A Phase 1/2, open label, first-in-human, dose escalation and expansion study for the evaluation of safety, pharmacokinetics, pharmacodynamics, and anti-tumor activity of SAR445877 administered as monotherapy or in combination with other anticancer therapies in adults with advanced solid tumors

Published: 16-01-2023
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This study has been transitioned to CTIS with ID 2023-507141-28-00 check the CTIS register for the current data. Primary- Dose escalation: To determine the maximum tolerated dose (MTD) or maximum administered dose (MAD), recommended dose(s), and the...

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

Summary

ID

NL-OMON53618

Source
ToetsingOnline

Brief title
TCD17620

Condition

- Miscellaneous and site unspecified neoplasms malignant and unspecified

Synonym
advanced stage cancer

Research involving
Human

Sponsors and support

Primary sponsor: Sanofi-aventis
Source(s) of monetary or material Support: Pharmaceutical company Sanofi-Aventis Recherche & Developpement

Intervention

Keyword: finst-in-human, SAR445877, Solid tumors

Outcome measures

Primary outcome

- Presence of dose limiting toxicities (DLTs) in Cycles 1 and 2

- Presence of treatment-emergent adverse events (TEAEs)

- Serious adverse events (SAEs)

- Presence of TEAEs, SAEs, and lab abnormalities, according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 and American Society for Transplantation and Cellular Therapy (ASTCT) consensus grading

- Objective response rate, which is defined as the proportion of participants who have a confirmed complete response (CR) or a partial response (PR), as the best overall response determined by the Investigator as per the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1

Secondary outcome

- Objective response rate (ORR) based on RECIST1.1 criteria

- Duration of response (DoR), defined as the time from the first documented evidence of confirmed CR or PR until progressive disease (PD) determined by Investigator per RECIST 1.1 or death from any cause, whichever occurs first

- SAR445877 PK parameters, cetuximab concentrations if relevant

- Proportion of participants with ADA against SAR445877

- Time to response, defined as the time from the first administration of investigational medicinal product (IMP) to the first documented evidence of confirmed PR or CR determined by Investigator per RECIST 1.1

- Duration of response (DoR), defined as the time from first documented evidence of confirmed CR or PR until progressive disease (PD) determined by Investigator per RECIST 1.1 or death from any cause, whichever occurs first

- Clinical benefit rate including confirmed CR or PR at any time or stable disease (SD) of at least 6 months determined by Investigator per RECIST 1.1

- Progression-free survival (PFS), defined as the time from the date of first administration of IMP to the date of the first documented disease progression determined by Investigator as per RECIST 1.1 or death from any cause, whichever occurs first

- Presence of TEAEs, SAEs, and lab abnormalities, according to the NCI-CTCAE Version 5.0 and the ASTCT consensus grading

Study description

Background summary

Immune checkpoint inhibitors (ICI) have revolutionized cancer treatments. PD1/PD-L1 inhibitors can block PD1/PD-L1 interactions, which is known to drive T cells dysfunction and the release of the brake on T cell anti-tumor immune responses. However, the responses of cancer patients to ICIs vary in success. Hence, unmet needs exist in predicting such ICI responses in cancer patients. Similarly, there is an unmet need to maximize the efficacy meanwhile minimizing the toxicity of the ICIs. CD8+ tumor-infiltrating lymphocytes are critical determinants of response to ICI treatments due to their direct role in tumor cell destruction.
SAR445877 is a fusion protein of high affinity anti-PD1 antibody combined with modified IL15R sushi domain and IL15 complex. SAR445877, via its anti-PD1 binding epitope, binds to T and NK cells expressing PD1 and potentially allows for a targeted expansion and activation of CD8+ T and NK cells expressing both PD1 and IL2/15Rβγ. Nonclinical studies have demonstrated the potential of SAR445877 as an immune-modulatory agent with good tolerability and therapeutic benefits in a number of different neoplastic and metastatic disease models including in PD-L1/PD-L1 resistant models as a monotherapy.
SAR445877 treatments in preclinical models resulted in increased cytotoxic immune cell recruitment to tumor microenvironment, prolonged survival and tumor clearance.

Study objective

This study has been transitioned to CTIS with ID 2023-507141-28-00 check the CTIS register for the current data.

