsequent antimyeloma therapy, their best response to the first subsequent antimyeloma therapy will be summarized.

4. EFFICACY

4.1. Analysis Specifications

4.1.1. Level of Significance

All statistical hypothesis tests will be based on 1-sided test at significance level of 0.025. All interval estimations will be reported using 2-sided 95% CI.

4.1.2. Independent Review Committee (IRC)

The independent review committee (IRC) will be composed of three physicians with expertise and clinical experience in the diagnosis and management of multiple myeloma. However, they will not have direct involvement in the conduct of the study. The IRC members will perform an independent review of data from all subjects treated with JNJ-68284528 in the study. The primary purpose of the IRC review will be to provide an independent determination of PD/response and ensure consistent evaluation of PD/response for all subjects in this study. The IRC will use the 2016 IMWG consensus criteria[5] (Attachment 1 of Protocol) in combination of clinical judgement to assess PD and response. The process and convention of the IRC will be detailed in a separate charter.

For each subject, the overall IRC-assessed response/PD and corresponding time will be determined based on a majority (2/3) quorum.

For overall IRC assessment of disease progression,

- If at least two reviewers determine that a subject had PD, then overall IRC will assess PD for this subject. The reason for IRC-assessed PD captures all reasons cited by individual reviewers. If there is any disagreement as to when it occurred, the time for PD will be determined as follows:
    - If PD is assessed by two reviewers on different dates, the latter PD date is used. The justification is that only by the latter date do 2 of the 3 reviewers agree that a subject's disease has progressed.
    - If PD is assessed by three reviewers, a majority (2/3) prevails. If there is no majority, the middle date is used. The justification for choosing the middle date is that 2 of the 3 (majority) reviewers assess PD by then.
- If one or none of the reviewers determines that a subject had PD, then overall IRC will assess censoring for this subject. The time for censoring is determined as follows:
    - If all three reviewers agree that a subject should be censored, the last time at which each reviewer assessed response of SD or better (including MR, PR, VGPR, CR, and sCR) will be determined and the middle time will be used as time of censoring. This is a majority in that 2 of the 3 reviewers will agree that a subject was stable or responding by the middle time.
    - If two reviewers agree on both censoring and timing of censoring, the common timing of censoring will be used as the time for censoring.
    - If two reviewers agree on censoring and disagree on timing, the time for censoring is determined by the following steps:
        - For the reviewer who assesses PD, all dates up to the last assessment prior to PD will be included.
        - All results from the 3 reviewers shall be used to determine the time of censoring, by applying the method described above when all three reviewers agree with censoring.

For overall IRC assessment of best response,

- If at least 2 reviewers indicate the same best response, that shall become the overall IRC-assessed best response.
- If all 3 reviewers disagree, the middle of the 3 response categories shall be assigned as the overall IRC-assessed best response.
- If there is disagreement as to when the best response occurs, the time for overall IRC-assessed best response is determined as follows:
    - If the same best response is assessed by all three reviewers, the majority (2/3) date will be used. If there is no majority, the middle date is used.
    - If the same best response is assessed by two reviewers, the later date will be used.
    - If the best response is assessed by only one reviewer, the later date between the corresponding assessment date from this reviewer and the assessment date with a better response from another reviewer will be used.

The overall IRC assessment of first response and the corresponding time is determined similar to that for best response.

4.1.3. Computerized Algorithm

Efficacy assessment will also be performed by the sponsor using a computerized algorithm, following the IMWG criteria[5] (Attachment 1 of Protocol). Detailed rules for response/PD assessment are provided in ATTACHMENT 1: Disease Progression and Response Assessment.

4.1.4. Data Handling Rules

There is no imputation planned for missing efficacy endpoint values.

4.2. Primary Efficacy Endpoint(s)

4.2.1. Definition

The primary endpoint is ORR, defined as the proportion of subjects who achieve a PR or better according to the IMWG response criteria[5], as assessed by IRC.

4.2.2. Estimand

The primary estimand, the main clinical quantity of interest to be estimated in the study, is defined by the following 5 components:

- Treatment: Treatment condition of interest is the sequence of conditioning regimen and JNJ-68284528
- Population: subjects with relapsed or refractory multiple myeloma who received at least 3 prior lines of therapy or are double refractory to a PI and an IMiD, and have received a PI, an IMiD, and anti-CD38 antibody
- Variable: overall response
- Intercurrent event: subsequent antimyeloma therapy or retreatment with JNJ-68284528. Response after the start of subsequent therapy or the retreatment with JNJ-68284528 will not be considered.
- Population-level summary: ORR

4.2.3. Analysis Methods

The analysis of ORR will be based on the mITT analysis set. Subjects with no postbaseline data will be considered as non-responders. Response after the start of subsequent therapy or the retreatment with JNJ-68284528 will not be considered. The ORR and its 2-sided 95% Clopper-Pearson exact CI will be presented. P-value from 1-sided exact binomial test for the null hypothesis of ORR ≤30% will be provided.

Descriptive summaries and forest plots will be provided for the subgroups as specified in Section 2.6.

Sensitivity analyses of ORR will be performed based on the mITT analysis set using disease response based on the computerized algorithm and investigator assessment according to the IMWG response criteria[4]. The prevalence-adjusted-bias-adjusted kappa (PABAK) statistics[1] and 95% CI will be calculated for agreement between IRC assessment and computerized algorithm assessment for response (response [PR or better] vs. no response).

Supplementary analyses of ORR will be performed:

- based on all enrolled analysis set
- based on all treated analysis set
- based on those subjects in the mITT analysis set who received the JNJ-68284528 product that met all the pre-specified release criteria

Other sensitivity analyses may also be performed as deemed appropriate.

4.3. Major Secondary Endpoints

The major secondary efficacy endpoints include VGPR or better rate, MRD negativity rate, CBR, DOR, TTR, PFS, OS.

4.3.1. Very Good Partial Response (VGPR) or Better Rate

4.3.1.1. Definition

Very good partial response (VGPR) or better rate is defined as the proportion of subjects who achieve a sCR, CR, or VGPR according to the IMWG response criteria[5].

4.3.1.2. Analysis Methods

The analysis will be based on the mITT analysis set. Very good partial response (VGPR), CR, or sCR after the start of subsequent therapy or the retreatment with JNJ-68284528 will not be considered. Very good partial response (VGPR) or better rate and its 2-sided 95% Clopper-Pearson exact CI will be presented.

Analyses will be performed based on IRC assessment, computerized algorithm assessment, and investigator assessment. Supplementary analyses will be performed based on all enrolled analysis set and all treated analysis set.

4.3.2. Minimal Residual Disease (MRD) Negativity Rate

4.3.2.1. Definition

Minimal residual disease negativity rate is defined as the proportion of subjects who have negative MRD by bone marrow aspirate at any timepoint after initial dose of JNJ-68284528 and before disease progression or starting subsequent therapy or retreatment with JNJ-68284528. Minimal residual disease positive subjects include subjects for whom all tested samples were found to be MRD positive or ambiguous. Subjects with missing or unevaluable MRD status will be grouped separately.

4.3.2.2. Analysis Methods

The analysis will be based on the mITT analysis set. The MRD negativity rate and its 2-sided 95% Clopper-Pearson exact CI will be presented. Reasons for missing or unevaluable MRD status will be provided.

For this study, the threshold value of 10^{-5} will be used for the primary MRD negativity analysis. Other threshold values may also be explored. Supplementary analyses will be performed based on all enrolled analysis set and all treated analysis set.

4.3.3. Clinical Benefit Rate

4.3.3.1. Definition

Clinical benefit rate is defined as the proportion of subjects with best response of MR or better (including sCR, CR, VGPR, PR, and MR).

4.3.3.2. Analysis Methods

The analysis will be based on the mITT analysis set. Responses after the start of subsequent therapy or retreatment with JNJ-68284528 will not be considered. Clinical benefit rate and its 2-sided 95% Clopper-Pearson exact CI will be presented.

Analyses will be performed based on IRC assessment, computerized algorithm assessment, and investigator assessment. Supplementary analyses will be performed based on all enrolled analysis set and all treated analysis set.

4.3.4. Duration of Response

4.3.4.1. Definition

Duration of response will be calculated among responders (with a PR or better) from the date of initial documentation of a response (PR or better) to the date of first documented evidence of progressive disease, as defined in the IMWG criteria[5], or death due to any cause, whichever occurs first. Subjects who have not progressed and are alive will be censored at the last disease evaluation before the start of subsequent antimyeloma therapy or retreatment with JNJ-68284528.

4.3.4.2. Analysis Methods

Analysis of DOR will be based on subjects in the mITT analysis set who achieve a response (PR or better response), using disease response based on IRC assessment. The distribution of DOR will be estimated using the Kaplan-Meier method. The Kaplan-Meier curve for DOR will be provided.

