A Phase 1/2, First-in-Human, Open-Label, Accelerated-Titration, Two-Part Clinical Trial of TK-8001 (MAGE-A1-Directed TCR-Transduced Autologous CD8+ T-cells) in Patients with HLA-A*02:01 Genotype and Advanced-Stage/Metastatic, MAGE-A1+ Solid Tumors that Either Have No Further Approved Therapeutic Alternative(s) or are not Eligible for them or are in a Non-Curable State and Have Received a Minimum of Two Lines of Systemic Therapy

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Phase 1 Part (Dose-escalation and Expansion):Primary objective:To evaluate the safety and tolerability of TK-8001Secondary objectives:To evaluate the preliminary anti-tumor activity of TK-8001 To determine the recommended Phase 2 dose (RP2D) of TK-...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Miscellaneous and site unspecified neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON53302

Source

ToetsingOnline

Brief title
Immunotherapeutic MAGE A-1 Directed Neoplasm Elimination

Condition

- Miscellaneous and site unspecified neoplasms malignant and unspecified

Synonym
Solid Tumor; Malignant Solid Tumor

Research involving
Human

Sponsors and support

Primary sponsor: T-knife GmbH
Source(s) of monetary or material Support: T-knife GmbH

Intervention

Keyword: HLA-A*02:01 Genotype, MAGE-A1+ Solid Tumors, TK-8001

Outcome measures

Primary outcome

Phase 1 Part (Dose-escalation and Expansion):

• Incidence and grade of treatment-emergent adverse events (AEs) and serious adverse events (SAEs)

• Number and type of dose limiting toxicities (DLT)

Phase 2 Part:

• Evaluation of ORR, SD, PR, and CR rate of TK-8001 monotherapy, according to RECIST Version 1.1 and iRECIST

• Incidence and grade of treatment-emergent AEs and SAEs

Secondary outcome

Phase 1 Part (Dose-escalation and Expansion):

• Evaluation of overall response rate (ORR), stable disease rate (SD), partial response rate (PR), and complete response (CR) rate of TK-8001 monotherapy, according to Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 and modified Response Evaluation Criteria in Solid Tumors (RECIST, V1.1) in cancer immunotherapy trials (iRECIST)

• Integrated evaluation of safety, efficacy and pharmacodynamic parameters

Phase 2 Part:

• Evaluation of PK parameters of TK-8001, such as the number and persistence of TCR-transduced T-cells in peripheral blood (e.g., vector copy)

• Evaluation of pharmacodynamic parameters of TK-8001, such as the treatment-emergent cytokine profile of TK-8001

Study description

Background summary

This trial is designed to evaluate the safety, tolerability, and preliminary antitumor activity of genetically modified autologous T-cells targeting the tumor antigen MAGE-A1 (TCR-transduced T-cells; TK-8001) in subjects with HLA-A*02:01 genotype and advanced-stage, MAGE-A1+ solid tumors (including but not limited to melanoma, squamous NSCLC, esophageal, gastric, breast [ductal, tubular, medullary], ovarian, mesothelioma, bladder, anal and sarcomas) in a non-curable state that have received a minimum of two lines of systemic therapy.

MAGE-A1 is a cancer testis antigen, exclusively expressed on human cancer cells

and in the testis (where no HLA-expression is present). MAGE-A1 has been shown to be widely expressed in various major tumor types and high medical need indications (advanced-stage, relapsed/refractory tumors with no therapeutic alternative). Importantly, MAGE-A1 follows a strict cancer-testis expression pattern and hast not been described to be expressed in any other healthy tissue outside testis.

TK-8001 is a cell therapy product consisting of autologous CD8+ T-cells retrovirally transduced with a high-affinity and high-specificity TCR generated with the humanized huTCR platform targeting a MAGE-A1 epitope and enabling elimination of MAGE-A1+ tumor cells.

Preclinical data have shown that the employed MAGE-A1-directed TCR recognizes, with high affinity and specificity, the MAGE-A1 epitope-expressing cells and that MAGE-A1+/ HLA-A*02:01+ tumor cells are effectively eliminated by TK-8001 T-cells. Non-clinical safety evaluation suggests cancer-testis-selective MAGE-A1 expression and a significantly reduced risk that MAGE-A1-targeting may result in off-target toxicity.

Clinical experiences made with TCR targeting MAGE-A1 also support further exploration of MAGE-A1-targeting via a TCR-based therapy. A trial by Immatics Inc., exploring a MAGE-A1-directed TCR for solid tumor treatment (IMA202, Clinical Trial Identifier: NCT03441100) infused total doses of 1.1 × 108, 0.9 × 108, 1.9 × 108, 5.1 × 108, 6.5 × 108 cells, with, to date, no DLT occurring. CRS was observed but did not reach Grade 3 or above in any subject treated. Encouragingly, 3 of 5 already heavily pretreated subjects experienced tumor shrinkage and disease stabilization.

