SAMENVATTING Studiecode

TITEL

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

INDICATIE

Multipel Myeloom

SCHEMA

Figure 2: Schematic Overview of the Study, Cohort A

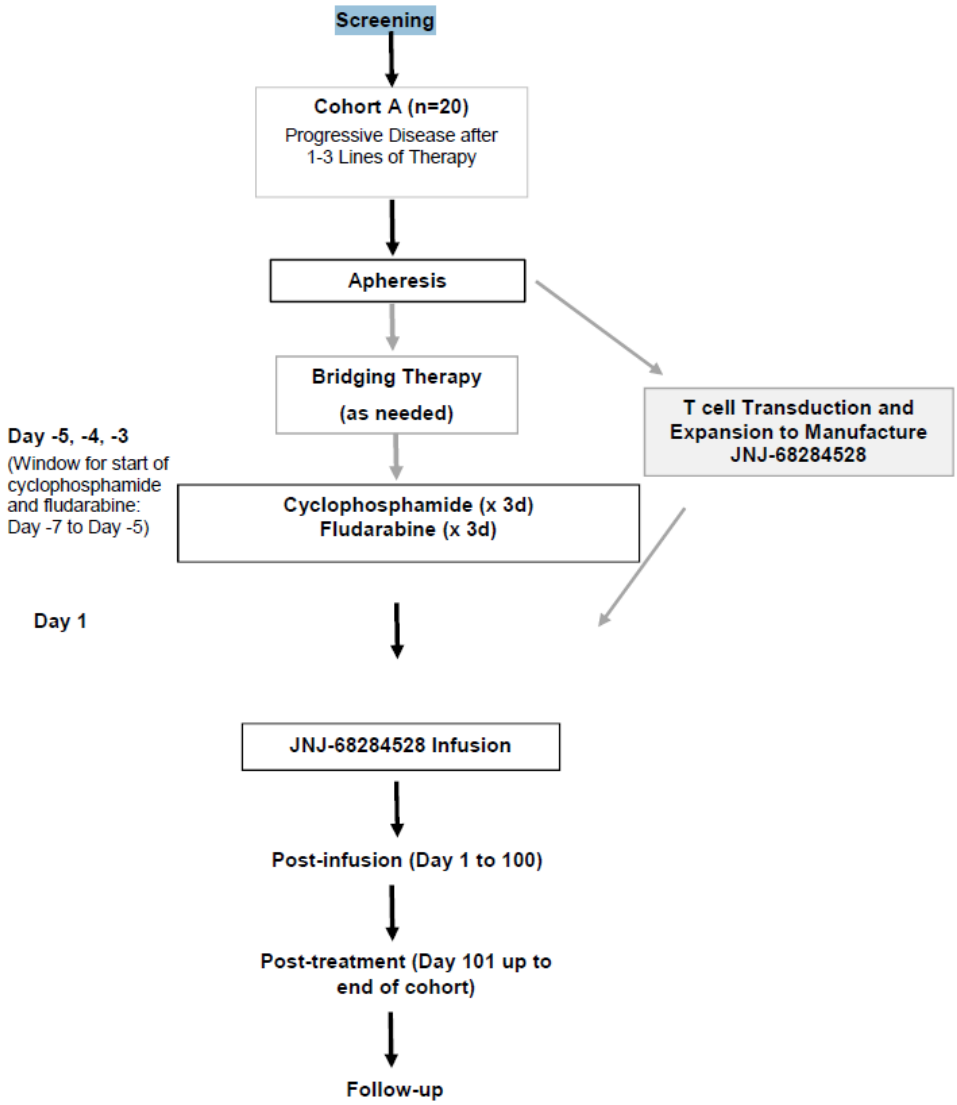


Figure 3: Schematic Overview of the Study, Cohort B

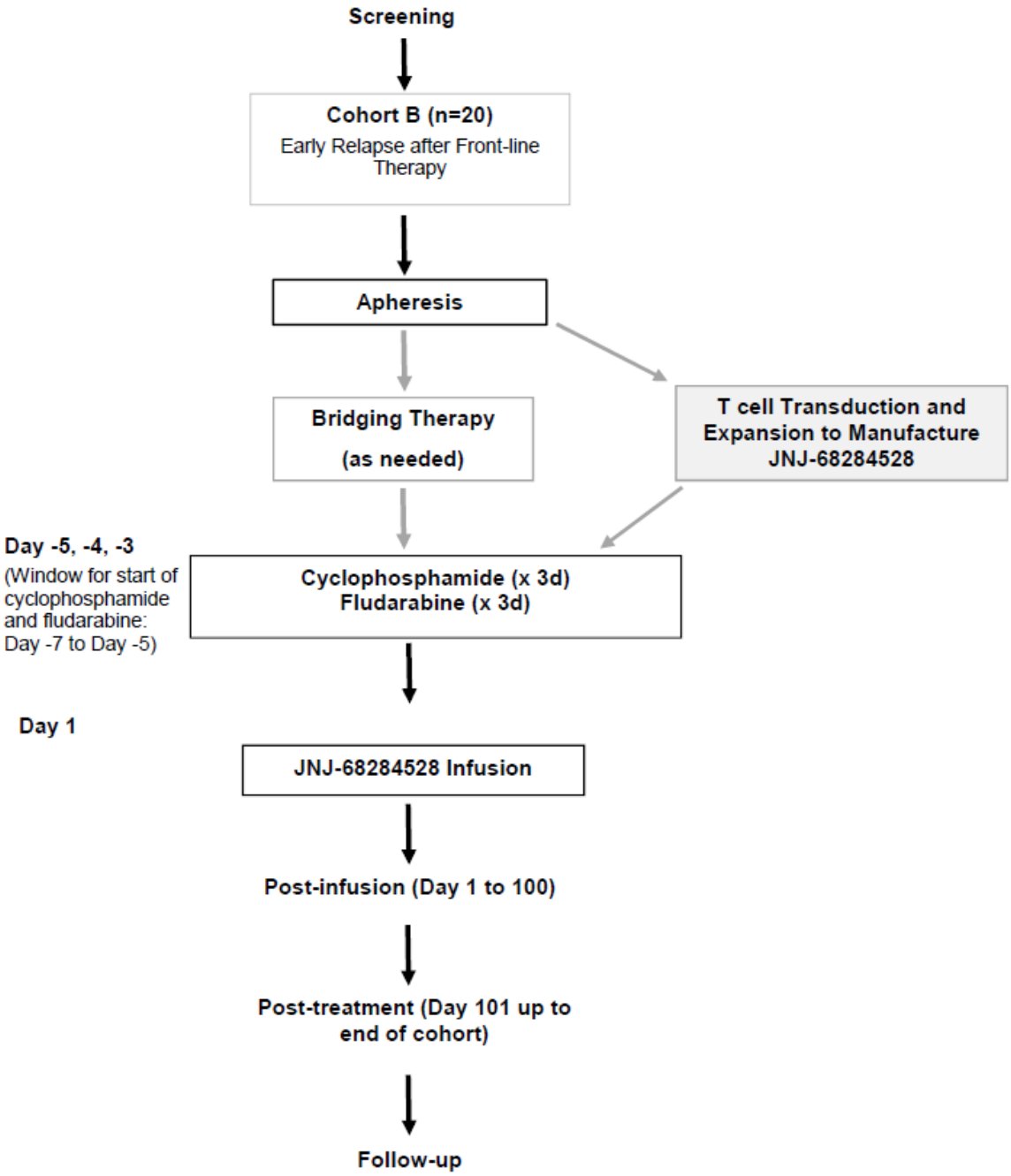


