A Phase 1, Open-Label, Multicenter, Dose Escalation and Cohort Expansion Study of the Safety and Efficacy of Allogeneic CRISPR-Cas9-Engineered T Cells (CTX130) in Adult Subjects with Advanced, Relapsed or Refractory Renal Cell Carcinoma (RCC) with Clear Cell Differentiation

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Primary Objective, Part A: To assess the safety of a single escalating dose and multiple dose regimen of CTX130 in subjects with unresectable or metastatic ccRCCPrimary Objective, Part B (Cohort Expansion): To assess the efficacy of CTX130 in...

Ethical review	Approved WMO
Status	Completed
Health condition type	Renal and urinary tract neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON54482

Source
ToetsingOnline

Brief title
CRSP-ONC-003 (3930/0017)

Condition

- Renal and urinary tract neoplasms malignant and unspecified

Synonym
clear cell renal cell carcinoma; kidney cancer

Research involving
Human

Sponsors and support

Primary sponsor: CRISPR Therapeutics AG
Source(s) of monetary or material Support: the study sponsor as listed in B7

Intervention

Keyword: CRISPR-Cas9 CAR-T cells, CTX130, Escalating doses, Relapsed or refractory renal cell carcinoma (RCC)

Outcome measures

Primary outcome

Parts A1, A3 (Single Dose Escalation): Incidence of adverse events (AEs),

defined asdose-limiting toxicities (DLTs).

Parts A2, A4 (Multiple Dose Regimen): Incidence of AEs after multiple doses of

CTX130.

Part B (cohort expansion): ORR, defined as the proportion of subjects who have

achieved a best overall response of complete response (CR) or partial response

(PR) according to RECIST v1.1, as assessed by an Independent Review Committee

(IRC).

Secondary outcome

• To further characterize the efficacy of CTX130 over time

• To further assess the safety of CTX130, and to describe and assess adverse

events (AEs) of interest, including cytokine release syndrome (CRS), tumor

lysis syndrome and Graft versus Host Disease (GvHD)

• To characterize pharmacokinetics (PK) (expansion and persistence) of CTX130

in blood

Study description

Background summary

Investigational Product Description:
CTX130 is a CD70-directed T cell immunotherapy comprised of allogeneic T cells that are genetically modified ex vivo using CRISPR-Cas9 (clustered regularly interspaced short palindromic repeats/CRISPR associated protein 9) gene editing components (single-guide ribonucleic acids [sgRNAs] and Cas9 nuclease). The modifications include targeted disruption of the T cell receptor alpha constant (TRAC), beta 2-microglobulin (B2M), and CD70 loci and the insertion of an anti-CD70 chimeric antigen receptor (CAR) transgene into the TRAC locus via an adeno associated virus (AAV) expression cassette. The CAR is composed of an anti CD70 single-chain variable fragment derived from a previously characterized anti CD70 hybridoma IF6, the CD8 transmembrane domain, a 4-1BB costimulatory domain, and a CD3* signaling domain.

Study rationale:
The study will be divided into 2 parts: Part A (dose escalation), which includes Parts A1 through A4, followed by Part B (cohort expansion). Parts A1 and A3 will evaluate the safety of a single escalating dose of CTX130 (with the option of additional doses of CTX130 following relapse, stable disease [SD], or disease progression with clinical benefit). Part A2 and A4 will evaluate the safety of a multiple dose schedule for CTX130. Part B will assess the safety and efficacy of the recommended dosing regimen for CTX130 in cohort expansion.
CAR T cell therapies are adoptive T cell therapeutics (ACTs) used to treat human malignancies. Currently approved ACTs are autologous and require patient-specific cell collection and manufacturing, which has led to reintroduction of residual contaminating tumor cells. Also, low response rates in patients with chronic lymphocytic leukemia (CLL) and lack of responses in patients with B-cell acute lymphoblastic leukemia (ALL) treated with autologous CAR T cell therapy have been partially attributed to the exhausted T cell phenotype. Finally, collection, shipment, manufacturing, and shipment back to the patient*s treating physician is time-consuming and, as a result, some patients have experienced disease progression or death while awaiting treatment. An allogeneic off-the-shelf CAR T cell product could provide benefits such as immediate availability and chemotherapy-naïve T cells from healthy donors, thus a more consistent product relative to autologous CAR T cell therapies.

