7. SELECTION, WITHDRAWAL, AND REPLACEMENT OF PATIENTS

7.1. Number of Patients Planned

Up to 91 patients are planned to be enrolled.

In the dose escalation portion, up to 54 patients may be enrolled. The actual sample size of these dose escalation cohorts will depend on the number of patients with DLT, and number of dose levels studied.

A total of up to 37 patients will be enrolled in the dose expansion phase at the RP2D determined in the dose escalation portion of the study across 2 expansion cohorts: cohort A and B (Section 6.1.4).

7.2. Study Population

The study population will consist of patients with aggressive B-NHL lymphoma according to the WHO criteria (Swerdlow, 2017) who have progressed after at least 2 lines of treatment including an anti-CD20 antibody and an alkylating agent.

7.2.1. Inclusion Criteria

A patient must meet the following criteria to be eligible for inclusion in the study:

1. Age 18 years or greater
2. Have documented $CD20^+$ aggressive B-NHL, with disease that has progressed after at least 2 lines of systemic therapy containing an anti-CD20 antibody and an alkylating agent. Lymphoma subtyping is based on the World Health Organization (WHO) classification (Swerdlow, 2017). Eligible subtypes include: DLBCL, primary mediastinal (thymic) large B-cell lymphoma, T-cell/histiocyte rich large B-cell lymphoma, follicular lymphoma grade 3b, and high-grade B-cell lymphoma (HGBL) (Appendix 1). Patients must, in the judgement of the investigator, require systemic therapy for lymphoma at the time of study enrollment.

   NOTES:

   - Patients who relapse after the most recent prior line, or patients who progress during or after the prior treatment, are eligible.
   - Patients who have received CAR-T therapy are eligible. Ongoing studies have demonstrated that odronextamab can be tolerated by and provides efficacy in these patients. CAR-T naïve and post-CAR-T failure patients are evaluated separately in Cohorts A and B respectively, in the dose expansion phase.
   - Patients should, in the judgment of the investigator, require systemic therapy for lymphoma at the time of study enrollment and should be deemed not appropriate for any other approved and locally available therapy with established benefit for that indication.

- DLBCL that is transformed from a lower grade neoplasm (eg, FL or CLL) may be enrolled. Patients with DLBCL transformation from prior CLL can only be enrolled in the absence of a leukemic CLL component. For patients with transformed DLBCL, prior systemic therapies administered for the lower grade neoplasm will not be considered among the prior lines of therapy for the purpose of determining eligibility.

3. Measurable disease on cross sectional imaging (defined as at least 1 bi-dimensionally measurable nodal lesion of ≥1.5 cm in the greatest transverse diameter (GTD) regardless of the short axis diameter) documented by diagnostic imaging (computed tomography [CT], or magnetic resonance imaging [MRI])
4. Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1
5. Adequate bone marrow function as documented by:
   a. Platelet count ≥50 x 10^9/L. A patient may not have received platelet transfusion therapy within 7 days prior to first dose of odronextamab to meet the platelet eligibility criterion
   b. Hemoglobin ≥9.0 g/dL; transfusions to meet this criteria are allowed per protocol.
   c. Absolute neutrophil count (ANC) ≥1.0 x 10^9/L. A patient may not have received G-CSF within 2 days prior to first dose of odronextamab in order to meet the ANC eligibility criterion

      NOTE: Patients with bone marrow involvement or splenic sequestration should meet the following hematologic parameters:

      - Platelet count ≥25 x 10^9/L. A patient may not have received platelet transfusion therapy within 3 days prior to first dose of odronextamab in order to meet the platelet eligibility criterion
      - Hemoglobin ≥7.0 g/dL
      - Absolute neutrophil count (ANC) ≥ 0.5 x 10^9/L. A patient may not have received G-CSF within 2 days prior to first dose of odronextamab in order to meet the ANC eligibility criterion
6. Adequate hepatic function:
   a. Total bilirubin ≤1.5 × upper limit of normal (ULN) (≤3 × ULN if attributed to lymphoma infiltration of liver)
   b. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤3 × ULN (≤5 × ULN if attributed to lymphoma infiltration of liver)
   c. Alkaline phosphatase (ALP) ≤2.5 × ULN (≤5 × ULN if attributed to lymphoma infiltration of liver)

   NOTES:

   *Irrespective of the presence of lymphoma infiltration of the liver, a patient with an AST >3 × ULN and/or ALT >3 x ULN concurrent with a total bilirubin >1.5 x ULN will be excluded

   *Patients with known Gilbert syndrome will be excluded if the total bilirubin value is >4 x ULN for the local general population

7. Calculated creatinine clearance by Cockcroft-Gault formula ≥50 mL/min

   NOTE: Patients with a calculated creatinine clearance <50 mL/min may be considered for enrollment if a measured creatinine clearance (based on 24-hour urine collection or other reliable method) is ≥50 mL/min

8. During dose expansion phase of the study, patient should be willing to undergo mandatory tumor biopsies, if in the opinion of the investigator, the patient has an accessible lesion that can be biopsied without significant risk to the patient. In the absence of such a lesion at screening, archival tissue samples up to 6 months prior (and without intervening treatment) can be considered acceptable for subject's study eligibility (after approval by the medical monitor).
9. Ability to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use protected health information (in accordance with national and local subject privacy regulations)
10. Willing and able to comply with clinic visits and study-related procedures
11. Provide informed consent signed by study patient or legally acceptable representative

7.2.2. Exclusion Criteria

A patient who meets any of the following criteria will be excluded from the study:

1. Prior treatments:
   - Prior allogeneic stem cell transplantation or solid organ transplantation
   - Patients who have received prior treatment with anti-CD20 x anti-CD3 bispecific antibody, such as odronextamab
2. Diagnosis of mantle cell lymphoma (MCL)
3. Primary central nervous system (CNS) lymphoma or known involvement by non-primary CNS lymphoma (even if treated into complete remission). Suspected CNS lymphoma should be evaluated by lumbar puncture, as appropriate, in addition to the mandatory head CT or MRI.
4. Treatment with any systemic anti-lymphoma therapy within 5 half-lives or within 14 days prior to first administration of study drug, whichever is shorter
   NOTE: (i) For patients who received prior CAR-T therapy, a washout period of at least 28 days is required before first dose of the study drug

   (ii) Patients with ongoing grade 2 or higher toxicity (assessed to be due to previous treatments) are not eligible. The following exceptions apply; laboratory thresholds will be as described in inclusion criteria, persistent but stable grade 2 toxicity and/or if not clinically significant in the Investigator's opinion.
5. Standard radiotherapy within 14 days of first administration of study drug.
   NOTE: Palliative radiotherapy to a symptomatic lymph node/lesion is allowed provided the irradiated lesion(s) or node(s) is not included as a target lesion for tumor assessments

6. Continuous systemic corticosteroid treatment with more than 10 mg per day of prednisone or corticosteroid equivalent within 72 hours of start of odronextamab
7. Co-morbid conditions:
   a. History of neurodegenerative condition or CNS movement disorder. Patients with a history of seizure within 12 months prior to study enrollment are excluded
   b. Patients with prior CAR-T cell therapy with unresolved-graft-versus-host disease are not eligible
   c. Patients with known history of hemophagocytic lymphohistiocytosis (HLH) are excluded
   d. Another malignancy in the past 5 years, with the exception of any tumor that is localized (eg, non-melanoma skin cancer or in-situ cervical carcinoma) and effectively treated with definitive local control (with or without continued adjuvant hormonal therapy)
   e. Cardiac ejection fraction <50% by echocardiogram (ECHO) or multigated acquisition (MUGA) scan
   f. Other significant concurrent disease or medical condition that, in the opinion of the investigator, could interfere with the conduct of the study or put the patient at significant risk, including but not limited to significant cardiovascular (eg, New York Heart Association Class III or IV cardiac disease, myocardial infarction within the previous 6 months, unstable arrhythmias, or unstable angina), pulmonary (eg, obstructive pulmonary disease and history of symptomatic bronchospasm), gastrointestinal, hepatic, renal, endocrine, hematologic, autoimmune, psychiatric or neurologic disorder
8. Infection:
   a. Any infection requiring hospitalization or treatment with IV anti-infectives within 2 weeks of first administration of study drug
   b. Uncontrolled infection with human immunodeficiency virus (HIV), hepatitis B (HBV) or hepatitis C (HCV) infection; or other uncontrolled infection
      - Patients with HIV who have controlled infection (undetectable viral load and CD4 count above 350 cells/microliter either spontaneously or on a stable antiviral regimen) are permitted
      - Patients with hepatitis B ($HepBsAg^+$) who have controlled infection (serum hepatitis B virus DNA polymerase chain reaction [PCR] that is below the limit of detection AND receiving anti-viral therapy for hepatitis B) are permitted
      - Patients who are hepatitis C virus antibody positive ($HCV\ Ab^+$) who have controlled infection (undetectable HCV RNA by PCR either spontaneously or in response to a successful prior course of anti-HCV therapy) are permitted
   c. Patients with active infection with Epstein-Barr virus are excluded
9. Cytomegalovirus infection as noted by detectable levels on peripheral blood PCR assay. Patients who show detectable levels of CMV at screening will need to be treated with appropriate antiviral therapy and demonstrate at least 2 undetectable levels of CMV by PCR assay (at least 7 days apart) before being re-considered for eligibility.