Another ongoing, single-center, phase 1 trial in subjects with MAGE-A1+/HLA-A*02:01+ relapsed/refractory multiple myeloma has demonstrated preliminary safety and tolerability of MAGE-A-1-directed TCR-transduced T-cells [DRKS00020221/German Clinical Trials Register; Sponsor: Charite/Max-Delbrück-Center, Berlin] at the starting dose of 1 × 105 cells/kg. As of May 2022, two subjects have been treated at this dose with no DLT or SAE reported, demonstrating safety of the approach.

The proposed accelerated -titration design appears reasonable and feasible as:
1. MAGE-A1-directed TCR cell therapies have already explored similar dose levels that were found to be safe (0.9 × 108 to 6.5 × 108),
2. MAGE-A1 is a true cancer-testis antigen with no expression in any healthy tissue outside testis, and
3. The target population comprises of subjects suffering from advanced-stage/metastatic tumors who have no further approved curative treatment option, making limited exposure to potentially subtherapeutic dose levels desirable.

In conclusion, MAGE-A1-directed TCR therapy may represent a novel treatment

strategy for advanced-stage solid tumor subjects. Therefore, a phase 1 exploration of TK-8001 in MAGE-A1+/ HLA-A*02:01+ solid tumors with the proposed trial appears warranted.

Study objective

Phase 1 Part (Dose-escalation and Expansion):

Primary objective:
To evaluate the safety and tolerability of TK-8001

Secondary objectives:
To evaluate the preliminary anti-tumor activity of TK-8001
To determine the recommended Phase 2 dose (RP2D) of TK-8001

Phase 2 Part:

Primary objectives:
To further evaluate the anti-tumoral activity of TK-8001
To further evaluate the safety and tolerability of TK-8001

Secondary objectives:
To further evaluate the PK of TK-8001
To further evaluate the pharmacodynamics of TK-8001

Study design

This two-part clinical trial will consist of a Phase 1 Part, which includes dose-escalation and expansion, and a Phase 2 Part.

In the Phase 1 Part dose-escalation, at least 6 subjects and up to 18 subjects (if DLT occurs) will receive escalating doses of TK-8001, with up to three dose levels explored.

In the Phase 1 Part expansion, up to 9 additional subjects may be treated on dose level 3 (DL3) if cleared during dose-escalation to further evaluate the safety and efficacy of TK-8001. The maximum total number of subjects to be treated on DL3 during Phase 1 will be
12 subjects.

If DL3 is not declared to be safe in the Phase 1 Part dose-escalation, but DL2 was safely completed, then up to 10 additional subjects may be treated on DL2 to gather more safety and efficacy data for TK-8001. The maximum total number of subjects to be treated on DL2 in this
case will be 12 subjects.

For Phase 1 Part expansion, if during manufacturing the cell number for a certain dose level cannot be reached, then the subject may undergo treatment at the reduced cell number obtained with agreement of the SRC and the treating Investigator.

In the Phase 2 Part, up to 30 subjects will receive TK-8001 in the RP2D derived from the Phase 1 Part. The start of the Phase 2 Part of the trial will be subject to submission and prior approval of a substantial amendment in which the eventual target population(s) and target doses of TK-8001 to be explored in the Phase 2 Part will be defined, including detailed enrolment criteria for the target population(s).

Dosing in the Phase 1 Part dose-escalation will be staggered; in each dose cohort, the first subject dosed must complete the full Monitoring Period to allow for initial assessment of safety before another subject may be dosed. Enrollment into the Phase 1 Part expansion can occur without a stagger; however, for safety purposes, no more than 3 subjects per cohort are permitted to be within the first 28 days of treatment simultaneously.

Available safety and pharmacodynamic data, as well as preliminary efficacy data from Phase 1 will be used to determine the RP2D. The RP2D may be at or below the maximum tolerated dose (MTD). The MTD is defined as the highest dose level of TK-8001 at which no more than 1 out of 6 subjects experienced a DLT during the first 28 days post-TK-8001 infusion within the Phase 1 Part dose-escalation. Depending on the overall safety profile observed, the Safety Review Committee (SRC) may, at any time, propose and request trial continuation with a dose below the MTD.

Intervention

TK-8001 are melanoma-associated antigen 1 (MAGE-A1) T-cell receptor (TCR)-transduced autologous cluster of differentiation (CD)8+ T-cells that are capable of eliminating MAGE-A1 epitope presenting tumor cells in subjects with the human leukocyte antigen (HLA)-A*02:01 genotype.

