SAMENVATTING Cartitude-4

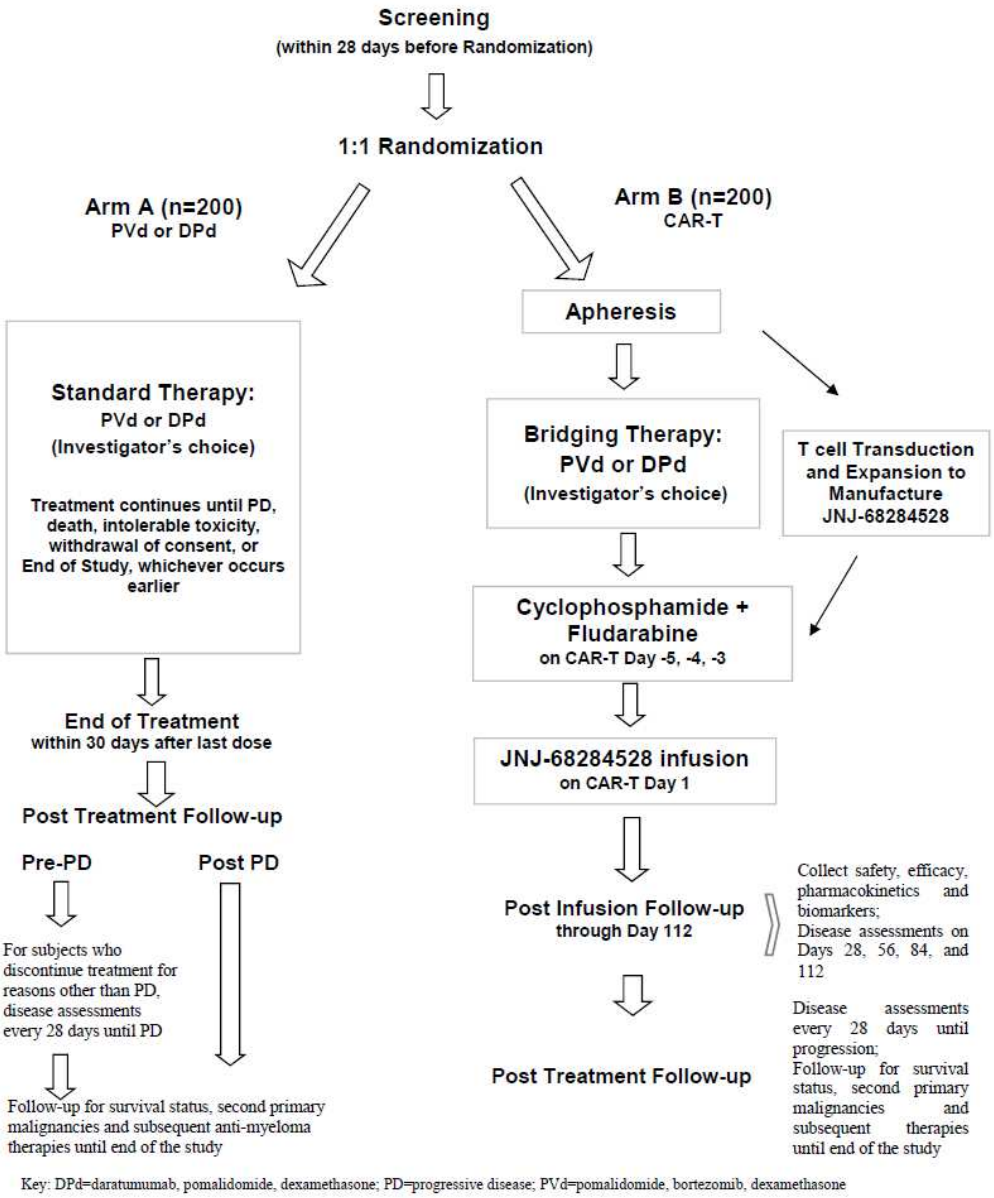
TITEL

A Phase 3 Randomized Study Comparing JNJ-68284528, a Chimeric Antigen Receptor T cell (CAR-T) Therapy Directed Against BCMA, versus Pomalidomide, Bortezomib and dexamethasone (PVd) or Daratumumab, Pomalidomide and Dexamethasone (DPd) in Subjects with Relapsed and Lenalidomide-Refractory Multiple Myeloma