Primary
- Dose escalation: To determine the maximum tolerated dose (MTD) or maximum administered dose (MAD), recommended dose(s), and the overall safety and tolerability profile of SAR445877 when administered as monotherapy
- Dose expansion: To determine the objective response rate (ORR) of SAR445877 administered as monotherapy at the recommended dose(s)

Secondary
- Dose escalation: to assess preliminary clinical activity of SAR445877 monotherapy at the recommended dose(s)
- Dose escalation and expansion: To characterize the pharmacokinetic (PK) profile of SAR445877 when administered in a monotherapy
- Dose escalation and expansion: To assess the potential immunogenicity of SAR445877
- Dose expansion: To assess other indicators of antitumor activity
- Dose expansion: To characterize the safety profile of SAR445877 monotherapy

Study design

Overall design:
This is a first-in-human (FIH), open-label, multicenter, dose escalation and expansion study for the evaluation of the safety, tolerability, pharmacokinetics, pharmacodynamics, and anti-tumor activities of SAR445877 administered intravenously (IV) as a single agent in adult participants with advanced unresectable or metastatic solid tumors.
A graphical presentation of the study schema is shown in Section 1.2.

Brief summary:
This is a Phase 1/2, open label, multiple cohort study to assess the safety and preliminary efficacy of SAR445877 as a monotherapy for participants aged at least 18 years with advanced unresectable or metastatic solid tumors.

The study will include 2 parts:
- A dose escalation Part 1: for finding the therapeutic dose(s) of SAR445877 in a monotherapy given every 2 weeks (Q2W) or weekly (QW).
- The dose expansion/optimization of this study will include cohorts with different solid tumors
regardless of the TPS/CPS and cohort with a negative expression of the PD-L1.

Intervention

Part 1 (Q2W or QW): SAR445877 single agent dose escalation in participants with advanced unresectable or metastatic solid tumor

Part 2A: SAR445877 single agent expansion
- Cohorts A1 and A2: in metastatic NSCLC not amenable to available SOC
- Cohort B: in advanced unresectable or metastatic HCC post ICI.
- Cohorts C1 and C2: in advanced unresectable or metastatic GC/GEJ, CPS <1, and ICI naïve
- Cohort D: in infiltrated tumor type
- Cohorts E1and E2: in advanced unresectable or metastatic CRC who have progressed on at least 2 prior regimens. Participants must have non-MSI-H disease to be eligible.

Part 2B: SAR445877 in combination with cetuximab expansion
- Cohort E3: in advanced unresectable or metastatic CRC who have progressed on at least one prior regimen. Participants must have non-MSI-H disease to be eligible.

The duration of each cycle is 14 days and the DLT observation period consists of the first 2 cycles of treatment.

Study burden and risks

In this study, we look at how safe the new medicinal product SAR445877 is and

how well it works. We are testing SAR445877 in different strengths in patients with advanced stage cancer.

The maximum time on the study will depend on the response to treatment, when the disease worsens and how well the study treatment is tolerated.

For the study, the patients need to visit the hospital 5 times in in a span of 2 weeks in Cycle 1-3, subsequent cycles will be a minimum of 1 visit every week. A visit normally lasts up to 8 hours and could maximally last 24 hours because patients will be admitted and monitored in the hospital at least 24 hours after each dose administration during Cycle 1 and Cycle 2; in Cycle 3 and beyond, hospitalization (in hospital monitoring) will be at least for 4 hours if no serious adverse reaction is observed in the prior SAR445877 administration.

The main side effect from SAR445877 observed during animal studies consisted of: Cytokine release syndrome (CRS), infusion related reactions, immune related reactions, vascular leak syndrome, cardiovascular effect, nephrotoxicity, cytopenia, esophagal disorder, immunogenicity, anaphylaxis, risks from study procedures, risks for the unborn baby or through breastfeeding.

Cetuximab can cause serious and fatal infusion reactions, cardiopulmonary arrest, interstitial lung disease, dermatologic toxicity, hypermagnesemia and accompanying electrolyte abnormalities, increased tumor progression, increased mortality, or lack of benefit in patients with Ras-Mutant mCRC and embryo-fetal toxicity.

There are no clinical data on the combination of SAR445877 and cetuximab.

Given the experimental nature of the study, it is not certain that patients will directly benefit from participating.

