Phase 1/2a, first-in-human, open-label, dose escalation trial with expansion cohorts to evaluate safety and preliminary efficacy of CLDN6 CAR-T with or without CLDN6 RNA-LPX in patients with CLDN6-positive relapsed or refractory advanced solid tumors

Published: 11-03-2020
Last updated: 19-09-2024

This study has been transitioned to CTIS with ID 2024-514962-38-00 check the CTIS register for the current data. -To assess the safety and tolerability of CLDN6 CAR-T +/- CLDN6 RNALPX and to assess the comparability of CLDN6 CAR-T from the manualand…

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Miscellaneous and site unspecified neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON54362

Source
ToetsingOnline

Brief title
BNT211-01 (4781/0008)

Condition

- Miscellaneous and site unspecified neoplasms malignant and unspecified

Synonym

1 - Phase 1/2a, first-in-human, open-label, dose escalation trial with expansion coh ... 23-06-2025

cancer, tumors

Research involving
Human

Sponsors and support

Primary sponsor: BioNTech Cell & Gene Therapies GmbH
Source(s) of monetary or material Support: By the sponsor as completed in section B7

Intervention

Keyword: CAR-T, CLDN6, GMO, Phase 1/2

Outcome measures

Primary outcome

Primary

- Occurrence of TEAEs within a patient including >= Grade 3, serious, fatal

TEAEs by relationship

- Occurrence of dose reduction and discontinuation of IMP within a patient due

to TEAEs

- Occurrence of DLTs within a patient during the DLT evaluation period

Long term follow-up - Primary

- Occurrence of AEs during the LTFU period suspected to be related to CLDN6

CAR-T/CLDN6 CAR-T(A) +/- CLDN6 (mod)RNA-LPX, such as:

o New malignancy (hematologic or solid)

o New neurologic disorder, or exacerbation of a pre-existing disorder

o New rheumatologic or autoimmune disorder, or exacerbation of a prior

rheumatologic or other autoimmune disorder

o New hematologic disorder

o Other new clinical condition considered by the Investigator to be related to

the prior genetically engineered T cell therapy

Long term follow-up - Secondary

- Progression-free survival

- Overall survival. Survival status will be collected until 15 years from last

genetically engineered T cell infusion or until death, whichever occurs first

Secondary outcome

-To describe the profile of soluble immune factors in CLDN6 CAR-T +/- CLDN6

RNA-LPX

-To evaluate anti-tumor activity of CLDN6 CAR-T +/- CLDN6 RNA-LPX according to

response evaluation criteria in solid tumors version 1.1

(RECIST 1.1)

Study description

Background summary

Outcome remains poor for patients with relapsed or refractory advanced solid tumors. Treatment options include further targeted therapies, immunotherapies, radiotherapy or palliative chemotherapy, which might be less tolerated after previous repeated exposure to cytotoxic compounds, or best supportive care. Therapy in this population is not curative with an expected OS of a few months. The oncofetal antigen CLDN6 has emerged as an attractive therapeutic target because of its absence from toxicity-relevant adult healthy tissues, and high expression in cancers with high unmet medical need. Thus, CLDN6 is a suitable target antigen for the development of a CAR-T against these cancers. The combination of CLDN6 CAR-T/CLDN6 CAR-T(A) with CLDN6 encoding RNA-LPX mediates controlled in vivo expansion, improved CAR-T persistence and anti-tumor efficacy in preclinical models, and constitutes an innovative concept for the specific and effective treatment of CLDN6-expressing tumors.

The main purpose of the trial is to determine a safe and potentially efficacious dose of CLDN6 CAR-T/CLDN6 CAR-T(A) +/- CLDN6 (mod)RNA-LPX. In a phase 1 dose escalation with CLDN6 CAR-T/CLDN6 CAR-T(A) (Part 1) and CLDN6 CAR-T/CLDN6 CAR-T(A) with CLDN6 (mod)RNA-LPX (Part 2) according to the classical 3+3 design, the RP2D of the CLDN6 CAR-T/CLDN6 CAR-T(A) +/- CLDN6 (mod)RNA-LPX will be determined. The RP2D will be further explored in phase IIa (Part 3) for efficacy signal seeking. So far, no drug targeting CLDN6 in cancer patients has been approved.

Study objective

This study has been transitioned to CTIS with ID 2024-514962-38-00 check the CTIS register for the current data.

-To assess the safety and tolerability of CLDN6 CAR-T +/- CLDN6 RNALPX and to assess the comparability of CLDN6 CAR-T from the manual and automated processes
-To identify the maximum tolerated dose (MTD)/RP2D for each IMP (i.e. CLDN6 CAR-T +/- CLDN6 RNA-LPX) based on the occurrence of doselimiting toxicities (DLT) using the following definitions:
-MTD is defined as the highest tolerated dose of CLDN6 CAR-T +/- CLDN6 RNA-LPX where less than 33% of the patients experience a DLT
-Recommended phase 2 dose (RP2D) of CLDN6 CAR-T +/- CLDN6 RNALPX based on integrated evaluation of safety and other data for all dose levels tested

Study design

This is a FIH, open-label, multicenter phase 1/2a dose escalation trial of CLDN6 CAR-T/CLDN6 CAR-T(A) with or without the CLDN6 (mod)RNA-LPX vaccine with expansion cohorts in patients with CLDN6 positive relapsed or refractory advanced solid tumors.

