Master Protocol to Assess the Safety and Recommended Phase 2 Dose of Next Generations of Autologous Enhanced NY-ESO-1/ LAGE-1a TCR Engineered T-cells, alone or in combination with other agents, in Participants with Advanced Tumors (study 209012)

Published: 25-09-2020
Last updated: 17-01-2025

Primary:To assess the safety, tolerability and determine recommended phase 2 dose (RP2D) of NY-ESO-1 and LAGE-1a specific T cells, alone or in combination with other agents, in HLA-A*02-positive participants with NY-ESO-1 and/or LAGE-1a positive...

Ethical review	Approved WMO
Status	Completed
Health condition type	Soft tissue neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON52650

Source
ToetsingOnline

Brief title
209012

Condition

- Soft tissue neoplasms malignant and unspecified
- Respiratory tract neoplasms

Synonym

non small cell lung cancer (NSCLC); synovial sarcoma; myxoid/round cell liposarcoma

Research involving
Human

Sponsors and support

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

Intervention

Keyword: GSK3845097, GSK3901961, LAGE-1a, NY-ESO-1

Outcome measures

Primary outcome

Dose-limiting toxicities, (serious) adverse events (of special interest).

Secondary outcome

Overall Response Rate (ORR), Duration of Response (DoR). T cell expansion and

persistence (peak expansion, Cmax, Tmax, AUC(0-t). Infiltration and phenotype

of transduced T cells in the tumor by RNA, DNA and/or protein levels.

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. In 2020 two clinical trials have been started in The Netherlands with GSK3377794, a form of ACT (study 208467, NL70428.000.19 and study 208471, NL69764.000.19). GSK3377794 is able 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 is a platform study, that will assess the effects of so called next generations of NY-ESO-1/LAGE-1a TCR engineered T cells that are efficacy enhanced using advances in technology (incl. multi-component engineering) and/or innovative ways of manufacturing. Each substudy will be performed with a next generation ACT alone or in combination with other agents, in HLA-A2-positive participants with NY-ESO-1 and/or LAGE-1a-positive advanced tumors.

At present 2 substudies are open:
Substudy 1:
GSK3901961 in previously treated advanced (metastatic or unresectable) synovial sarcoma and previously treated metastatic NSCLC.
Substudy 2:
GSK3845097 in previously treated advanced synovial sarcoma.

Protocol amendment 1: July 1, 2021 Main changes:
1. Changes to Substudy 1 and 2 Inclusion criteria relative to disease status requirements to allow participants with advanced disease diagnosis to undergo target expression screening; participants with evidence of radiological or clinical disease progression will be able to undergo leukapheresis; initiation of lymphodepletion will require evidence of disease progression from prior line of therapy by RECIST v1.1.
2. Changes to Substudy 1 Inclusion and Exclusion criteria language relative to prior lines of treatments for NSCLC participants to allow those who have received any PD-1/PD-L1 checkpoint blockade therapy and, in the same or different line of treatment, any platinum containing chemotherapy. NSCLC participants with actionable genetic aberrations may also be included if they have exhausted the targeted standard of care therapy.
3. Clarifications to Substudy 1 and 2 lymphodepleting chemotherapy dose adjustments to ensure adequate consideration given to prior anti-cancer therapies (systemic and radiation exposure), renal function (for fludarabine) as well as use of adjusted body weight (for cyclophosphamide when necessary).
4. Allowing potential future inclusion of a limited number of patients who progressed following clinical benefit (PR, CR, SD >=3 months) from infusion with GSK3377794 (letetresgene autoleucel, lete-cel) on a GSK sponsored trial.

Protocol amendment 2: November 4, 2021; Main changes:
1. Implementation of additional safety monitoring measures in accordance with a recent Dear Investigator Letter and safety events.
2. For participants treated as of protocol amendment 2, the cyclophosphamide dose in the lymphodepleting chemotherapy was reduced on Day -7 thru Day -4 to further optimize and reduce potential for acute and prolonged cytopenias while also minimizing impact on efficacy.
3. For NSCLC participants in Substudy 1 Cohort 2 treated as of Protocol Amendment 2, the lymphodepleting chemotherapy schedule was changed from Day -8 through Day -5 to Day -7 through Day -4 to align with the schedule for the

sarcoma participant cohort.
4. Inclusion of myxoid/round cell liposarcoma as a second translation-related sarcoma indication.