Study burden and risks

Due to the use of a conditioning regimen, intense hematotoxicity and early and late infectious complications may occur. Also, various specific organ toxicities (e.g., hemorrhagic cystitis with cyclophosphamide) may occur. These toxicities may be severe but are well known to cancer treating physicians and are part of their daily clinical practice and experience.

Clinical syndromes associated with the cell therapy infusion may occur, such as CRS and neurologic toxicities/encephalopathies (e.g., immune effector cell-associated neurotoxicity [ICAN] syndromes). These phenomena are rarely

seen in standard clinical care situations and; therefore, require intense attention and early and medically competent intervention.

Other potential toxicities may include graft-versus-host-disease (GvHD), tumor lysis syndrome (TLS), and the possibility of conditions linked to retroviral transformation.

Another specific consideration for this trial is the currently ongoing pandemic with coronavirus disease (COVID)-19. Subjects ideally should be vaccinated by the time point of trial entry, in line with common practice for tumor subjects at many oncology centers around the world being rapidly vaccinated at the start of their tumor treatment. If a subject is not yet vaccinated, the Investigator should, together with the subject, evaluate the risks for waiting for trial participation until vaccination has been completed versus participating without being vaccinated.

In light of all the available preclinical, affinity, and specificity data, identified target selectivity for MAGE-A1, overall subject selection criteria, conditioning regimen, safety monitoring, and interventional recommendations made in case of occurrence of specific toxicities, the risk-benefit assessment for TK-8001 is currently regarded as positive, and a Phase 1 exploration of TK-8001 in subjects with MAGE-A1+/ HLA-A*02:01+ advanced-stage/metastatic, MAGE-A1+ solid tumors (including but not limited to melanoma, squamous NSCLC, esophageal, gastric, breast [ductal, tubular, medullary], ovarian, mesothelioma, bladder, anal and sarcomas) that either have no further approved therapeutic alternative or are not eligible for them or that are in a non-curable state as per the Investigator*s assessment and have received a minimum of two lines of systemic therapy appears warranted.

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

Each subject must meet all of the following inclusion criteria to be eligible to enroll in this trial and to proceed to TK-8001 treatment:
1. Ability to understand the intent of the trial and provision of a signed and dated informed consent from the subject prior to performing any protocol-related procedures (including screening evaluations), and ability to comply with the trial procedures and any locally required authorization
2. Age >= 18 years
3. Presence of an advanced-stage/metastatic, solid tumor in non-curable state:
a. For which there is either no approved therapeutic alternative available or the subject is not eligible for them or
b. For which the subject has received a minimum of two lines of approved systemic therapy
NB: Screening I and apheresis may take place during the line of treatment immediately preceding the planned TK-8001 treatment to avoid delays due to manufacturing time in progressing subjects
4. HLA-A*02:01 genotype
5. MAGE-A1+ tumor as per IHC
6. As per most recent tumor assessment, presence of radiologically measurable disease - with at least 1 lesion, not previously irradiated, that can be accurately measured as per RECIST V1.1 with CT or MRI and that is not considered for on-treatment biopsy
7. ECOG performance status <= 1
8. Life expectancy > 3 months as assessed by the Investigator
9. Adequate organ function, defined as:
a. Bone marrow function: hemoglobin >= 10 g/dL (equal to 6.2 mmol/L); platelet count >= 100 × 109 /L; leukocyte count >= 3.0 × 109 /L; absolute lymphocyte count >= 0.65 × 109/L. Note: absolute lymphocyte count >= 0.65 × 109/L criterion only applies to Screening I.

