A Phase I, Open-Label Study of GSK1795091 Administered in Combination with Immunotherapies in Participants with Advanced Solid Tumors.

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Primary objective: To evaluate the safety and tolerability of GSK1795091 when administered in combination with either GSK3174998, GSK3359609, orpembrolizumab.Secondary objectives: * To evaluate the antitumor activity of GSK1795091 when administered...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON46814

Source
ToetsingOnline

Brief title
204686

Condition

- Other condition

Synonym
Advanced Solid Tumors, cancer

Health condition

Advanced Solid Tumors

Research involving

Human

Sponsors and support

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

Intervention

Keyword: Advanced solid tumor, combination therapy, safety, tolerability

Outcome measures

Primary outcome

AEs, SAEs, DLTs, withdrawals due to AEs, dose reductions or delays, and changes in safety assessments (e.g., laboratory parameters, vital signs, and cardiac parameters).

Secondary outcome

-Objective response rate (ORR) and disease control rate (DCR) (complete response [CR]+ partial response [PR]+ stable disease [SD] * 12 weeks), time to response, duration of response, progression-free survival (PFS), and overall survival.

- GSK1795091 concentrations in plasma and assessment of PK parameters (e.g., maximum observed concentration [Cmax], AUC(0-*) and trough plasma concentration [Ctrough]) if data permit.

- Number and percentage of participants who develop detectable antidrug antibodies against GSK3174998, GSK3359609, or pembrolizumab.

Study description

Background summary

The combination of two or more immunotherapies holds promise in treating patients with cancer. One model of a *cancer-immune cycle* describes a series of feed- forward steps by which the immune system recognizes and kills tumor cells, a cycle which is counterbalanced by tumor and host derived factors which suppress anti-tumor immune activation [Chen, 2013; Chen, 2017]. These steps include:

- Release of cancer cell antigens
- Cancer antigen presentation
- Priming and activation
- Trafficking of T-cells to tumors
- Infiltration of T-cells into tumors
- Recognition of cancer cells by T-cells
- Killing of cancer cells

Rational combination strategies, such as immunotherapies acting at different steps in the immune cycle, could produce meaningful and synergistic activity compared to monotherapies [Hoos, 2016]. Combining a TLR4 agonist with a checkpoint modulator, such as an OX40 agonist, targets two complementary steps in the cancer-immunity cycle; TLR engagement results in the production of various inflammatory cytokines/chemokines such as tumor necrosis factor (TNF)alpha, interleukin (IL) 6, granulocyte colony-stimulating factor (G-CSF), and type I interferons (i.e., IFNalpha, IFN beta) and enhanced uptake, processing, and presentation of antigens. OX40 agonism is expected to increase priming and activation of T-cells. Based on nonclinical data, the combination of GSK1795091 (a TLR4 agonist) and GSK3174998 (an OX40 agonist) is anticipated to have antitumor activity greater than either of the monotherapies. The combination will be evaluated for the first time in this clinical study. Additional combinations will be introduced by protocol amendment.

Study objective

Primary objective:
To evaluate the safety and tolerability of GSK1795091 when administered in combination with either GSK3174998, GSK3359609, or pembrolizumab.

Secondary objectives:
* To evaluate the antitumor activity of GSK1795091 when administered in combination with either GSK3174998, GSK3359609, or pembrolizumab.
* To characterize the pharmacokinetics (PK) of GSK1795091 when administered in combination with either GSK3174998, GSK3359609, or pembrolizumab.
* To evaluate the immunogenicity of GSK3174998, GSK3359609, or pembrolizumab when administered in combination with GSK1795091.

Study design

This is a Phase I, open-label, non-randomized, multicenter and multi-country study designed to evaluate the safety, tolerability, PK, pharmacodynamic, and preliminary clinical activity of GSK1795091 administered in combination with other immunotherapies to participants with advanced solid tumors.