Protocol amendment 4 dated 27-05-2022:
This amendment concerns the Master protocol and sub-studies 1 and 2 (worldwide); in the US this amendment also concerns substudy 3. Protocol amendment 3 concerned changes related to substudy 3 which is only being conducted in the US.
Main changes of amendment 4:
- Change of inclusion and exclusion criteria; a detailed overview of the changes can be found on page 2-4 of the clean version of the Master protocol.
- Changes to the protocol amendment have been incorporated into the ICF
A detailed overview of the changes can be found on page 2-4 of the clean version of the Master protocol.

Study objective

Primary:
To assess the safety, tolerability and determine recommended phase 2 dose (RP2D) of NY-ESO-1 and LAGE-1a specific T cells, alone or in combination with other agents, in HLA-A*02-positive participants with NY-ESO-1 and/or LAGE-1a positive advanced tumors
Secondary:
To investigate the efficacy of NY-ESO-1 and LAGE-1a specific T cells, alone or in combination with other agents, in HLA-A*02+ participants with NYESO-1 and/or LAGE-1a positive advanced tumors. To describe the expansion and persistence of NYESO-1 and LAGE-1a specific T cells, alone or in combination with other agents, over time. To evaluate T cell trafficking to and activity at tumor site.

Substudy objectives: see protocol chapter 13.

Study design

This is a master protocol (platform study).
The protocol will evaluate next generation NY-ESO-1/LAGE-1a specific TCR engineered T cells in HLA-A*02-positive participants with NY-ESO-1 and/or LAGE-1a-positive previously treated advanced synovial sarcoma, myxoid/round cell liposarcoma and NSCLC (substudy 1) or advanced synovial sarcoma or myxoïd/ rondcel liposarcoom (substudy 2).

Steps: Preselection (HLA-A*02 and NY-ESO-1 and LAGE-1a) and further screening - Leukapheresis - 3 days of chemotherapy (fludarabine and cyclophosphamide) - 1 infusion of GSK3901961 (substudy 1) or GSK3845097 (substudy 2) - Follow-up max. 1 year.

The protocol may be amended later to investigate other next generations of NY-ESO-1/LAGE-1a TCR engineered T cells and/or other NY-ESO-1+ or LAGE-1a positive tumor types and/or combinations with other agents.
After the study participants will be entered into a long term follow up protocol.
Approx. 20 participants in substudy 1 and 10 in substudy 2. The total number may be increased to 48.

Intervention

Treatment with NY-ESO-1 and LAGE-1a specific T cells, alone or in combination with other agents.
Substudy 1: GSK3901961 and substudy 2: GSK3845097.

Study burden and risks

Risk: Adverse events of the study medication.
Burden:
Pre-selection: 1-2 visits, 10 ml blood and (if no archival material available) 1 tumor biopsy.
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 (2-3 days, 1200-1800 mg/m2 in 200-500 ml NaCl 0,9% in 60 min.). Administration GSK3901961 or GSK3845097 (1 day, 1 x 109 - 8 x 109 cells) *). Hospital stay min. 3 days *). Thereafter 2 weeks with regular hospital visits. In total 17 hospital visits during the first 6 months and every 3 months thereafter.
*) For the first patient receiving GSK3901961 and the first patient receiving GSK3845097: 30% of the dose will be administered. The remaining 70% will be administered one week later. Both patients will stay in the hospital for 10 consecutive days.
Tests:
• Physical examination: every visit during treatment period.
• Blood pressure, pulse, pulse oximetry etc.: every visit.
• ECG: 6 times.
• Echocardiography (alternative: MUGA scan): twice.
• Telemetry (if tumor location near heart): 3-7 days post administration of study medication.
• Blood draws: every visit. 5-110 mL blood per occasion; total during first 6 months (excl. 210-300 mL for leukaferesis): 820 mL.
• CT/MRI scan: every 6-12 weeks.
• Tumor biopsy: 3x.
Optional:
• Blood test for pharmacogenetic research (6 ml).

• Photographs of skin abnormalities in case of adverse events.

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

SUBSTUDY 1:
SCREENING:
• Male or female, age 18 years and above.
• Measurable disease (RESIST v1.1).
• Tumor sample plus report is available for NY-ESO-1 analysis. See protocol section 6.1.1 item 3.