10. Allergy/hypersensitivity: Known hypersensitivity to both allopurinol and rasburicase
11. History of severe allergic reaction attributed to compounds with a similar chemical or biologic composition as that of the study drug or excipient
12. Vaccination within 28 days prior to first study drug administration with a vector that has replicative potential
13. Member of the clinical site study team or his/her immediate family unless prior approval granted by the sponsor.
14. Women of childbearing potential (WOCBP) with a positive serum β-hCG pregnancy test.
15. Pregnant or breastfeeding women.
16. Women of childbearing potential* or men who are unwilling to practice highly effective contraception prior to the initial dose/start of the first treatment, during the study, and for at least 6 months after the last dose. Sperm or egg donation is prohibited during the study and for 6 months after the last dose of study drug. Highly effective contraceptive measures include:
    a. stable use of combined (estrogen and progesterone containing) hormonal contraception (oral, intravaginal, transdermal) or progesterone-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation initiated 2 or more menstrual cycles prior to screening
    b. intrauterine device (IUD); intrauterine hormone releasing system (IUS)
    c. bilateral tubal ligation
    d. vasectomized partner† (provided that the male vasectomized partner is the sole sexual partner of the study participant and that the partner has obtained medical assessment of surgical success for the procedure).
    e. and/or sexual abstinence ‡,§.
    f. Male study participants with WOCBP partners are required to use condoms unless they are vasectomized† or practice sexual abstinence.‡,§

    * Women of childbearing potential are defined as women who are fertile following menarche until becoming post-menopausal, unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.
    A post-menopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient to determine the occurrence of a post-menopausal state. The above definitions are according to Clinical Trial Facilitation Group (CTFG) guidance.
    Pregnancy testing and contraception are not required for women with documented hysterectomy.
    † Vasectomized partner or vasectomized study participant must have received medical assessment of the surgical success.
    ‡ Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated

with the study drugs. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient.

§ Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception. Female condom and male condom should not be used together.

17. Patients who are committed to an institution by virtue of an order issued either by the judicial or the administrative authorities.

Van: Els Klaver - van der Bel e.klaver-vanderbel@erasmusmc.nl
Onderwerp: FW:
Datum: 14 januari 2025 om 09:07
Aan: bklaver.bk@gmail.com

Van: Petra Cornelisse <p.cornelisse@erasmusmc.nl>
Verzonden: maandag 13 januari 2025 06:45
Aan: Pim Mutsaers <p.mutsaers@erasmusmc.nl>; Els Klaver - van der Bel <e.klaver-vanderbel@erasmusmc.nl>
Onderwerp: RE:

Ja, zal ik doen!

Met vriendelijke groet, with kind regards,

Petra Cornelisse, MSc.

Sr. Global CPM & IT developer / administrator

Clinical Operations

HOVON

From: Pim Mutsaers <p.mutsaers@erasmusmc.nl>
Sent: Friday, January 10, 2025 9:23 PM
To: Els Klaver - van der Bel <e.klaver-vanderbel@erasmusmc.nl>
Cc: Petra Cornelisse <p.cornelisse@erasmusmc.nl>
Subject:

Dag Els,
Zou jij aan Petra Cornelisse Pagina 78 t/m 83 van het Athena-1 protocol op KMS kunnen sturen? (ik heb TM even in de cc gezet, zij weten wat ik bedoel) Dit als link voor de LLPC site voor de studie Athena-1
@ Petra: op de LLPC site staan nu onder athena-1 de verkeerde in-en exclusie criteria
Als Els ze stuurt, kun jij ze dan vervangen? Dank

Kind regards,

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