INDICATIE

Multipel myeloom

SCHEMA



Key: DPd=daratumumab, pomalidomide, dexamethasone; PD=progressive disease; PVd=pomalidomide, bortezomib, dexamethasone

INCLUSIE CRITERIA

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

1. Be at least 18 years of age.
2. Have documented diagnosis of MM as defined by the criteria below:
   - Multiple myeloma diagnosis according to the IMWG diagnostic criteria
   - Measurable disease at screening as defined by any of the following:
     - Serum monoclonal paraprotein (M-protein) level ≥1.0 g/dL or urine M-protein Level ≥200 mg/24 hours; or
     - Light chain MM without measurable M-protein in the serum or the urine:

       Serum free light chain ≥10 mg/dL and abnormal serum free light chain ratio.

   Note: Local laboratory assessments may be used to establish measurable disease at Screening, with local laboratory result ≥125% of requirements. However, subjects must have laboratory studies for diseases assessment received by central laboratory prior to randomization.
3. Have received 1 to 3 prior lines of therapy including a PI and IMiD. Subject must have undergone at least 1 complete cycle of treatment for each line of therapy, unless PD was the best response to the line of therapy

Note: induction with or without hematopoietic stem cell transplant, consolidation and maintenance therapy is considered a single line of therapy.

4. Have documented evidence of PD by IMWG criteria based on investigator's determination on or within 6 months of their last regimen.
5. Subjects with only 1 prior line of therapy must have progressed within 36 months of a stem cell transplant, or if not transplanted, then within 42 months of starting initial therapy.
6. Criterion modified per Amendment 1

   6.1. Be refractory to lenalidomide per IMWG consensus guidelines (Rajkumar 2011) (failure to achieve minimal response or progression on or within 60 days of completing lenalidomide therapy). Progression on or within 60 days of the last dose of lenalidomide given as maintenance will meet this criterion. For subjects with more than 1 prior line of therapy, there is no requirement to be lenalidomide refractory to the most recent line of prior therapy.
7. Have an ECOG Performance Status score of 0 or 1
8. Have clinical laboratory values meeting the following criteria during the Screening Phase (re-testing is allowed but the below criteria must be met in the latest test prior to randomization):
   - Hemoglobin ≥8 g/dL (without prior RBC transfusion within 7 days before the laboratory test; recombinant human erythropoietin use is permitted);

- Absolute neutrophil count (ANC) ≥1 × 10^9/L (without recombinant human granulocyte colony-stimulating factor [G-CSF] within 7 days and without pegylated G-CSF within 14 days of the laboratory test);
- Platelet count ≥75 × 10^9/L (without prior platelet transfusion within 7 days before the laboratory test) in subjects in whom <50% of bone marrow nucleated cells are plasma cells; platelet count ≥50 x 10^9/L (without prior platelet transfusion within 7 days before the laboratory test) in subjects in whom ≥50% of bone marrow nucleated cells are plasma cells;
- Lymphocyte count ≥0.3 × 10^9/L;
- Aspartate aminotransferase (AST) ≤3 × upper limit of normal (ULN);
- Alanine aminotransferase (ALT) ≤3 × ULN;
- 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);
- Estimated glomerular filtration rate ≥40 mL/min per 1.73 m^2 (to be calculated using the Modification of Diet in Renal Disease (MDRD) formula.

9. Women of childbearing potential must have 2 negative pregnancy tests prior to starting PVd or DPd. The first, 10-14 days prior to the start of PVd or DPd and prior to randomization. The second pregnancy test will need to be done within 24 hours prior to the start of PVd or DPd. The investigator must verify that the results of these tests are negative prior to starting PVd or DPd. See Section 10.12 for definition of females who are not of reproductive potential.
10. When a woman is of childbearing potential, the subject must commit either to abstaining continuously from heterosexual intercourse or agree to use 2 methods of reliable birth control simultaneously. One of them 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 agree to remain on both methods from the time of signing the ICF until at least 3 months after receiving the last dose of daratumumab or bortezomib or 28 days after the last dose of pomalidomide, whichever is later (Arm A) or at least 1 year after receiving a JNJ-68284528 infusion or at least 3 months after receiving the last dose of daratumumab or bortezomib or 28 days after the last dose of pomalidomide, whichever is later (Arm B) (Section 10.12). Reliable contraception is indicated even where there has been a history of infertility, unless due to hysterectomy. Women of childbearing potential should be referred to a qualified provider of contraceptive methods, if needed.

