A prospective Phase I/IIa, open-label, multicenter trial to evaluate the safety and efficacy of oNKord®, an off-the-shelf, ex vivo-cultured allogeneic NK cell preparation, in subjects with acute myeloid leukemia who are in morphologic complete remission with measurable residual disease and who are currently not proceeding to allogeneic hematopoietic stem cell transplantation.

Published: 20-03-2020
Last updated: 08-04-2024

Primary ObjectivesThe primary objectives are:• The primary safety objective is to evaluate the safety and tolerability of the infusion of up to three doses of oNKord®• The primary efficacy objective is to assess the cumulative incidence of MRD...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Leukaemias
Study type	Interventional

Summary

ID

NL-OMON52744

Source
ToetsingOnline

Brief title
WiNK

Condition

- Leukaemias

Synonym
bone marrow cancer cells, leukemia

Research involving
Human

Sponsors and support

Primary sponsor: Glycostem Therapeutics
Source(s) of monetary or material Support: Glycostem therapeutics

Intervention

Keyword: Acute myeloid leukemia, ATMP, Open label, Phase I-IIa

Outcome measures

Primary outcome

Primary endpoints:

Safety and Tolerability:

To evaluate the safety and tolerability of oNKord® using the cumulative

incidence of the adverse events of special interest (AESI), including:

• Grade 3-4 infusion-related toxicity of oNKord®, as rated by the National

Cancer Institute (NCI)*s Common Terminology Criteria for Adverse Events (CTCAE)

version 5.0

• Acute graft versus host disease (GVHD) grade III and IV / Extensive chronic

GVHD

• Cytokine Release Syndrome (CRS) >= Grade 2, as rated by the American Society

for Transplantation and Cellular Therapy (ASTCT) Consensus Grading for Cytokine

Release Syndrome

• Immune effector cell-associated neurotoxicity syndrome (ICANS) >= Grade 2, as rated by the ASTCT Consensus Grading for Neurologic Toxicity Associated with Immune Effector Cells

Efficacy:

To evaluate the efficacy of oNKord® using:

• The cumulative incidence of MRD response as assessed via centralized assessment in bone marrow at 1, 2, 3, 6, 9 and 12 months post-RP2D oNKord® infusion. Subjects with responses are defined as MRD negative (as per the European LeukemiaNet [ELN] MRD Working Party 2021 recommendations) subjects still in morphologic CR at any time during the follow-up period of the trial after receiving oNKord® at RP2D.

Secondary outcome

Secondary endpoints

Safety and Tolerability:

To evaluate the safety and tolerability of the trial treatment using the cumulative incidence of AESIs, including:

• Grade 3-4 infusion-related toxicity, as rated by CTCAE v5.0

• Acute GVHD grade III and IV / Extensive chronic GVHD

• CRS >= Grade 2, as rated by the ASTCT Consensus Grading for Cytokine Release Syndrome

• ICANS >= Grade 2, as rated by the ASTCT Consensus Grading for Neurologic Toxicity Associated with Immune Effector Cells

• Haemorrhagic cystitis

• Death related to the trial treatment

• Incidence and severity of viral, fungal, and bacterial infections with onset during the first two months following trial treatment, including viral reactivations, and Infection Related Mortality (IRM) defined as death due to infectious disease

Efficacy:

To evaluate the efficacy of the trial treatment at the RP2D by assessing:

• EFS, defined as the time from enrolment until disease relapse (morphologic and/or clinical relapse) after morphologic CR or death due to any cause, whichever occurs first

• CIR, defined as the cumulative incidence of relapse throughout the course of the trial

• Duration of MRD response, defined as duration between MRD negativity to returning to MRD positivity, as determined by centralized assessment

• OS rate (defined as the time from enrolment until death from any cause) at 12 months

• Changes in QoL using the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 and SF-36 questionnaires, assessed at 1, 3 and 12 months post-treatment compared to baseline

Exploratory Endpoints

• Analysis of biomarkers predictive of response may include:

o Analysis of responders and non-responders, as assessed by the efficacy primary endpoint, in relation to secondary efficacy endpoints

o Targeted DNA sequencing of commonly mutated genes in AML, performed by next

generation sequencing (NGS) on bone marrow samples, compared to diagnosis tumour genetic profiling (if available), and associated to response/ non-response

o Assessment of oNKord® immunogenicity

o Number of oNKord® infusions and corresponding enumeration of oNKord®-derived NK-cells in combination with relevant cytokine levels, including chimerism as determined by genomic assays and/or flow cytometry

o MRD negativity, baseline physical and functional conditions associated to occurrence of relapse and survival