Descriptive summaries and forest plots will be provided for the subgroups as specified in Section 2.6.

Supplementary analyses will be performed based on subjects in the all enrolled analysis set and all treated analysis set who achieve a response using IRC assessment, respectively.

In addition, DOR will be summarized for subjects who achieved CR, MRD-negative CR, and VGPR or better, respectively.

4.3.5. Time to Response

4.3.5.1. Definition

Time to first response is defined as the time between date of the initial infusion of JNJ-68284528 and the first efficacy evaluation that the subject has met all criteria for PR or better. Time to best response is defined as the time between date of the initial infusion of JNJ-68284528 and the first efficacy evaluation that the subject has his/her best response to treatment.

4.3.5.2. Analysis Methods

Time to first response and time to best response will be analyzed for subjects in the mITT analysis set who achieve a response (PR or better). Descriptive statistics (N, mean, SD, median, and range) will be provided. Time to CR or better response will be summarized similarly for subjects in the mITT analysis set who achieve CR or better.

Analyses will be performed based on both IRC assessment and computerized algorithm assessment. Descriptive summaries will be provided to characterize the difference in timing of first response and best response between IRC assessment and computerized algorithm assessment.

Supplementary analyses will be performed based on subjects in the all enrolled analysis set and all treated analysis set who achieve a response using IRC assessment and computerized algorithm assessment, respectively, according to the IMWG response criteria[5] in a similar manner as described above.

4.3.6. Progression-free Survival

4.3.6.1. Definition

Progression-free survival is defined as the time from the date of the initial infusion of JNJ-68284528 to the date of first documented disease progression, as defined in the IMWG criteria[5], or death due to any cause, whichever occurs first. For subjects who have not progressed and are alive, data will be censored at the last disease evaluation before the start of any subsequent antimyeloma therapy or retreatment with JNJ-68284528.

Determinations of dates of PFS event and dates for censoring are summarized in Table 4 as follows.

Table 4: PFS Event and Censoring Method

Situation	Outcome	Date of Event or Censoring
Disease progression prior to start of subsequent antimyeloma therapy or retreatment with JNJ-68284528	PFS event	Earliest date that indicates disease progression
Death	PFS event	Date of death
No postbaseline disease assessment	Censored	Date of initial infusion of JNJ-68284528
Other, such as: • Withdrawal of consent to study participation, • Lost to follow-up	Censored	Date of last disease assessment prior to withdrawal of consent to study participation*, lost to follow-up, or

• Start of subsequent antimyeloma therapy or retreatment with JNJ-68284528 prior to disease progression or death		start of subsequent antimyeloma therapy or retreatment with JNJ-68284528

*Subjects who died after consent withdrawal will be censored at the date of consent withdrawal for PFS analysis

4.3.6.2. Analysis Methods

The analysis will be based on the mITT analysis set using progressive disease based on IRC assessment. The distribution of PFS will be estimated using the Kaplan-Meier method. The Kaplan-Meier curve for PFS will be provided.

In addition, landmark PFS rate with 95% CI will be estimated by Kaplan-Meier method. The reasons for PFS censoring will be summarized as well.

Descriptive summaries and forest plots will be provided for the subgroups as specified in Section 2.6.

Kaplan-Meier curves for PFS will be provided by responder vs. non-responder and CR/sCR vs. non-CR/sCR based on IRC assessment.

Sensitivity analyses of PFS, in which progressive disease is based on the computerized algorithm assessment and investigator assessment according to the IMWG response criteria[5], will be performed in a similar manner as described above.

Supplementary analyses will be performed based on all treated analysis set, and based on all enrolled analysis set where PFS is calculated from the date of the initial apheresis to the date of first documented disease progression, as defined in the IMWG criteria[3], or death due to any cause, whichever occurs first. For subjects who underwent apheresis but did not receive JNJ-68284528 infusion, additional event and censoring method in Table 5 will be used.

Table 5: Sensitivity Analysis All Enrolled Analysis Set - PFS Event and Censoring Method for Subjects Who Apheresed but Did Not Received JNJ-68284528 Infusion

Situation	Outcome	Date of Event or Censoring
Discontinued study before JNJ-68284528 infusion due to progressive disease	PFS event	Date of study discontinuation
Discontinued study before JNJ-68284528 infusion due to death	PFS event	Date of death
No disease assessment after apheresis	Censored	Date of apheresis
If none of the above	Censored	Date of last disease assessment prior to study discontinuation

4.3.7. Overall Survival

4.3.7.1. Definition

Overall survival is defined as the time from the date of the initial infusion of JNJ-68284528 to the date of the subject's death. If the subject is alive or the vital status is unknown, then the subject's data will be censored at the date the subject was last known to be alive. Subjects who died after consent withdrawal will be considered as having an OS event.

4.3.7.2. Analysis Methods

Overall survival will be analyzed using similar statistical methods as described in Section 4.3.6.2 for PFS analysis.

Supplementary analyses will be performed based on all treated analysis set, and based on all enrolled analysis set where OS is calculated from the date of the initial apheresis to the date of the subject's death.

4.4. Other Efficacy Variable(s)

Other efficacy endpoints related to retreatment evaluation include VGPR or better rate, MRD negativity rate, DOR and TTR after retreatment with JNJ-68284528.

4.4.1. Definitions

Very good partial response (VGPR) or better rate after retreatment with JNJ-68284528 is defined as the proportion of subjects who achieve sCR, CR, or VGPR, according to the IMWG response criteria[5], after retreatment with JNJ-68284528.

Minimal residual disease (MRD) negativity rate after retreatment with JNJ-68284528 is defined as the proportion of subjects who have negative MRD by bone marrow aspirate at any timepoint after retreatment with JNJ-68284528 and before disease progression or starting subsequent therapy. Minimal residual disease positive subjects include subjects for whom all tested samples after retreatment with JNJ-68284528 were found to be MRD positive or ambiguous. Subjects with missing or unevaluable MRD status after retreatment with JNJ-68284528 will be considered as MRD positive.

Duration of response (DOR) after retreatment with JNJ-68284528 will be calculated among responders after retreatment (with a PR or better after retreatment) from the date of initial documentation of a response (PR or better) after retreatment to the date of first documented evidence of progressive disease after retreatment, as defined in the IMWG criteria[5], or death due to PD, whichever occurs first. Subjects who have not progressed or who die due to causes other than disease progression will be censored at the last disease evaluation before the start of subsequent antimyeloma therapy. Subjects who start subsequent antimyeloma therapy without PD will be censored at the last disease evaluation before the start of subsequent antimyeloma therapy.

Time to first response after retreatment with JNJ-68284528 is defined as the time between date of the retreatment with JNJ-68284528 and the first efficacy evaluation that the subject has met all criteria for PR or better after retreatment with JNJ-68284528.

4.4.2. Analysis Methods

The analysis of VGPR or better rate and MRD negativity rate after retreatment will be based on subjects who received retreatment with JNJ-68284528. Responses after the start of subsequent anti-cancer therapy will not be considered. The response rates and their 2-sided 95% Clopper-Pearson exact CIs will be presented.

The analysis of DOR and time to first response after retreatment will be based on subjects who received retreatment with JNJ-68284528. The distribution of DOR after retreatment will be estimated using the Kaplan-Meier method. The Kaplan-Meier curve for DOR after retreatment will be provided. Time to first response after retreatment will be analyzed for subjects who achieve a response (PR or better) and descriptive statistics (N, mean, SD, median, and range) will be provided.

Subjects listings may be provided instead of summary tables for retreatment evaluation if only a limited number of subjects received retreatment with JNJ-68284528.

5. SAFETY

Safety assessment will be evaluated through AEs, clinical laboratory tests, vital sign measurements, physical examination findings, cardiac variables (ECG, echocardiogram/MUGA scan) and assessment of ECOG performance status. Safety analyses will be based on the all treated analysis set and presented by the dose level and overall.

5.1. Adverse Events

Adverse Events will be recorded in standard medical terminology and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 5.0, with the exception of (1) Immune effector Cell-associated Neurotoxicity (ICANS) reported in Phase 2 portion of the study and CRS, which will be evaluated according to the ASTCT[4] consensus grading system, and (2) AE associated with changes in handwriting, which will be graded according to the protocol criteria (Attachment 15 of Protocol). The verbatim terms used in the eCRF by investigators to identify AEs will be coded using the latest Medical Dictionary for Regulatory Activities (MedDRA).

Unless otherwise specified, at each level (e.g., system organ class [SOC] and/or preferred term [PT]) of subject summarization in reporting the incidence of the AE, a subject is counted once if one or more events were recorded.

