A Phase 1b/2a Pilot Study to Evaluate the Safety and Tolerability of Autologous T-Cells Expressing Enhanced TCRs (T Cell Receptors) Specific for NY-ESO-1/LAGE-1a (GSK3377794) Alone, or in Combination with Pembrolizumab in HLA-A2+ Participants with NY-ESO-1- or LAGE-1a-Positive Advanced or Recurrent Non-Small Cell Lung Cancer (study 208471)

Published: 29-07-2019
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Primary:• To evaluate the safety and tolerability of autologous genetically modified T-cells (GSK3377794) in human leukocyte antigen (HLA) HLA-A*02:01, HLA-A*02:05 and/or HLA-A*02:06 positive participants with NY-ESO-1 and/or LAGE-1a positive...

Ethical review	Approved WMO
Status	Completed
Health condition type	Respiratory tract neoplasms
Study type	Interventional

Summary

ID

NL-OMON52531

Source
ToetsingOnline

Brief title
208471

Condition

- Respiratory tract neoplasms

Synonym
non small cell lung cancer (NSCLC); lung cancer

Research involving
Human

Sponsors and support

Primary sponsor: GlaxoSmithKline
Source(s) of monetary or material Support: GlaxoSmithKline BV

Intervention

Keyword: GSK3377794, NSCLC, NY-ESO-1 LAGE-1a, Pembrolizumab

Outcome measures

Primary outcome

Adverse events, ECOG performance status, Overall Response Rate (ORR) (RECIST

1.1).

Secondary outcome

Progression-Free Survival (PFS). Disease Control Rate (DCR). Duration of

Response (DoR). Time to Response (TTR). Pharmacokinetic (PK) parameters.

NB: exploratory parameters, see protocol paragraph 3.

Study description

Background summary

Adoptive T-cell therapy (ACT) is a therapeutic approach that uses a cancer patient*s own T lymphocytes obtained by leukapheresis, engineered to express a tumor specific T-cell receptor, expanded in vitro and re-infused into the participant, with the aim of generating an anti-tumor T-cell immune response. NY-ESO-1 and LAGE-1a antigens are tumor-associated proteins that have been

found in several tumor types, including non-small cell lung cancer (NSCLC).
Previous clinical trials using ACT with T-cells directed against NY-ESO-1/LAGE-1a have shown objective responses between 40-60% in participants with synovial sarcoma, metastatic melanoma, and multiple myeloma. Pembrolizumab is a monoclonal antibody that acts specifically on tumor targeting T-cells to block PD-1/PD-L1 interaction and increase T-cell anti-tumor function; pembrolizumab will be used in combination with NY-ESO-1/LAGE-1a TCR engineered patient T-cells (GSK3377794) to potentially further improve therapy for patients.
The ability of GSK3377794 to achieve objective responses in diverse tumor types supports a hypothesis that HLA and antigen expression are biomarkers that identify a population of participants that may benefit from GSK3377794.
This study will further assess the effects of GSK3377794 monotherapy and the combination of GSK3377794 and pembrolizumab in HLA-A*02:01, HLA-A*02:05 and/or HLA-A*02:06 patients with NY-ESO-1- or LAGE-1a-positive advanced or recurrent NSCLC.

Protocol amendment 5 27-03-2020; main changes: Randomisation has been dropped. At screening fresh biopsy tumour tissue may be considered if no achival material is available. New inclusion criterion platinum-based chemotherapy. Clarification exisiting inclusion criterion measurable disease. Removal exclusion criterion docetaxel treatment. Removal supportive therapy with docetaxel between leukapheresis and the start of lymphodepletion.

Protocol amendment 6 dd 19-05-2021; main changes: Simplify/enhance screening and enrollment efforts. Broaden patient eligibility. Include additional safety tests and measures.

Protocol amendment 7 November 2021. Main changes:
1. Implementation of additional safety monitoring measures in accordance with a recent Dear Investigator Letter and safety events for GSK3377794.
2. For participants treated as of protocol amendment 7, the upper end of the target dose range of transduced T cells was increased from to 8×109 to 15×109 in order to maximize the delivery of cells for participants whose manufacture yields >8×109 transduced T cells.

