Phase I First Time in Human Open Label Study of GSK3745417 administered with and without Anticancer Agents in Participants with Advanced Solid Tumors (study 208850)

Published: 10-04-2019
Last updated: 09-04-2024

Primary (PART 1A ONLY):Dose escalation: To determine the safety, tolerability, and the recommended phase 2 dose (RP2D) of GSK3745417 alone administered intravenously to participants with selected advanced/recurrent solid tumors.Secondary: (PART 1A...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON56334

Source
ToetsingOnline

Brief title
study 208850

Condition

- Other condition

Synonym
solid tumors

Health condition

solide tumoren

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Dose escalation, Dostarlimab, GSK3745417, Solid tumors

Outcome measures

Primary outcome

PART 1A: Dose limiting toxicities, adverse events.

Secondary outcome

PART 1A: Best objective response (RECIST 1.1). GSK3745417 concentrations in

plasma and PK parameters.

Study description

Background summary

The immune system plays a critical role in protecting the body from neoplastic disease. Immune checkpoint inhibitors anti-PD(L)-1 and anti-CTLA-4 have demonstrated therapeutic benefit across multiple tumor types, yielding durable responses in some patients. However, a majority of patients do not respond to monotherapy with checkpoint inhibitors, at least in part due to the non-inflamed nature of the tumor. Therefore, strategies to increase the tumor immunogenicity are being actively explored.
Pre-clinical data strongly suggest that the STimulator of INterferon Genes (STING) pathway is the tumor sensing pathway of the immune system. Therefore, activation of the STING pathway has the potential to boost tumor antigen presentation and the tumor immunogenicity. Potent and durable anti-tumor response has been demonstrated in tumor models with STING agonist treatment. In addition, the effect of STING activation in boosting tumor antigen presentation suggests potential combination benefit with immune check point modulators. Given their non-overlapping mechanisms of action, the combination of the two could simultaneously accelerate separate steps in the

cancer-immunity cycle, i.e., the tumor antigen presentation process and the T cell activation process, therefore generating synergistic anti-tumor effect. GSK3745417 is a synthetic STING agonist that is being developed as an immune stimulatory agent for the treatment of cancer. This study will be the first time in human study of GSK3745417 administered alone and in combination with other immunotherapies to participants with advanced solid tumors. The initial combination partner is pembrolizumab, but subsequent combination partners and/or additional routes of administration may be evaluated (following protocol amendment/s) based on biologic rationale, nonclinical data, and/or emerging clinical data.
This FTIH, open label, dose escalation study will assess the safety, PK, pharmacodynamics, and preliminary clinical activity of GSK3745417 in participants with selected advanced or recurrent solid tumors as monotherapy (Part 1), in combination with pembrolizumab (Part 2), and potentially in combination with additional therapies. The monotherapy cohort expansion (Part 1B) and the combination with pembrolizumab (Part 2) of the study will only be opened by protocol amendment.

The current application is focussed to the dose escalation part of GSK3745417 alone (part 1A).

Amendment 03 (December 2020):
The study originally consisted of part 1A, 1B, 2A and 2B. Part 1B and 2B, the desired and undesirable effects of the doses in a larger group of participants, has been removed. In part 2A, the study medication pembrolizumab has been replaced by dostarlimab. The Netherlands did not participate in part 2A and 2B of the study and will now also only participate in part 1A. Furthermore, the optional PK / PD cohorts have been removed.

Amendment 04 (May 2021):
This protocol amendment was generated in response to the Dear Investigator Letter (dated 11-02-21) and mainly contains risk mitigating changes: requirements for improved cardiac monitoring, reduced dosage and the side effects section is updated. After approval of this protocol, enrollment of patients will be resumed in all cohorts.

Amendment October 2021:
In May 2021 the addition of Dostarlimab has been realized per protocol amendment. The Netherlands could not be included in this amendment due to patent issues for Dostarlimab. At present NL is able to participate in the Dostarlimab arm. Hence this protocol amendment.

Amendment March 2022
Introduction of an Imaging Sub-study to be conducted in the Netherlands. The aim of the Imaging Sub-study consisting of 2 parts is a) to investigate if GSK3745417 monotherapy followed by combination with dostarlimab results in T-cell activation as assessed by the T-cell uptake of an investigational marker

of T-cell activation, 18F-labeled analog of arabinofuranosyl guanine ([18F]F-AraG) visualized by positron emission tomography (PET) imaging, and b) to investigate the biodistribution of radiolabelled GSK3745417 ([11C]GSK3745417). Hence this protocol amendment.

Amendment 9 (October 2023):
The sponsor has decided to halt further inclusion in the study, after the decision to stop further development of GSK3745417 in solid tumours. This decision is based on recent data that show a lack of expectted activity tresholds. As a consequence planned monotherapy (1B) and combination therapy (2B) cohort expansioins will not be opened for inclusion. In addition: the sub study will be stopped and part B of the sub study has not started.

Study objective

Primary (PART 1A ONLY):
Dose escalation: To determine the safety, tolerability, and the recommended phase 2 dose (RP2D) of GSK3745417 alone administered intravenously to participants with selected advanced/recurrent solid tumors.
Secondary: (PART 1A ONLY):
Dose expansion: Antitumor activity and PK properties of GSK3745417 alone.