In Part 1, the safety and tolerability of escalating doses of GSK1795091 and GSK3174998, GSK3359609, or
pembrolizumab. will be evaluated in participants with advanced solid tumor cancers according to an Neuenschwander-Continual Reassessment Method (N-CRM) design to identify doses for evaluation in Part 2 [Neuenschwander, 2008]. Part 1 will include a GSK1795091 run-in period of 2 weeks (i.e., GSK1795091 administration on Days 1 and 8) prior to administration of the combination beginning at Day 15. Approximately 5 dose levels of GSK1795091 in combination with a single dose level of GSK3174998, GSK3359609, or
pembrolizumab are planned to be evaluated in Part 1. Following protocol amendment, GSK1795091 may also be evaluated with additional immunotherapies and/or by additional routes of administration.

In Part 2, an expansion cohort of approximately 6 to 15 participants with squamous cell carcinoma of the head and neck will be enrolled to further evaluate safety and activity of dose identified in Part 1. The dose of GSK1795091 administered with GSK3174998, GSK3359609, or
pembrolizumab. will be determined based on data from Part 1. Following protocol amendment, additional expansion cohorts in other tumor types may be enrolled, based on emerging nonclinical and clinical data.

In addition, a PK/Pharmacodynamic cohort will be opened to enrollment during Part 1 to obtain additional PK and pharmacodynamic data, with an emphasis to obtain insight on the potential impact of the combination treatments on the immune cells and status of the tumor microenvironment, in conjunction with PK and pharmacodynamic markers obtained from blood. Tumor biopsies are required for enrollment to the PK/Pharmacodynamic cohort, whereas biopsies are strongly encouraged but not mandatory for Part 1 dose escalation cohorts. Participants in the PK/Pharmacodynamic cohort may be enrolled to any dose level which has already been completed and supported by adequate safety and tolerability from dose escalation. Up to approximately
3 participants per dose level may be enrolled into the PK/Pharmacodynamic cohort.

Intervention

Patients will be treated with study medicines for up to 2 years. They will receive study treatment every week from Week 1 through Week 12 (in Part 1) or till Week 13 (in Part 2) and then every 3 weeks after that.

Furthermore their data of Medical history and demographic data will be collected They must undergo physical and vital signs examinations. An 12-lead ECG, Echocardiogram and MRI or CT scans will be made. Tissue samples, blood and urine will be collected.

Study burden and risks

This is an open-label, dose escalation study and the first study of the combination of GSK1795091 and GSK3174998, GSK3359609, or pembrolizumab. conducted in humans; this study will enroll participants with advanced solid tumors. There is biologic rationale to study this combination for the treatment of cancer based on complementary modes of action on the immune system, and GSK1795091 and GSK3174998, GSK3359609, or pembrolizumab. have antitumor activity when used in combination that exceeds either agent*s monotherapy activity in preclinical models. However, it is unknown if the combination will have clinical activity for patients with cancer.

Based on nonclinical in vivo and ex vivo combination evaluations and clinical experience to date, and the conservative starting dose of GSK1795091, the safety profile of the combination is not expected to exceed that of monotherapy GSK3174998 and monotherapy GSK1795091. In contrast to experience to date with GSK3174998, GSK3359609, or
pembrolizumab. , it is expected that increasing the dose of GSK1795091 past a certain threshold will be associated with DLTs given the TLR4 agonist mechanism of action and experience with other TLR agonists including LPS. Consistent with other Phase 1 trials for the treatment of cancer, a target DLT frequency has been set as 16-33%, and a Bayesian adaptive dose escalation design is employed to efficiently determine the dose(s) associated with this DLT frequency. In addition, it is possible that infrequent events unrelated to dose, such as increases in hepatic laboratory values, might be observed. This risk will, in part, be mitigated by a run-in period for GSK1795091 prior to the initiation of combination study treatment. Overall, the benefit:risk is typical of a Phase I study of participants with advanced cancer.

