A Phase 1, Multicenter, Open-Label Study of SQZ-AAC-HPV as Monotherapy and in Combination with Immune Checkpoint Inhibitors in HLA-A*02+ Patients with HPV16+ Recurrent, Locally Advanced or Metastatic Solid Tumors

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Primary ObjectivesPart 1 (Monotherapy Dose Escalation Phase):* To determine the recommended Phase 2 dose (RP2D) of SQZ AAC HPV monotherapy. * To characterize the safety and tolerability of SQZ AAC HPV administered as monotherapy. Part 2 (Combination...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Miscellaneous and site unspecified neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON50875

Source
ToetsingOnline

Brief title
SQZ-AAC-HPV

Condition

- Miscellaneous and site unspecified neoplasms malignant and unspecified

Synonym

Cancer caused by the human papilloma virus (HPV), Late-stage cancer

Research involving
Human

Sponsors and support

Primary sponsor: SQZ Biotechnologies
Source(s) of monetary or material Support: pharmaceutische industrie

Intervention

Keyword: HLA-A*02+, HPV16+, locally advanced or metastatic cancer', 'Recurrent, SQZ-AAC-HPV

Outcome measures

Primary outcome

1. The primary endpoint for safety is the number of patients with any AE and observed toxicity to SQZ-AAC-HPV administration, where the severity is assessed using NCI CTCAE version 5.0. All AEs with onset after the first administration of SQZ-AAC-HPV will be included in the analysis. Adverse events will be collected beginning at signing informed consent; however, analyses will be performed focusing on treatment-emergent AEs.

Secondary outcome

1. Preliminary evidence of antitumor activity of SQZ-AAC-HPV monotherapy and in combination with an immune checkpoint inhibitor(s) will be evaluated per RECIST 1.1 and iRECIST:

* Progression-free survival

* Disease control rate

* Objective response rate

* Stable disease lasting at least 12 weeks

* Time to best overall response

* Duration of response

* Overall survival

2. Manufacturing feasibility: Individual patient batch yield, product failure

prohibiting use of out-of-specification product, and any additional information

from blood collection for manufacture of autologous blood product through

SQZ-AAC-HPV production that is deemed relevant.

Study description

Background summary

SQZ-AAC-HPV is a red blood cell (RBC)-derived product of activating antigen carriers (AACs), as a treatment for human papillomavirus (HPV) strain 16 positive (HPV16+) cancer in human leukocyte antigen (HLA) serotype within the HLA-A serotype group positive (HLA-A*02+) patients.

SQZ-AAC-HPV-101 includes patients who are HLA A*02+ with advanced-stage, previously treated HPV16+ solid tumors (head and neck, cervical cancer, and other tumor types). There are several reasons to suggest that the proposed patient population will provide the most favorable risk-benefit ratio for SQZ-AAC-HPV and, therefore, is the appropriate population for this first in-human (FIH) study. First, the AAC-HPV drug substance is prepared by incorporating E6 SLP and E7 SLP, which contain HLA-A*02 antigenic epitopes to HPV16 (E6 and E7 proteins), into the autologous AACs using the Cell Squeeze process. Second, based on the hypothesized mechanism of action of SQZ-AAC-HPV, it is anticipated that the CD8+ T cells induced by SQZ AAC HPV will migrate into the tumor and recognize tumor cells presenting E6 or E7 epitopes and target them for destruction. Third, the nonclinical syngeneic tumor efficacy study was conducted in mice with HPV16+ tumors, and this study showed encouraging results (delayed tumor growth and extended survival due to cytotoxic T cells infiltrating the tumor).

Study objective

Primary Objectives
Part 1 (Monotherapy Dose Escalation Phase):
* To determine the recommended Phase 2 dose (RP2D) of SQZ AAC HPV monotherapy.

* To characterize the safety and tolerability of SQZ AAC HPV administered as monotherapy.
Part 2 (Combination Safety Phase):
* To determine the RP2D of SQZ AAC HPV in combination with (1) ipilimumab, (2) nivolumab, and (3) nivolumab plus ipilimumab.
* To characterize the safety and tolerability of SQZ AAC HPV at the RP2D administered in combination with (1) ipilimumab, (2) nivolumab, and (3) nivolumab plus ipilimumab.

Secondary Objectives (Parts 1 and 2)
* To assess the antitumor activity of SQZ AAC HPV in patients with recurrent, locally advanced or metastatic solid tumors.
Part 1 only:
* To assess the manufacturing feasibility of SQZ-AAC-HPV.
Exploratory Objectives (Parts 1 and 2)
* To explore changes in blood cytokines after treatment with SQZ AAC HPV.
* To characterize the immunogenic and pharmacodynamic effects (on selected pharmacodynamic parameters) and duration of pharmacodynamic response following SQZ AAC-HPV administration.