All reported treatment-emergent adverse events (TEAEs), all second primary malignancies during the entire duration of the study and hepatitis B virus (HBV) reactivations and neurotoxicity during the first year post-dosing of JNJ-68284528 will be included in the analysis. TEAEs are defined as any AE that occurs at or after the JNJ-68284528 infusion through 100 days after the JNJ-68284528 infusion or the start of subsequent anti-myeloma therapy, whichever is earlier; or any AE that is considered related to study drug (very likely, probably, or possibly related) regardless of the start date of the event; or any AE that is present at baseline but worsens in toxicity grade or is subsequently considered drug-related by the investigator. If the event occurs on the day of the initial infusion and either event time or time of infusion are missing, then the event will be assumed to be treatment-emergent. If the event date is recorded as partial or completely missing, then the event will be considered as treatment-emergent unless it is known to be prior to the infusion based on partial onset date or resolution date.

The following AE summaries will be presented by dose level and overall. The TEAEs after retreatment with JNJ-68284528 will be summarized similarly and separately.

- An overview of TEAE, including subjects with TEAE, treatment-emergent SAE, TEAE related to study drug, TEAE of maximum grade of 1 to 5, TEAE with outcome death

- TEAE by SOC and PT
- TEAE by SOC, PT, and relationship to study drug
- TEAE by SOC, PT and toxicity grade 3 or higher
- Most common (>10%) TEAE by SOC, PT, and toxicity grade 3 or higher
- TEAE by SOC, PT, and worst grade

- Treatment-emergent SAE by SOC and PT
- Treatment-emergent SAE by SOC, PT, and toxicity grade 3 or higher
- Most common (>5%) Treatment-emergent SAE by SOC, PT, and toxicity grade 3 or higher

- Toxicity grade 3 or 4 TEAE by SOC and PT
- Toxicity grade 3 or 4 TEAE by SOC, PT, and relationship to study drug
- Most common (>5%) toxicity grade 3 or 4 TEAE by SOC and PT

- TEAE with outcome death by SOC, PT and relationship to study drug

In addition, the following AEs will be tabulated.

- AE that occurs from administration of the conditioning regimen and before study drug infusion by SOC, PT, and toxicity grade 3 or higher
- AE that occurs from apheresis and before administration of the conditioning regimen by SOC, PT, and toxicity grade 3 or higher
- AE as primary reason for treatment discontinuation (between the start of the conditioning regimen and JNJ-68284528 infusion) by SOC, PT and relationship to conditioning regimen
- AE related to bridging therapy by SOC, PT, and toxicity grade 3 or higher
- AE related to apheresis procedure by SOC, PT, and toxicity grade 3 or higher
- AE leading to conditioning regimen delay by SOC, PT, and toxicity grade 3 or higher
- AE leading to JNJ-68284528 infusion delay ~~of ≥14 days~~ by SOC, PT, and toxicity grade 3 or higher

5.2. Deaths

Number of subjects who died during the study and the primary cause of death will be summarized overall and by dose level for the all treated analysis set. In addition, all deaths within 30 days and within 100 days after the initial dose of JNJ-68284528 infusion will be summarized respectively.

A listing will be generated for all treated subjects who died during the study.

5.3. Adverse Events of Special Interest

5.3.1. Cytokine Release Syndrome

Subjects with any cytokine release syndrome (CRS) will be summarized by the maximum toxicity grades (according to ASTCT[4] consensus grading system). Cytokine release syndrome (CRS) events that were initially graded per the Lee criteria[3] in Phase 1b portion of the study will be re-evaluated according to ASTCT[4] consensus grading system. In addition, the time from initial JNJ-68284528 infusion to first onset of CRS, the duration of CRS in days, the outcome of CRS, and the treatment for CRS will be summarized as well.

Additionally, subjects with any symptom of CRS will be summarized by MedDRA SOC, PT and maximum toxicity grade (according to NCI-CTCAE version 5.0).

Listings will be provided respectively for subjects who reported any CRS or any symptom of CRS.

5.3.2. Neurologic Adverse Events

Neurologic adverse events include CAR-T cell neurotoxicity (ICANS, other neurotoxicities) and other neurologic adverse events. CAR-T cell neurotoxicity (ICANS, other neurotoxicities) events are adverse events of special interest. Other neurologic adverse events, while not a protocol-defined adverse event of special interest, will be included to allow a comprehensive summary on the neurologic adverse events.

Subjects with any neurologic adverse event reported after JNJ-68284528 infusion will be summarized by MedDRA SOC, HLGT, HLT, PT, and grade 3/4.

CAR-T cell neurotoxicity (ICANS, other neurotoxicities)

Subjects with any ICANS will be summarized by the maximum toxicity grades (according to ASTCT[4] consensus grading system). CAR-T cell Related Encephalopathy Syndrome (CRES) events that were initially grade per NCI-CTCAE version 5.0 in Phase 1b portion of the study will be re-evaluated according to ASTCT[4] consensus grading system. In addition, the time from initial JNJ-68284528 infusion to first onset of ICANS, the duration of ICANS in days, the outcome of ICANS, the treatment of ICANS, and concurrent/non-concurrent CRS will be summarized as well. One shift table from baseline to worst ICE scores during the post infusion period will be provided.

Subjects with any other neurotoxicities will be summarized by the maximum toxicity grades (according to NCI-CTCAE version 5.0). In addition, the time from initial JNJ-68284528 infusion to first onset of other neurotoxicities, the duration of neurotoxicities in days, and the outcome of other neurotoxicities will be summarized. Subject listing will be provided for other neurotoxicities after JNJ-68284528 infusion. Exploratory analysis of other neurotoxicities (yes vs. no) by clinical tumor assessment (high vs. intermediate vs. low burden, according to the categorization tabulated below) at baseline, by ICANS (yes vs. no), and by worst toxicity grade of CRS (<2 vs. ≥2) will be performed.

Tumor Burden Category	Criteria
High	Any of the following parameters at baseline were met: • Bone marrow % plasma cell ≥ 80% • Serum M-spike ≥ 5g/dL • Serum free light chain ≥ 5000 mg/L
Low	All of the following (as applicable to the subject) parameters at baseline were met: • Bone marrow % plasma cell < 50% • Serum M-spike < 3g/ dL • Serum free light chain < 3000 mg/L
Intermediate	Did not fit either criteria of high or low tumor burden

Other neurologic adverse events

Subject listing will also be provided for other neurologic adverse events observed after JNJ-68284528 infusion. In addition, subjects with other neurologic adverse events will be summarized by MedDRA SOC, PT and relationship to study drug.

5.3.3. Tumor Lysis Syndrome

Subjects with any TLS will be summarized by MedDRA SOC, PT and maximum toxicity grade (according to NCI-CTCAE version 5.0). A listing of subjects who reported any treatment-emergent TLSs during the study will be provided.

5.3.4. Second Primary Malignancies

A listing of subjects who reported second primary malignancies during the study will be provided. This listing will include diagnosis, study day of diagnosis, stage of disease, recurrence of a prior existing malignancy (yes, no) and pathology diagnosis (biopsy, aspirate, etc.) information whenever a second primary malignancy is observed. In addition, the treatment for second primary malignancy and the outcome information will also be presented in the listing. Second primary malignancies will be clinically reviewed and categorized as cutaneous/non-invasive, non-cutaneous/invasive, or hematologic malignancies, which will be summarized accordingly.

5.4. Other Safety Observations

Cytopenia associated AEs, hypogammaglobulinemia, hypersensitivity reactions, and infections (including the HBV reactivation) will be summarized.

5.5. Clinical Laboratory Tests

All clinical laboratory tests will be displayed for the subjects included in the all treated analysis set.

Descriptive statistics (N, mean, SD, median, range) will be used to summarize observed laboratory values and change from baseline in observed value at each scheduled visit for each dose level. Line plots of the mean with standard error for each laboratory analyte over time will be displayed by dose level for selected laboratory analytes.

Applicable laboratory results will be graded according to NCI-CTCAE version 5.0. The worst toxicity grade in hematology and chemistry during the post infusion period will be summarized by dose level and toxicity grade. Shift tables from baseline to worst toxicity grade during the post infusion period will be provided for selected laboratory analytes. These tables will summarize the number of subjects with each baseline CTC grade and changes to the maximum CTC grade.

5.6. Vital Signs and Physical Examination Findings

Vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, oxygen saturation, and temperature) values and change from baseline will be summarized at each scheduled time point by dose level. The percentage of subjects with values beyond clinically important limits will be summarized.

A listing of subjects with treatment-emergent clinically important abnormalities in vital signs will be presented.

Incidence of treatment-emergent clinically important abnormalities in vital signs, as defined in Table 6, will be summarized for subjects who had a baseline assessment and at least one post-baseline assessment for that vital sign.