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. Participant must be *18 years of at the time of signing the informed consent.
2. Histological documentation of advanced solid tumor, other than TNBC (defined per ASCO/CAP guidelines) [Hammond, 2010; Wolff, 2013].
3. Archival tumor tissue obtained at any time from the initial diagnosis to study entry. Although a fresh biopsy obtained during screening is preferred, archival tumor specimen is acceptable if it is not feasible to obtain a fresh biopsy.
Note: Participants enrolled in a PK/Pharmacodynamic Cohort must provide a fresh biopsy of a tumour lesion not previously irradiated during the screening period and must agree to provide at least one additional on-treatment biopsy.
4. Disease that has progressed after standard therapies or for which standard therapy is otherwise unsuitable (e.g., intolerance).
5. Measurable disease, i.e., presenting with at least 1 measurable lesion per Response Evaluation Criteria in Solid Tumors (RECIST version 1.1).
6. Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0-1.
7. Life expectancy of at least 12 weeks.
8. Adequate organ function
9. applicable for France only
10. Male or female
a. Female participants:
A female participant is eligible to participate if she is not pregnant, not breastfeeding, and at least 1 of the following conditions applies:
i. Not a woman of childbearing potential (WOCBP)
OR
ii. A WOCBP who agrees to follow the contraceptive guidance

during the treatment period and for at least 120 days after the last dose of study treatment.
11. Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.
Additional Inclusion Criteria for Patients in Part 2
12. Histological or cytological documentation of SCCHN (oral cavity, oropharynx, hypopharynx, or larynx) that is recurrent, locally advanced, or metastatic and is not amenable to curative treatment options, surgery or definitive chemoradiation therapy.
13. Received or ineligible for platinum-based therapy and PD-1/PD-L1 therapy.
14. Received no more than 3 prior lines of systemic therapy for metastatic disease.

Exclusion criteria

1. Malignancy other than disease under study with the exception of those from which the participant has been disease-free for more than 2 years and not expected to affect the safety of the participant or the endpoints of the trial.
2. Symptomatic central nervous system (CNS) metastases or asymptomatic CNS metastases that have required steroids within 2 weeks prior to first dose of study treatment.
3. Active autoimmune disease that has required systemic disease modifying or immunosuppressive treatment within the last 2 years.
Note: Replacement therapy (e.g., thyroxine or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is permitted.
4. Concurrent medical condition requiring the use of systemic immunosuppressive treatment within 28 days before the first dose of study treatment.
5. Known human immunodeficiency virus infection.
6. Current unstable liver or biliary disease per investigator assessment defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminaemia, oesophageal or gastric varices, persistent jaundice, or cirrhosis.
NOTE: Stable chronic liver disease (including Gilbert*s syndrome or asymptomatic gallstones) or hepatobiliary involvement of malignancy is acceptable if participant otherwise meets entry criteria.
7. Presence of Hepatitis B surface antigen (HBsAg) at screening or within 3 months prior to first dose of study treatment
8. Positive Hepatitis C test result at screening or within 3 months prior to first dose of study treatment.
NOTE: Participants with positive Hepatitis C antibody due to prior resolved disease can be enrolled, only if a confirmatory negative Hepatitis C RNA test is obtained. Participants with negative Hepatitis C antibody test are not required to also undergo Hepatitis C RNA testing
9. QTcF >450 msec or QTcF >480 msec for participants with bundle branch block
The QTcF is the QT interval corrected for heart rate according to Fridericia*s formula, machine-read or manually over-read.
10. Recent history (within the past 6 months) of acute diverticulitis, inflammatory bowel disease, intra-abdominal abscess, or gastrointestinal obstruction.
11. Recent history of allergen desensitization therapy within 4 weeks of starting study treatment.
12. History of severe hypersensitivity to mAbs.