Synovial sarcoma and myxoid/round cell liposarcoma:
• Diagnosis of synovial sarcoma or myxoid/round cell liposarcoma confirmed by

local histology and with evidence of disease-specific translocation.
• Advanced (metastatic or unresectable) synovial sarcoma or myxoid/round cell liposarcoma. See protocol section 6.1.1 for details.

NSCLC:
• Histologically or cytologically confirmed Stage IV NSCLC.

LEUKAPHERESIS:
• HLA-A*02:01, HLA-A*02:05 and/or HLA-A*02:06 positive and NY-ESO-1 positive. See protocol section 6.1.2 item 8-9.
• Measurable disease (RECIST v1.1).
• For sarcoma: Has completed at least one standard of care treatment including anthracycline
containing regimen OR is intolerant to the therapy. See protocol section 6.1.2, item 12.
• For NSCLC: Has been previously treated with or is intolerant to PD-1/PD-L1 checkpoint blockade therapy and a platinum-based chemotherapy, or is intolerant to it. See protocol section 6.1.2, item 13 and 14.
• Left ventricular ejection fraction >=45%. See protocol section 6.1.2 item 15.
• ECOG performance status 0-1.
• Adequate organ function (see protocol Table 9).
• Contraception guidelines for males and females should be followed, see chapter 6.1.2 item 19 of the protocol for details.
• Negative pregnancy test for female participants able to become pregnant.

TREATMENT:
• Documented radiographic evidence of disease progression from prior line of therapy.
• A biopsy of non-target tumor tissue obtained within 28 days prior to initiating the chemotherapy is mandatory. See protocol section 6.1.3 item 23 for details.
For a detailed list of Iclusion Critera, please refer to the protocol for substudy 1 (page 54-59).

SUBSTUDY 2
SCREENING:
• Male or female, age 18 years and above.
• Tumor sample plus report is available for NY-ESO-1 analysis. See protocol section 6.1.1 item 3.
• Diagnosis of synovial sarcoma or myxoid/round cell liposarcoma confirmed by local histology. and with evidence of disease-specific translocation.
• Advanced (metastatic or unresectable) synovial sarcoma or myxoid/round cell liposarcoma. See protocol section 6.1.1 for details.

LEUKAPHERESIS:
• HLA-A*02:01, HLA-A*02:05 and/or HLA-A*02:06 positive and NY-ESO-1 positive. See protocol section 6.1.2 item 7.

• Measurable disease (RECIST v1.1).
• Evidence of radiographic or clinical disease progression.
• Has completed at least one standard of care treatment including anthracycline containing regimen OR is intolerant to the therapy. See protocol section 6.1.2, item 12.
• Left ventricular ejection fraction >=45%. See protocol section 6.1.2 item 15.
• ECOG performance status 0-1.
• Adequate organ function (see protocol Table 10).
• Contraception guidelines for males and females should be followed, see chapter 6.1.2 item 18 of the protocol for details.
• Negative pregnancy test for female participants able to become pregnant.

TREATMENT:
• Documented radiographic evidence of disease progression from prior line of therapy.
• A biopsy of non-target tumor tissue obtained within 28 days prior to initiating the chemotherapy is mandatory. See protocol section 6.1.3 item 21 for details.

For a detailed list of Inclusion Criteria please refer to the protocol for substudy 2 (Page 56-60).

Exclusion criteria

SUBSTUDY 1:
SCREENING:
• CNS metastases. See protocol section 6.2.2 item 6 for exceptions.
• Clinically significant systemic illness, see protocol section 6.2.1, item 2 for details.
• Previous treatment with genetically engineered NY-ESO-1-specific T cells NY-ESO-1 vaccine or NY-ESO-1 targeting antibody. See protocol section 6.2.1 item 3.
• Prior gene therapy using an integrating vector. See protocol section 6.2.1 item 4.
• Prior allogeneic hematopoietic stem cell transplant within the last 5 years or solid organ transplant.

LEUKAPHERESIS:
• CNS metastases. See protocol section 6.2.2 item 6.
• History of chronic or recurrent (within the last year prior to leukapheresis) severe autoimmune or immune mediated disease requiring steroids or other immunosuppressive treatments.
• Uncontrolled intercurrent illness. See protocol chapter 6.2.2, item 9 for details.
• Insufficient pulmonary function with mechanical parameters <40% predicted.