Figure 4: Schematic Overview of the Study, Cohort C

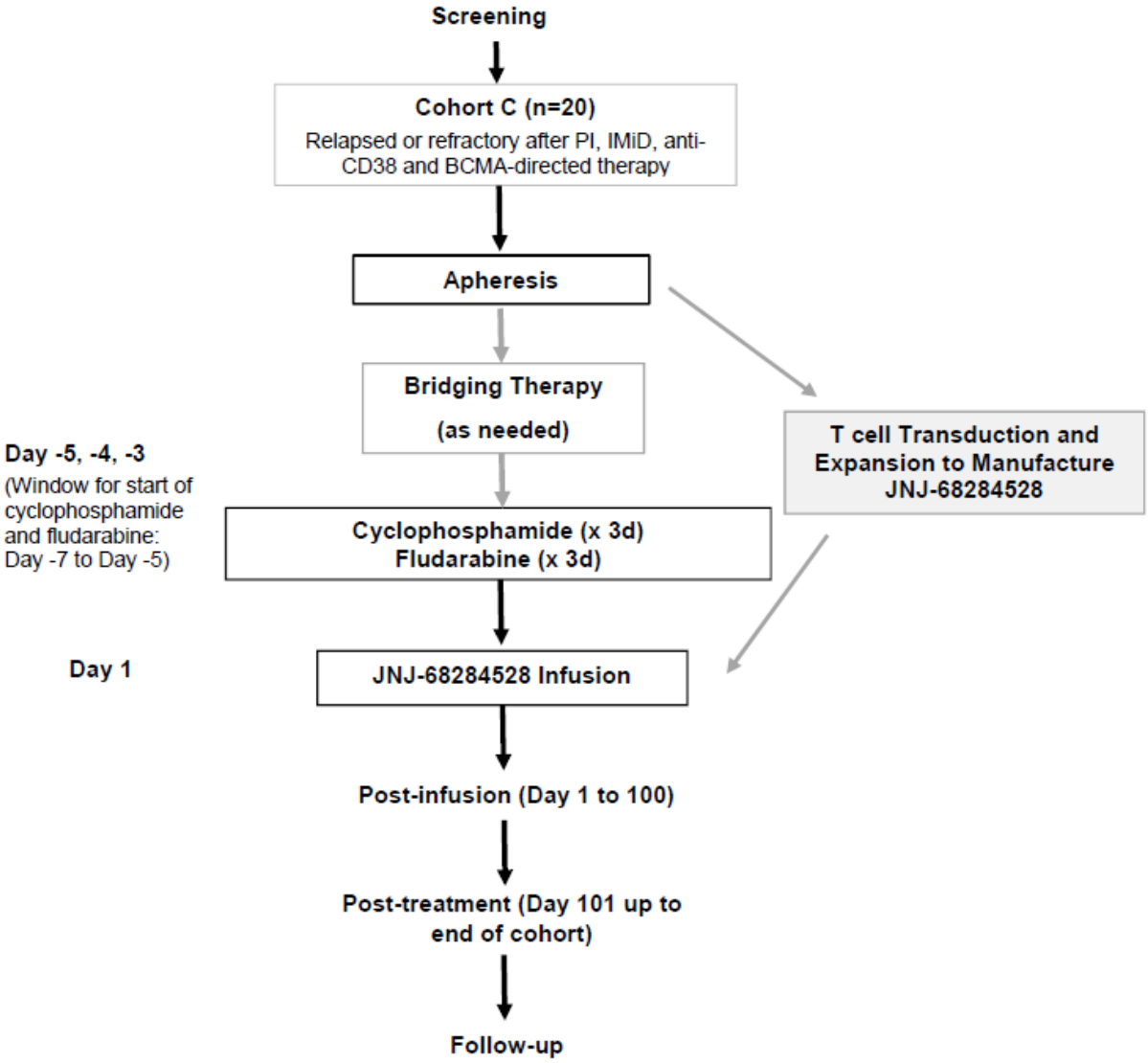
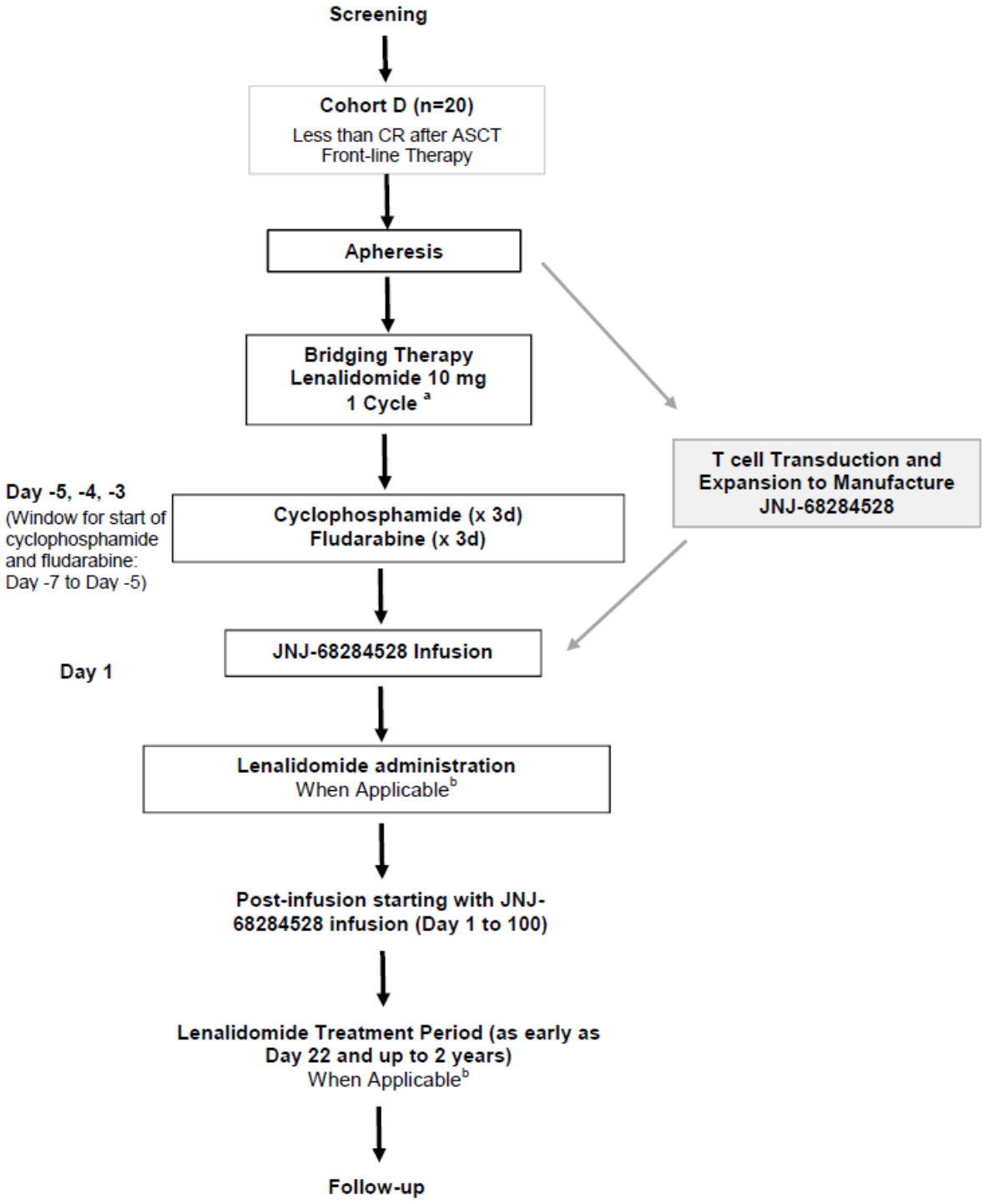