Table 6: Clinically Important Abnormalities in Vital Signs

Vital Sign	Criteria
Pulse	>110 bpm and with >20 bpm increase from baseline
	<50 bpm and with >15 bpm decrease from baseline
Systolic blood pressure	>180 mm Hg and with >20 mm Hg increase from baseline
	<90 mm Hg and with >20 mm Hg decrease from baseline
Diastolic blood pressure	>105 mm Hg and with >15 mm Hg increase from baseline
	<50 mm Hg and with >15 mm Hg decrease from baseline
Temperature	>38°C and with ≥1°C increase from baseline
Respiratory rate	>20 or <7 breaths per minute
Oxygen saturation	<95%

5.7. Cardiac Function Assessments

The interpretation of the electrocardiogram (ECGs) as determined by the site personnel will be displayed by the number and percentage of subjects meeting the normality criteria. The interpretation will be summarized at baseline and Day 56 by dose level and overall.

For echocardiogram or MUGA scan, subject listings will be provided for left ventricular ejection fraction (LVEF) and the overall interpretation as determined by the site personnel.

5.8. ECOG Performance Score

ECOG performance status evaluates the effect of the disease status on the activities of daily living. Descriptive statistics will be used to summarize ECOG performance status at baseline, scheduled post-baseline timepoints (including change from baseline), worst score during post infusion period (including change from baseline) for each dose level. Shift table from baseline to worst score during the post infusion period may be provided.

6. PHARMACOKINETICS/PHARMACODYNAMICS

Unless specified otherwise, descriptive statistics will be used to summarize pharmacokinetics data. In addition, coefficient variation and geometric mean will be provided in the pharmacokinetic concentration summary.

6.1. Pharmacokinetics

Pharmacokinetic analyses will be performed on the pharmacokinetic-evaluable analysis set. All concentrations below the lowest quantifiable concentration or missing data will be labeled as such in the concentration database. Concentrations below the lowest quantifiable concentration will be treated as zero in the summary statistics. Descriptive statistics will be used to summarize CAR-T positive cell count and transgene level at each sampling timepoint.

Pharmacokinetic parameters, including, but not limited to Cmax, AUC, and Tmax, will be summarized descriptively at each sampling timepoint and displayed with line plots over time. In addition, correlation of PK parameters with clinical endpoints may be explored, as appropriate.

If sufficient data are available, population-PK analysis of peripheral JNJ-68284528 cellular concentration and transgene level-time data of JNJ-68284528 may be performed. If the population-PK analysis is conducted, details will be given in a population-PK analysis plan and the results of the analysis will be presented in a separate report. Exposure-response analyses may also be performed; if performed, details will be provided in a separate analysis plan and report.

6.2. Immune Response

The incidence of anti-JNJ-68284528 antibodies will be summarized for the immunogenicity analysis set. The results will be summarized by dose level for subjects with appropriate samples for the detection of antibodies to JNJ-68284528.

Immunogenicity analyses will be descriptive and will include the number and percentage of subjects who developed anti-JNJ-68284528 antibodies. The effect of anti-JNJ-68284528 antibodies on pharmacokinetics, safety, and efficacy may also be evaluated.

6.3. Pharmacodynamics

Exploratory analyses may be conducted to summarize pharmacodynamic markers (e.g., sBCMA, M-protein).

6.4. Pharmacokinetic/Pharmacodynamic Relationships

Pharmacokinetic/pharmacodynamic modeling may be performed, including exploring the relationship between JNJ-68284528 cellular concentrations, transgene levels, pharmacodynamic markers (e.g., sBCMA, M-protein) and endpoints of clinical efficacy and safety. If performed, details and results of the analysis will be presented in a separate report.

7. BIOMARKER

Biomarker studies are designed to identify markers predictive of response (or resistance) to JNJ-68284528. Planned analyses are based on the availability of clinically valid assays and may

be deferred if emerging study data show no likelihood of providing useful scientific information. Results of biomarker analyses may be presented in a separate report.

7.1. Minimal Residual Disease (MRD)

MRD will be monitored in subjects using next generation sequencing (NGS) on bone marrow aspirate DNA.

7.1.1. Sampling Timepoints

For all subjects, a fresh bone marrow aspirate will be obtained at baseline, as well as after infusion at Day 28, and at 6 months, 12 months, 18 months (Day 520), and 24 months (Day 744) (± 16 days) regardless of the status of disease measured in blood and urine. For subjects with suspected CR/sCR, a sample will be obtained at the time of CR/sCR, and then yearly until disease progression.

7.1.2. Analysis Methods

Details on MRD negativity rate analyses are described in Section 4.3.2.

Time to MRD negativity will be summarized descriptively, as well as the proportion of subjects with durable MRD negativity (i.e., achieved MRD negative status at 2 bone marrow aspirate examinations that are a minimum of 1 year apart, without any examination showing MRD positive status in between) if sufficient data becomes available. MRD negativity rate will be summarized for subjects who achieved CR/sCR, and VGPR, respectively.

In addition, exploratory landmark analyses may be conducted to correlate MRD negativity results (as either binary or continuous values) with clinical endpoints such as DOR, PFS, and OS. Similar analysis may be performed for subjects who achieved CR or better.

7.2. Replication competent lentivirus

Whole blood from subjects will be evaluated for the presence of lentiviral vesicular stomatitis virus-G using a qPCR assay.

7.2.1. Sampling Timepoints

Whole blood sample for replication competent lentivirus (RCL) will be collected at prior to first dose of conditioning regimen, on Day 1 before JNJ-68284528 infusion, and approximately 3, 6, and 12 months then yearly for 15 years post infusion.

7.2.2. Analysis Methods

The subject incidence of RCL detected in blood samples will be tabulated by assessment timepoint and by dose level and overall.

7.3. Molecular Subtyping

7.3.1. Molecular Subtypes

Bone marrow aspirate samples will be assessed for specific molecular subtypes having chromosomal aberrations such as del17p, t(4;14), and t(14;16).

7.3.2. Molecular Risk Subgroup Analysis

To determine if JNJ-68284528 will lead to improved clinical responses in standard as well as high-risk molecular subgroups, the following exploratory analysis will be conducted by using similar analysis methods to those specified in Sections 4.2.3, 4.3.2, 4.3.6, and 4.3.7.

- To evaluate ORR and CR or better rate for subjects in high-risk molecular subgroup and subjects with specific molecular subtypes such as del17p, t(14;16), and t(4;14).
- To evaluate MRD negativity rate for subjects in standard-risk and high-risk molecular subgroups.
- To evaluate PFS and OS for subjects in high-risk molecular subgroup and subjects with specific molecular subtyping such as del17p, t(14;16), and t(4;14).

Subgroup exploratory analysis of ORR and PFS by molecular risk may be conducted.

7.4. Cytokine profiling

Cytokines (such as IL-6, IL-10, and IFN-γ) level will be summarized descriptively at each scheduled timepoint. Additionally, exploratory analysis summarizing cytokines (Cmax and exposure -$AUC_{0\text{-}56d}$-) grouped by response categories (responder vs. non-responder, CR/sCR vs. non-CR/sCR), by worst CRS toxicity grade, or by CAR-T cell neurotoxicity (ICANS and Other neurotoxicities) might be generated.

7.5. Immunophenotyping

Immune cell populations (including CAR-T cells) in peripheral blood and malignant plasma cells in bone marrow from subjects will be evaluated for expression of several markers including but not limited to immune-specific markers (CD4 and CD8) and tumor associated markers (such as BCMA) using multiparametric flow cytometry.

7.5.1. Sampling Timepoints

Whole blood and bone marrow samples will be collected at several times prior and after JNJ-68284528 infusion.

7.5.2. Analysis Methods

Frequencies of relevant immune cell populations (including but not limited to CAR-T CD4 and CD8 cells) might be summarized descriptively at relevant timepoints (such as T_{max} of CD3+CAR+ cells). A summary of these values grouped by response categories (responder vs. non-responder, CR/sCR vs. non-CR/sCR), by worst CRS toxicity grade, or by CAR-T cell neurotoxicity (ICANS and Other neurotoxicities) might be generated.

8. PATIENT EXPERIENCE DATA

8.1. Health-Related Quality of Life (HRQoL)

Subjects HRQoL (symptoms, functioning, and overall well-being) during Phase 2 will be assessed using the following PRO instruments: EORTC QLQ-C30, EQ-5D-5L, PGIC, PGIS, and four single items from EORTC QLQ-MY20.

