A Phase I, Open-Label Study of GSK3174998 Administered Alone and in Combination with Anticancer Agents including Pembrolizumab in Subjects with Selected Advanced Solid Tumors

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OX40 agonists have been shown to increase antitumor immunity and improve tumor-free survival in non-clinical models and OX40 agonist monoclonal antibodies (mAbs) are currently being evaluated in Phase I clinical trials. GSK3174998 is a humanized...

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

Summary

ID

NL-OMON47867

Source
ToetsingOnline

Brief title
201212

Condition

- Other condition
- Metastases

Synonym
selected advanced or recurrent solid tumors

Health condition

selected advanced or recurrent solid tumors

Research involving
Human

Sponsors and support

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

Intervention

Keyword: GSK3174998, open-label, Phase I

Outcome measures

Primary outcome

The primary objectives of the study are to evaluate the safety and tolerability and to identify the maximum tolerated dose (MTD) or maximum administered dose (MAD) of GSK3174998 when administered intravenously as monotherapy (Part 1) or in combination with pembrolizumab (Part 2) to subjects with selected advanced or recurrent solid tumors.

Secondary outcome

Secondary objectives include: the evaluation of antitumor activity;

characterization of pharmacokinetics (PK) for GSK3174998 when administered alone; characterization of PK for GSK3174998 and pembrolizumab when administered in combination; and determination of the immunogenicity of GSK3174998 when administered alone or for GSK3174998 and pembrolizumab when administered in combination. Exploratory objectives include evaluation of pharmacodynamic activity in the blood and tumor microenvironment.

* Safety endpoints: Adverse events (AEs), serious adverse events (SAEs),

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

* Antitumor activity endpoints: Objective response rate (ORR) and Disease Control Rate (DCR) (complete response [CR]+partial response [PR]+stable disease [SD] *12 weeks), time to response (TTR), duration of response (DOR), progression free survival (PFS), and overall survival (OS). Unless otherwise specified, all response endpoints will be assessed by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 and by irRECIST (immune-related RECIST); the primary endpoint analysis will use irRECIST.

* PK endpoints: Plasma GSK3174998 and serum pembrolizumab concentrations and PK parameters including maximum observed concentration (Cmax), area under the concentration-time curve over the dosing interval (AUC(0-*)), and minimum observed concentration (Cmin).

* Pharmacodynamic endpoints: Assessment of lymphocyte OX40 receptor membrane expression and occupancy by GSK3174998, along with the phenotype, quantity, and activation state of T cells in the periphery, T-cell receptor (TCR) diversity, expression of circulating soluble factors, and changes in genomic DNA and gene expression, and mutational load. Assessment of tumor biopsies via immunohistochemistry (IHC) for the numbers of tumor infiltrating lymphocytes and other immune cells expressing key phenotypic markers.Changes in gene expression (RNA and protein), TCR diversity or mutational load (genomic DNA).

* Immunogenicity endpoints: Number and percentage of subjects who develop

detectable antidrug antibodies (ADA).

Study description

Background summary

The stimulation of antitumor T-cell activity, through inhibition of negative T-cell regulatory pathways with immunotherapeutic checkpoint inhibitors, has been very successful in the treatment of melanoma and non-small cell lung cancer (NSCLC). Another approach that provides an attractive target for the development of immunotherapy anticancer agents is the modulation of costimulatory pathways to enhance T-cell function. OX40 is a potent costimulatory receptor expressed primarily on activated CD4+ and CD8+ T cells. OX40 agonists have been shown to increase antitumor immunity and improve tumor-free survival in non-clinical models and OX40 agonist monoclonal antibodies (mAbs) are currently being evaluated in Phase I clinical trials. GSK3174998 is a humanized wild-type immunoglobulin G1 (IgG1) anti-OX40 agonistic mAb and will be evaluated as a single-agent treatment in Part 1 of the current study. The anticancer immune response is a multi step process and it is expected that tumors may utilize redundant mechanisms to block the anti tumor response; in these instances, combination therapies will likely be required. Combining an OX40 agonist with a programmed death receptor-1 (PD-1) inhibitor targets two different steps in the cancer immunity cycle; OX40 agonism is expected to increase priming/activation of T cells, while inhibition of PD-1 blocks its interaction with programmed death ligand 1 (PD-L1) and programmed death ligand 2 (PD-L2), releasing the PD-1 pathway-mediated inhibition of the immune response. Based on non-clinical data, combination treatment with an OX40 agonist and a PD-1 inhibitor is anticipated to have synergistic anti tumor activity, compared with single-agent treatment. The combination of GSK3174998 with the PD-1 inhibitor pembrolizumab will be evaluated in Part 2 of the current study.

Study objective

OX40 agonists have been shown to increase antitumor immunity and improve tumor-free survival in non-clinical models and OX40 agonist monoclonal antibodies (mAbs) are currently being evaluated in Phase I clinical trials. GSK3174998 is a humanized wild-type immunoglobulin G1 (IgG1) anti-OX40 agonistic mAb and will be evaluated as a single-agent treatment in Part 1 of the current study.