Study objective

Primary:
• To evaluate the safety and tolerability of autologous genetically modified T-cells (GSK3377794) in human leukocyte antigen (HLA) HLA-A*02:01, HLA-A*02:05 and/or HLA-A*02:06 positive participants with NY-ESO-1 and/or LAGE-1a positive advanced NSCLC alone [Arm A1] or GSK3377794 in combination with pembrolizumab [Arm A].
• To determine the response to GSK3377794 alone [Arm A] or in combination with pembrolizumab [Arm B].
Secondary:

• To further investigate the anti-tumor activity of GSK3377794.
• To describe the persistence of GSK3377794 over time.
NB: exploratory objectives, see protocol paragraph 3.

Study design

Parallel group, open-label, study of GSK3377794.
Screening.
Leucapheresis.
Standard of care until disease progression.
When disease progression has been confirmed: wash-out from previous standard of care.
Four days chemotherapy with fluderabine (4 days) and cyclophosphamide (3 days).
Start study treatment:
Allocation to Arm /B or C, based on changes in tumour genes No (Arm A/B) or Yes (Arm C).
Arm A/B: First Arm A will be filled, thereafter Arm B will be filled
Arm A: GSK3377794 will be administered as a single intravenous (IV) infusion of 1 to 6 x109 transduced cells. Participants who subsequently progress may optionally receive rescue therapy with pembrolizumab 200 mg Q3W for up to 35 cycles at or until disease progression.
In Arm B, participants will receive a single IV infusion of GSK3377794 on Day 1 followed by pembrolizumab 200 mg starting on Day 22. Pembrolizumab will be administered for up to 35 cycles Q3W or until disease progression.
Arm C: All participants will be treated with GSK3377794 plus pembrolizumab.
After the study participants will be entered into a long term follow up protocol.
Approx. 55 participants.

Intervention

Treatment with GSK3377794 with or without pembrolizumab.

Study burden and risks

Risk: Adverse events of the study medication. Combination GSK3377794-pembrolizumab has not been administered before.
Burden:
Pre-selection: 1-2 visits, 60 ml blood.
Visits from screening onwards:
3 visits before the start of the study treatment (including screening and leukapheresis).
Chemotherapy: fludarabine (3-4 days, 30 mg/m2 in 50-100 ml NaCl 0,9% in 30 min.) and cyclophosphamide (3 days, 900 mg/m2 in 100-250 ml Na Cl 0,9% in 60 min.). Administration GSK3377794 (1 day, 5 x 109 T-cells in 100 ml in 15-30 min.). Admission to hospital 3-7 days. Thereafter 7 weeks every week and

thereafter from week 8 until week 25 every 3 weeks.
Pembrolizumab (max. 35 days with an interval of 3 weeks, 200 mg in 100 ml in 30 min.)
From week 25 onwards the number of visits differs from one treatment group to the other:
• Group 1: every 12 weeks from week 34 until the end of treatment.
• Group 2 and 3: every 3 weeks from week 28 until the end of treatment (because of the pembrolizumab infusions).
Tests:
• Physical examination: during screening and during every visit during treatment period.
• Blood pressure, pulse, pulse oximetry etc.: every visit.
• Blood draws 15-240 ml, 800 ml in first 6 months.
• ECG: 5x.
• Echocardiography (alternative: MUGA scan): 2x.
• CT/MRI scan: every 6-12 weeks (cf. standard).
• Tumor biopsy: 3x.
• Additional renal function tests in the elderly.
Optional:
• Blood test for pharmacogenetic research (6 ml).
• Photographs of skin abnormalities in case of adverse events.
• Interview during week 3 and end of trial.

Contacts

Public
GlaxoSmithKline

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GlaxoSmithKline

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

SCREENING:
• Male or female, age 18 years and above.
• Histologically or cytologically diagnosed unresectable Stage IIIb or Stage IV NSCLC. Measurable disease is not an indispensable requirement for enrollment/leukapheresis.
• ECOG performance status 0-1.
• Life expectancy of at least 3 months.
• Left ventricular ejection fraction >=50% or as per institution*s guidelines.
• Adequate venous access for leukapheresis.
• Participant is positive for any of the following alleles: HLA-A*02:01, HLA A*02:05, HLA-A*02:06.
• Tumor tissue (archival biopsy) obtained at any time from the initial diagnosis to time of study entry is mandatory for tumor antigen expression analysis (NY-ESO-1 and/or LAGE1a). In case an archival biopsy is not available a fresh biopsy may be considered in consultation with the sponsor.
LEUKAPHERESIS:
• Successfully completed screening: HLA-A*02:01, HLA-A*02:05 and/or HLA-A*02:06 positive and meeting the threshold for expression of NY-ESO-1 and/or LAGE1a.
• Suitable for leukapheresis, including the laboratory parameters mentioned in chapter 5.1.2, item 12 of the protocol.
• Time point of leukapheresis the treatment scheme: see chapter 5.1.2, item 13 of the protocol for details.
CHEMOTHERAPY/TREATMENT:
• Must have received or are receiving at least 1 line of prior systemic therapy. See chapter 5.1.3, item 15 of the protocol for details.
• Following treatment with a PD-1/PD-L1 checkpoint blockade therapy administered either as monotherapy or in combination with other checkpoint inhibitors or other therapies, progression is defined by meeting all of the criteria defined in chapter 5.1.3, item 15b of the protocol.
• Histologically or cytologically diagnosed unresectable Stage IIIb or Stage IV NSCLC with measurable disease per RECIST v1.1.
• Prior radiotherapy: For prior chest radiotherapy see D5a (exclusion criteria)