8.1.1. PRO Instruments

The PRO endpoints include the following:

- Summary Scores
  - EORTC-QLQ-C30 functional scales (physical, role, emotional, cognitive, social), global health status (GHS) scale, symptom scales (pain, fatigue, nausea/vomiting)
  - EQ-5D-5L utility score
- Single Item Scores
  - EORTC QLQ-C30 single symptom items
  - EORTC-QLQ-MY20 four single items
  - EQ-5D-5L VAS
  - PGIS
  - PGIC

PRO instruments will be scored based on the instrument developer guidelines. No imputation for missing data will be done for the PRO data. Sensitivity analyses on missing data and methods of imputation will be included in a separate analysis plan. If a subject has multiple records at the same visit, the closest one to the visit date will be selected as the scheduled assessment.

8.1.2. Analysis Methods

Descriptive Statistics

Descriptive analysis of PRO data will be performed on the mITT analysis set.

For each of the PRO instruments, compliance rates at each scheduled timepoint will be provided based on the number and percentage of expected, received and missing PRO assessments. The missing PRO assessments are defined as the expected number for a visit minus the actual number received and the expected number will be determined by subject-level study completion status.

Descriptive statistics (n, mean, standard deviation, median, and range) will be provided for all PRO endpoints at each time point. Line plot of mean with standard error over time will be displayed. For key PRO endpoints (EORTC QLQ-C30 GHS, Pain, Fatigue, Physical Functioning, EQ-5D-5L VAS and utility value), the descriptive statistics will be summarized for the following subgroups: subjects who achieve a sCR/CR, MRD-negative CR, VGPR, PR, and no response/stable disease.

Within Group Change

Mixed effects model with repeated measures will be conducted for all subjects in the mITT analysis set with at least one post-baseline (screening visit) assessment. Within group change from baseline will be calculated for all PRO endpoints (except for the PGIC) by fitting a mixed effects model including subjects as a random effect, and baseline value and time as fixed effects.

As a subgroup analysis, the within group change for subjects who met the primary clinical endpoint (ORR) will be calculated for the key PRO endpoints: EORTC QLQ-C30 GHS, Pain, Fatigue, Physical Functioning, and EQ-5D-5L VAS and utility value.

Time to Event

Time to event analyses will be conducted for the key PRO endpoints (EORTC QLQ-C30 GHS, Pain, Fatigue, Physical Functioning, EQ-5D-5L VAS and utility value).

A distribution-based method will be used to define improvement/worsening in scores, i.e., half SD away from the mean score at baseline. Time to improvement and time to worsening will be summarized by using descriptive statistics such as mean, SD, median and range. Death due to disease progression will be considered as worsening.

Estimation of Meaningful Change

Meaningful change for the EORTC QLQ-C30 subscales and EORTC QLQ-MY20 single items will be determined using the EORTC meaningful change values provided in the literature[1] and anchor-based methodology. The number and percent of subjects meeting the literature-based minimum importance difference (MID) during the post-infusion period will be summarized.

For the anchor-based approach, the PGIC will be used as an anchor to determine the MID of the key PRO endpoints (EORTC QLQ-C30 GHS, Pain, Fatigue, Physical Functioning). The MID will be estimated as the mean change score on the EORTC endpoints of subjects who improved by one point (improvement) on the PGIC "A little better now" from baseline to each PRO visit during the post-infusion period.

8.2. Qualitative Interview Assessment

Content analysis of the interview transcripts will be described in a separate analysis plan.

9. MEDICAL RESOURCE UTILIZATION

Analyses of medical resource utilization will be specified in a separate analysis plan. Results of these analyses will be presented in a separate report.

10. ADDITIONAL EXPLORATORY ANALYSES

For selected efficacy and safety endpoints of interests, including rate of sCR, CRS onset, and time to CRS onset, univariate and multivariate regression modeling will be performed for the individual endpoint to identify potential predictive markers. Candidate covariates will include but not limited

to demographics, baseline disease characteristics, and key manufacturing parameters. Potential early clinical, translational, and imaging markers for neurotoxicity will also be explored. Results of these exploratory analyses may be presented in a separate report.

11. ADDITIONAL ANALYSES FOR COVID-19

Supplementary analysis may be performed for PFS, in which subjects who died due to COVID-19 infection would be censored at the last disease evaluation before COVID-19 infection and the start of any subsequent antimyeloma therapy or retreatment with JNJ-68284528. Major and minor protocol deviations due to COVID-19 will be provided as appropriate.

REFERENCES

1. Byrt T, Bishop J, Carlin JB. Bias, prevalence and kappa. J Clin Epidemiol. 1993;46(5):423-429. doi:10.1016/0895-4356(93)90018-v
2. EORTC Quality of Life Group. Guidelines for assessing quality of life in EORTC clinical trials. https://www.eortc.org/app/uploads/sites/2/2018/02/clinical_trials__guidelines_qol.pdf.
3. Lee DW, Gardner R, Porter DL, et al. Current concepts in the diagnosis and management of cytokine release syndrome. Blood. 2014;124(2):188-195
4. Lee DW, Santomasso BD, Locke FL, et al. ASTCT consensus grading for cytokine release syndrome and neurological toxicity associated with immune effector cells. Biol Blood Marrow Transplant. 2019 Apr;25(4):625-638. DOI: https://doi.org/10.1016/j.bbmt.2018.12.758
5. Kumar S, Paiva B, Anderson KC, et al. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. Lancet Oncol. 2016;17(8):e328-e346.
6. Rajkumar SV, Harousseau JL, Durie B, et al. Consensus recommendations for the uniform reporting of clinical trials: report of the International Myeloma Workshop Consensus Panel 1. Blood. 2011;117(18):4691-4695.

ATTACHMENTS

ATTACHMENT 1: PROGRESSIVE DISEASE AND RESPONSE ALGORITHM BASED ON IMWG CRITERIA FOR MULTIPLE MYELOMA

Progressive Disease and Response Algorithm Based on IMWG Criteria for Multiple Myeloma

Protocol: 68284528MMY2001

The scope of this algorithm document is summarized in Table 1.

Table 1: Scope

Progressive Disease (PD)	• Whether or not the disease progressed • If disease progressed, - Date of progression - Reason(s) for PD • If disease never progressed, determine the date of censoring
Response	• The date and category of best response • The date and category of first response • Duration of response (DOR)

1. Determination of PD

1.1. IMWG Criteria

1.1.1. Progressive Disease

PD is to be used for calculation of time to disease progression and progression-free survival for all subjects.

PD is defined as satisfying any one of the criteria listed below. These are identical to the IMWG criteria as described in the protocol. Further explanations (noted in superscript) pertaining to particular PD criteria are provided in Section 1.2, Clarifications and Modifications.

a. Increase [1.2.2] of ≥25% in the level of serum M-protein and absolute increase [1.2.2] must be ≥0.5 g/dL (5 g/L) [1.2.3; 1.2.4; 1.2.5].

b. Increase [1.2.2] of ≥25% in the 24-hour urinary light chain excretion (urine M-protein) and absolute increase [1.2.2] must be ≥200 mg/24 hours [1.2.3].

c. Only in subjects without measurable serum and urine M-protein levels at baseline: increase [1.2.2] of ≥25% in the difference between involved and uninvolved FLC levels [1.2.13] and absolute increase [1.2.2] must be >10 mg/dL [1.2.3].

d. Only in subjects without measurable serum and urine M-protein levels and without measurable disease by FLC levels: increase [1.2.2] of ≥25%

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in the level of bone marrow plasma cells percentage and absolute increase [1.2.2] must be ≥10% [1.2.3].

e. Definite increase [1.2.7] in the size of existing bone lesions [1.2.8] or soft tissue plasmacytomas [1.2.8; 1.2.9].

f. Definite development of new bone lesions or soft tissue plasmacytomas [1.2.10; 1.2.11].

g. ≥50% increase in circulating plasma cells (minimum of 200 cells per μL) if this is the only measure of disease

h. Development of plasma cell leukemia

1.2. Clarifications and Modifications

In order to allow these rules to be applied consistently and to be programmed, the Sponsor has added certain clarifications and modifications for using the IMWG criteria.

1.2.1. Measurable disease is defined in the protocol by at least one of the following measurement: (1) serum M-protein ≥ 1g/dL (≥ 10 g/L) (2) urine M-protein ≥ 200 mg/24h; (3) serum FLC assay: involved FLC level ≥ 10 mg/dL (≥ 100 mg/L) provided serum FLC ratio is abnormal.

1.2.2. The reference point for calculating increase and % of increase for M-protein, FLC and bone marrow plasma cells will be the lowest response value and the "lowest response value" does not need to be a confirmed value.

1.2.3. Requires 2 consecutive (i.e., no intermediate values that do not meet the definition of PD) assessments made at any time before the institution of any new therapy (i.e., subsequent anti-cancer therapy).