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 (vasectomy must be confirmed by 2 negative semen analyses);
- User-dependent method: progestogen-only hormone contraception associated with inhibition of ovulation (oral or injectable). Estrogen-containing hormonal contraception is contraindicated due to increased risk of thromboembolic events with pomalidomide. Note: Hormonal contraception may be susceptible to interaction with the study

treatment, which may reduce the efficacy of the contraceptive method. Refer to Section 10.12 for further information.

- Women of childbearing potential must follow the contraception criteria outlined in the local pomalidomide pregnancy prevention program.

11. A man must commit either to abstaining continuously from heterosexual sexual

intercourse or a man:

- Who is sexually active with a woman of childbearing potential or a pregnant woman must agree to use a barrier method of contraception (eg, latex or synthetic condom with spermicidal foam/gel/film/cream/suppository) from the time of signing the ICF until at least 3 months after receiving the last dose of daratumumab or bortezomib or 28 days after the last dose of pomalidomide, whichever is later (Arm A) or at least 1 year after receiving a JNJ-68284528 infusion or at least 3 months after receiving the last dose of daratumumab or bortezomib or 28 days after the last dose of pomalidomide, whichever is later (Arm B), even if they have
- undergone a successful vasectomy;
- Should agree to practice contraception according to and for the time frame specified in the local pomalidomide pregnancy prevention program.

12. Women and men must agree not to donate eggs (ova, oocytes) or sperm, respectively, during the study and for at least 3 months after receiving the last dose of daratumumab or bortezomib, or 28 days after the last dose of pomalidomide, whichever is later (Arm A) or at least 1 year after receiving a JNJ-68284528 infusion or at least 3 months after receiving the last dose of daratumumab or bortezomib or 28 days after the last dose of pomalidomide, whichever is later (Arm B).
13. Must sign an informed consent form (ICF) (or their legally acceptable representative must sign) indicating that he or she understands the purpose of, and procedures required for, the study and is willing to participate in the study. Subjects must be willing and able to adhere to the prohibitions and restrictions specified in this protocol, as referenced in the ICF.
14. Willing and able to adhere to the lifestyle restrictions specified in this protocol

EXCLUSIE CRITERIA

Any potential subject who meets any of the following criteria will be excluded from participating in the study. The subject will be excluded if he or she has or had:

1. Prior treatment with CAR-T therapy directed at any target.
2. Any previous therapy that is targeted to BCMA.
3. Ongoing toxicity from previous anticancer therapy that has not resolved to baseline levels or to Grade 1 or less; except for alopecia.
4. Subjects with Grade 1 peripheral neuropathy with pain or Grade 2 or higher peripheral neuropathy will not be permitted to receive PVd as standard therapy or bridging therapy; however, subject may receive DPd as standard therapy or bridging therapy.
5. Received a cumulative dose of corticosteroids equivalent to ≥70 mg of prednisone

within the 7 days prior to randomization

6. Was vaccinated with live attenuated vaccines within 4 weeks prior to randomization
7. Subject received any antitumor therapy as follows, prior to randomization:
    - Targeted therapy, epigenetic therapy, or treatment with an investigational drug or used an invasive investigational medical device within 14 days or at least 5 half-lives, whichever is less;
    - Investigational vaccine within 4 weeks;
    - Monoclonal antibody treatment 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 is given for palliative purposes and the radiation portal covered ≤5% of the bone marrow reserve, the subject is eligible irrespective of the end date of radiotherapy. Radiotherapy within 14 days on measurable extramedullary plasmacytoma(s) is not permitted even in the setting of palliation for symptomatic management.
8. 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 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.
9. Plasma cell leukemia at the time of screening, Waldenström's macroglobulinemia, POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes), or primary AL amyloidosis.

10. Criterion modified in Amendment 1

    10.1. Contraindications or life-threatening allergies, hypersensitivity, or intolerance to JNJ-68284528 or its excipients, including dimethyl sulfoxide (refer to Investigator's Brochure), or to fludarabine, cyclophosphamide, tocilizumab, pomalidomide, dexamethasone.