The trial is outlined in Figure 1 and consists of three parts:
For CLDN6 CAR-T manufactured using a manual process (IMP-1), the following applies:
1. Part 1 will be a CLDN6 CAR-T dose escalation in lymphodepleted patients until the maximum tolerated dose and/or recommended phase 2 dose of CLDN6 CAR-T as monotherapy are defined (Figure 2).
2. Part 2 will be a vaccine-modulated dose escalation until the maximum tolerated dose and/or recommended phase 2 dose of CLDN6 CAR-T + CLDN6 (mod)RNA-LPX are defined. Patients will be pretreated with an LD regimen (standard, Figure 3), or they may be pretreated with a reduced-dose LD regimen (optional, Figure 4) or without LD (optional Figure 5), as decided by the SRC per SRC charter. If satisfactory expansion and persistence is seen at a certain dose level, cohorts testing vaccine-modulated CLDN6 CAR-T without may also be

activated. All decisions concerning opening the LD-free cohorts will be made by the safety review committee.
*Patients treated in Part 1 may be additionally treated with CDLN6 RNA-LPX according to the SoTP (Section 1.3.2) under the following conditions:
• The dose level has been deemed safe by the SRC.
• The patient consents to the additional treatment in a separate consent form.
• The SRC approves the use of CLDN6 RNA-LPX based on the available safety and CLDN6 CAR T expansion data of the respective patient.
• Safety criteria include:
o No significant, unacceptable or irreversible toxicities related to trial treatment.
o The patients must meet the inclusion criteria for hematologic, renal, hepatic and coagulation functions.

This is a summary, for more detailed information please refer to the protocol section 4.

Intervention

All patients will receive one infusion of CLDN6 CAR-T/CLDN6 CAR-T(A) with or without additional treatment with the CLDN6 (mod)RNA-LPX vaccine. Patients in Part 1 may be re-dosed at month 2.

Study burden and risks

Benefit-Risk Assessment
Since CLDN6 is exclusively expressed by tumor cells and no protein expression has been detected on any analyzed adult normal tissue, no off-tumor on-target toxicities are expected. Importantly, CLDN6 is known to be expressed on embryonic stem cells, thus pregnant women must not participate in the trial and should not become pregnant thereafter. qRT-PCR analysis suggest that CLDN6 mRNA expression was either negative in the vast majority of normal tissues or slightly above the defined cut-off in a single sample each of a few tissue types (placenta, testis and umbilical cord, cerebellum, lung). Notably, CLDN6 protein was not detected in any of these samples. Even though on-target, off-tumor toxicities are not expected, they cannot be ruled out, hence patients will be observed clinically for 14 d after CLDN6 CAR-T/CLDN6 CAR-T(A) and (mod)RNA-LPX administration.

To date, RNA-LPX based cancer vaccines have demonstrated a favorable safety and tolerability profile in different indications, in different treatment settings (metastatic, post neo-adjuvant, adjuvant), and with different types of cancer vaccine antigens (see IB for details). In the clinical trials with RNA-LPX, no DLTs were reported during dose escalation, the TEAEs considered related to trial drug were transient, mostly Grade 1 and 2, and associated with the specific format of encoding and delivering the vaccine antigens, namely

single-stranded RNA formulated as a 1,2 di O octadecenyl-3-trimethylammonium propane chloride/dioleoly-sn-glycero-phophoethanolamine (DOTMA/DOPE) lipoplex. None of the potential risks, except for class-intrinsic risks, described above is considered likely and relevant for the patients. Based on the experience from the ongoing clinical trials with RNA-LPX, the class-intrinsic potential risks are expected to manifest as mild-to-moderate, transient and manageable flu-like AEs and transient lymphopenia (by sequestration).

The occurrence of AEs related to LD, CLDN6 CAR-T/CLDN6 CAR-T(A) and CLDN6 (mod)RNA-LPX may overlap making it difficult to assess the causality at the time of occurrence.

As of 10th of March 2022 15 patients have been treated with the combination of CLDN6 CAR-T and CLDN6 RNA-LPX in the BNT211-01 trial. Apart from the anticipated flu-like symptoms occurring within hours of CLDN6 RNA-LPX injection, no aggravation of adverse events (AEs) attributed to CLDN6 CAR-T could be confirmed although it is premature to draw conclusions based on the limited number of CLDN6 RNA-LPX injections administered.

