A Phase 1/1b First-in-human Dose Escalation and Expansion Study for the Evaluation of Safety, Pharmacokinetics, Pharmacodynamics, and Anti-tumor Activity of SAR439459 Administered Intravenously as Monotherapy and in Combination with cemiplimab in Adult Patients with Advanced Solid Tumors

Published: 20-12-2018
Last updated: 10-01-2025

Primary Objectives:Dose escalation (Part 1)Part 1A (SAR439459 monotherapy)-To determine the maximum tolerated dose (MTD) and/or maximum administered dose (MAD) of SAR439459 when administered intravenously as monotherapy in adult patients with...

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

Summary

ID

NL-OMON55468

Source
ToetsingOnline

Brief title
TCD14678

Condition

- Miscellaneous and site unspecified neoplasms malignant and unspecified

Synonym
Advanced solid tumors

Research involving
Human

Sponsors and support

Primary sponsor: Genzyme Europe BV
Source(s) of monetary or material Support: Genzyme Europe B.V.

Intervention

Keyword: anti-PD1 mAb, anti-TGF-beta, cancer, solid tumors

Outcome measures

Primary outcome

- Incidence of DLTs at Cycle 1 and 2 (Day 1 to Day 28) in Parts 1A and 1B.

- Objective Response Rate (ORR) for Part 2B: Efficacy as documented by ORR will be assessed by evaluation of anti-tumor response information according to RECIST 1.1 (Part 2A and 2B).

Secondary outcome

- Overall safety profile: The overall safety profile of SAR439459 administered in monotherapy (Part 1A and Part 2A) or in combination with cemplimab (Part 1B and Part 2B).

- Immunogenicity evaluation: Blood samples will be assessed for human anti-SAR439459 antibodies (all cohorts) and for human anti- cemiplimab antibodies (Parts 1B and 2B).

- Progression free survival (PFS): The time from first IMP administration until objective tumor progression or death (Part 2A and Part 2B).

- Time to progression (TTP): The time from first IMP administration until objective tumor progression (Part 2A and 2B).

- Objective Response Rate (ORR) for Part 2A: Efficacy as documented by ORR will be assessed by evaluation of antitumor response information according to RECIST 1.1 (Part 2A).

- Cmax for SAR439459 and for cemiplimab: Maximum plasma concentration observed.

- AUC for SAR439459: Area under the serum concentration versus time curve extrapolated to infinity.

- AUClast for SAR439459 and for cemiplimab: Area under the plasma concentration versus time curve calculated using the trapezoidal method from time zero to last post-dose corresponding to the last concentration above the limit of quantification.

- AUC0-14d for SAR439459 and for cemiplimab: Area under the plasma concentration versus time curve calculated using the trapezoidal method from time zero to 14 days post-dose.

- t1/2z for SAR439459: Terminal half-life associated with the terminal slope

(*z).

- CL for SAR439459: Total body clearance of a drug from plasmacalculated using

the following equation from AUC: CL= Dose/AUC on cycle 1.

- Vss for SAR439459: Estimate of Volume of distribution at the steady state

after single IV dose.

Study description

Background summary

Although immunotherapies, particularly anti-PD-1 treatment have transformed the treatment landscape of melanoma, there are currently no effective treatment options for patients after failure of anti-PD-1 therapeutics.

TGFβ regulates several biologic processes including cell proliferation, angiogenesis, and immune suppression. Importantly, each of these contributes to tumor progression, and thus the overall role of TGF-β in oncology is likely an integrated combination of these functions.

It is hypothesized that inhibition of TGF-β will alleviate the suppressive tumor microenvironment and allow checkpoint modulators, such as PD-1 (or programmed cell death-ligand 1 [PD-L1]) inhibitors to better induce immune responses and thus increase the proportion of patients benefitting from anti-PD-1 treatment.

The TCD14678 study will be conducted in patients with advanced cancer. This study is a Phase 1/1b first-in-human, dose escalation, and dose expansion study for the evaluation of safety, PK, PD, and anti-tumor activity of SAR439459 administered intravenously as monotherapy and in combination with cemiplimab in adult patients with advanced solid tumors.

