A phase II non-inferiority study comparing point-of-care produced CAR T-cell to commercial CAR T-cells in patients with relapsed/refractory Non-Hodgkin Lymphoma

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This study has been transitioned to CTIS with ID 2024-511979-15-00 check the CTIS register for the current data. Primary objective: • To compare progression free survival (PFS, of patients randomized to investigational point-of-care (PoC) ARI-0001...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Lymphomas non-Hodgkin's B-cell
Study type	Interventional

Summary

ID

NL-OMON54144

Source
ToetsingOnline

Brief title
HOVON 161 CAR T

Condition

- Lymphomas non-Hodgkin's B-cell

Synonym
Non-Hodgkin Lymphoma

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen
Source(s) of monetary or material Support: Zorginstituut Nederland

Intervention

Keyword: Efficacy, Non Hodgkin Lymphoma, Point-of -care CAR T-cell, Safety

Outcome measures

Primary outcome

• PFS from date of IMP infusion (if applicable)

Secondary outcome

• PFS from date of randomization

• Safety and toxicity assessment of ARI-0001 CAR T-cells and Axi cel per AE reporting classified according to CTCAE Version 5 and CRS and ICANS classified according to the ASTCT criteria

• Overall response rate (ORR, sum of CR and PR), as well as CR, PR, SD and PD/relapse at 4 weeks, 12 weeks, 6, 12 and 24 months after infusion of CAR T-cells

• Best overall response (BOR) rate at 4 weeks, 12 weeks, 6, 12 and 24 months after infusion of CAR T-cells

• Duration of response (DOR)

• OS from date of randomization, and from date of CAR T-cell infusion (if applicable)

• Patient Reported Outcome/Quality of Life (PRO/QOL)

• CAR T-cell expansion, persistence, and T-cell characteristics in both treatment arms (ARI-0001 vs Axi-cel)

• PoC CAR T-cell production characteristics (e.g. number of viable T-cells, transduction efficiency, T-cell subsets (activated T-cells, memory T-cells)), including the functional characteristics (e.g. potency tests) between the different production sites

• The association of the functional characteristics (e.g. potency tests) of the CAR T-cell products (ARI-0001 CAR T-cells) with CAR T-cell expansion, persistence, adverse events, response rates and progression free survival.

• Proportion of successful batches between the different production sites

• Number of days between leukapheresis and infusion of CAR T-cells (vein-to-vein time)

• Fludarabine pharmacokinetics.

Study description

Background summary

Chimeric antigen receptor (CAR)T-cell therapy is an innovative form of adoptive cell therapy that has proven its efficacy in the treatment of various hematological malignancies, including B-cell non-Hodgkin lymphoma (NHL), and B-cell acute lymphoblastic leukemia (ALL). CD19 has been the most studied target antigen for CAR T-cell immunotherapy. Anti-CD19 CAR T-cell therapy has shown durable responses in patients with different B-NHLs, including Diffuse Large B-cell Lymphoma (DLBCL). Unfortunately, up to 50-60% of the patients do not respond to CD19-directed CAR T-cell therapy. There are several shortcomings of current CD19-directed CAR T-cell therapy, that likely underpin these, namely:
i) Due to centralized production at commercial sites, the production is time consuming (about 4 weeks), meaning that patients with rapidly progressive lymphoma may not reach the moment of the infusion of the anti-CD19 CAR T-cells.
ii) Furthermore, for the current production processes, the autologous T-cells need to be cryopreserved for shipment from the hospital to the production sites and vice versa. This (double) cryopreservation process can decrease the quality of the CAR T-cells.

This trial aims to address these shortcomings and will study the feasibility and clinical efficacy of local manufacturing CD19-directed CAR T-cells, (ARI-0001 CAR T-cells), in a completely closed system using the CliniMACS Prodigy device. This randomized phase II study will compare the clinical efficacy of locally produced CAR T-cells with commercially available CAR T-cells (for example axicabtagene ciloleucel) in patients with relapsed or refractory (R/R) diffuse large B-cell lymphoma (DLBCL).
This in-house (point-of-care) production process of ARI-0001 will take approximately 7 or 12 days and thus will generate CAR T-cells *faster* which will be infused in the patient preferably without cryopreservation (*fresh*). Furthermore, the point-of-care production process can be replicated in academic institutions with the appropriate cellular manufacturing facilities. If successful, this study will show feasibility of local production of CAR T-cell therapy, improving their rapid accessibility and quality.

Study objective

This study has been transitioned to CTIS with ID 2024-511979-15-00 check the CTIS register for the current data.

Primary objective:
• To compare progression free survival (PFS, of patients randomized to investigational point-of-care (PoC) ARI-0001 CAR T-cells versus PFS of patients randomized to commercial standard-of-care (SoC) (axicabtagene ciloleucel (Axi cel, Yescarta)) CAR T-cells in patients with R/R DLBCL.

Secondary objectives:
• To evaluate response rates (ORR and CR)
• To evaluate safety and toxicity of ARI-0001 and Axi-cel
• To assess overall survival (OS)
• To evaluate quality of life (QoL)
• To assess costs associated with both treatment regimens (ARI-0001 vs Axi-cel)
• To evaluate CAR T-cell expansion, persistence, and T-cell characteristics in both treatment arms (ARI-0001 vs Axi-cel)
• To evaluate PoC CAR T-cell production characteristics (e.g. number of viable T-cells, transduction efficiency, T-cell subsets (activated T-cells, memory T-cells)), including the functional characteristics (e.g. potency tests) between the different production sites
• To evaluate the association of the functional characteristics (e.g. potency tests) of the CAR T-cell products (ARI-0001 CAR T-cells) with CAR T-cell expansion, persistence, adverse events, response rates and progression free survival
• To assess the proportion of successful batches between the different production sites
• To evaluate the number of days between leukapheresis and infusion of CAR T-cells (vein-to-vein time)

• To evaluate fludarabine pharmacokinetics.