Study design

This is a first time in human (FTIH), open-label, non-randomized, multicenter study designed to evaluate the safety, tolerability, PK, pharmacodynamics, and preliminary clinical activity of GSK3174998 administered intravenously to subjects with selected
advanced or recurrent solid tumors. The study will be conducted in 2 parts, each part starting with a dose-escalation phase followed by a cohort expansion phase. Part 1 will evaluate GSK3174998 monotherapy, while Part 2 will evaluate GSK3174998 in combination with pembrolizumab. GSK3174998 will first be evaluated as monotherapy in escalating doses. Once a dose of GSK3174998 has been identified that is both
tolerable and demonstrates pharmacodynamic activity, enrollment of Part 2 may begin. In Part 2, escalating doses of GSK3174998 will be evaluated with fixed doses of pembrolizumab. The transition of the study from dose-escalation to cohort expansion and from monotherapy (Part 1) to combination therapy with pembrolizumab (Part 2) will be performed under the guidance of a Protocol Steering Committee. The remit,
membership, roles, and responsibilities of the Steering Committee are described in a Steering Committee Charter. Pending a review of emerging data from this study and under the guidance of the Steering Committee, the protocol may be subsequently amended to include investigation of additional anticancer agent combinations with GSK3174998.

Intervention

subjects participating in part 1 of the study and will receive the last tolerated dose, in part 2 of the study subjects will receive combination therapy all subjects will receive the same dose of pembrolizumab but another dose of OX40.

Study burden and risks

see C4

Contacts

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Scientific
GlaxoSmithKline

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Subjects eligible for enrollment in the study must meet all of the following criteria:
1. Provide signed, written informed consent.;2. Male and female subjects, age 18 years (at the time consent is obtained).;3. Histological documentation of locally advanced, recurrent or metastatic solid malignancy that has progressed after standard therapy appropriate for the specific tumor type, or for which standard therapy has proven to be ineffective, intolerable, or is considered inappropriate (with the possible exception of the PD-(L)1 naive populations described in inclusion criterion 4). Subjects should not have received more than 5 prior lines of therapy for advanced disease including both standards of care and investigational therapies. Subjects whose cancers harbor molecular alterations for which targeted therapy is standard of care should have received health authority approved appropriate targeted therapy for their tumor types before enrollment.;4. Subjects with the following solid tumors are eligible for screening: NSCLC, SCCHN, RCC, melanoma, bladder, STS, TNBC, and MSI CRC. In Part 2B (Cohort Expansion), specific subgroups of the above solid tumors will be studied. These subgroups may be defined by specific lines of treatment, types of prior treatment, histological subtypes, and may be enriched for selected biomarkers or patient characteristics. Populations
to be studied in Amendment 3 include but are not limited to the following. Enrolment of additional populations will be communicated in writing.
- Subjects with dedifferentiated liposarcoma who have not received prior treatment with a PD-(L)1 inhibitor
- Subjects with melanoma who have received a prior PD-(L)1 inhibitor, had a CR, PR or SD and subsequently progressed while on PD-(L)1 therapy. Subjects who have received prior treatment with a PD-(L)1 inhibitor must have documented disease progression as defined by meeting all of the following criteria:

o Has received at least 2 doses of an approved PD-(L)1 inhibitor
o Has demonstrated disease progression as defined by RECIST v1.1. The initial evidence of disease progression is to be confirmed by a second assessment no less than four weeks from the date of the first documented PD, in the absence of rapid clinical progression.
o Progressive disease has been documented within 18 weeks from the last dose of the PD-(L)1 inhibitor.;5. In Parts 1A and 2A,a biopsy of the tumor tissue obtained at anytime 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. Subjects enrolled in Part 1A or Part 2A Pharmacodynamic Cohorts or in Part 2B of the study 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.In addition, an archived tumor tissue should be submitted for subjects in Part 2B, if available. The criterion for collection of fresh biopsies may be waived once GSK has determined an appropriate number of viable tissue samples have been analysed.;6. Measurable disease per RECIST version 1.1 - please refer to Appendix 5 of the Study Protocol. Palpable lesions that are not measurable by radiologic or photographic evaluations may not be utilized as the only measurable lesion.;7. Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0-1.;8. Life expectancy of at least 12 weeks.;9. Adequate organ function (see Table 7 of study protocol, p46).;10. QT duration corrected for heart rate by Fridericia's formula (QTcF) <450 msec or QTcF <480 msec for subjects 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.;11. In France, a subject will be eligible for inclusion in this study only if either affiliated to or a beneficiary of a social security category.;12. Female subject: is eligible to participate if she is not pregnant (as confirmed by a negative serum beta-human chorionic gonadotrophin (*-hCG) test), not lactating, and at least one of the following conditions applies:
a. Non-reproductive potential defined as:
- Pre-menopausal females with one of the following:
- Documented tubal ligation
- Documented hysteroscopic tubal occlusion procedure with follow-up confirmation of bilateral tubal occlusion
- Hysterectomy
- Documented Bilateral Oophorectomy
- Postmenopausal defined as 12 months of spontaneous amenorrhea [in questionable cases a blood sample with simultaneous follicle stimulating hormone (FSH) and estradiol levels consistent with menopause (refer to laboratory reference ranges for confirmatory levels)].;*For the complete remaining inclusion criteria, please see study protocol p53-54.*