    - Subjects with contraindications or life-threatening allergies, hypersensitivity, or intolerance to daratumumab will not be permitted to receive DPd as standard therapy or bridging therapy; however, subjects may receive PVd as standard therapy or bridging therapy. Likewise, subjects with contraindications or lifethreatening allergies, hypersensitivity, or intolerance to bortezomib will not be permitted to receive PVd as standard therapy or bridging therapy; but may receive DPd as standard therapy or bridging therapy.

11. Pregnant or breast-feeding or planning to become pregnant while enrolled in this study or within 3 months of receiving the last dose of daratumumab or bortezomib, or within 28 days after the last dose of pomalidomide, whichever is later (Arm A) or at least within 1 year after receiving JNJ-68284528 infusion or at least within 3 months after receiving the last dose of daratumumab or bortezomib or within 28 days after the last dose of pomalidomide, whichever is later (Arm B).
12. Plans to father a child while enrolled in this study or within 3 months of receiving the last dose daratumumab or bortezomib, or within 28 days after the last dose of pomalidomide, whichever is later (Arm A) or at least within 1 year after receiving JNJ-68284528 infusion or at least within 3 months after receiving the last dose of daratumumab or bortezomib or within 28 days after the last dose of pomalidomide, whichever is later (Arm B).
13. Stroke or seizure within 6 months of signing ICF.
14. Received either of the following:

    - An allogenic stem cell transplant within 6 months before apheresis. Subjects who received an allogeneic transplant must have stopped all immunosuppressive medications for 6 weeks without signs of graft-versus-host disease. Subjects with active graft-versus-host disease are excluded.
    - An autologous stem cell transplantation ≤12 weeks before apheresis.

15. Known active, or prior history of central nervous system (CNS) involvement or exhibits clinical signs of meningeal involvement of MM.
16. Subject with chronic obstructive pulmonary disease (COPD) with a forced expiratory volume in 1 second (FEV1) <50% of predicted normal will not be able to receive DPd as standard therapy or bridging therapy; however, subject may receive PVd as standard therapy or bridging therapy. Note that FEV1 testing is required for subjects who are planned to receive treatment with DPd and are suspected of having COPD.
17. Criterion revised per Amendment 1

    17.1. Any of the following:

    a) Seropositive for human immunodeficiency virus (HIV)

    b) Hepatitis B infection: In the event the infection status is unclear, quantitative viral levels are necessary to determine the infection status. Subjects who are anti-HBs positive and without

history of vaccination or for subjects who are anti-HBc positive with or without positive anti-HBs should have hepatitis B virus (HBV)-DNA quantification test done. Please consult Section 10.6 for further details.

c) 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 is required for study eligibility, defined as ≥24 weeks after completion

of antiviral therapy.

18. Criterion revised per Amendment 1

    18.1. Serious underlying medical or psychiatric condition or disease, that is likely to interfere with study procedures or results, or that in the opinion of the investigator would constitute a hazard for participating in this study, such as:

    - Requirement of supplemental oxygen to maintain oxygen saturation;
    - Evidence of serious active viral or bacterial infection, requiring systemic antimicrobial therapy, or uncontrolled systemic fungal infection;
    - Active autoimmune disease or a history of autoimmune disease within 2 years;
    - Clinical evidence of dementia or altered mental status;
    - Any history of Parkinson's disease or other neurodegenerative disorder
    - Clinically significant cardiac disease, such as:
        - New York Heart Association Class III or IV congestive heart failure (see Section 10.14);
        - 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 (LVEF <45%) as assessed by echocardiogram or multiple-gated acquisition (MUGA) scan performed ≤8 weeks before randomization.

19. Major surgery within 2 weeks before randomization, or has not fully recovered from an earlier surgery, or has major surgery planned during the time the subject is expected to participate in the study.

    Note: Kyphoplasty or vertebroplasty are not considered major surgery. If there is a question about whether a procedure is considered a major surgery, the investigator must consult with the sponsor and resolve any issues before enrolling a subject in the study.

20. 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.

NOTE: Investigators should ensure that all study enrollment criteria have been met at screening and before randomization. If a subject's clinical status changes (including any available laboratory results or receipt of additional medical records) after screening but before randomization such that he or she no longer meets all eligibility criteria, then the subject should be excluded from participation in the study.

Section 5.4 (Screen Failures) describes options for retesting. The required source documentation to support meeting the enrollment criteria is noted in Section 10.3 - Regulatory, Ethical, and Study Oversight Considerations.