• Determination of the biological parameters related to oNKord® derived NK-cells may include analysis of the in-vivo lifespan (immunophenotyping), cytolytic activity (persistence of oNKord® derived NK-cell functionality after infusions), and extent of oNKord® derived NK-cell expansion and persistence (chimerism) at multiple time points after oNKord® infusion(s)

• Cumulative incidence of molecular response on MRD as assessed by error-corrected NGS at various timepoints post oNKord® infusion(s) in bone marrow and peripheral blood

Study description

Background summary

Transfusion of allogeneic natural killer (NK)-cells is a promising therapeutic approach for patients with acute myeloid leukaemia (AML). NK cells are major effector cells of the innate immune system and play a key role in controlling viral infections as well as tumour immunosurveillance. In the setting of haplo-identical allogeneic haematopoietic stem cell transplantation (HSCT), NK cell alloreactivity has proven to decrease relapse rates and improve survival

among AML patients. Therefore, there is an emerging interest in exploiting adoptive NK cell transfer in the treatment of AML.
For the current trial, allogeneic NK cells are generated from umbilical cord blood (UCB) CD34+ hematopoietic stem and progenitor cells (HSPCs) using an ex vivo expansion and differentiation method that was developed by Glycostem Therapeutics B.V. via oNKord®.
The approach is supported by the capability of the oNKord® NK cells to migrate to the bone marrow (BM) and to mediate a cytotoxic effect on leukaemia cells following adoptive transfer. In addition, efficient oNKord® cell survival in vivo in the presence of low dose human interleukin-15 (IL-15) was observed. Transient elevation of IL-15 plasma levels was reported in AML patients following lymphodepletion by cyclophosphamide and fludarabine (Cy/Flu) conditioning, which could favour the in vivo expansion and maturation of oNKord® NK cells, as well as clinical responses to AML following oNKord® adoptive transfer.
Measurable residual disease (MRD) is a predictive factor of relapse and mortality in patients with AML who are in morphologic complete remission (CR). Since BM is the primary site of AML development and encloses niches essential for leukaemic stem cells causing relapse, BM targeting is essential for elimination of MRD before morphologic relapse in patients having reached morphologic CR and thus induction of optimal and persistent clinical responses against AML during this window of opportunity before relapse. Reaching a threshold dose of functionally active NK cells with or without repeat dosing might be a prerequisite for NK cell therapy to be effective in this population of patients when HSCT is not a suitable or preferred option.
In this phase I-IIa trial, oNKord® will be evaluated for its safety, tolerability and clinical benefit in AML patients in morphologic CR (including CR with incomplete blood recovery [CRi]) with MRD and who are currently not proceeding to allo-HSCT.. The safety and tolerability of oNKord® intravenous infusion (IV) of a single dose of up to 30 x 106 NK cells/kg bodyweight has been established in a phase I trial (PMLA25 study).
Stage A of the present trial (dose-escalation stage) is designed to assess the safety and tolerability of up to three oNKord® infusions, either on a single day or four days apart, at a dose of 325 - 1,000 x 106 viable NK-cells per intravenous infusion (IV) infusion, and to determine the oNKord® recommended phase II dose (RP2D) to be used in Stage B.
Stage B of the trial (expansion stage) will evaluate the safety and tolerability of oNKord® at the RP2D, as identified in Stage A, and efficacy on MRD (cumulative incidence of response and duration of response), Event Free Survival (EFS), Overall Survival (OS), and Cumulative Incidence of Relapse (CIR).
The starting material (umbilical cord blood) for the up to three doses of oNKord® to be infused in each individual subject is collected from the same donor. Dosing of oNKord® by intravenous infusion is not bodyweight related.

