A Phase 1/2, open-label, multicenter, dose escalation and dose expansion study of SAR442720 in combination with other agents in participants with advanced malignancies

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The primary goal of Part 3 of this study is to evaluate the safety, recommended phase 2 dose (RP2D), antitumor effect and PK of SAR442720 in combination with KRAS G12C inhibitor adagrasib, in participants with NSCLC with KRAS G12C mutationsPart-3a...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Respiratory tract neoplasms
Study type	Interventional

Summary

ID

NL-OMON51317

Source
ToetsingOnline

Brief title
TCD16210

Condition

- Respiratory tract neoplasms

Synonym
metastatic non small cell lungcancer; metastatic lung cancer

Research involving
Human

Sponsors and support

Primary sponsor: Genzyme Europe BV
Source(s) of monetary or material Support: Sanofi

Intervention

Keyword: KRASG12C mutations, NSCLC (non small cell lung cancer)

Outcome measures

Primary outcome

Part 3a:

Incidence, nature and severity of TEAEs and SAEs according to NCI CTCAEv5.0 for the combination of SAR442720 and adagrasib.

Part 3b:

Objective response rate (ORR) defined as the percentage of participants with a confirmed complete response (CR) or partial response (PR) determined by the investigator, per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1

Secondary outcome

Part 3 of the study:

Duration of response (DOR) of SAR442720 and adagrasib in all participants.

Overall Response Rate (ORR) of the combination treatment with SAR442720 and adagrasib, based on RECIST v1.1

Part 3a:

- plasma concentrations of SAR442720 and plasma concentrations of adagrasib

- ORR of SAR442720 and adagrasib in all participants (based on RECIST v1.1).

Part 3b: the determination of

- the duration of the response

- the incidence of adverse reactions

- the time to response (TTR)

- the clinical benefit rate (CBR)

- disease control rate (DCR)

- progression free survival (PFS)

Study description

Background summary

The RAS-MAPK pathway is frequently dysregulated in human cancers, typically as a result of genomic alterations that lead to hyperactivation. These alterations can occur at 3 levels: 1) upstream of RAS in RTKs, 2) directly within mediators of the RAS catalytic cycle (RAS isoforms and RAS GTPase activating proteins [GAPs], such as neurofibromin 1 [NF1]), or 3) in downstream effector kinases, such as BRAF or MEK.
SAR442720 is a potent, selective, and orally bioavailable SHP2 allosteric inhibitor. SHP2 is a positive upstream regulator of RAS activation, and thus, presents a suitable therapeutic target for patients whose tumors harbor oncogenic mutations that remain dependent on active RAS cycling between GTP- and GDP-bound state. Examples of these include subsets of KRASG12, NF1 LOF mutations, class 3 type mutations in BRAF or amplification of wild-type KRAS.
SHP2 is also involved in signaling in T-cells. It binds with PD-1 following PD-L1 stimulation and inhibits T-cell activation. Therefore, targeting SHP2 may restore or even enhance T-cell functions. The costimulatory receptor CD-28, and to some extent the T-cell receptor, are dephosphorylated and de-activate some critical components of the interferon gamma (IFNγ) signaling cascade, defects in which have been described as a key component of resistance to anti-PD1 therapy. SHP2 inhibition may increase the efficacy of PD1 inhibitors in patients with high PD-L1 expression but may also sensitize patients with low PD-L1 expression to a PD1 inhibitor.
SHP2 is expressed in immune cells and plays a role in signal transduction downstream of regulatory immunoreceptors, including PD-1. Preclinical studies have demonstrated a role for SHP2 in tumor immunity through modulation of both innate and adaptive mechanisms. Consistent with a pleiotropic effect on the immune system, SHP2 inhibition has been shown to attenuate tumor growth in

syngeneic models of mouse tumors that are apparently insensitive to a direct, cell intrinsic effect of SHP2 inhibition. Given the potential complementary mechanisms of action, SAR442720 plus anti-PD-1 represents a rational combination which was evaluated in preclinical models.
Preclinical testing confirms that SHP2 inhibition does not confer sensitivity to PD1 refractory tumors. In addition, the preliminary observations from patients receiving single agent SAR442720 suggest increased T-cell infiltration and activation of innate immune system in tumors during SHP2i treatment. Considering that SHP2 plays vital roles in tumor growth and tumor immunity, so combination of SAR442720 with anti-PD1 therapy would provide a promising therapeutic strategy.
The TCD16210 study consists of 4 parts.
The purpose of the escalation part (Part-1) is to evaluate the safety, PK, and preliminary efficacy of escalating doses of SAR442720 in combination with pembrolizumab in adult participants with relapsed/refractory solid tumors with specific mutations/rearrangements that result in hyperactivation of the RAS-MAPK pathway and to identify the RP2D for this combination. The purpose of the expansion part (Part-2) is to evaluate the anti-tumor activity and safety of SAR442720 combined with pembrolizumab in first-line treatment of participants with advanced NSCLC. The purpose of Part-3 (Part-3A: dose escalation and Part-3B: dose expansion) of this study is to evaluate the safety, recommended Phase 2 dose (RP2D), anti-tumor effect, and PK of SAR442720 in combination with KRAS G12C inhibitor, adagrasib in participants with NSCLC harboring KRAS G12C mutations. The purpose of Part-4 of this study is to evaluate the effect of food on the PK of SAR442720 tablet and the relative bioavailability of SAR442720 tablet formulation (test) compared to the SAR442720 capsule formulation (reference), when dosed in combination with pembrolizumab to participants with advanced malignancies.
Netherlands will only take part in part 3 of the trial where SAR442720 will be combined with adagrasibin patients with KRAS 12G3 mutant NSCLC.
The rationale for combining SAR442720 with adagrasib is that the addition of SAR442720 to adagrasib may promote anti-tumor activity by inhibiting the cycling to GTP-bound KRAS for both mutant and wild type KRAS species, therefore theoretically preventing resistance. Nonclinical and clinical studies observations with RAF inhibitors have suggested that inhibition of RAS signaling may be transient due to feedback activation. Mechanistic studies have shown that such adaptive resistance may be mediated by SHP2, and clinical trial observations have implicated RTK signaling. The combination of SAR442720 and adagrasib may augment anti-tumor activity through inhibition of feedback activation and consequently prevent resistance.
The KRAS G12C mutation occurs frequently in NSCLC (14%) and effective targeted therapies for cancers with KRAS mutations remain an unmet medical need. KRAS G12C mutant NSCLC patients showed a variable and submaximal response to KRAS G12C inhibitors; objective response rate (ORR) to sotorasib, another KRAS G12C inhibitor that was granted accelerated approval for NSCLC patients, was 37% and ORR to adagrasib was 45%. In addition, it was shown in mouse model that treatment with MRTX849 remodeled the tumor immune microenvironment and was able