b. Hepatic function: aspartate transaminase (AST) and alanine transaminase (ALT) <= 3.0×upper limit of normal (ULN); bilirubin <= 2.0xULN
c. Renal function: serum creatinine < 1.5×ULN and/or creatinine clearance >= 50 mL/min (Cockcroft-Gault equation).
d. International normalized ratio (INR) < 1.5 and partial thromboplastin time (PTT) within 1.25 × of upper and lower limit of normal
10. All toxicities related to prior radiotherapy, chemotherapy, or surgical procedure must have recovered to baseline or Grade <= 1 based on the National Cancer Institute - Common Terminology Criteria for AEs v5.0, except alopecia (any grade), and AEs that are regarded clinically nonsignificant or stable on supportive therapy as per treating physician's assessment
Note: In case of Screening I and apheresis taking place during a prior line of treatment this criterion applies only to Screening II
11. Ongoing immune-related adverse events from previous therapies must have recovered to baseline or Grade <= 1 except vitiligo, hair loss, and stable endocrinopathies with physiologic hormone repletion
NB: In case of Screening I and apheresis taking place during a prior line of treatment, this criterion applies only to Screening II
12. Women of non-childbearing potential due to surgical sterilization (at least 6 weeks following surgical bilateral oophorectomy with or without hysterectomy or tubal ligation) confirmed by medical history or menopause (i.e., no menstrual bleeding for more than 12 months in a woman aged >= 45 years).
13. Women of childbearing potential who test negative for pregnancy at Screening based on serum pregnancy test must be using a highly effective method of contraception from the time of Screening until the persistence of TK-8001 is no longer detected by droplet digital PCR or up to 12 months after the last dose of cyclophosphamide, whatever comes later
• Note: Highly effective methods of contraception that result in a low failure rate (i.e., < 1% per year) when used consistently and correctly include combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, or transdermal), progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, or implantable), intrauterine device, intrauterine hormone-releasing system, bilateral tubal occlusion, vasectomized partner, or sexual abstinence.
• True abstinence, when in line with the preferred and usual lifestyle of the subject, is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of trial participation and until the persistence of TK-8001 is no longer detected by ddPCR or up to 6 (men with female partner) or 12 months (women of childbearing potential) after the last dose of cyclophosphamide, whatever comes later. 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 subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, and post-ovulation method) and withdrawal are not acceptable methods of contraception
14. Men with female partners of childbearing potential must agree to use highly

effective methods of contraception during the trial until the persistence of TK-8001 is no longer detected by ddPCR or up to 6 months after the last dose of cyclophosphamide, whatever comes later.

Exclusion criteria

Each subject fulfilling any of the following exclusion criteria is not eligible to enroll in this trial and to proceed to TK-8001 treatment:
1. Has received any approved or non-approved tumor-directed therapy within 14 days before start of conditioning therapy
2. Has received any other MAGE-A1-targeting therapy
3. Pre-existing arrhythmia, considered to be of concern as per clinical assessment (e.g. uncontrolled atrial fibrillation, significant ventricular tachy-/arrhythmia [CTCAE Grade >= 2], significant bradycardia, or highergrade AV-block among others) ,uncontrolled angina pectoris, diagnosed with at present uncontrolled heart failure (New York Heart Association II-IV), or any myocardial infarction/coronary event as well as any CNS-ischemic event and any thromboembolic event within 6 months prior to screening
4. Left ventricular ejection fraction (LVEF) <45% as measured by an echocardiogram or multigated acquisition (MUGA) scan
5. Corrected QT interval by the Fredericia formula (QTcF) >450 ms for men or >470 ms for women
6. History of CNS disease such as stroke, seizure, encephalitis or multiple sclerosis (within 6 months prior to screening)
7. Active allergy requiring continuous systemic medication or active infections requiring IV/orally (PO) anti-infectious therapy within 7 days prior to conditioning therapy
8. History of or clinical evidence of CNS primary tumors or metastases (including leptomeningeal metastases), unless they have been previously treated are asymptomatic, considered inactive by brain imaging and have been stable for at least 4 weeks prior to trial entry/TK-8001 treatment
9. Systemic steroids at a daily dose of >5 mg of prednisolone except non-systemic (inhaled, topical, or nasal), for the last 14 days prior to planned date for leukapheresis
10. Evidence of any form of active rheumatoid arthritis or active joint inflammation
11. Subjects with rapidly progressing disease (as per Investigator assessment), which may predispose to inability to tolerate treatment and/or trial procedure
12. Major surgery within last 4 weeks prior to consent
13. Known/expected hypersensitivity against TK-8001, dimethyl sulfoxide (DMSO), and/or other cellular therapy components
14. Active disease/ongoing infection in regard to human immunodeficiency virus (HIV), hepatitis B virus (HBV), hepatitis C virus (HCV), tuberculosis (TB), syphilis (Treponema pallidum [TPHA]), or
severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (by PCR)

15. Any other diseases, metabolic dysfunction, physical examination finding, or clinical laboratory abnormality giving reasonable suspicion of a disease or condition that in the opinion of the Investigator would contraindicate the use of the IP
16. Receipt of any organ transplantation, including autologous or allogeneic hematopoietic cell transplantation, but with the exception of transplants that do not require immunosuppression (e.g., corneal transplant, hair transplant)
17. Any vaccine administration within 4 weeks of IP administration. Vaccination with live vaccines while on trial is not permitted unless of vital medical necessity and outside the Conditioning, TK-8001 Treatment, and Monitoring Periods
18. Subject is pregnant or breastfeeding
19. Known active drug or alcohol abuse

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	3
Type:	Anticipated

Ethics review

Approved WMO Date:	02-05-2023
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	22-09-2023

Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	29-09-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	02-10-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	27-11-2023
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	EUCTR2021-004158-49-NL
ClinicalTrials.gov	NCT05430555
CCMO	NL83771.000.23