The overall objective of the trial is to evaluate whether oNKord® therapy is

safe and if it can reduce the relapse risk and therefore mortality in AML subjects who are in morphologic CR with MRD and who are currently not proceeding to allo-HSCT

Study objective

Primary Objectives
The primary objectives are:
• The primary safety objective is to evaluate the safety and tolerability of the infusion of up to three doses of oNKord®
• The primary efficacy objective is to assess the cumulative incidence of MRD response following the infusion of oNKord® at the recommended phase 2 dose (RP2D)
Secondary Objectives
The secondary objectives are:
• In Stage A, to determine oNKord® RP2D
• To further evaluate the safety and tolerability of the trial treatment
• To further assess the efficacy of the trial treatment on event-free survival (EFS), duration of MRD response, cumulative incidence of relapse (CIR) and overall survival (OS)
• To evaluate the effect of the trial treatment on quality of life (QoL)
Exploratory Objectives
The exploratory objectives are:
• To identify biomarkers predictive of response for MRD, EFS and OS
• To evaluate biological parameters related to oNKord® mechanism of action following up to three oNKord® infusions
• To assess the cumulative incidence of molecular response on MRD following up to three oNKord® infusions

Study design

This trial will be conducted as a multicentre, open label, phase I-IIa trial to evaluate the safety and efficacy of oNKord® alone (all cohorts) and as part of the overall trial treatment, consisting of the non-myeloablative conditioning regimen (Cy/Flu) followed by up to three oNKord® infusions (for cohorts A1, A2, A3, A5 and cohort B if applicable), in AML subjects who are in morphologic CR (including CRi) with MRD and have no strong indication for HSCT.
The trial uses a 2-stage, single arm design in 40 subjects (Stage A with 16 subjects and Stage B with 24 subjects). The overall design is shown in Figure 1 in the Synopsis section.

The trial will start with Stage A, a dose-escalation stage, in which 3 cohorts (A1-A3) of 3 subjects each will receive escalating repeat doses of oNKord®, while a fourth and fifth cohorts will receive the dose of the third cohort (A3) but will undergo either an adjusted conditioning strategy (A4) or a different oNKord® dosing schedule (A5).

Dose cohort A4 will enroll three subjects undergoing treatment with azacitidine-venetoclax as per standard of care who will receive the same number of oNKord® doses as cohort A3, but without the use of Cy/Flu (the immunosuppressive effect of the azacitidine-venetoclax treatment alleviates the need for the Cy/Flu lymphodepleting conditioning regimen to prevent/minimize immune rejection of the allogeneic NK cells).
Dose cohort A5 will enroll three subjects who will receive the Cy/Flu conditioning regimen followed by the same cumulative total dose of oNKord® (3 x 325 - 1,000 x 106 viable NK cells) as cohorts A3 and A4, but as a single day infusion on Day 0 (same day infusion of three bags of oNKord®).
Due to the acute nature of the disease, the time it takes for screening and the attrition due to the inclusion criteria (specifically MRD positivity), an over-enrollment of up to one more patient per dose escalation cohort will be allowed (up to four patients total per dose cohort).
Upon completion of Stage A, the trial treatment at the RP2D to take forward to Stage B of the trial (expansion stage) will be selected and studied in 24 additional subjects.
Eligibility criteria for participation in the trial and follow-up duration are the same for subjects in both Stage A and Stage B.
Stage A (dose escalation stage) will investigate the safety and tolerability of one, two, and three doses of oNKord® at 325 - 1,000 x 106 viable NK cells/infusion in five cohorts of a minimum of three subjects each:
• Subjects within each of the five cohorts will be enrolled sequentially to ensure a time window of at least 72 hours in between the infusion of the first dose of oNKord® to the previous subject and the infusion of the first dose of oNKord® to the following subject within a cohort.
• Up to four subjects in cohort A1 will receive Cy/Flu and one oNKord® infusion on Day 0 .
• Under the condition that no dose-limiting toxicity (DLT) is observed during the DLT observation ending at the Month 1 Follow-up Visit after oNKord® infusion of the last subject enrolled in cohort A1, and the positive recommendation by the IDMC, up to four subjects will be included in cohort A2 to receive Cy/Flu and two oNKord® reapeat infusions, 4 days apart (i.e., Day 0 and Day +4).
• Under the condition that no DLT is observed during the DLT observation period ending at the Month 1 Follow-up Visit after oNKord® infusions of the last subject enrolled in cohort A2, and with the positive recommendation by the IDMC, up to four subjects will be included in cohort A3 to receive Cy/Flu and three oNKord® repeat infusions, 4 days apart (i.e., Day 0, Day +4 and Day +8).
• Under the condition that no DLT is observed during the DLT observation period ending at the Month 1 Follow-up Visit after oNKord® infusions of the first subject enrolled in cohort A3:
o Up to four subjects will be included in cohort A4 to receive three oNKord® repeat infusions, 4 days apart (i.e., Day 0, Day +4 and Day +8) without the use of Cy/Flu. The removal of the Cy/Flu conditioning regimen in this cohort is expected to further increase the safety of the experimental treatment, and therefore cohort A4 will enroll patients in parallel with cohort