Study design

This is a Phase 1 open-label, multicenter study of the safety and tolerability, antitumor activity, and immunogenic and pharmacodynamic effects of SQZ AAC HPV as monotherapy and in combination with (1) ipilimumab, (2) nivolumab, and (3) nivolumab plus ipilimumab, in HLA A*02+ patients with recurrent, locally advanced or metastatic HPV16+ solid tumors.

This study will be conducted in 2 parts, with Part 1 consisting of a dose escalation phase to determine the safety profile, preliminary efficacy, and RP2D of SQZ-AAC-HPV monotherapy. Part 2 of the study will evaluate the safety and preliminary efficacy of SQZ-AAC-HPV when combined with immune checkpoint inhibitors, the Combination Safety Phase.

Intervention

In both parts of the study, SQZ AAC-HPV will be administered at 3 week intervals until the SQZ AAC-HPV supply is exhausted, treatment discontinuation criteria are met (protocol section 7.1), or for a maximum of 1 year, whichever comes first. Patients who experience disease progression per Response Evaluation Criteria for Solid Tumors version 1.1 (RECIST 1.1) may continue dosing if considered in their best interest by the treating Investigator to allow for confirmation of disease progression; ie, immune confirmed progression (iCPD) according to modified RECIST criteria for incorporation into solid tumor studies of immunotherapeutics (iRECIST) (Seymour et al, 2017).

Study burden and risks

Please refer to SISICF and section E9a

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

1. Male or female patients *18 years of age who are HLA-A*02+, as confirmed by genotyping assay from blood.
2. Histologically confirmed incurable or metastatic solid tumors (including but not limited anal, to cervical and head and neck tumors) that are HPV16+.
3. For cervical cancer, which is not amenable to curative treatment with surgery, radiation, and/or chemoradiation therapy, the cancer must have

progressed after prior systemic chemotherapeutic treatment with a platinum-based regimen in the adjuvant or recurrent setting. Patients must have progressive disease (PD) while receiving or after the completion of the most recent prior treatment.
4. For recurrent and metastatic head and neck cancer, which is not amenable to curative treatment with surgery, radiation, and/or chemoradiation therapy, the cancer must have progressed following at least 1 prior platinum-based chemotherapy in the primary, adjuvant, or recurrent setting and been offered checkpoint immunotherapy. Patients who relapsed after platinum-containing definitive chemoradiation or after adjuvant chemoradiation are eligible if a platinum re-challenge at time of relapse is not seen as beneficial.
5. Patients with incurable or metastatic HPV16+ cancers other than cervical or head and neck cancer must have progressed after at least 1 available standard therapy for incurable disease, or the patient is intolerant to or refuses standard therapy(ies) or has a tumor for which no standard therapy(ies) exist.
6. Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 to 1.
7. Patients must agree to venous access for the blood collection for manufacture of autologous blood product and be willing to have a central line inserted if venous access is an issue.
8. Patients with unresectable or metastatic solid tumors must have a lesion that can be biopsied with acceptable clinical risk and agree to have a fresh biopsy at Screening and on Cycle 2 Day 8 (±2 days). The second biopsy must be taken from the same lesion of the biopsy at Screening.
9. At least 1 measurable lesion according to RECIST 1.1.
10. Adequate organ function and bone marrow reserve as indicated by the following laboratory assessments performed within 14 days prior to the blood collection for manufacture of autologous blood product:
a. Bone marrow function: absolute neutrophil count *1000/µL; hemoglobin *9 g/dL; platelet count *75,000/µL.
b. Hepatic function: total serum bilirubin *1.5 × ULN; serum AST/ALT, *2.5 × ULN (*5 × ULN in the presence of hepatic metastases); alkaline phosphatase <2.5 × ULN with the following exception: patients with liver and bone involvement: alkaline phosphatase *5 × ULN.
c. Renal function: serum creatinine *2.5 × ULN or creatinine clearance *30 mL/min based either on urine collection or Cockcroft-Gault estimation.
d. Coagulation profile: prothrombin time (PT), international normalized ratio (INR)/partial thromboplastin time (PTT) *1.5 × ULN. Patients on a stable, maintenance regimen of anticoagulant therapy for at least 30 days prior to blood collection for manufacture of autologous blood product may have PT/INR measurements >1.5 × ULN if, in the opinion of the Investigator, the patient is suitable for the study. An adequate rationale must be provided to the Sponsor prior to enrollment.
11. Patients with immune-mediated endocrinopathies following treatment with immune checkpoint inhibitors requiring hormone replacement therapy are eligible.
a. Patients requiring prednisone as part of hormone replacement therapy are eligible if the daily doses do not exceed 10 mg.
12. Female patients of childbearing potential must:

a. Have a negative serum beta human chorionic gonadotropin (*-hCG) pregnancy test at Screening, and
b. Agree to use highly effective contraception from the time of informed consent until at least 5 months after the last dose of immune checkpoint inhibitor or SQZ AAC-HPV (CTFG, 2020).
13. Male patients who are not vasectomized must be willing to use condoms from the time of informed consent until at least 5 months after the last dose of immune checkpoint inhibitor or SQZ AAC HPV.
14. The patient is capable of understanding and complying with the protocol and has signed the required informed consent form (ICF). The appropriate ICF must be signed before relevant study procedures are performed. If applicable, the female partner of a male patient understands and signs the pregnant partner ICF.