Study design

Phase II, multi-center, randomized, open label, non-inferiority study.

Intervention

Patients are randomized between treatment with
- PoC CAR T-cell (ARI-0001)
- SoC CAR T-cell (Axi-cel)

Study burden and risks

All patients participating in this clinical trial are suffering from progressive malignant B-cell lymphoma with no available approved curative therapy. At this stage, patients are treated with palliative therapy or with best supportive care. The survival rate and life expectancy are very poor. Published clinical data lead to the assumption that a treatment with the IMP could lead to tumor regression, response and long-term remission.
Anticipated risks
The risk of trial related procedures (blood sampling, leukapheresis, tumor biopsies) are known and standard procedures will be applied to minimize risks. The risks of the lympho-depleting chemotherapy with fludarabine (FLU) and cyclophosphamide (CY) are known and include myelosuppression with neutropenia and infections, gastrointestinal side effects with nausea and diarrhea, alopecia and renal toxicities and cystitis.
Infusion of CAR T-cells can be associated with toxicities including high-grade fever (usually starting about 24 h after CAR T cells infusion) and flu-like symptoms such as myalgia, but can also lead to life-threatening complications with hypotension and vascular leak, cytopenias, coagulopathy and renal and respiratory failure, hypoxia, and neurologic disturbances. This syndrome of toxicities has been termed cytokine release syndrome (CRS), likely related to a progressive systemic inflammatory process initiated and maintained by the infused CAR T-cells activated in vivo upon encounter with the targeted antigen. In addition, neurotoxicity (immune effector cell-associated encephalopathy (ICANS) eg encephalopathy, somnolence, aphasia) has been observed with CAR T-cell therapy. Both CRS and ICANS are manageable, and the vast majority of patients will recover from CRS and ICANS.

There will be no extra burden for the patients. because this trial will compare treatment with commercial CAR T-cells with treatment with PoC CAR T-cells, and in both arms standard of care (including lympho-depleting chemotherapy, toxicity management, blood collections, cerebral spine fluid (CSF) collections, and response evaluations) will be applied.

Contacts

Public
Universitair Medisch Centrum Groningen

Hanzeplein 1
Groningen 9713 GZ
NL
Scientific
Universitair Medisch Centrum Groningen

Hanzeplein 1
Groningen 9713 GZ
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Histologically confirmed DLBCL and associated subtypes, defined by WHO 2016 classification: DLBCL not otherwise specified (NOS), High-grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements with DLBCL histology (DHL/THL) and FL3B, T-cell/histocyte rich B-cell lymphoma, Primary mediastinal B-cell lymphoma, EBV+ DLBCL, transformed lymphoma (transformed follicular) and R/R after at least 2 lines of systemic therapy
• Age >= 18 years
• ECOG/WHO performance status >2
• Secondary central nervous system (CNS) involvement is allowed however, then he/she must have
- No signs or symptoms of CNS involvement that would hamper adequate ICANS assessment

• Estimated life expectancy of >3 months other than primary disease
• Patients of child-bearing or child-fathering potential must be willing to practice birth control from the time of enrollment on this study and for four months after receiving the preparative regimen
• Signed and dated informed consent before conduct of any trial-specific procedure
• Patient is capable of giving informed consent

Exclusion criteria

• Absolute neutrophil count (ANC) <1.0x109/L
• Platelet count <50x109/L
• Absolute lymphocyte count <0.1x109/L
• Primary CNS lymphoma
• Known history of infection with hepatitis C or B virus unless treated and confirmed to be PCR negative
• Active HIV infection with detectable viral load or CD4 T-cell count below 0.20x109/L
• Known history or presence of seizure activities or on active anti- seizure medications within the previous 12 months
• Known history of CVA within prior 12 months
• Unstable neurological deficits
• Known history or presence of autoimmune CNS disease, such as multiple sclerosis, optic neuritis or other immunologic or inflammatory disease
• Active systemic autoimmune disease for which immunnosupressive therapy is required
• Presence of CNS disease that, in the judgment of the investigator, may impair the ability to evaluate neurotoxicity, baseline dementia that would interfere with therapy or monitoring, determined using mini-mental status exam at baseline
• Active systemic fungal, viral or bacterial infection
• Clinical heart failure with NYHA class >=2 or LVEF <40%
• Resting oxygen saturation <92% on room air
• Liver dysfunction as indicated by total bilirubin, AST and/or ALT >5 x institutional ULN, unless directly attributable to the lymphoma or Gilbert disease
• GFR <40 mL/min calculated according to the modified formula of Cockcroft and Gault or by direct urine collection
• Pregnant or breast-feeding woman
• Active other malignancy requiring treatment
• Medical condition requiring prolonged use of systemic immunosuppressives with exception of prednisolon<10 mg/day
• History of severe immediate hypersensitivity reaction against any drug or its Ingredients/ impurities that is scheduled to be given during trial participation e.g. as part of the mandatory lymphodepletion protocol, premedication for infusion, or rescue medication/salvage therapies for

treatment related toxicities
• Any psychological, familial, sociological and geographical condition potentially hampering compliance with the study protocol and follow-up schedule

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	18-10-2022
Enrollment:	300
Type:	Actual

Ethics review

Approved WMO Date:	07-09-2021
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	25-08-2022
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Approved WMO Date:	08-12-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	17-01-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	02-05-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	04-09-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	02-05-2024
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	09-07-2024
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
EU-CTR	CTIS2024-511979-15-00
EudraCT	EUCTR2021-000937-15-NL
CCMO	NL76854.000.21