Study objective

Primary Objectives:

Dose escalation (Part 1)

Part 1A (SAR439459 monotherapy)
-To determine the maximum tolerated dose (MTD) and/or maximum administered dose (MAD) of SAR439459 when administered intravenously as monotherapy in adult patients with advanced solid tumors.

Part 1B (SAR439459 and REGN2810 combination therapy)
-To determine the MTD and/or MAD of SAR439459 administered intravenously in combination with cemiplimab administered intravenously in adult patients with advanced solid tumors.

Dose expansion (Part 2)

Part 2A (SAR439459 monotherapy)
-To determine optimal dose of SAR439459 administered intravenously in adult patients with advanced melanoma who have failed a prior therapy based on anti-PD-1 (programmed cell death-1) or anti-PD-L1.

Part 2B (SAR439459 and REGN2810 combination therapy)
-To determine the objective response rate (ORR) of SAR439459 in combination with cemiplimab in adult patients with selected advanced solid tumors by evaluation of antitumor response according to RECIST1.1

Secondary Objectives:

-To characterize the PK profile of SAR439459 administered as monotherapy (Part 1A/2A) and in combination with cemiplimab (Part 1B/2B) and PK profile of cemiplimab in combination with SAR439459 (Part 1B/2B).
-To assess the immunogenicity of SAR439459 monotherapy (Part 1A/2A) and SAR439459 and cemiplimab combination (Part 1B/2B).

Dose escalation (Part 1)
-To characterize the overall safety and tolerability profile of SAR439459 administered as monotherapy and in combination with cemiplimab.
-To identify the preliminary recommended phase 2 dose (pRP2D) of SAR439459 as monotherapy or in combination with cemiplimab.

Dose expansion (Part 2)
-To determine the progression free survival (PFS), time to progression (TTP), ORR, and safety of SAR439459 as monotherapy and PFS, TTP and safety in combination with cemiplimab in adult patients with selected advanced solid tumors.
-To confirm the optimal dose of SAR439459 administered in combination with cemiplimab.

Study design

- Phase 1, open-label, parallel sutudy.

- Escalation monotherapy (Part 1A) and escalation combination (Part 1B) followed by expansion monotherapy (Part 2A) and expansion combination (Part 2B).

- Escalation phases will not be randomized while expansion phases will be randomized.

Intervention

Part 1A:

SAR439459 administered intravenously every 2 weeks in a 14-day cycle with escalating doses between 0.05 - 15 mg/kg

Part 1B:

SAR439459 + cemiplimab combination administered intravenously every 2 weeks in a 14-day cycle or every 3 weeks in a 21-day cycle with escalating SAR439459 doses and cemiplimab at a standard dose

Part 2A:

SAR439459 administered intravenously every 3 weeks in a 21-day cycle with two previously determined recommended doses from part 1A

Part 2B:

SAR439459 + cemiplimab combination administered intravenously every 3 weeks in a 21-day cycle with up to two previously determined SAR439459 doses in combination with cemiplimab at a standard dose

Study burden and risks

The risks are related to the blood samples and the possible side effects of the study medication.

The burden on the patient will be the frequency of visits to the research center.

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

Dose escalation (Part 1A and Part 1B):, -Patients with histologically confirmed, advanced unresectable or metastatic solid tumor whom in the opinion of the Investigator does not have a suitable alternative therapy.,

Dose expansion (Part 2A):, -Patients with histologically confirmed, advanced unresectable melanoma whom in the opinion of the Investigator does not have a suitable alternative therapy

-Patients must have failed any prior therapy based on anti-PD-1 or anti-PD-L1 as defined by disease progression within 26 weeks of initiating anti-PD-1 or anti-PDL-1-based therapy without any evidence of a response.

-Patients must have a site of disease amenable to biopsy and be a candidate for tumor biopsy.