CRISPR-Cas9 engineering employs a recombinant AAV vector to insert an anti-CD70 CAR expression cassette into the TRAC locus, disrupting expression of the T

cell receptor (TCR), which is intended to minimize the probability of graft vs host disease (GvHD). Expression of B2M, a component of major histocompatibility (MHC) class I molecules, is also targeted for disruption, which is intended to minimize the host*s MHC mediated immune rejection of the allogeneic T cell product, thus improving persistence of CTX130. This first-in-human trial in subjects with unresectable or metastatic clear cell renal cell carcinoma (ccRCC) will evaluate the safety and efficacy of this CRISPR Cas9 modified allogeneic CAR T cell approach.

CTX130, a CD70-directed genetically modified allogeneic T cell immunotherapy, is manufactured from the cells of healthy donors; therefore, the resultant manufactured cells are intended to provide each subject with a consistent final product of reliable quality. Furthermore, the manufacturing of CTX130, through precise delivery and insertion of the CAR at the TRAC site using AAV and homology-directed repair, does not present the risks associated with random insertion of lentiviral and retroviral vectors.

Finally, CD70 is the membrane-bound ligand of the CD27 receptor, which belongs to the tumor necrosis factor receptor superfamily. It is commonly expressed at elevated levels in multiple carcinomas and lymphomas, and it is a diagnostic biomarker for ccRCC. The tightly controlled normal tissue expression in humans is mostly limited to transient surface expression in blood and lymphoid tissues, specifically activated peripheral T and B lymphocytes, scattered T cells in tonsils, skin and intestine, germinal B cell centers, thymic epithelial cells, and natural killer cells. Based on studies in knockout animal models, CD70/CD27 does not seem to be essential for the development and function of the immune system in mice. Therefore, the above characteristics of CD70 render CTX130 a promising therapy for CD70-positive malignancies.

Study objective

Primary Objective, Part A: To assess the safety of a single escalating dose and multiple dose regimen of CTX130 in subjects with unresectable or metastatic ccRCC

Primary Objective, Part B (Cohort Expansion): To assess the efficacy of CTX130 in subjects with unresectable or metastatic ccRCC, as measured by objective response rate (ORR) according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1)

Secondary Objectives (Parts A and B)
1. To further characterize the efficacy of CTX130 over time
2. To further assess the safety of CTX130, and to describe and assess adverse events of special interest, including cytokine release syndrome (CRS), tumor lysis syndrome and GvHD
3. To characterize pharmacokinetics (expansion and persistence) of CTX130 in

blood

Study design

This is an open-label, multicenter, Phase 1 study evaluating the safety and efficacy of CTX130 in subjects with unresectable or metastatic RCC with clear cell differentiation. The study will be divided into 2 parts: Part A (dose escalation), which includes Part A1 through A4, followed by Part B (cohort expansion).

Each part of the study will consist of 3 main stages:
Stage 1 - Screening to determine eligibility for treatment (up to 14 days)
Stage 2 - Treatment (Stage 2A and Stage 2B); see Table S1 in protocol synopsis for treatment in each part of the study
Stage 3 - Follow-up (5 years after last CTX130 infusion)

Subjects* clinical eligibility must be reconfirmed according to the protocol-specified criteria prior to the initiation of daratumumab administration (subjects in Parts A3 and A4 only), prior to lymphodepleting (LD) chemotherapy (all subjects), and prior to CTX130 infusion (all subjects).

During the post-CTX130 infusion period, subjects will be monitored for acute toxicities (Days 1-28), including CRS, immune effector cell-associated neurotoxicity syndrome (ICANS), GvHD, and other adverse events (AEs). Toxicity management guidelines are provided in the study protocol. During Part A, subjects will be hospitalized for the first 7 days following each CTX130 infusion, or longer if required by local regulation or site practice. In Part A and Part B, subjects must remain within proximity of the investigative site (i.e., 1-hour transit time) for 28 days after each CTX130 infusion.

After the acute toxicity observation period, subjects will be subsequently followed for up to 5 years after last CTX130 infusion with physical exams, regular laboratory and imaging assessments, and AE assessments. After completion of this study, subjects will be asked to participate in a separate long-term follow-up study for an additional 10 years to assess long-term safety and survival.

Dose escalation in Part A will be performed using a standard 3+3 design in which 3 to 6 subjects will be enrolled at each dose level depending on the occurrence of dose limiting toxicities (DLTs), as defined in the protocol. The DLT evaluation period will begin with the initial CTX130 infusion and last for 28 days.