A3, after the first subject enrolled in cohort A3 has completed the DLT observation period with no DLT. Dose cohort A4 might also enroll three additional patients upon recommendation of the independent data monitoring committee (IDMC) and decision by the Sponsor.
o Up to four subjects will be included in cohort A5 to receive Cy/Flu and three back-to-back oNKord® infusions on Day 0 (same day infusion of three bags of oNKord®). Dose cohort A5 will enroll patients in parallel with cohort A4.

If one subject develops a DLT in any of the five dose cohorts, an additional three subjects will be enrolled into that same cohort. Development of DLTs in more than one of all subjects treated at a specific dose level indicates that the maximum tolerated dose (MTD) has been exceeded, and the previous dose level is considered the RP2D. In the unlikely case that two or more DLTs occur at the lowest dosing cohort (cohort A1 with one oNKord® infusion), a decision to stop the trial will be taken by the Sponsor after review and recommendation by the IDMC, the Sponsor, and the Medical Monitor.

Stage B (expansion stage) will investigate the safety, tolerability and efficacy of oNKord® infusion(s) at the RP2D in 24 subjects: after the DLT observation period ending at the Month 1 follow-up visit after oNKord® infusions of the last subject enrolled in cohort A4 and/or cohort A5, and dependent on the determination of the RP2D and positive recommendation of the IDMC to proceed to Stage B, 24 subjects will be included in cohort B to receive the trial treatment at the RP2D.

An interim analysis of the safety and tolerability, as well as preliminary oNKord® efficacy signals of the trial treatment, will be conducted when 14 subjects reach three months follow-up (around 50% of subjects at the RP2D). The IDMC will review the safety data from the interim analysis and issue an opinion on the safety and tolerability of the trial treatment at the RP2D.

Intervention

For cohorts A1, A2, A3 and A5: Five days before the first infusion of oNKord®, eligible subjects will receive cyclophosphamide (300 mg/m2/day IV) and fludarabine (30 mg/m2/day IV) on Days -5, -4, and -3. The Cy/Flu regimen will be administered in an inpatient (hospitalized) setting, as per institutional practice.

oNKord® will be administered intravenously at a dose of 325 - 1,000 x 106 viable NK-cells per infusion:
Cohort A1: one oNKord® infusion at Day 0.
Cohort A2: two oNKord® infusions, 4 days apart (Day 0 and Day +4).
Cohort A3: three oNKord® infusions, 4 days apart (Day 0, Day +4 and Day +8).
Cohort A4: three oNKord® infusions, 4 days apart (Day 0, Day +4 and Day +8).
Cohort A5: three back-to-back oNKord® infusions on Day 0

Cohort B: RPD2, as determined in Stage A.

Study burden and risks

Known and potential risks are related both to the reduced intensity conditioning as a prerequisite for oNKord® infusion and to oNKord® as the IMP of the trial. Overall, the most common toxicities that might be expected from Cy/Flu conditioning and oNKord® infusion includes fever, chills, myalgias, malaise, lymphopenia, and neutropenia.
The most common risks for the patient are associated with the Cy/Flu conditioning regimen. Cy/Flu conditioning can induce acute toxicity related to the agents themselves (cyclophosphamide and fludarabine), as well as pancytopenia requiring transfusions and increasing the probability of (severe) infections.
See protocol for tables for commonly according adverse reactions associated with cyclophosphamide and fludarabine.