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

I 01. Participant must be at least 18 years of age inclusive, at the time of signing the informed consent.
Dose escalation Part 1:
I 02. Participants with advanced unresectable or metastatic solid tumors for which, in the judgement of the investigator, no standard alternative therapy is available or is not in the best interest of the participant.
Dose expansion/optimization Part 2:
Cancer diagnosis:
I 03. Participants in Cohorts 1A and A2: Histologically or cytologically confirmed diagnosis of metastatic NSCLC.
I 04. Participants in Cohort B: Histologically or cytologically confirmed diagnosis of advanced unresectable or metastatic HCC, or clinically by American Association for the Study of Liver Diseases (AASLD) criteria in cirrhotic patients (participants without cirrhosis must have had histological confirmation of diagnosis).
I 05. Participants in Cohorts C1 and C2: Histologically or cytologically confirmed diagnosis of advanced unresectable or metastatic GC or Siewert Type 2 & 3 GEJ.
I 06. For participants in Cohorts C1 and C2: Disease with CPS scoring of <1 as determined at local laboratory with an Agency approved test (for the other cohorts: Disease with any CPS scoring. No need for CPS determination at local laboratory).
I 07. For participants in Cohorts C1 and C2: Participants must have MSI or MMR status known or determined locally and must have non-MSI-H or proficient MMR (pMMR) disease to be eligible.

I 08. For participants in Cohorts C1 and C2: Participants with unknown HER2/neu status must have their HER2/neu status determined locally. Participants with HER2/neu negative are eligible.
Participants with HER2/neu positive tumors must have documentation of disease progression on treatment containing an approved HER2 targeted therapy to be eligible.
Prior anticancer therapy (For dose expansion/optimization Part 2 only):
I 09. Participants in Cohorts A1 and A2: Participants must have received at least 1 systemic therapy for the metastatic setting and must not be amenable to the available SOC.
Participants in Cohort B: Participants who have received at least 1 prior anticancer therapy, including an anti-PD1/PD-L1 containing regimen, and for whom have progressed after a primary or secondary resistance to an anti-PD1/PD-L1.
Primary resistance: participant must have experienced PD or SD lasting <6 months since the initiation of the anti-PD1/PD-L1 inhibitor-based treatment and the participant must have received PD1/PD-L1 for at least 6 weeks. Radiographic confirmation of the PD must be documented after a minimum of 4 weeks after the initial identification of progression, unless: 1) investigator confirms clinical progression/deterioration attributed to PD, or 2) the first radiographic assessment indicated critical tumor growth by imaging (size or location).
Secondary resistance: participants must have experienced PD, either during or within 3 months of discontinuing treatment with an anti-PD1 based therapy, occurring after previous clear benefit (any complete [CR] or partial response [PR]), or after previous SD of >6 months. There is no requirement for radiographic confirmation of the progression.
I 10. Participants in Cohorts C1 and C2: Participants should have failed or relapsed after at least 1 prior line of treatment, which does not include an anti-PD1/PD-L1-based treatment.
Measurable Disease:
I 11. At least 1 measurable lesion per RECIST 1.1 criteria. Target lesions may be located in a previously irradiated field if there is a documented radiographic disease progression in that site.
Provision of tumor tissue:
I 12. Mandatory baseline biopsy for all participants treated in the Escalation Part from DL3 in Part 1 Q2W schedule and from DL1 QW schedule, and for all participants in the Expansion Part 2: Biopsies will be obtained if considered to be an acceptable risk by the treating physician. The slide specifications are detailed in the Lab Manual. Mandatory on-treatment biopsy for all participants treated in the Escalation Part from DL3 in Part 1, and for participants in the Expansion Part 2, if clinically feasible and considered to be an acceptable risk per investigator's discretion.
Note:
Tumor site used for biopsy must not have been irradiated previously and must not be the only measurable lesion.
Not applicable to cohort D: The Sponsor may approve the written request to

enroll, on a case-by-case basis, for participants with:
• the location of the tumor not amenable to biopsy due to a significant risk, OR
• less than required number of slides or with an archival tumor tissue sample collected more than 6 months prior to screening
Weight
I 13. Body weight within 40-150 kg (inclusive).