Figure 5: Schematic Overview of the Study, Cohort D



Cohorts A t/m C zijn vol en geen deelnemers kunnen verder geïncludeerd worden.

INCLUSIE CRITERIA Cohort D

Each potential subject must satisfy all of the following criteria to be enrolled in Cohort D of the study:

1. Have newly diagnosed multiple myeloma per IMWG criteria (Rajkumar 2014) with a

   history of 4 to 8 total cycles of initial therapy, including induction, high-dose therapy, and ASCT with or without consolidation (Subjects previously treated for smoldering myeloma are not eligible).
   Subject treated with consolidation must have received ≤2 cycles.

- Received an IMID or PI or both in combination with a steroid as a part of the induction or consolidation regimen
- Treatment with alkylating therapy (for example cyclophosphamide) and/or monoclonal antibodies (for example, daratumumab) during induction/consolidation is permitted
- Subjects who have not received consolidation therapy should be approximately 100 days post-ASCT during screening
- Subjects treated with consolidation therapy should be approximately 160 days post-ASCT during screening

2. Have overall best response <CR and ≥stable disease, and have not yet evolved to

   Progressive Disease as assessed per IMWG 2016 criteria

3. ≥18 years of age.
4. ECOG Performance Status score of 0 or 1
5. Clinical laboratory values meeting the following criteria during the Screening Phase:

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Hematology	
Hemoglobin	≥8.0 g/dL (≥5 mmol/L) (without prior red blood cell [RBC] transfusion within 7 days before the laboratory test; recombinant human erythropoietin use is permitted)*
Platelets	≥75 x 10^9/L (must be without transfusion support in the 7 days prior to the laboratory test)
Absolute Lymphocyte Count (ALC)	≥0.3 x 10^9/L
Absolute Neutrophil Count (ANC)	≥1×10^9/L (prior growth factor support is permitted but must be without support in the 7 days prior to the laboratory test)
Chemistry	
AST and ALT	≤3.0 × upper limit of normal (ULN)
Estimated Glomerular Filtration Rate	≥40 mL/min/1.73 m^2 based upon Modified Diet in Renal Disease formula calculation (Attachment 8) or a 24-hour urine collection.