13. History or evidence of cardiovascular (CV) risk including any of the following:
* Recent (within the past 6 months) history of serious uncontrolled cardiac arrhythmia or clinically significant ECG abnormalities including second degree (Type II) or third degree atrioventricular block.
* Cardiomyopathy, myocardial infarction, acute coronary syndromes (including unstable angina pectoris), coronary angioplasty, stenting, or bypass grafting within the past 6 months before enrollment.
* Congestive heart failure (Class II, III, or IV) as defined by the New York Heart Association functional classification system [NYHA, 1994].
* Recent (within the past 6 months) history of symptomatic pericarditis.
14. History of idiopathic pulmonary fibrosis, pneumonitis, interstitial lung disease, or organizing pneumonia, or evidence of active, non-infectious pneumonitis. Note: post-radiation changes in the lung related to prior radiotherapy and/or asymptomatic radiation-induced pneumonitis not requiring treatment may be permitted if agreed by the investigator and Sponsor.
15. Recent history (within 6 months) of uncontrolled symptomatic ascites or pleural effusions.
16. Any serious and/or unstable pre-existing medical, psychiatric disorder, or other condition that could interfere with the participant*s safety, obtaining informed consent, or compliance to the study procedures.
17. Is or has an immediate family member (e.g., spouse, parent/legal guardian, sibling or child) who is investigational site or sponsor staff directly involved with this trial, unless prospective Institutional Review Board (IRB) approval (by chair or designee) is given allowing exception to this criterion for a specific participant.
18. Prior treatment with the following agents:
* Tumor necrosis factor receptor (TNFR) agonists, including OX40, CD27, CD137 (4-1BB), CD357 (glucocorticoid-induced TNFR family-related gene) at any time.
* TLR4 agonist at any time.
* Anticancer therapy or investigational therapy within 30 days or 5 half-lives of the drug, whichever is shorter.
* Prior radiation therapy: permissible if at least 1 non-irradiated measurable lesion is available for assessment according to RECIST version 1.1 or if a solitary measurable lesion was irradiated, objective progression is documented. A wash out of at least 14 days before start of study treatment for radiation of any intended use to the extremities for bone metastases and 28 days for radiation to the chest, brain, or visceral organs is required.
19. Prior allogeneic or autologous bone marrow transplantation or other solid organ transplantation.
20. Toxicity from previous treatment including:
* Toxicity Grade *3 related to prior immunotherapy and that lead to study treatment discontinuation.
* Toxicity related to prior treatment has not resolved to Grade *1 (except alopecia, or endocrinopathy managed with replacement therapy).
21. Received transfusion of blood products (including platelets or red blood cells) or administration of colony stimulating factors (including G-CSF, granulocyte- macrophage colony-stimulating factor, and recombinant erythropoietin) within 2 weeks before the first dose of study treatment.
22. Major surgery within 4 weeks before the first dose of study treatment. Participants must have also fully recovered from any surgery (major or minor) and/or its complications before

initiating study
treatment.
23. Known drug or alcohol abuse.
24. Receipt of any live vaccine within 4 weeks.

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	13-09-2018
Enrollment:	4
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	GSK1795091
Generic name:	na
Product type:	Medicine
Brand name:	GSK3174998
Generic name:	na
Product type:	Medicine
Brand name:	GSK3359609
Generic name:	na
Product type:	Medicine
Brand name:	Pembrolizumab
Generic name:	L01XC18
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	27-03-2018
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	13-09-2018
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	24-09-2018
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	27-09-2018
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	31-10-2018
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	15-01-2019
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	06-02-2019
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO	

Date:	15-02-2019
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO

Date:	11-03-2019
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO

Date:	23-05-2019
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO

Date:	08-10-2019
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO

Date:	14-11-2019
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO

Date:	27-02-2020
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO

Date:	11-03-2020
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO

Date:	16-04-2020
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van

	Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	30-11-2020
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

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	EUCTR2017-003545-23-NL
Other	IND136203
CCMO	NL64368.031.18