Cohort A4 leverages the immunosuppression induced by azacitidine-venetoclax standard of care treatment, as conditioning regimen. Azacitidine-venetoclax standard of care treatment is not administered as part of the trial (azacitidine-venetoclax are not non-investigational medicinal products [NIMPs] in the WiNK trial). See Investigator's Brochure (IB) for common adverse reactions associated with azacitidine and venetoclax.

oNKord® infusion
Potential adverse reactions after the infusion could include allergic or hypersensitivity reactions to some of the constituents of oNKord® (e.g. the excipient dimethyl sulfoxide [DMSO] or impurity): immediate fever or chills, skin rash, bronchospasm, or anaphylactic shock, and delayed serum-sickness-like reactions.
Because oNKord® contains mismatched donor NK lymphocytes, a causal relationship between acute or chronic GVHD and oNKord® administration cannot be ruled out.
oNKord® infusion will also be closely monitored for two unique and immunotherapy-specific toxicities: cytokine release syndrome (CRS) and neurotoxicity, called immune effector cell-associated neurotoxicity syndrome (ICANS).
CRS is a systemic inflammatory response that can be triggered by a variety of factors including immunotherapy drugs like chimeric antigen receptor (CAR)-T cell (Shimabukuro-Vornhagen et al. 2018). The early CRS manifestations are comparable to flu-like symptoms, including high fever, malaise, arthralgia/myalgia, nausea and headaches. Within hours, symptoms can progress to hypotension, vascular leakage, disseminated intravascular coagulation (DIC), and respiratory failure ultimately leading to multi-organ system failure (Garcia Borrega et al. 2019).
ICANS is the second major side effect developing in a substantial proportion of patients treated with CD19-targeted CAR-T cells (Santomasso et al. 2019). The symptoms and the presentation of ICANS are heterogeneous and can progress from

headaches, fatigue, and mild aphasia to more severe and potentially life-threatening symptoms including seizures, raised intracranial pressure with cerebral oedema, and coma (Garcia Borrega et al. 2019).
However, the probability of occurrence of CRS and ICANS following oNKord® infusion is reduced compared to CAR-T cell therapies. Indeed, allogeneic NK cells have limited in vivo persistence after adoptive transfer as they do not clonally expand, and are rapidly (within days to weeks) rejected by the immune system (Rezvani et al. 2017; Dolstra et al. 2017).
Moreover, oNKord® manufacturing process includes a washing step allowing for elimination of residual cytokines in the final product. Potential trace amounts detected are more than 5-logs below what have been used in direct IL-2, IL-7 and IL-15 administration to patients with cancer or viral infections (Miller et al. 2005; Curti et al. 2011).
oNKord® immunogenicity
The development of an immune response against oNKord® allogeneic NK cells may trigger the apparition of anti-HLA antibodies after the oNKord® infusion(s). The impact of these antibodies on efficacy or safety of oNKord® is still to be evaluated.
Epstein-Barr Virus (EBV) infection
The high prevalence of EBV-positive cord blood donors implies a poor feasibility of EBV-negative product manufacturing. In order to mitigate the risk of infection for EBV-negative subjects, these subjects are excluded from the WiNK trial (see Section 1.5.3).
Further information on the risks associated with oNKord® can be found in Chapter 6.9. of the IB.

The tests used during this study may also cause complications or discomforts for patients

ECG
The ECG procedure may cause some mild discomfort during the placement and removal of the leads to and from the skin. Patients may also experience some local irritation, redness, or burning in the areas where the leads are attached.

ECHO/MUGA Scan
An ECHO is generally well tolerated by patients and safe. If patients require a multigated acquisition (MUGA) scan, they will receive a radioactive substance through an injection in the vein. This injection may cause pain. The dose of radioactivity is very low and it is considered safe. Your body will get rid of the substance within about 24 hours.

CT scan/Chest X-ray
Patients will be exposed to radiation when undergoing a CT scan or chest X-ray. The extra radiation falls within the limits set for this type of extra radiation exposure.
For some CT scans, it is necessary that patients are injected with a contrast agent. There is a small risk of developing an allergic reaction to the agent.

This reaction can be mild (itching, rash, nausea) or severe (difficulty breathing or state of shock). Most allergic reactions can be controlled with medication.
The contrast agent can also cause dehydration or damage the kidneys, which at worst results in kidney failure. If patients are dehydrated or have poor kidney function, the study doctor can decide to take a blood sample to check whether your kidneys are functioning well enough, prior to performing a CT scan.