1.2.4. If nadir serum M-protein is ≥ 50g/L (≥5 g/dL), M-protein increases of ≥ 10g/L (1g/dL) is sufficient for progressive disease. It does not require meeting "increase of ≥ 25% in the level of serum M-protein".

1.2.5. Any 2 consecutive increase of serum M-protein ≥5 g/L (≥0.5 g/dL) is consistent with progressive disease, assuming that increase of ≥25% is met or not applicable, even if the serum M-protein level is below measurable disease threshold.

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1.2.6. The baseline value for assessing disease progression is the measurement closest to the conditioning regimen and before CAR-T infusion (it applies to SPEP, UPEP, FLC, plasmacytomas and bone lesions).

1.2.7. The program computes the date of progression as the earliest date of any of the tests listed in Section 1.1.1 (a, b, e, f, or g for subjects with measurable serum or/and urine M-protein; or a, b, c, e, f or g for subjects without measurable serum and urine M-protein) that indicate PD.

1.2.8. For PD due to bone lesions, the algorithm will rely on information collected on the eCRF regarding skeletal survey (i.e., increase in the size of lytic bone lesions or increase in the total number of lytic bone lesions) and other radiology reports. At any time, study sites may report progressive disease based on an increase in the size or number of lytic bone lesions. The algorithm accepts this determination as definitive.

1.2.9. For plasmacytomas, the Sponsor has defined "definite increase in size" as either an increase of over 50% in the sum of the products of the two longest perpendicular diameters when available > 1 lesion, using the smallest previous product as the reference point; or an increase of over 50% in the longest diameter when available, using the previous lesion dimensions with >1 cm in short axis.

In the case that a plasmacytoma appears to have split, this will not be considered as a new plasmacytoma, but total size will be calculated as the sum of the products of the two longest perpendicular diameters of all the split parts.

1.2.10. New post-baseline bone lesions are evidence of PD. If no baseline bone lesions are available, then any subsequent data that report a bone lesion will be considered as development of new bone lesions.

1.2.11. New post-baseline plasmacytomas are evidence of PD, even if the measurements are not available. If no baseline plasmacytoma data are available, then any subsequent data that report a plasmacytoma will be considered as a "new" plasmacytoma and will be considered as evidence of PD.

1.2.12. Imputation of UPEP and SPEP values: If the serum immunofixation result is "Not Detected" and the SPEP value is missing or not done, then SPEP value is treated as 0. If the urine immunofixation is "Not Detected" and the UPEP is missing or not done, then UPEP value is treated as 0.

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1.2.13. Difference between involved and uninvolved FLC level is defined as absolute value of kappa FLC level minus lambda FLC level in the serum.

1.2.14. Development of plasma cell leukemia is considered as disease progression. The date of PD is the date of event onset.

2. Determination of Date of Censoring and Reason for PD

The date of last post-baseline efficacy measure is used as the censoring date for all subjects without progressive disease. Subjects that have no post-baseline efficacy data are censored at the infusion date for CAR-T treated subjects.

The reason(s) for PD is defined as the initial reason(s) that caused the program to indicate PD as well as any other criteria that were met by the time of confirmation of PD. Indicator variables for each reason (SPEP, UPEP, FLC, bone marrow, bone lesion [increase in number, increase in size], extramedullary plasmacytoma [new extramedullary plasmacytoma, increase in size] and plasma cell leukemia) are created.

3. Determination of Response Category and Duration of Response

3.1. IMWG Criteria

According to IMWG criteria, response categories include complete response (CR), stringent complete response (sCR), very good partial response (VGPR), partial response (PR), Minimal disease (MR), stable disease (SD), and progressive disease (PD) (defined in Section 1). Categories of sCR, CR, VGPR, PR, MR, and SD are determined using the IMWG criteria for subjects with relapsed refractory myeloma as outlined below.

Further explanations (noted in superscript) pertaining to particular response criteria are provided in Section 3.2, Clarifications and Modifications. The definition for duration of response is also covered in Section 3.2.15.

3.1.1. Definition of CR

Requires all of the following:

a. Negative immunofixation of serum and urine [3.2.4; 3.2.5; 3.2.6].

b. Disappearance of any soft tissue plasmacytomas.

c. <5% plasma cells in the bone marrow [3.2.7].

d. In subjects where serum and urine M-protein are not measurable, normal FLC ratio [3.2.5; 3.2.6; 3.2.8]

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3.1.2. Definition of sCR

Requires all of the following:

a. CR as defined above.

b. Normal FLC ratio [3.2.5, 3.2.8].

c. Absence of clonal bone marrow plasma cell (PCs) by immunohistochemistry, or 2- to 4-color flow cytometry.

3.1.3. Definition of VGPR

Requires any of the following:

a. Serum and urine M-component detectable by immunofixation but not on electrophoresis [3.2.3, 3.2.5, 3.2.11], or

b. ≥90% reduction [3.2.10] in serum M-protein plus urine M-protein <100 mg/24 hours [3.2.3, 3.2.5]

c. If the serum and urine M-protein are not measurable, a reduction [3.2.10] of ≥90% in the difference between involved and uninvolved FLC levels [3.2.5; 3.2.12] is required.

d. In addition to the above criteria, if present at baseline, >90% reduction [3.2.10] in the size of soft tissue plasmacytomas is also required.

3.1.4. Definition of PR

Requires all of the following:

a. ≥50% reduction [3.2.10] of serum M-protein [3.2.5] and reduction [3.2.3, 3.2.10] in 24-hour urinary M-protein by ≥90% or to <200 mg/24 hours [3.2.5].

b. If the serum and urine M-protein are not measurable, a reduction [3.2.10] of ≥50% in the difference between involved and uninvolved FLC levels [3.2.5; 3.2.12] is required.

c. If serum and urine M-protein are not measurable, and serum free light assay is also not measurable, ≥50% reduction in bone marrow plasma cells is required in place of M-protein, provided baseline percentage was ≥30%

d. In addition to the above criteria, if present at baseline, ≥50% reduction [3.2.10] in the size of soft tissue plasmacytomas is also required.

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3.1.5. Definition of MR

Requires all of the following:

a. 25% to <50% reduction [3.2.10] of serum M-protein [3.2.5] and reduction [3.2.10] in 24-hour urine M-protein by 50% to <90% [3.2.5].

b. In addition to the above criteria, if present at baseline, >=50% reduction [3.2.10] in the size of soft tissue plasmacytomas is also required.

3.1.6. Definition of SD

Not meeting the criteria for sCR, CR, VGPR, PR, MR, or PD.

3.2. Clarifications and Modifications

As was the case with PD, developing a program to assess response requires adding certain clarifications, minor modifications and additions to the IMWG criteria.

3.2.1. Only subjects with measurable disease at baseline are eligible for assessment of response except CR or better (Measurable disease is defined in Section 1.2.1); only legitimated on treatment serum M-protein and urine paraprotein measurements are used for assessment of response.

3.2.2. CR, sCR, VGPR, PR, MR and SD response categories require no known evidence of progressive or new bone lesions if radiographic studies were performed. Once the program has determined PD for a subject, no subsequent response assessments are performed.

3.2.3. Subjects with measurable disease (defined in Section 1.2.1) in serum (SPEP) and urine (UPEP) need to be followed by both SPEP and UPEP for response assessment and categorization; Except for assessment of VGPR or better, subjects with measurable disease restricted to the SPEP will need to be followed only by SPEP (i.e., urine M-protein need not show a reduction, but the available urine M-protein values must not meet the criteria for PD); correspondingly, subjects with measurable disease restricted to the UPEP will need to be followed only UPEP for response categories less than VGPR (i.e., serum M-protein need not show a reduction, but the available serum M-protein values must not meet the criteria for PD).

3.2.4. To be considered CR, both serum and urine immunofixation must be carried out and be negative regardless of the size of baseline M-protein in the serum or

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urine; subjects with negative UPEP values pre-infusion still require UPEP testing to confirm CR and VGPR.

3.2.5. Requires 2 consecutive (i.e., no intermediate values that do not meet the definition of response) assessments made at any time before the institution of any new therapy (i.e., subsequent anti-cancer therapy).

3.2.6. For coding CR in subjects in whom the only measurable disease is by serum FLC levels: it requires a normal FLC ratio (Kappa/Lambda) in addition to CR criteria.

3.2.7. If all criteria for confirmed CR were met, except that bone marrow aspirate and biopsy were not performed, and baseline bone marrow evaluation showed <5% plasma cells, then the algorithm accepts this as a CR.

3.2.8. Normal FLC ratio is required to conclude sCR for all subjects regardless of whether disease at baseline was measurable on serum, urine, both or neither.

3.2.9. Presence/absence of clonal cells is based upon the kappa/lambda ratio. An abnormal kappa/lambda ratio by immunohistochemistry requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is kappa/lambda of >4:1 or <1:2.