I 17. For participants in Cohort D: Participants with tumors that are usually considered immunogenic "hot" tumors infiltrated by T cells as any of the following: histologically or cytologically confirmed diagnosis of advanced unresectable or metastatic melanoma, non-small cell lung cancer, bladder, head and neck, kidney, and liver cancer or other indications known to be immunogenic at the discretion of the investigator with agreement of the study medical monitor.
I 18. Participants in Cohort D: Participants must have received at least 1 systemic therapy for their advanced/ metastatic setting and must not be amenable to the available SOC.
I 19. Participants in Cohorts E1, E2 and E3: Histologically or cytologically confirmed diagnosis of advanced unresectable or metastatic colorectal cancer.
I 20. Participants in Cohorts E1, E2 and E3 MSI status: Participants must have MSI status known or determined locally and must have non-MSI-H disease to be eligible.
I 21. Participants in Cohorts E1, E2 and E3: Participants with RAS-mutant and BRAF-mutant colorectal cancer are eligible for enrollment.
I 22. Prior anticancer therapy: Participants in cohorts E1 and E2 should have failed or relapsed on at least 2 prior regimens.
I 23. Participants in cohort E3 should have failed or relapsed on at least 1 prior regimen. Participants who have received cetuximab or other anti-EGFR therapy as part of their prior line of treatment are eligible.

Exclusion criteria

E 01. Eastern Cooperative Oncology Group (ECOG) performance status of >=2.
E 02. Predicted life expectancy <=3 months.
E 03. For participants with HCC- Cohort B (Part 2): Child Pugh Class B or C liver score. Participants with Child Pugh Class B-7 score are allowed for Part 1.
E 04. Diagnosed of any other malignancies, either progressing or requiring active treatments, within 2 years prior to enrollment, except for basal cell carcinoma or squamous cell carcinoma of the skin, which are in-situ malignancies, as well as superficial bladder carcinoma, or low risk prostate cancer, and any tumors that have been deemed as effectively treated with definitive local control.
E 05. Active brain metastases or leptomeningeal metastases:
• Participants with previously treated brain metastases are eligible, provided

they are clinically stable for at least 4 weeks with no evidence of new or enlarging brain metastases, and have not received corticosteroids for at least 2 weeks prior to the first IMP administration.
• Participants with asymptomatic brain metastases (ie, no neurological symptoms, no requirements for corticosteroids, and no lesion >1.5 cm) are eligible but will require regular imaging of the brain at the site of the disease.
E 06. History of treatment-related immune-mediated (or immune-related) AEs from immune modulatory agents (including but not limited to anti-PD1/PD-L1 agents and anti-cytotoxic T lymphocyte associated protein 4 monoclonal antibodies) that caused permanent discontinuation of the agent, or that were Grade 4 in severity, or have not resolved to Grade <=1.
E 07. Has any condition requiring ongoing/continuous corticosteroid therapy (>10 mg prednisone/day or an anti-inflammatory equivalent) within 1 week prior to the first dose of the study medicine. Physiologic replacement doses are allowed even if they are >10 mg of prednisone/day or equivalent, as long as they are not being administered for immunosuppressive intent. Inhaled or topical steroids are permitted, provided that they are not for treatment of an autoimmune disorder. Note: Participants who require a brief course of steroids (up to 2 days in the week before enrollment) or physiologic replacement are eligible to be enrolled in the study.
E 08. Any clinically significant cardiac (including valvular) or vascular (thromboembolic disorders) disease, within 6 months prior to the first IMP administration, such as:
• Congestive heart failure (New York Heart Association Class II to IV, or left ventricular ejection fraction <50%).
• Increased troponin (higher than upper limit of normal [ULN] per local laboratory) at screening. Participants with a higher troponin may be allowed upon cardiologist consultation and discussion with the Study Medical Monitor on a case-by-case basis.
• Unstable or poorly controlled angina, myocardial infarction, coronary artery revascularization procedure (eg, coronary artery bypass graft, percutaneous coronary intervention).
• Transient ischemic attack, cerebral infarction (stroke), symptomatic pulmonary embolism, and peripheral artery revascularization procedure.
• Uncontrolled cardiac arrhythmia requiring medication (>= Grade 2, according to the NCI-CTCAE V5.0).
E 09. History of congenital long QT syndrome, torsades de pointes or prolonged QTc interval >480 msec using Fridericia*s formula (unless a pacemaker is in place).
E 10. Ongoing AEs >=Grade 2 (NCI CTCAE V5.0) caused by any prior anti-cancer therapy with the exception of Grade 2 alopecia, vitiligo, fatigue, and active hypothyroidism, and stable neuropathy.
E 11. Ongoing or recent (within 2 years) evidence of significant autoimmune disease that required treatment with systemic immunosuppressive treatments, which may suggest risk for immune-related AEs (irAEs). Participants with the following conditions are eligible: vitiligo, childhood asthma that has