Total bilirubin	≤2.0 × ULN; except in subjects with congenital bilirubinemia, such as Gilbert syndrome (in which case direct bilirubin ≤1.5 × ULN is required)
Corrected serum calcium	≤12.5 mg/dL (≤3.1 mmol/L) or free ionized calcium ≤6.5 mg/dL (≤1.6 mmol/L)

* For subjects who meet the inclusion criteria at screening, transfusion of RBCs is permitted after screening as needed to maintain a hemoglobin level ≥8.0 g/dL

6. Women of childbearing potential must have a negative highly sensitive serum pregnancy test (β-human chorionic gonadotropin [β-hCG]) at screening.

7. Criterion modified per Amendment 2
    a. When a woman is of childbearing potential (See Attachment 16) the following are required:

- Subject must agree to practice 2 methods of reliable birth control simultaneously from 4 weeks prior to initiating treatment with lenalidomide until 1 year after receiving a JNJ-68284528 infusion or for 4 weeks following discontinuation of lenalidomide (whichever is later). One of the birth control methods should be a highly effective method of contraception (failure rate of <1% per year when used consistently and correctly; see examples below) and one other effective method (ie, male latex or synthetic condom, diaphragm, or cervical cap) and subject must agree to remain on both methods. Examples of highly effective contraceptives include:
    - user-independent methods: 1) implantable progestogen-only hormone contraception associated with inhibition of ovulation; 2) intrauterine device; intrauterine hormone-releasing system; 3) vasectomized partner;
    - user-dependent method: progestogen-only hormone contraception associated with inhibition of ovulation (oral or injectable). Estrogen-containing hormonal contraception is contraindicated due to increase risk of thromboembolic events with lenalidomide.
    - women of childbearing potential must follow the contraception criteria outlined in the local REVLIMID® pregnancy prevention program.

In addition to the highly effective method of contraception a man:

- Must always use a condom during any sexual contact with a woman of childbearing potential, even if they have undergone a successful vasectomy, from the time of signing the ICF until 1 year after receiving a JNJ-68284528 infusion or
- for 4 weeks after discontinuing lenalidomide (whichever is later).
- Who is sexually active with a woman who is pregnant must use a condom.
- Should agree to practice contraception according to and for the time frame
- specified in the local REVLIMID pregnancy prevention program.

Women and men must agree not to donate eggs (ova, oocytes) or sperm, respectively, during the study and for 1 year after receiving a JNJ-68284528 infusion or for 4 weeks after discontinuing lenalidomide (whichever is later).

Note: Hormonal contraception may be susceptible to interaction with the study treatment, which may reduce the efficacy of the contraceptive method.

8. Subject must sign an ICF indicating that he or she understands the purpose of and

procedures required for the study and is willing to participate in the study. Consent is to be obtained prior to the initiation of any study-related tests or procedures that are not part of standard-of-care for the subject's disease.

9. Willing and able to adhere to the prohibitions and restrictions specified in this protocol.

EXCLUSIE CRITERIA Cohort D

Any potential subject who meets any of the following criteria will be excluded from participating in Cohort D of the study:

1. Received prior treatment with CAR-T therapy directed at any target.
2. Received any therapy that is targeted to BCMA.
3. Criterion modified per Amendment 2
    a. Active malignancies (ie, progressing or requiring treatment change in the last 24 months) other than the disease being treated under study. The only allowed exceptions are:

- non-muscle invasive bladder cancer (NMIBC) treated within the last 24 months that is considered completely cured.
- skin cancer (non-melanoma or melanoma) treated within the last 24 months that is considered completely cured.
- non-invasive cervical cancer treated within the last 24 months that is considered completely cured.
- localized prostate cancer (N0M0):
    - with a Gleason score of ≤6, treated within the last 24 months or untreated and under surveillance,
    - with a Gleason score of 3+4 that has been treated more than 6 months prior to full study screening and considered to have a very low risk of recurrence, or
    - history of localized prostate cancer and receiving androgen deprivation therapy and considered to have a very low risk of recurrence.
- breast cancer: adequately treated lobular carcinoma in situ or ductal carcinoma in situ, or history of localized breast cancer and receiving antihormonal agents and considered to have a very low risk of recurrence.
- malignancy that is considered cured with minimal risk of recurrence.