3.2.10. Reductions are based on changes from baseline.

3.2.11. Serum and urine M-protein via SPEP and UPEP must be reported as 0, not detected, or below level of quantification and positive serum or urine immunofixation.

3.2.12. Difference between involved and uninvolved FLC level is defined as absolute value of kappa FLC level minus lambda FLC level in the serum.

3.2.13. Skeletal survey is not required for assessment of response unless clinically indicated. However, if skeletal survey is performed, there should be no indication of disease progression before confirmation of response.

3.2.14. The date of first/best response is the earliest date that all available and required response criteria are met and confirmed by following evaluation. The date of serum immunofixation response is the initial date of response, not the date of confirmation. The date of urine immunofixation response is the initial date of

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response, not the date of confirmation. The latest date of response (date at which all criteria were met) among all the relevant response criteria will also be stored in the analysis dataset.

3.2.15. Duration of response (DOR) applies to subjects achieving at least PR by IMWG criteria, and is measured from start of achieving PR (first observation of PR before confirmation) to the time of disease progression, with deaths owing to causes other than progression not counted, but censored. DOR is derived as (date of PD or date of censoring – date of first response + 1).

3.2.16. Subjects with at least one post-baseline disease assessment corresponding to the type of measurable disease at baseline and also not falling into any response category or progressive disease are assigned as response category- stable disease (SD)

3.2.17. For cases that all criteria of VGPR are met, the baseline serum M-protein value with $\geq$ 0.5 g/dL would be used as the reference point to calculate the reduction.

4. References

1. BGM Durie *et al*. International uniform response criteria for multiple myeloma. *Leukemia 2006*

2. Rajkumar *et al*. Consensus recommendations for the uniform reporting of clinical trials: report of the International Myeloma Workshop Consensus Panel 1. *Blood 2011*

3. Shaji Kumar *et al*. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. *Lancet Oncology 2016*.

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ATTACHMENT 2: SUPPLEMENTARY STATISTICAL ANALYSIS PLAN FOR THE EUROPEAN MEDICINES AGENCY (EMA)

Janssen Research & Development

Supplementary Statistical Analysis Plan

Supportive Evidence Generation Leveraging Real-World Data

JNJ-68284528

Status:	Final Draft
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Prepared by:	Janssen Research & Development, LLC

Compliance: The study described in this report was performed according to the principles of Good Clinical Practice (GCP).

TABLE OF CONTENTS

ABBREVIATIONS

ATT	average treatment effects on the treated
CI	confidence interval
HR	hazard ratio
IMiD	immunomodulatory drug
IMWG	International Myeloma Working Group
ISS	International Staging System
KM	Kaplan-Meier
MM	multiple myeloma
MoAB	monoclonal antibody
ORR	overall response rate
OS	overall survival
PH	proportional hazards
PI	proteasome inhibitor
PR	partial response
PS	propensity score
RWD	real-world data
RWE	real-world evidence
SAP	statistical analysis plan
sIPTW	stabilized inverse probability treatment weighting

1. BACKGROUND

This document provides the statistical analysis plan (SAP) for supportive evidence generation to help contextualize the study outcome from 68284528MMY2001.

The objective of the analyses is to build an external control arm using real-world data (RWD) and provide context for the efficacy outcome from the single arm study 68284528MMY2001. The SAP consists of two sections. The first section provides background and definitions specific to the MAMMOTH Study (Gandhi 2019). The second section will lay out the statistical methods for the planned analyses.

2. DATA SOURCE - MAMMOTH STUDY

2.1. Introduction

The MAMMOTH study was a multi-center, retrospective study to investigate the natural history and outcomes of patients with multiple myeloma refractory to CD38 monoclonal antibodies (MoAB) (Monoclonal Antibodies in Multiple Myeloma: Outcomes after Therapy Failure, the MAMMOTH Study). A total of 275 patients were identified at 14 academic institutions in the US with diagnosis of active multiple myeloma who were refractory to CD38 MoAB administered alone or in combination. Eligibility for the study required patients with multiple myeloma to be treated for at least 4 weeks with a CD38 MoAB-containing index regimen and with evidence of progressive disease (PD), as defined by the International Myeloma Working Group (IMWG) response criteria, having progressed while on therapy or within 60 days after last dose of the index regimen.

2.2. Study Objective

The primary objective is to evaluate the efficacy of JNJ-68284528 in the context of an external control arm based on the MAMMOTH study.

2.3. General Analysis Definitions

2.3.1. Analysis Sets

JNJ-68284528 Population – Definition A

The JNJ-68284528 population consists of subjects in study 68284528MMY2001 who underwent apheresis. The specific inclusion criteria for prior therapies are as follows:

- Received at least 3 prior multiple myeloma treatment lines of therapy or are double refractory to an IMiD and PI (refractory multiple myeloma as defined by IMWG consensus criteria). Note: induction with or without hematopoietic stem cell transplant and with or without maintenance therapy is considered a single line of therapy
- Undergone at least 1 complete cycle of treatment for each line of therapy, unless PD was the best response to the line of therapy
- Received as part of previous therapy a PI, an IMiD, and an anti-CD38 antibody (prior exposure can be from different monotherapy or combination lines of therapy)

JNJ-68284528 Population – Definition B

The JNJ-68284528 population consists of subjects in study 68284528MMY2001 who received JNJ-68284528 infusion. The specific inclusion criteria for prior therapies are the same as in the Definition A.

Another two sub-populations are defined as below for potential sensitivity analyses:

- Definition B1: Subjects who received bridging therapies from apheresis to JNJ-68284528 infusion period in the JNJ-68284528 population B.
- Definition B2: Subjects who haven't received bridging therapies from apheresis to JNJ-68284528 infusion period in the JNJ-68284528 population B.

MAMMOTH Population – Definition A

The MAMMOTH population includes subjects satisfying all the following criteria:

- Received at least 3 prior multiple myeloma treatment regimens or are double refractory to an IMiD and PI (refractory multiple myeloma as defined by IMWG consensus criteria)
- Exposed to at least a PI, an IMiD, and a CD38 MoAB (prior exposure can be from different monotherapy or combination regimens) as part of previous therapy
- Received a subsequent therapy after becoming refractory to CD38 MoAB

MAMMOTH Population – Definition B

The MAMMOTH population consists of subjects who were alive and have not experienced disease progression 47 days (i.e., the median duration from apheresis to JNJ-68284528) from the initiation of the first subsequent therapy after meeting the inclusion criteria described as in the Definition A.

2.3.2. Study Day and Baseline

Study Day 1 (index date) is used to define baseline covariates, starting time of time to event endpoints (i.e., PFS and OS) and start of the time window to capture overall response rate. The baseline characteristics are defined as the last measurements prior to the index date.

Study Day 1 for JNJ-68284528

Study day 1 for JNJ-68284528 population A is defined as the date of apheresis.

Study day 1 for JNJ-68284528 population B, population B1, and population B2 is defined as the date of JNJ-68284528 infusion.

Study Day 1 for MAMMOTH

Study day 1 for MAMMOTH population A is defined as the start date of the first therapy after meeting inclusion criteria as defined in section 2.3.1.

Study day 1 for MAMMOTH population B is defined as the start date of the first therapy after meeting inclusion criteria as defined in section 2.3.1 plus 47 days.

2.3.3. Demographics and Baseline Disease Characteristics

Table 1 presents demographics and baseline characteristics that are commonly available in both the JNJ-68284528 and MAMMOTH data. Note that these variables are subject to change if warranted.

Table 1: Commonly Available Demographics and Baseline Characteristics

Continuous Covariates	Summary Type
Age (at baseline)	Descriptive statistics (N, mean, standard deviation [SD], median and range [minimum and maximum])
Years since diagnosis	
Creatinine	
Categorical Covariates	
Sex	Frequency distribution with the number and percentage of subjects in each category
Race	
ISS	
Type of MM	
Number of prior lines of therapy	
Prior exposure or refractoriness to commonly used MM agents (considering following categories: penta-/quad-/triple-/double/single refractory and non-refractoriness)	
High-risk myeloma as defined by chromosome abnormalities at any time prior to the index date	
Prior stem cell transplantation (yes/no)	

2.3.4. Efficacy Endpoints

2.3.4.1. Overall Response Rate

JNJ-68284528

ORR for the JNJ-68284528 population is defined as the proportion of subjects who achieve a partial response (PR) or better according to the IMWG criteria and adjudicated by the independent review committee (IRC). Response after the start of subsequent therapy or retreatment with JNJ-68284528 will not be considered.

MAMMOTH

ORR for MAMMOTH is defined as the proportion of subjects who achieve a PR or better according to the IMWG criteria based on investigator assessment of response for the first subsequent therapy after becoming refractory to CD38 MoAB.