See protocol chapter 6.2.2, item 12 for details
• Current active liver or biliary disease. See protocol chapter 6.2.2, item 11 for details.
• QTc >480 msec. See protocol chapter 6.2.2, item 12 for details.
• Active infections. See protocol chapter 6.2.2, item 14 for details.
• NSCLC: Radiotherapy that involves the lung or bone marrow exposure or heart exposure. See protocol chapter 6.2.2, item 18 for criteria and other details.

TREATMENT:
• Cytotoxic therapy within the last 3 weeks prior to chemotherapy.
• Systemic corticosteroids or any other immunosuppressive therapy within the last 2 weeks prior to chemotherapy. See protocol chapter 6.2.3, item 23 for details.
• >=50 Gy to a significant volume of the pelvis, long bones or spine. See protocol section 6.2.3 item 20.
• Radiotherapy to the target lesions within the last 3 months. See protocol chapter 6.2.3, item 24 for details.
• Anti-cancer vaccine within the last 2 months prior to chemotherapy in the absence of tumor response. See protocol chapter 6.2.3, item 23 for details.
• Live vaccine within the last 4 weeks prior to chemotherapy.
• Immune therapy within the last 4 weeks prior to chemotherapy. See protocol chapter 6.2.3, item 25 for details.
• Washout periods for prior therapy see protocol chapter 6.2.3, Table 10.
For a detailed list of Exclusion Criteria please refer to the Substudy 1 protocol (Page 60-65).

SUBSTUDY 2:
SCREENING:
• Any other prior malignancy that is not in complete remission. See protocol section 6.2.1 item 1 for exceptions.
• Clinically significant systemic illness, see protocol section 6.2.1, item 2 for details.
• Previous treatment with genetically engineered NY-ESO-1-specific T cells NY-ESO-1 vaccine or NY-ESO-1 targeting antibody. See protocol section 6.2.1 item 3.
• Prior gene therapy using an integrating vector. See protocol section 6.2.1 item 4.
• Prior allogeneic hematopoietic stem cell transplant within the last 5 years or solid organ transplant.

LEUKAPHERESIS:
• CNS metastases.
• History of chronic or recurrent (within the last year prior to leukapheresis) severe autoimmune or immune mediated disease requiring steroids or other immunosuppressive treatments.
• Uncontrolled intercurrent illness. See protocol chapter 6.2.2, item 9 for details.

• Insufficient pulmonary function with mechanical parameters <40% predicted. See protocol chapter 6.2.2, item 10 for details
• Current active liver or biliary disease. See protocol chapter 6.2.2, item 11 for details.
• QTc >480 msec. See protocol chapter 6.2.2, item 12 for details.
• Active infections. See protocol chapter 6.2.2, item 14 for details.

TREATMENT:
• Cytotoxic therapy within the last 3 weeks prior to chemotherapy.
• Systemic corticosteroids or any other immunosuppressive therapy within the last 2 weeks prior to chemotherapy. See protocol chapter 6.2.3, item 23 for details.
• >=50 Gy to a significant volume of the pelvis, long bones or spine. See protocol section 6.2.3 item 20.
• Radiotherapy to the target lesions within the last 3 months. See protocol chapter 6.2.3, item 21 for details.
• Anti-cancer vaccine within the last 2 months prior to chemotherapy in the absence of tumor response. See protocol chapter 6.2.3, item 22 for details.
• Live vaccine within the last 4 weeks prior to chemotherapy.
• Immune therapy within the last 4 weeks prior to chemotherapy.
• Washout periods for prior therapy see protocol chapter 6.2.3, Table 11.
For a detailed list of Exclusion Criteria please refer to the Substudy 2 protocol (Page 61-65).

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	01-12-2021
Enrollment:	5
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:	GSK3845097
Generic name:	GSK3845097
Product type:	Medicine
Brand name:	GSK3901961
Generic name:	GSK3901961

Ethics review

Approved WMO Date:	25-09-2020
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	08-03-2021
Application type:	First submission
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:	30-04-2021

Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	02-06-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	06-08-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	12-08-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	16-09-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	20-01-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
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Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	02-06-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Approved WMO Date:	29-06-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	21-07-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	29-08-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	30-09-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	06-12-2022
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	EUCTR2019-004446-14-NL
CCMO	NL74331.000.20
Other	www.gsk-studyregister.com, 209012

Study results

Date completed: 04-11-2022

Results posted: 02-11-2023

First publication
18-08-2023