Bone marrow biopsy/Bone marrow aspiration
Patients will be given anaesthetic to numb the area and reduce the pain. This procedure may nevertheless be very painful. However, the pain only lasts for about 15 to 30 seconds. The bone area may be sore for a day or two. It is possible, but not likely that patients could get an infection or have a large amount of bleeding. In very rare cases, people might have an allergic reaction to the numbing medicine. The allergic reaction could include rash/hive, flushing of the face, itching, wheezing and tightness in the throat.

Blood collection
Taking blood samples can cause pain, bleeding, bruising, infection or thrombosis (a blood clot) around the site where the needle was inserted. These problems usually disappear naturally. You could faint while or after taking the blood. There is a small risk of nerve damage with permanent pain. Taking blood samples regularly can cause anaemia for which you could require a blood transfusion. The staff who take the blood will do all they can to minimize discomforts.

Contacts

Public
Glycostem Therapeutics

Kloosterstraat 9
Oss 5349 AB
NL
Scientific
Glycostem Therapeutics

Kloosterstraat 9
Oss 5349 AB
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

To be eligible to participate in this trial, subjects must meet all of the following eligibility criteria:
1. Male or female subjects >= 18 years old
2. Subjects with a diagnosis of AML and related precursor neoplasms according to the World Health Organization (WHO) 2016 classification (excluding acute promyelocytic leukaemia), including secondary AML after an antecedent haematological disease (e.g. myelodysplastic syndrome) and therapy-related AML
3. a. For cohorts A1, A2, A3, A5 (and cohort B if applicable): Subjects who have achieved morphologic CR, including CRi, and complete clinical remission, with MRD documented at screening, after one or two courses of remission induction chemotherapy and who have completed consolidation chemotherapy or who achieved morphologic CR with documented MRD with hypomethylating agents (HMAs) or other relevant appropriate therapies (e.g. HMAs in combination with venetoclax)
b. For cohort A4 (and cohort B if applicable): Subjects with newly diagnosed AML who have achieved morphologic CR, including CRi while undergoing azacitidine-venetoclax standard of care treatment, and who are MRD-positive on the 28th day (+/- 7 days) of at least treatment cycle 3 or later cycles (>=3)
4.Subjects who are currently (at the time of screening) not proceeding to allo-HSCT, i.e.:
a. Subjects who have a contraindication for allo-HSCT (e.g. age > 75 years old, diffusing capacity of the lung for carbon monoxide [DLCO] < 60%, left ventricular ejection fraction [LVEF] < 40%, liver cirrhosis, creatinine clearance < 30 mL/min, hematopoietic stem cell transplantation-specific comorbidity index [HCT-CI] >= 5); or
b. Subjects who have no contraindication for allo-HSCT but do not proceed:
i. By personal choice; or
ii. Because there is no compatible donor expected to be available in a timely manner; or

iii. Due to unfavorable patient-specific risk-benefit assessment discussed between the treating physician and the patient and his/her close relatives. Factors taken into consideration include the disease-related risk (risk of relapse, toxicity or other treatment options if any), the patient-related risk (age, comorbidities including the HCT-CI score) and the curative potential of allo-HSCT versus toxicity (treatment intensity, graft versus leukemia effect, non-relapse mortality risk) (Muller and Muller-Tidow 2015)
5. Life expectancy >= 6 months at screening
6. Adequate renal and hepatic functions within 14 days of trial screening, unless clearly disease-related, as indicated by the following laboratory values:
a. Serum creatinine <= 3 times the upper limit of normal (ULN) and estimated glomerular filtration rate (eGFR) >= 30 mL/min/1.73 m2
b. Serum total bilirubin < 2.0 mg/dL, unless due to Gilbert*s syndrome
c. Alanine transaminase (ALT) <= 2.5 x ULN
7. Karnofsky Status >= 50%
8.Seropositivity to Epstein-Barr virus (EBV)
9. Male subjects with partners who are women of childbearing potential must use an effective contraceptive method during the trial and for a minimum of 6 months after trial treatment, or have undergone successful vasectomy at least 6 months prior to entry into the trial (confirmed by semen analysis)
10. Female subjects of childbearing potential must have a negative serum pregnancy test at screening and agree to use an effective contraceptive method during the trial and for a minimum of 6 months after trial treatment
11. Able to understand and willing to provide written informed consent to participate in the trial
12. Affiliation to a national health insurance scheme (according to applicable local requirements)

Exclusion criteria

Subjects who meet any of the following criteria at screening will be excluded from trial entry:

1. Subjects having received prior allo- HSCT
2. Subjects with acute promyelocytic leukaemia
3. Diagnosis of any previous or concomitant malignancy is an exclusion criterion, except when the subject completed treatment (chemotherapy and/or surgery and/or radiotherapy) with curative intent for this malignancy at least 6 months prior to enrolment
4. Blast crisis of chronic myeloid leukaemia
5. Concurrent severe and/or uncontrolled medical condition (e.g. uncontrolled diabetes, uncontrolled infection, hypertension active or controlled infection), including abnormal laboratory values that could compromise compliance with the trial protocol or cause unacceptable safety risks.
6. Known allergy to any of the components of oNKord® (e.g., dimethyl sulfoxide

[DMSO]) or to any of the drugs to be administered in the preparative regimen to oNKord® infusion
7. For cohorts A1, A2, A3, A5 (and cohort B if applicable): contraindication to any of the drugs to be administered in the lymphodepleting conditioning regimen. This includes Cy, Flu, and medications associated with prophylaxis of AEs
8. Cardiac dysfunction as defined by:
a. Myocardial infarction within the last 3 months of trial entry, or
b. Reduced left ventricular function with an ejection fraction < 40% as measured by multi-gated acquisition (MUGA) scan or echocardiogram (echo) within 28 days before screening, or
c. Unstable angina, or
d. New York Heart Association (NYHA) Class IV congestive heart failure, or
e. Unstable cardiac arrhythmiase trial
9. Pulmonary dysfunction as defined by oxygen saturation < 90% on room air. Pulmonary function test (PFT) is required only in the case of symptomatic or prior known impairments within 28 days before screening - with pulmonary function < 50% corrected (DLCO) and forced expiratory volume in 1 second (FEV1)
10. Major surgery within 4 weeks prior to screening or a major wound that has not fully healed
11. Vaccination with live, attenuated vaccines within 4 weeks prior to screening
12. Subjects must be able to be off prednisone or other immunosuppressive medications for concomitant disease for at least 3 days prior to the:
a. Start of the Cy/Flu regimen in cohorts A1, A2, A3, A5 (and cohort B if applicable)
b. First oNKord® infusion in cohort A4 (and cohort B if applicable)
13. History of stroke or intracranial haemorrhage within 6 months prior to screening
14. Active infections (viral, bacterial or fungal) that requires specific therapy. Acute anti-infectious therapy must have been completed within 14 days prior to trial treatment
15. History of human immunodeficiency virus (HIV) or active infection with hepatitis B virus (HBV) or hepatitis C virus (HCV)
16. a. For cohorts A1, A2, A3, A5 (and cohort B if applicable): Subjects who are undergoing or will be undergoing chemotherapy (including HMAs), radiation therapy, targeted therapy or immunotherapy that cannot be finished or stopped at least 1 week prior to initiating the Cy/Flu conditioning regimen
b. For cohort A4 (and cohort B if applicable): Subjects who are undergoing or will be undergoing chemotherapy (excluding HMAs), radiation therapy, targeted therapy or immunotherapy that cannot be finished or stopped at least 1 week prior to the first oNKord® infusion
17. Positive pregnancy test or breastfeeding for women of childbearing potential
18. Use of other investigational drugs/therapies within 3 weeks prior to trial treatment (within 6 weeks in the case of drugs/therapies with long half-life) or participation in a concomitant interventional clinical trial
19. Any serious concomitant medical condition, medication or therapy which could, in the opinion of the Investigator, compromise participation in the trial

20. Subjects under legal protection measure (guardianship, trusteeship or safeguard of justice) and/or inability or unwillingness to comply with the requirements and procedures of this trial

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	30-11-2020
Enrollment:	8
Type:	Actual

Medical products/devices used

Product type:	Medicine
Generic name:	Somatic cels allogenic

Ethics review

Approved WMO Date:	20-03-2020
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	07-08-2020
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den

	Haag)
Approved WMO Date:	05-10-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	27-10-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	21-01-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	05-02-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	22-03-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	29-04-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	27-05-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	22-09-2021

Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	08-11-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	17-03-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	31-03-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	27-05-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	07-07-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	15-12-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	22-02-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2019-003686-17-NL
ClinicalTrials.gov	NCT04632316
CCMO	NL73236.000.20