for details. Allowed in case of prior palliative or stereotactic radiosurgery to solitary lesions outside of the chest.
• Acceptance of CNS metastases: see chapter 5.1.3, item 19 of the protocol for details.
• Acceptance of initiation of the chemotherapy: see chapter 5.1.3, item 20 of the protocol for details.
• Acceptance of standard of care line of therapy between leukapheresis and treatment: see chapter 5.1.3, item 21 of the protocol for details.
• Contraception guidelines for males and females should be followed, see chapter 5.1.3, item 23 and 5.3.3 of the protocol for details.
• Pembrolizumab treatment (rescue) for Arm A: see chapter 5.1.4 of the protocol for details.

Exclusion criteria

SCREENING:
• Has received >=3 lines of prior systemic therapy. See protocol section 5.2.1 item 2.
• Prior treatment: See protocol section 5.2.1:
a. Previous treatment with genetically engineered NY-ESO-1-specific T-cells.
b. Previous NY-ESO-1 vaccine or NY-ESO-1 targeting antibody.
c. Prior gene therapy using an integrating vector.
d. Previous allogeneic hematopoietic stem cell transplant.
• Prior malignancy other than NSCLC. Exceptions: see chapter 5.2.1, item 2.
• Active autoimmune disease or history. See chapter 5.2.2 item 6,7.
• Uncontrolled intercurrent infection, cardiac, pulmonary, demyelinating disease, or unstable liver or biliary disease. See chapter 5.2.2, item 8.
• Active infection with HIV, hepatitis B, hepatitis C, EBV, CMV, syphilis, HTLV. See chapter 5.2.2, item 9 of the protocol for details.
• QTc >450 msec or QTc >480 msec for patients with BBB. See chapter 5.2.2, item 13 of the protocol for details.
LEUKAPHERESIS:
• Investigational treatment within 30 days or 5 half-lives (whichever is shorter). See chapter 5.2.2, item 15 of the protocol for details.
• Radiotherapy that involves the lung or >25% bone marrow exposure, or mean heart dose >20Gy within 3 months. See chapter 5.2.2, item 19 of the protocol for details.
CHEMOTHERAPY/TREATMENT:
• Corticosteroids other than inhaled or topical or any other immunosuppressive therapy within 2 weeks.
• Live vaccine within 30 days prior to the first dose of study drug. See chapter 5.2.2, table 12 of the protocol for details.
• Pembrolizumab treatment (rescue) for Arm A: see chapter 5.2.4 of the protocol for details.

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):	21-02-2020
Enrollment:	9
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Cyclophosphamide
Generic name:	cyclophosphamide
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Fludarabine
Generic name:	fludarabine
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	GSK3377794
Generic name:	GSK3377794
Product type:	Medicine
Brand name:	Keytruda
Generic name:	Pembrolizumab
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	29-07-2019
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	23-01-2020
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	06-04-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	14-04-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	14-05-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	24-07-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	10-08-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Approved WMO

Date:	25-08-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	24-09-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	16-10-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	09-11-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	20-11-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	08-12-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	15-12-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	16-12-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den

	Haag)
Approved WMO Date:	05-01-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	15-03-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	02-04-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	26-05-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	01-06-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	08-07-2021
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:	14-07-2021

Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	22-07-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	16-12-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	12-01-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	08-07-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	14-07-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	09-12-2022
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	EUCTR2018-003949-42-NL
CCMO	NL69764.000.19
Other	www.gsk-clinicalstudyregister.com; 208471

Study results

Date completed: 04-11-2022

Results posted: 24-07-2023

URL result
URL
Type
int
Naam
M2.2 Samenvatting voor de leek
URL

Internal documents
File