Part A1: In DL1, subjects will be treated in a staggered manner such that a subject will only receive
CTX130 once the previous subject has completed the DLT evaluation period (i.e., staggered by 28

days). If the occurrence of a DLT in >=2 of 3 subjects at DL1 has resulted in dose de-escalation, dosing
of all subjects at DL -1 will also be staggered by 28 days. If no DLT occurs at DL1, dose escalation
will progress to DL2, and dosing between each subject will be staggered by 14 days. If no DLT occurs
at the first 2 dose levels (DL1 and DL2), dosing will be staggered by 7 days between each subject at
subsequent dose levels (DL3 and DL4).
Part A2: Enrollment into a Part A2 dose level may begin at a dose level that has been deemed safe by
the SRC in Part A1. Each subject will receive a total of up to 3 doses of CTX130: 1 dose administered
every 8 weeks (1 dose per cycle in Cycles 1-3).
Part A3: Dosing of CTX130 at any dose level in Part A3 will not begin unless the dose level has been
deemed safe by the SRC in Part A1. Dose escalation/de-escalation is allowed according to the 3+3
design (see Section 4.3). Sentinel dosing will be implemented for the starting dose level, i.e., the first
subject will complete the DLT evaluation period before the second and third subjects are dosed. The
second and third subjects may be dosed concurrently. In subsequent dose levels or expansion of the
same dose level, cohorts of up to 3 subjects may be enrolled and dosed concurrently.
Part A4: Enrollment into a Part A4 dose level may begin if that dose level has been deemed safe by
the SRC in Part A3. Each subject will receive a total of up to 3 doses of CTX130: 1 dose administered
every 8 weeks (1 dose per cycle in Cycles 1-3). Dosing of subjects may occur concurrently.

Subjects must receive CTX130 to be evaluated for DLT, as defined in the protocol. If a subject discontinues the study any time prior to the initial CTX130 infusion, the subject will be deemed nonevaluable for DLT and will be replaced. If a DLT evaluable subject (i.e., a subject that has been administered CTX130) has signs or symptoms of a potential DLT, the DLT evaluation period will be extended according to the protocol-defined window to allow for improvement or resolution before a DLT is declared.

The SRC will review available data when the DLT observation period ends for the last subject treated in each dose level. The SRC will be responsible for making dose escalation decisions based on review of all available safety data. Throughout dose escalation, for cases in which a dose had been cleared and dose escalation is permitted, the sponsor in consultation with the SRC may alternatively decide to enroll an additional 6 subjects at the current dose

level. Based on ongoing assessment of benefit and risk, the SRC may stop dose escalation before a maximum tolerated dose (MTD) is determined.

The sponsor will declare the recommended Part B dose (RPBD)with a preferred dosing schedule for cohort expansion at or below the MTD (if determined). At least 6 subjects will be administered CTX130 before an RPBD is declared.

Toxicities will be graded and documented according to National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0 (CTCAE v5.0), except for CRS (American Society for Transplantation and Cellular Therapy criteria), neurotoxicity ICANS criteria and CTCAE v5.0), and GvHD (Mount Sinai Acute GvHD International Consortium criteria).

Intervention

Subjects will receive an intravenous (IV) infusion of CTX130 following lymphodepleting (LD) chemotherapy.

Study burden and risks

The completed nonclinical studies adequately demonstrate the safety of CTX130 and support the first-in human (FIH) clinical studies in subjects with advanced, relapsed, or refractory renal cell carcinoma.

Please refer to the complete risk benefit analysis document.

Contacts

Public
CRISPR Therapeutics AG

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Scientific
CRISPR Therapeutics AG