2.3.4.2. Progression-free Survival (PFS)

JNJ-68284528

To mimic the MAMMOTH PFS definition, PFS for the JNJ-68284528 population is defined as the time from the index date to the date of any subsequent antimyeloma therapy (for those with disease progression but without recording subsequent antimyeloma therapy, the date of confirmed disease progression will be used) OR death due to any cause, whichever occurs first. For subjects who have not developed event of interest, data will be censored at their last disease evaluation.

MAMMOTH

PFS for the MAMMOTH population is defined as the time from the index date to the date of subsequent antimyeloma therapy after disease progression OR death, whichever occurs first. For subjects who are alive and have not reported disease progression after the index date, data will be censored at their last follow-up date. The start date of next line of therapy is used as the date of progression in MAMMOTH data collection.

2.3.4.3. Overall Survival (OS)

JNJ-68284528

OS for the JNJ-68284528 population is defined as the time from the index date to the date of the subject's death. If the subject is alive or the vital status is unknown, then the subject's data will be censored at the date the subject was last known to be alive. Subjects who died after consent withdrawal will be considered as having an OS event.

MAMMOTH

OS for the MAMMOTH population is defined as the time from the index date to the date of the subject's death. If the subject is alive or the vital status is unknown, then the subject's data will be censored at the date the subject was last known to be alive.

3. EFFICACY

3.1. General Analysis Specifications

The efficacy analyses outlined below will be performed within each set of the 2 populations:

- JNJ-68284528 population A vs MAMMOTH population A
- JNJ-68284528 population B vs MAMMOTH population B

In addition, sensitivity analyses of efficacy endpoints might be performed for the two comparisons:

- JNJ-68284528 population B1 vs MAMMOTH population B
- JNJ-68284528 population B2 vs MAMMOTH population B

3.1.1. Level of Significance

There is no pre-specified significance level for these analyses but 2-sided nominal p-values and 2-sided 95% confidence interval (CI) will be provided for descriptive purposes.

3.1.2. Propensity Score Approaches

All available baseline covariates which are considered as potential confounders will be adjusted for using propensity score weighting schemes. The average treatment effects on the treated (ATT) approach and stabilized inverse probability treatment weighting (sIPTW) approach will be considered. The weight is calculated for each patient via a logistic regression model including the potential confounding covariates as independent variables. Summary statistics of these covariates

will be provided before and after the adjustment to describe the impact of weight adjustment on balancing the covariates. The distributions of weights under each approach will also be presented.

3.1.3. Data Handling Rules

Missing covariate values are not to be imputed unless otherwise specified. If substantial amount of data is missing for a specific covariate, that covariate will not be included in the logistical model for propensity score weight generation or any outcome regression model as a covariate. In such cases, the sub-population of patients who had all non-missing covariates for adjustment may be used as part of a sensitivity analysis. Methods based on multiple imputation may be conducted as sensitivity analysis as well.

3.2. Analysis Methods

3.2.1. Overall Response Rate (ORR)

The weighted logistic regression model containing treatment group indicator only will be adopted to estimate the treatment effect in terms of the odds ratio and its 95% CI. Additionally, unweighted analyses using a multivariate logistic regression model including treatment and confounding covariates, as well as doubly robust estimation combining propensity scores weighting and logistic regression including treatment and confounding covariates will also be performed. ATT and sIPTW weights will be used, respectively. The judgment on which of both approaches is most appropriate will be based on the level of overlap between propensity score distributions from both cohorts.

If ORR information is substantially missing in the MAMMOTH population, the corresponding analyses will not be performed.

3.2.2. Time to Event Endpoints (PFS or OS)

The weighted KM estimates will be presented to describe the distributions of PFS and OS. The median PFS and OS (including the 95% CI) will also be reported for each population. The weighted Cox proportional hazard (PH) model using ATT will be applied to estimate the treatment effect in terms of the hazard ratio (HR) with 95% Wald-type CI using robust sandwich variance estimator (Lin 1989). Analyses using the sIPTW approach will also be performed. Additionally, unweighted multivariate Cox proportional hazard regression model including treatment and confounding covariates, as well as doubly robust estimation combining propensity score weighting and Cox PH regression with treatment and confounding covariates will also be explored. Analyses excluding covariates with missing values as well as analyses using multiple imputation for missing covariates may be conducted as sensitivity analysis.

REFERENCES

1. Curtis, Melissa D., Sandra D. Griffith, Melisa Tucker, Michael D. Taylor, William B. Capra, Gillis Carrigan, Ben Holzman et al. "Development and validation of a high-quality composite real-world mortality endpoint." Health services research 53, no. 6 (2018): 4460-4476.
2. Gandhi UH, Cornell RF, Lakshman A, Gahvari ZJ, McGehee E, Jagosky MH, Gupta R, Varnado W, Fiala MA, Chhabra S, Malek E. Outcomes of patients with multiple myeloma refractory to CD38-targeted monoclonal antibody therapy. Leukemia. 2019 Mar 11:1.
3. Klein, JP, Moeschberger, MM. Survival Analysis: Techniques for Censored and Truncated Data (Second Edition). Springer-Verlag, NY: Springer; 2003.
4. Xie J, and Liu C. Adjusted Kaplan–Meier estimator and log-rank test with inverse probability of treatment weighting for survival data. Statist. Med. (2005) 24, 3089–3110.
5. Cole SR and Hernán MA. Adjusted survival curves with inverse probability weights, Computer Methods and Programs in Biomedicine 2004:45-49.
6. Li Fan, Morgan KL, and Zaslavsky AM. Balancing Covariates via Propensity Score Weighting, Journal of the American Statistical Association, 2018 - Issue 521113.
7. Robins JM, Rotnitzky A, Zhao LP. Estimation of regression coefficients when some regressors are not always observed. J Am Stat Assoc. 1994;89(427):846–866.
8. Bang H, Robins JM. Doubly robust estimation in missing data and causal inference models. Biometrics. 2005;61(4):962–973.
9. Funk MJ, Westreich D, Wiesen C Stürmer T, Brookhart MA, Davidian M. Doubly Robust Estimation of Causal Effects American Journal of Epidemiology, Volume 173, Issue 7, 1 April 2011, Pages 761–767.
10. Lin DY, Wei LJ. The robust inference for the Cox proportional hazards model. Journal of the American statistical Association. 1989 Dec 1;84(408):1074-8.

ATTACHMENTS

Attachment 1 Weights for Propensity Score Methods

This attachment is to describe the details of weights generation of propensity score methods used in the analysis. The theoretical details can be found in Xie and Liu (2005), Cole and Hernán (2004) and Li et al (2018).

Based on the selected the baseline covariates, fit a logistic regression of exposure to JNJ-68284528 (Yes or No) to obtain estimates of the propensity score for each patient by the predicted probabilities from the fitted model.

Average treatment effects on the treated (ATT). This approach is to create a pseudo-sample by assigning a weight to each patient in the control cohort so that the control cohort had a similar distribution to that of the study cohort in the covariates. Specifically, suppose the sample sizes for the study and control cohorts are n_1 and n_0, respectively; the propensity score $(\tilde{p}_k)$ for a specific subject k is the probability of being assigned to the study cohort given baseline covariates. For patients in the study cohort the ATT weight is $\widetilde{ATT}w_{1k} = 1$ $(k = 1, 2, \cdots, n_1)$; but, for a patient in the control cohort, the ATT weight for this patient is $\widetilde{ATT}w_{0k} = \frac{\tilde{p}_k}{1-\tilde{p}_k}$ $(k = (n_1 + 1), (n_1 + 2), \cdots, (n_1 + n_0))$.

Stabilized inverse probability treatment weighting (sIPTW). This approach is to create a pseudo-sample by assigning a weight to each patient in the study cohort and the control cohort so that the two cohorts have a similar distribution in the covariates. Specifically, suppose the sample sizes for the study and control cohorts are n_1 and n_0, respectively; the propensity score $(\tilde{p}_k)$ for a subject k is the probability of being assigned to the study cohort given baseline covariates. Let $p_1 = \frac{n_1}{n_1+n_0}$ and $p_0 = \frac{n_0}{n_1+n_0}$. Propensity scores are calculated using logistic regression model. For a patient in the study cohort , the sIPTW weight for this patient is $\tilde{w}_{1k} = p_1/\tilde{p}_k$ $(k = 1, 2, \cdots, n_1)$; similarly, for a patient in the control cohort , the sIPTW weight for this patient is $\tilde{w}_{0k} = p_0/(1 - \tilde{p}_k)$ $(k = (n_1 + 1), (n_1 + 2), \cdots, (n_1 + n_0))$.