Exclusion criteria

A subject will not be eligible for inclusion in this study if any of the following criteria apply:
1. Prior treatment with the following agents (from last dose of prior treatment to first dose of GSK3174998):
- TNFR agonists, including OX40, CD27, CD137 (4-1BB), CD357 (GITR): at any time.
NOTE: Subjects treated in Part 1/monotherapy with GSK3174998 may be enrolled into Part 2/combination with pembrolizumab upon disease progression and upon discussion and

approval from the GSK Medical Monitor.;- Checkpoint inhibitors, including PD-1, PD-L1, and CTLA-4 inhibitors: within 4 weeks.NOTE: Subjects entering the PD-(L)1 naive expansion cohort may not have received any prior PD-(L)1 anti-cancer treatment.
- Other anticancer therapy, including chemotherapy, targeted therapy, and biological therapy: within 4 weeks or 5 half lives of the drug, whichever is shorter. Prior radiation therapy is permissible if at least one unirradiated measurable lesion is available for assessment via RECIST version 1.1. A wash out of at least two weeks before start of study drug for palliative radiation to the extremities for osseous bone metastases and 4 weeks for radiation to the chest, brain, or visceral organs is required.
- Investigational therapy: if the subject has participated in a clinical trial and has received an investigational product: within 30 days or 5 halflives of the investigational product (whichever is shorter). At least 14 days must have passed between the last dose of prior investigational agent and the first dose of study drug. Note: if the agent is a TNFR agonist or a checkpoint inhibitor, the above exclusions take precedence.;2. Prior allogeneic or autologous bone marrow transplantation or other solid organ transplantation.;3. Toxicity from previous treatment:
- Subjects with *Grade 3 toxicity related to prior immunotherapy leading to study treatment discontinuation are not eligible.
- Subjects whose toxicity related to prior treatment has not resolved to * Grade 1 (except alopecia, hearing loss, grade * 2 neuropathy or endocrinopathy managed with replacement therapy) are not eligible.;4. Malignancy other than disease under study, except as noted below:
- Any other malignancy from which the subject has been disease-free for more than 2 years and, in the opinion of the principal investigators and GSK Medical Monitor, will not affect the evaluation of the effects of this clinical trial treatment on currently targeted malignancy, can be included in this clinical trial.;5. Central nervous system (CNS) metastases, with the following exception:
- Subjects who have previously-treated CNS metastases, are asymptomatic, and have had no requirement for steroids for 2 weeks prior to first dose of study drug.
Note: Subjects with carcinomatous meningitis are excluded regardless of clinical stability.;6. Has received transfusion of blood products (including platelets or red blood cells) or administration of colony stimulating factors (including granulocyte colonystimulating factor [G-CSF], granulocyte-macrophage colony-stimulating factor [GMCSF], recombinant erythropoietin) within 2
weeks before the first dose of study drug.;7. Major surgery * 4 weeks before the first dose of study treatment. Subjects must have also fully recovered from any surgery (major or minor) and/or its complications before initiating study treatment.;8. Active autoimmune disease (see Appendix 2) that has required systemic treatment within the last 2 years (i.e., with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g., thyroxine or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.;9. Concurrent medical condition requiring the use of systemic immunosuppressive medications within 28 days before the first dose of study treatment. Physiologic doses of corticosteroids for treatment of endocrinopathies or steroids with minimal systemic absorption, including topical, inhaled, or intranasal corticosteroids may be continued if the subject is on a stable dose.;10. Active infection, known human immunodeficiency virus infection, or positive test for hepatitis B surface antigen or hepatitis C.;11. Current active liver or biliary disease (with the

exception of Gilbert's syndrome or asymptomatic gallstones, liver metastases, or otherwise stable chronic liver disease per investigator assessment).
NOTE: Stable chronic liver disease should generally be defined by the absence of ascites, encephalopathy, coagulopathy, hypoalbuminemia, esophageal or gastric varices, persistent jaundice, or cirrhosis.;12. Known, current drug or alcohol abuse.;*For the complete reminaining exclusion criteria, please see study protocol p56.*

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):	11-09-2015
Enrollment:	40
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	GSK3174998
Generic name:	GSK3174998
Product type:	Medicine
Brand name:	KEYTRUDA
Generic name:	Pembrolizumab
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	01-12-2015
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	17-03-2016
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	10-06-2016
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	26-08-2016
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	22-11-2016
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	20-12-2016
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	11-04-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	20-09-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek

	(Assen)
Approved WMO Date:	20-11-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	12-04-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	16-05-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	18-06-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	21-06-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	27-08-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	31-08-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	20-09-2018

Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	12-02-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	15-02-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

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	EUCTR2015-000152-14-NL
CCMO	NL54280.056.15