Exclusion criteria

1. Treatment with anticancer therapy, including investigational therapy, within 2 weeks prior to blood collection for manufacture of autologous blood product. For prior therapies with a half-life longer than 3 days, timing of discontinuation of the therapy should be discussed with Sponsor.
2. Patients with >Grade 1 AEs (except Grade 2 alopecia) according to NCI CTCAE version 5.0 related to previous treatment with anticancer or investigational therapy that do not resolve (ie, to >Grade 2) at least 2 weeks prior to blood collection for manufacture of autologous blood product.
3. History of any Grade 4 irAE from prior immunotherapy (patients with endocrinopathy managed with replacement therapy or asymptomatic elevation of serum amylase or lipase are eligible), any irAE that led to permanent discontinuation of prior immunotherapy, or any Grade 3 irAE that occurred *6 months prior to blood collection for manufacture of autologous blood product.
4. Patients treated with non-corticosteroid based immunosuppressive agents within the last 6 months may not be eligible and should be discussed with Sponsor.
5. Patients with active, known, or suspected autoimmune disease may not be eligible and should be discussed with Sponsor.
6. Patients who have undergone splenectomy.
7. Patients who have received or who are anticipated to require blood transfusion within 4 weeks prior to the blood draw for autologous investigational product manufacture.
8. Patients with prior allogeneic bone marrow or solid organ transplantation may not be eligible and should be discussed with Sponsor.
9. Live virus vaccination within 4 weeks prior to blood collection for manufacture of autologous blood product.
10. Systemic treatment with either corticosteroids (>10 mg of prednisone or the equivalent per day) or other immunosuppressive medications within 14 days prior to blood collection for manufacture of autologous blood product.

11. Known active central nervous system metastases and/or carcinomatous meningitis. Patients with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least 4 weeks prior to the first dose of investigational product and any neurologic symptoms have returned to Baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 7 days prior to blood collection for manufacture of autologous blood product. This exception does not include carcinomatous meningitis, which is excluded regardless of clinical status.
12. History of interstitial lung disease requiring steroids, idiopathic pulmonary fibrosis, pneumonitis (including drug induced), or organizing pneumonia (eg, bronchiolitis obliterans, cryptogenic organizing pneumonia).
13. Clinically significant cardiac disease, including unstable angina, acute myocardial infarction within 6 months prior to blood collection for manufacture of autologous blood product, New York Heart Association class III or IV congestive heart failure, and arrhythmia requiring therapy.
14. Systemic arterial thrombotic or embolic events, such as cerebrovascular accident (including ischemic attacks) within 1 month prior to blood collection for manufacture of autologous blood product.
15. Systemic venous thrombotic events (eg, deep vein thrombosis) or pulmonary arterial events (eg, pulmonary embolism) within 1 month prior to blood collection for manufacture of autologous blood product.
16. History or presence of an abnormal ECG that, in the Investigator*s opinion, is clinically meaningful.
17. Left ventricular ejection fraction (LVEF) <50%.
18. Major surgery within 2 weeks of blood collection for manufacture of autologous blood product; following major surgeries >2 weeks prior to blood collection for manufacture, all surgical wounds must be healed and free of infection or dehiscence.
19. Any other clinically significant comorbidities, such as active infection, known psychiatric or neurological disorder, or any other condition, which in the judgment of the Investigator, could compromise compliance with the protocol, interfere with the interpretation of study results, or predispose the patient to safety risks.
20. Known active hepatitis B or hepatitis C, or active mycobacterium tuberculosis infection.
21. History of alcohol and/or illicit drug abuse within 12 months of entry.
22. Female patients who are breastfeeding or have a positive serum pregnancy test at the Screening visit.
23. History of allergy or hypersensitivity to any component of SQZ AAC HPV.
24. History of severe allergic anaphylactic reactions to chimeric, human, or humanized antibodies or infusion proteins (combination cohorts only).
25. Known hypersensitivity to ipilimumab, nivolumab, Chinese hamster ovary cell products, or any component of the ipilimumab or nivolumab formulation (combination cohorts only).
26. Enrollment of HIV+ patients should be discussed with Sponsor.

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
Generic name:	Somatic cells autologous
Product type:	Medicine
Brand name:	Opdivo
Generic name:	Nivolumab
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Yervoy
Generic name:	Ipilimumab
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	23-07-2021
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Approved WMO

Date:	02-02-2022
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	25-02-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	10-03-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	08-04-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	11-04-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	05-08-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	15-08-2022
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	EUCTR2021-000992-35-NL
ClinicalTrials.gov	NCT04892043
CCMO	NL77147.000.21