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CH

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. >=18 years of age and body weight >=42 kg.
2. Able to understand and comply with protocol-required study procedures and voluntarily sign a written informed consent document.
3. Diagnosed with unresectable or metastatic RCC with clear cell differentiation:
• Have previous exposure to both a CPI and a VEGF inhibitor and documented progression after adequate exposure for favorable risk by International Metastatic RCC Database Consortium criteria or a lack of response and/or progression after adequate exposure for intermediate and poor risk characteristics.
• Have a previously pathologically confirmed diagnosis of RCC with clear cell differentiation.
• Availability of tumor tissues.
• Have measurable disease as assessed by the investigator/site radiologist per RECIST v1.1. Target lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions.
• Have at least 1 nontarget lesion that is suitable for biopsies.
4. Karnofsky performance status >=80% as assessed during the screening period.
5. Meets protocol-specified criteria to undergo daratumumab administration (Parts A3 and A4 only), LD chemotherapy and CAR T cell infusion.
6. Adequate organ function:
• Renal: Creatinine clearance >=50 mL/min.
• Liver:
* Aspartate aminotransferase and alanine aminotransferase < 3 x upper limit of normal (ULN)
* Total bilirubin <2 x ULN (for Gilbert*s syndrome: total bilirubin < 3 mg/dL and normal conjugated bilirubin)
* Albumin >90% of lower limit of normal.
• Cardiac: Hemodynamically stable and left ventricular ejection fraction >=45%

by echocardiogram.
• Pulmonary: Oxygen saturation level on room air >92% per pulse oximetry.
• Hematologic: Platelet count >100,000/mm^3, absolute neutrophil count >1500/mm^3, and hemoglobin >9 g/dL without prior blood cell transfusion before screening.
• Coagulation: Activated partial thromboplastin time or partial thromboplastin time <=1.5 x ULN.
7. Female subjects of childbearing potential (postmenarcheal, has an intact uterus and at least 1 ovary, and is less than 1 year postmenopausal) must agree to use a highly effective method of contraception (as specified in the protocol) from enrollment through at least 12 months after last CTX130 infusion.
8. Male subjects must agree to use acceptable effective method of contraception (as specified in the protocol) from enrollment through at least 12 months after last CTX130 infusion.

Exclusion criteria

1. Prior treatment with any anti-CD70 targeting agents.
2. Prior treatment with any CAR T cells or any other modified T or natural killer cells.
3. Known contraindications to daratumumab (Parts A3 and A4 only) any LD chemotherapy agent(s) or any of the excipients of CTX130 product.
4. Subjects with central nervous system (CNS) manifestation of their malignancy as evidenced by positive screening MRI or past history.
5. History or presence of clinically relevant CNS pathology such as seizure, stroke, severe brain injury, cerebellar disease, history of posterior reversible encephalopathy syndrome with prior therapy, or another condition that in opinion of the investigator may increase CAR T cell-related toxicities.
6. Ongoing, clinically significant pleural effusion, or ascites or any pericardial effusion, or a history of
pleural effusion or ascites in the last 2 months.
7. Unstable angina, clinically significant arrhythmia per investigator*s judgement, or myocardial infarction within 6 months prior to screening.
8. Diabetes mellitus with a current hemoglobin A1c level of >7.0%.
9. Ongoing bacterial, viral, or fungal infection, requiring systemic anti-infectives.
10. Positive for presence of human immunodeficiency virus type 1 or 2, or active hepatitis B virus or hepatitis C virus infection. Subjects with prior history of hepatitis B or C infection who have documented undetectable viral load (by quantitative polymerase chain reaction or nucleic acid testing) are permitted.
11. Previous or concurrent malignancy, except those treated with curative approach not requiring systemic therapy and have been in remission for >12 months, or any other localized malignancy that has a low risk of developing

into metastatic disease, per investigator*s judgement.
12. Primary immunodeficiency disorder or active autoimmune disease requiring steroids and/or any other immunosuppressive therapy.
13. Prior solid organ transplantation or bone marrow transplant.
14. Use of systemic antitumor therapy or investigational agent, including radiotherapy, within 14 days prior to enrollment. Use of physiological doses of steroids (e.g. <=10mg/day prednisone or equivalent) will be permitted for subjects previously on steroids if clinically indicated.
15. Received live vaccines or herbal medicines as part of traditional Chinese medicine or non-over-the-counter herbal remedies within 28 days prior to enrollment.
16. Diagnosis of significant psychiatric disorder that could seriously impede the subject*s ability to participate in the study.
17. Pregnant or breastfeeding females.

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	15-03-2021
Enrollment:	8
Type:	Actual

Ethics review

Approved WMO

Date:	29-07-2020
Application type:	First submission

Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	23-11-2020
Application type:	First submission
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:	11-06-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	07-07-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	18-10-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	15-12-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	17-01-2022
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:	25-03-2022
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:	07-06-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	09-03-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	13-03-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	28-06-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	04-07-2023
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	EUCTR2019-004513-14-NL
ClinicalTrials.gov	NCT04438083
CCMO	NL74278.000.20