resolved, residual hypothyroidism that required only hormone replacement or psoriasis that does not require systemic treatment.
E 12. Has a known history or any evidence of interstitial lung disease or active, non-infectious pneumonitis within 3 years prior to the first dose of the study drug. A history of radiation pneumonitis in the radiation field is permitted.
E 13. Organ transplant requiring immunosuppressive treatment.
E 14. Uncontrolled or active infection with human immunodeficiency virus (HIV), hepatitis B, or hepatitis C infection, or has a diagnosis of immunodeficiency.
• Participants will be tested for hepatitis C virus (HCV) and hepatitis B virus (HBV) at screening.
• Participants with a known HIV infection, if controlled (undetectable viral load [HIV RNA PCR] and CD4 count above 350, either spontaneously or on a stable antiviral regimen), are permitted. For participants with a controlled HIV infection, monitoring will be performed per local standards.
• Participants with a controlled hepatitis B (HBsAg+) infection (serum HBV DNA PCR that is below the limit of detection and receiving anti-viral therapy for hepatitis B) are permitted. Participants with controlled infections must undergo periodic monitoring of the HBV DNA. Participants must remain on anti-viral therapy throughout the study treatment.
• Participants who are hepatitis C virus antibody positive (HCV Ab+), and whose infection is controlled (undetectable HCV RNA by PCR either spontaneously or in response to a successful prior course of anti-HCV therapy), may be enrolled into the study.
E 15. Clinically not controlled chronic or ongoing infectious disease requiring hospitalization or treatment within the 14 days prior first IMP administration.
E 16. Known severe hypersensitivity (>= Grade 3) to or contraindication for the use of any study intervention or components thereof, including premedication that may be administered in this study. Otherwise, sensitivity of any grade or allergies that, in the opinion of the investigator contraindicates participation in the study. For Cohort E3 (receiving cetuximab) Participant has a history of allergic reactions attributed to compounds of chemical or biologic composition similar to those of cetuximab, or if the participant had red meat allergy/tick bite history.
Prior/concomitant therapy
E 17. Is unable or unwilling to take the premedication that may be used.
E 18. Last administration of prior antitumor therapy within 21 days or less than 5 times the half-life, whichever is shorter; major surgery or local therapy within 21 days prior to first dose of IMP. Participants who received anti-PD-1 therapy require an interval of 90 days prior to first dose.
E 19. Washout period of less than 2 weeks prior to radiotherapy. A 1-week washout is permitted for palliative radiation for a non-central nervous system disease.
E 20. Receipt of a live-virus vaccination within 28 days of the planned treatment start date.
E 21. For participants in Cohorts C1 and C2: Prior treatment with an agent (approved or investigational) that blocks the PD1/PD-L1 pathway (participants

who had joined a study with an anti-PD1/PD-L1 but have a written confirmation they were on the control arm are allowed).
Prior/concurrent clinical study experience
E 22. Participation in any other clinical study in which the last investigational study treatment administration was within 5 half-lives from this study*s intervention initiation ie, prior to the first IMP administration.
Diagnostic assessments
E 23. Inadequate organ and bone marrow functions as evidenced by:
• Absolute neutrophil count (ANC) <1500 cells/µL (1.5 × 109/L). No granulocyte colony stimulating factor (G-CSF) is permitted in order to reach this value.
• Platelets <100 × 10^3/µL or <100 × 109/L. Platelet transfusion is not allowed within 3 days prior to the screening hematological test.
• Hemoglobin <9 g/dL (transfusion support within prior 2 weeks i

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	09-10-2023
Enrollment:	37
Type:	Actual

Medical products/devices used

Registration:	No

Ethics review

Approved WMO

Date:	16-01-2023

Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	03-04-2023
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	10-08-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	21-09-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	05-02-2024
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	21-02-2024
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	10-06-2024
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	07-10-2024
Application type:	Amendment
Review commission:	METC NedMec

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
EU-CTR	CTIS2023-507141-28-00
EudraCT	EUCTR2022-001239-95-NL
ClinicalTrials.gov	NCT05584670
CCMO	NL83123.041.22