to produce sustained complete response when combined with check point inhibitors in immune competent animals but not in T-cell deficient mice. These data suggest that SHP2 inhibition in combination with KRAS G12C inhibitor has potential to enhance the anti-tumor activity by blocking the receptor tyrosine kinase resistance mechanisms as well as by contributing to immune permissive tumor microenvironment.

Study objective

The primary goal of Part 3 of this study is to evaluate the safety, recommended phase 2 dose (RP2D), antitumor effect and PK of SAR442720 in combination with KRAS G12C inhibitor adagrasib, in participants with NSCLC with KRAS G12C mutations

Part-3a is the dose escalation part involving safety. the tolerability and the recommended phase 2 dose is identified and part-3b is the dose extension at which the anti-tumor activity is determined.

The secondary goal of Part 3 in this study is:
in Part 3A characterizing the PK of SAR442720 with adagrasib, and the PK of adagrasib with SAR442720 to estimate the anti-tumor effects of SAR442720 with adagrasib
in Part 3B, assessing the safety profile of SAR442720 with adagrasib, to assess other indicators of anti-tumor activity, and
assessing the PK of SAR442720 with adagrasib, and the PK of adagrasib with SAR442720.

Study design

A phase 1/2, open-label, multicenter, dose escalation and dose expansion study

Intervention

Dose-escalation part 3A;
SAR442720 and adagrasib are administered orally on a continuous basis.

Dose-expansion part 3B:
The dose of SAR442720 confirmed in Part 3a and a fixed dose of adagrasib will be administered orally continuously.

Study burden and risks

The risks are related to the blood samples and the tumor biopsies taken and to the possible side effects of the study drugs.
The increased burden on the patient are the more frequent visits to the

hospital.

Contacts

Public
Genzyme Europe BV

Paasheuvelweg 25
Amsterdam 1105 BP
NL
Scientific
Genzyme Europe BV

Paasheuvelweg 25
Amsterdam 1105 BP
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

- Participants must be >= 18 years of age
- Histologically proven diagnosis of advanced solid tumors
- Participants must have one or more of the following molecular aberrations:
KRAS mutations and amplifications, BRAF Class 3 mutations, or NF1 LOF mutations
- Participants must have following molecular aberration (Part 3A and 3B): -
KRAS G12C mutation
- At least 1 measurable disease per RECIST 1.1 criteria.
- Eastern Cooperative Oncology Group (ECOG) performance status 0-1
- Woman of childbearing potential must agree to follow contraceptive guidance

- Capable of giving signed informed consent

Exclusion criteria

- Predicted life expectancy <3 months.
- Primary central nervous system (CNS) tumors.
- Symptomatic or impending cord compression. Stable CNS disease is allowed.
- History of cerebrovascular stroke or transient ischemic attack within previous 6 months.
- Prior solid organ or hematologic transplant.
- History or current retinal pigment epithelial detachment (RPED), central serous retinopathy, retinal vascular occlusion (RVO), neovascular macular degeneration
- Any clinically significant cardiac disease
- Active, known or suspected autoimmune disease
- History of or current interstitial lung disease or pneumonitis
- Receipt of a live-virus vaccination within 28 days, viral vaccine that do not contain live virus within 7 days of planned treatment start. Seasonal flu vaccines that do not contain live virus are permitted.
- Known infection with human immunodeficiency virus (HIV), known uncontrolled hepatitis B infection, active tuberculosis, or severe infection requiring parenteral antibiotic treatment.
- Inadequate hematologic, hepatic and renal function
- Known second malignancy
- Impairment of gastrointestinal function
- Any unstable or clinically significant concurrent medical condition that would, in the opinion of the investigator, jeopardize the safety of a participant, impact their expected survival through the end of the study participation, and/or impact their ability to comply with the protocol.
- History of severe allergic reaction to any of the study intervention components

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	5
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	nvt
Generic name:	adagrasib

Ethics review

Approved WMO Date:	17-05-2022
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	30-06-2022
Application type:	First submission
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
EudraCT	EUCTR2020-000436-22-NL
ClinicalTrials.gov	NCT04418661
CCMO	NL81060.041.22