Study design

Phase I, first time in humans (FTIH), open-label, repeat-dose, non-randomized study to evaluate the safety, tolerability, and preliminary clinical activity and establish a recommended dose of GSK3745417 administered intravenously (IV) alone (Part 1) or co-administered (Part 2) with pembrolizumab in participants with refractory/relapsed solid tumors. Each part consists of a dose escalation phase and a cohort expansion phase.
It is estimated that a total of approximately 300 participants will be enrolled in this study, approximately 120 for dose escalation cohorts, and approximately 180 in the expansion cohorts, including PK/PD, and 6 tumor specific expansion cohorts. Additional tumor specific cohort(s) and combinations may be added based upon emerging pre-clinical data, or clinical data from the dose escalation portion of the study.
Participants will initially receive GSK3745417 as monotherapy during dose escalation in Part 1A. Part 2A will be conducted following protocol amendment. GSK3745417 will be administered every week or every three weeks. The investigator determines the frequency of administration.
In Part 2A, escalating doses of GSK3745417 in combination with 200 mg pembrolizumab will be evaluated. In Part 1B and 2B, participants will receive a single dose level of GSK3745417 as identified based on data from Part 1, either alone or in combination with pembrolizumab. Part 1b and 2B will not be opened anymore.

Intervention

PART 1A: Treatment with GSK3745417 alone.

Study burden and risks

Risk: Adverse events of the study medication. First in human study.
Burden:
• Weekly visits during 2 years.
• Approx. 104 infusions met GSK3745417, 5 min. per infusion of 10 ml.
• Possibility for 24 hour observation period after the first 6 infusions.
• Physical examination: every visit.
• Neurological examination: once
• Blood draws: every visit. 15-90 mL blood per occasion.
• ECG en echocardiography (alternative: MUGA scan): once.
• Holter monitoring: once.
• telemetry: once, only by patients who receive GSK3745417 every week.
• CT/MRI scan every 9 weeks.
• Tumor biopsy: 0-1 times.
• Photos to measure the size of the tumor if you have tumors on your skin
Optional:
• Request images of 3 scans (CT/MRI) during last year: once

Burden Imaging substudy:
• Deel A: 3 AraG scans, 1 FDG PET scan

Contacts

Public
GlaxoSmithKline

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Amersfoort 3811 LP
NL
Scientific
GlaxoSmithKline

Van Asch van Wijckstraat 55H
Amersfoort 3811 LP
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

• Male or female, age 18 years and above.
• Histologically or cytologically confirmed advanced/recurrent solid tumors, who have progressed on, be intolerant of, or ineligible for, all available therapies for which clinical benefit has been established.
• Fresh tumor sample. For further details: see protocol section 5.1, item 5.
• Measurable disease. For further details: see protocol section 5.1, item 6.
• ECOG performance status 0-1.
• Life expectancy of at least 12 weeks.
• Adequate organ function. For further details: see protocol section 5.1, item 9.
• Not pregnant or breastfeeding females and females of non-reproductive potential or reproductive potential and agrees to follow a required contraceptive method. For further details: see protocol section 5.1, item 11.
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Exclusion criteria

• Malignancy other than disease under study. For further details: see protocol section 5.2, item 1.
• CNS metastases. For further details: see protocol section 5.2, item 2.
• Active autoimmune disease that has required systemic treatment within the last 2 years. Replacement therapy is not considered a form of systemic treatment. For further details: see protocol section 5.2, item 3.
• Concurrent medical condition requiring the use of systemic immunosuppressive treatment within 28 days before the first dose of study treatment. For further details: see protocol section 5.2, item 4.
• Current unstable liver or biliary disease per investigator assessment. For

further details: see protocol section 5.2, item 5.
• History of vasculitis.
• Active infection requiring systemic therapy, known human immunodeficiency virus infection, positive test for hepatitis B or hepatitis C. See protocol section 5.2, item 8.
• Within the past 6 months: acute diverticulitis, inflammatory bowel disease, intra-abdominal abscess, or gastrointestinal obstruction.
• Allergen desensitization therapy within 4 weeks of starting study treatment.
• History or evidence of cardiac and pulmonary abnormalities. For further details: see protocol section 5.2, item 12-15.
• Within 6 months: uncontrolled symptomatic ascites or pleural or pericardial effusions.
• Prior or concomitant therapies listed in protocol section 5.2, item 19-24.
• Recent (within the past 6 months) history of any grade of immune myocarditis or pericarditis.

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	30-09-2020
Enrollment:	25
Type:	Actual

Medical products/devices used

Registration:	No
Product type:	Medicine
Brand name:	GSK3745417
Generic name:	GSK3745417
Product type:	Medicine

Brand name:	Jemperli
Generic name:	Dostarlimab
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	10-04-2019
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	22-10-2019
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	11-02-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	18-02-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	14-05-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	09-07-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	10-07-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	05-01-2021

Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	06-01-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	14-01-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	18-01-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	25-02-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	08-06-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	11-06-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	04-11-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	17-12-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	01-04-2022

Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	03-05-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	02-08-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	16-08-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	26-11-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	06-12-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	05-05-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	23-05-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	01-11-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	14-11-2023

Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	20-02-2024
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	13-03-2024
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

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
Other	208850 (www.gsk-clinicalstudyregister.com)
EudraCT	EUCTR2018-001924-20-NL
CCMO	NL68710.031.19