Risks such as myelosuppression with associated cytopenias and febrile neutropenias are known risks of the LD chemotherapy. Lymphodepletion as such cannot be avoided at this stage of clinical development as it was shown to be beneficial for T-cell engraftment and persistence. To account for the fact that patients may experience febrile neutropenias at the same time as the signs and symptoms of cytokine release syndrome (CRS) typically occurred in patients treated with CD19 CAR-T, all patients will be monitored as in-patients for 14 days after the administration of CLDN6 CAR-T/CLDN6 CAR-T(A). IN BNT211-01, pronounced cytopenias were observed in patients with testicular cancers who were pretreated with a recent HDCT/ASCT..

After careful assessment of all emerging safety, expansion and persistence data the sponsor opened a LD-free cohort in Part 2 of the trial, to further lower the risk for the patients. However, due to unsatisfactory expansion of CLDN6 CAR-T cells, this cohort was closed and all patients with a recent HDCT/ASCT are now treated with a reduced dose of lymphodepletion. To further mitigate the risk of cytopenias, patients receiving LD after a HDCT/ASCT should have an autologous stem cell back-up.

Based on inclusion criteria and published literature, eligible patients will not have available standard treatment options, leaving a very poor prognosis for this population. It is possible that the CLDN6 CAR-T/CLDN6 CAR-T(A) therapy alone or with CLDN6 RNA-LPX will exert an anti-tumor effect, as demonstrated by first clinical data as well as preclinical data in mice, for patients with advanced CLDN6 expressing solid tumors.

Taken together, the risk-benefit ratio in the heavily pretreated patient population suffering from advanced tumor diseases is regarded as positive.

Nevertheless, all ongoing and planned clinical trials contain regular safety monitoring of laboratory and clinical parameters to ensure patient safety and well-being.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

-Must have a CLDN6-positive tumor regardless of tumor histology defined as >= 50% of tumor cells expressing >= 2+ CLDN6 protein using a semi-quantitative immunohistochemistry (IHC) assay for specific detection of CLDN6 protein expression in formalin-fixed, paraffinembedded neoplastic tissues.
-Must have measurable disease per RECIST 1.1 (except for germ cell tumor or ovarian cancer patients).
-Germ cell cancer patients without initial measurable disease per RECIST 1.1

and evaluable by cancer antigen (CA)-125, alphafetoprotein (AFP) or human chorionic gonadotropin (hCG; as applicable) are eligible for the trial.
-Ovarian cancer patients without initial measurable disease per RECIST 1.1. and evaluable by CA-125 are eligible for the trial.
-Must have a histologically confirmed solid tumor that is metastatic or unresectable and for which there is no available standard therapy likely to confer clinical benefit, or patient who is not a candidate for such available therapy.

Exclusion criteria

-Have received prior CAR-T therapy, except CLDN6 CAR-T therapy.
-Have received vaccination with live virus vaccines within 6 weeks prior to the start of lymphodepletion (LD).
-Receives concurrent systemic (oral or intravenous [i.v.]) steroid therapy > 10 mg prednisolone daily, or its equivalent, for an underlying condition.
-Current evidence of new or growing brain or spinal metastases during screening. Patients with known brain or spinal metastases may be eligible if they:
-Have had radiotherapy or another appropriate therapy for the brain or spinal metastases,
-Have no neurological symptoms,
-Have stable brain or spinal disease on the computer tomography or magnetic resonance imaging scan within 4 weeks before signing of the informed consent,
-Must not be undergoing acute corticosteroid therapy or steroid taper. Chronic steroid therapy is acceptable provided that the dose is stable for the last 14 d prior to screening (<= 10 mg prednisolone daily or equivalent),
-Do not require steroid therapy within 7 d before the first dose of CLDN6 CAR-T,
-Do not have anticipated imminent fracture or cord compression due to spinal bone metastases.
-Has history of another primary cancer within the 2 years prior to enrollment except for the following: non-melanoma skin cancer, cervical carcinoma in situ, superficial bladder cancer, prostate cancer with currently undetectable prostate specific antigen, or other non-metastatic carcinoma that has been in complete remission without treatment for more than 2 years.

Study design

Design

Study phase: 2

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	16-09-2020
Enrollment:	30
Type:	Actual

Medical products/devices used

Registration:	No
Product type:	Medicine
Brand name:	n/a
Generic name:	CLDN6 CAR-T
Product type:	Medicine
Brand name:	n/a
Generic name:	CLDN6 CAR-T(A)

Ethics review

Approved WMO Date:	11-03-2020
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	15-07-2020
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	18-08-2020

Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	16-11-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	10-03-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	28-04-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	12-05-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	21-05-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	13-07-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	27-07-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Approved WMO Date:	04-10-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	02-12-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	17-12-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	02-02-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	23-03-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	22-04-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	13-05-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	19-08-2022
Application type:	Amendment

Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	25-10-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	18-11-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	22-12-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	14-02-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	24-05-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	20-11-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	21-12-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO	

Date:	26-02-2024
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	06-03-2024
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	22-04-2024
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	25-04-2024
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	CTIS2024-514962-38-00
EudraCT	EUCTR2019-004323-20-NL
CCMO	NL72581.000.20