4. Prior anti-tumor therapy, as follows, prior to apheresis:

- Targeted therapy, epigenetic therapy, or treatment with an investigational drug or used as invasive investigational medical device within 14 days or at least 5 half-lives, whichever is less.
- Monoclonal antibody treatment for multiple myeloma within 21 days.
- Cytotoxic therapy within 14 days.
- Proteasome inhibitor therapy within 14 days.
- Immunomodulatory agent therapy within 7 days.
- Radiotherapy within 14 days. However, if the radiation portal covered ≤5% of the bone marrow reserve, the subject is eligible irrespective of the end date of radiotherapy.

5. Ongoing toxicity from previous anticancer therapy must resolve to baseline levels or to Grade 1 or less, except for alopecia or peripheral neuropathy.
6. Received a cumulative dose of corticosteroids equivalent to ≥70 mg of prednisone within the 14 days prior to apheresis.
7. The following cardiac conditions:
   - New York Heart Association (NYHA) stage III or IV congestive heart failure Myocardial infarction or coronary artery bypass graft ≤6 months prior to enrollment
   - History of clinically significant ventricular arrhythmia or unexplained syncope, not believed to be vasovagal in nature or due to dehydration
   - History of severe non-ischemic cardiomyopathy
   - Impaired cardiac function (left ventricular ejection fraction <45%) as assessed by echocardiogram or multiple-gated acquisition (MUGA) scan (performed ≤8 weeks of apheresis)
8. Known active, or prior history of central nervous system involvement of myeloma or exhibits clinical signs of meningeal involvement of multiple myeloma.
9. Stroke or seizure within 6 months of signing ICF.
10. Plasma cell leukemia at the time of screening (>2.0 x 10^9/L plasma cells by standard differential), Waldenström's macroglobulinemia, POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes), or primary (AL) amyloidosis.
11. Seropositive for human immunodeficiency virus (HIV).
12. Vaccinated with live, attenuated vaccine within 4 weeks prior to apheresis.
13. Subject must not require continuous supplemental oxygen.
14. Known life threatening allergies, hypersensitivity, or intolerance to cyclophosphamide, fludarabine, lenalidomide, JNJ-68284528 or its excipients, including DMSO (refer to Investigator's Brochure).
15. Hepatitis B infection as defined according to Attachment 10. In the event the infection status is unclear, quantitative levels are necessary to determine the infection status. (Hwang 2015)
16. Hepatitis C infection defined as (anti-hepatitis C virus [HCV] antibody positive or HCV-RNA positive) or known to have a history of hepatitis C. For subjects with known history of HCV infection, confirmation of sustained virologic response [SVR] is required for study eligibility, defined as ≥24 weeks after completion of antiviral therapy.
17. Criterion modified per Amendment 2
    a. Serious underlying medical condition, such as:
   - Evidence of active viral or bacterial infection requiring systemic antimicrobial therapy, or uncontrolled systemic fungal infection
   - Active autoimmune disease or a history of autoimmune disease within 3 years
   - Overt clinical evidence of dementia or altered mental status
   - Any history of Parkinson's disease or other neurodegenerative disorder
18. Any issue that would impair the ability of the subject to receive or tolerate the planned treatment at the investigational site, to understand informed consent or any condition for which, in the opinion of the investigator, participation would not be in the best interest of the subject (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments.

19. Pregnant or breast-feeding, or planning to become pregnant while enrolled in this study and until 1 year after receiving a JNJ-68284528 infusion or for 4 weeks following discontinuation of lenalidomide (whichever is later).
20. Plans to father a child while enrolled in this study until 1 year after receiving a JNJ-68284528 infusion or for 4 weeks following discontinuation of lenalidomide (whichever is later).
21. Major surgery within 2 weeks prior to apheresis, or has surgery planned during the study or within 2 weeks after JNJ-68284528. (Note: subjects with planned surgical procedures to be conducted under local anesthesia may participate)