-Patients must be able and willing to provide mandatory tumor biopsies prior to and during study treatment.,

Dose expansion (Part 2B):, -Patients with avanced unresectable or metastatic melanoma who failed after one prior therapy based on anti-PD-1 or anti-PD-L1 or colorectal adenocarcinoma with mesenchymal molecular subtype or urothelial cancer and have failed platinum-containing chemotherapy or non-small cell lung cancer (NSCLC) after failure of anti-PD-1 or anti PD-L1, or hepatocellular carcinoma (HCC) after failure of anti-PD-1 or anti PD-L1, with or without bevacizumab.

For all indications patients must not have a suitable alternative approved standard therapy available in the opinion of the investigator or must be refused by the patient., Dose expansion parts 2A and 2B:, -At least 1 measurable lesion by RECIST v1.1.

Exclusion criteria

-Age < 18 years.
-Eastern Cooperative Oncology Group (ECOG) performance status >1.
-Concurrent treatment with any other anticancer therapy (including radiotherapy or investigational agents) or participation in another clinical study.
-Washout period of less than 3 weeks to prior anticancer therapy.
-Significant and uncontrolled concomitant illness, including any psychiatric condition.
-Active infections, including unexplained fever (temperature >38.1ºC), or antibiotic therapy within 1 week prior to enrollment.
-Any prior organ transplant including allogeneic bone marrow transplant.
-History within the last 5 years of an invasive malignancy other than the one treated in this study.
-History of known HIV, unresolved viral hepatitis.
-Any major surgery within the last 28 days.
-Patients with primary central nervous system (CNS) tumors and/or CNS metastases of non-CNS primary tumors that are untreated.
-History of severe, acute or chronic heart diseases.
-History of severe, acute or chronic renal diseases or inadequate renal function.
-History of significant valvular heart disease (including valve replacement), vascular malformation and anurysm
-Any of the following within 6 months prior to study enrollment: pulmonary embolism, deep vein thrombosis, active uncontrolled bleeding, infectious or inflammatory bowel disease, diverticulitis, intestinal obstruction or

perforation and gastrointestinal hemorrhage.
-Inadequate hematological, renal or liver function.
-Non-resolution of any prior treatment related toxicity to Grade <2.
-Prior treatment with any anti-TGF-β inhibitors.
-Known allergies to any component of SAR439459 and/or REGN2810.
-Patients with uveal melanoma and patients with prior or ongoing uveitis.
-Patients who received prior immunotherapy who developed toxicity leading to a permanent discontinuation of immunotherapy.
-Ongoing or recent (within 2 years) evidence of significant autoimmune disease that required treatment with systemic immunosuppressive treatments.
-Immunosuppressive corticosteroid doses (>10 mg prednisone daily or equivalent) within 4 weeks prior to the first dose of SAR439459 and/or REGN2810 (occasional use of inhaled, intraocular, nasal or topical steroids for symptomatic relief allowed).
-History of pneumonitis or bowel perforation.
-Patients with underlying cancer predisposition syndromes.
-Therapeutic doses of anticoagulants or antiplatelet agents within 7 days prior the first dose of SAR439459
-Receipt of a live vaccine within 30 days of planned start of study medication.
-Prothrombin time (PT) or international normalized ratio (INR) > 1.5 × ULN

Study design

Design

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

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	18-11-2019
Enrollment:	12
Type:	Actual

Medical products/devices used

Product type:	Medicine

Ethics review

Approved WMO Date:	20-12-2018
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	28-08-2019
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	02-10-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	13-02-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	23-03-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	02-04-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	15-05-2020

Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	17-08-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	19-08-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	01-04-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	21-04-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	27-06-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	07-07-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	09-07-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	28-07-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	25-08-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	02-11-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	08-11-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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	EUCTR2018-001113-32-NL
CCMO	NL66868.078.18

Register	ID
Other	U1111-1187-5425

Study results

Date completed: 05-11-2021

Results posted: 21-11-2022

Summary results
Trial ended prematurely

First publication
08-07-2022