A Phase I, first-in-human, multicenter, open-label, dose escalation followed by an expansion phase clinical study of KBA1412 given as monotherapy or in combination with pembrolizumab in adults with advanced solid malignant tumors

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DOSE ESCALATION PHASE: PART A: Primary Objectives: • To assess the safety and tolerability of KBA1412 when given as monotherapy. • To determine the maximum tolerated dose (MTD) and/or Recommended Phase II dose (RP2D) of KBA1412 when given as...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Haematopoietic neoplasms (excl leukaemias and lymphomas)
Study type	Interventional

Summary

ID

NL-OMON53468

Source
ToetsingOnline

Brief title
Study of KBA1412 in patients with advanced solid malignant tumors

Condition

- Haematopoietic neoplasms (excl leukaemias and lymphomas)

Synonym
melanoma, Solid Tumors

Research involving
Human

Sponsors and support

Primary sponsor: Kling Biotherapeutics B.V.
Source(s) of monetary or material Support: Kling Biotherapeutics B.V.

Intervention

Keyword: Advanced Solid Malignant Tumors, Monotherapy, Pembrolizumab

Outcome measures

Primary outcome

Dose Escalation Phase: Part A & mini-dose escalation part C:

Primary endpoint:

• To determine the DLT's.

• To establish the MTD and/or RP2D of single agent KBA1412 and KBA1412 plus pembrolizumab

Expansion Phase: Parts B and C:

Primary endpoint:

• To determine safety and tolerability using the secondary safety outcome measures: Incidence, nature, and severity of adverse events; changes in physical examination findings, laboratory test results, and vital signs over time.

• To establish the MTD and/or RP2D of single agent KBA1412 and KBA1412 plus pembrolizumab. • To evaluate the objective response rate (ORR) in each of the

cohorts using iRECIST.

Dose Escalation Phase: Part A & mini-dose escalation part C:

Timepoint of evaluation:

• at completion of DLT observation period

Expansion Phase: Parts B and C:

Timepoint of evaluation:

• at completion of cycle 8

Secondary outcome

Dose Escalation Phase: Part A & mini-dose escalation part C:

Secondary endpoint:

• To determine the serum PK profile of KBA1412 monotherapy and KBA1412 plus pembrolizumab.

• To determine the Incidence of antibody formation to KBA1412 monotherapy and KBA1412 plus pembrolizumab.

•To determine the objective response rate (ORR) in each of the cohorts using iRECIST.

Expansion Phase: Parts B and C:

Secondary endpoint:

• To determine the serum PK profile of KBA1412 monotherapy and KBA1412 plus pembrolizumab.

• To determine the Incidence of antibody formation to KBA1412 monotherapy and

KBA1412 plus pembrolizumab.

Timepoint of evaluation:

• at completion of treatment of the last patient in Part A (patients of Part C

mini-dose escalation will continue in dose expansion)

Expansion Phase: Parts B and C:

Timepoint of evaluation:

• at completion of treatment of the last patient in Part B and Part C

Study description

Background summary

It has been long described that patients suffering from cancer, especially those undergoing successful treatment, can develop antibodies that specifically bind cancer cells. From the B-cell repertoire of a melanoma patient in long-term remission, a B-cell clone was isolated that showed strong reactivity towards various melanoma cancer cell lines (including the patient*s autologous tumor).

KBA1412 is a fully human, patient-derived, monoclonal antibody.

KBA1412 is currently being developed for the treatment of solid tumors, and subsequent development will consider B cell acute lymphoblastic leukemias (B-ALL). Preclinical data suggest that KBA1412 combined with checkpoint inhibitors provide additional therapeutic benefit, and, therefore, this combination will also be investigated in clinical studies.

Study objective

DOSE ESCALATION PHASE:
PART A:
Primary Objectives:
• To assess the safety and tolerability of KBA1412 when given as monotherapy.
• To determine the maximum tolerated dose (MTD) and/or Recommended Phase II

dose (RP2D) of KBA1412 when given as monotherapy.

Secondary Objectives:
• To investigate the pharmacokinetic (PK) properties of KBA1412.
• To investigate the incidence of anti-drug antibody (ADA) formation to KBA1412.
• To investigate the pharmacodynamic properties of KBA1412.
• To evaluate the efficacy of KBA1412.

EXPANSION PHASE:
PARTS B and C:
Primary Objectives:
• To assess the safety and tolerability of KBA1412 when given as monotherapy (Part B) or in combination with pembrolizumab (Part C).
• To determine the MTD and/or RP2D of KBA1412 when given as monotherapy (Part B) or in combination with pembrolizumab (Part C).
• To evaluate the efficacy of KBA1412 at the MTD and/or RP2D as monotherapy (Part B) or in combination with pembrolizumab (Part C).

Secondary Objectives:
• To investigate the PK properties of KBA1412 when given as monotherapy (Part B) or in combination with pembrolizumab (Part C).
• To investigate the incidence of ADA formation to KBA1412 when given as monotherapy (Part B) or in combination with pembrolizumab (Part C).
• To investigate the pharmacodynamic properties of KBA1412 when given as monotherapy (Part B) or in combination with pembrolizumab (Part C).

Study design

KBA1412-101 is a Phase I, first-in-human, multicenter, open-label, clinical study in adults with advanced solid malignant tumors.

This study will characterize the safety, tolerability, PK and biological activity (pharmacodynamics) of KBA1412 when given as monotherapy or in combination with pembrolizumab.

The study will consist of 3 parts - the study will start with the KBA1412 monotherapy dose escalation Part A and once the MTD and/or RP2D is established, the study will then proceed to the simultaneous conduct of Parts B (monotherapy expansion phase) and C (combination therapy with pembrolizumab mini-dose escalation from the modified MTD [MTD-1] followed by expansion phase).

PART A
Part A - Monotherapy Dose-Escalation Phase
Part A, the KBA1412 monotherapy dose escalation phase (every 3 weeks [Q3W] dosing), will include 36 patients with solid tumors. All cohorts will consist of 3 patients and might be expanded.

The dose escalation will be conducted to assess the MTD of KBA1412. Part A will involve 6 planned dose levels for KBA1412 starting at 0.1 mg/kg.
The dose escalation will stop when the MTD has been reached.

PART B
Part B - Monotherapy Expansion Phase
Part B will assess the RP2D monotherapy dose of KBA1412 (Q3W dosing) based on the safety, biomarker and PK profiles observed during the dose escalation phase (Part A) of the study in a wider range of tumor types. Part B will include approximately 35 patients. This part will initially consist of 4 cohorts of 5 patients of the following tumor types: melanoma; ovarian cancer; gastric cancer; colorectal cancer.

PART C
Part C - Combination Therapy Mini-Dose-Escalation Phase
Part C will include a mini-dose escalation phase of the combination therapy (Q3W dosing KBA1412 with pembrolizumab) followed by an expansion phase in a wider range of tumor types. Part C will include approximately 35 patients. This part will initially consist of 4 cohorts of 5 patients of the following tumor types: melanoma; ovarian cancer; gastric cancer; colorectal cancer.
Dose escalation will be conducted with the objective of determining an MTD and/or RP2D for the combination therapy.
For Part C, the starting dose of KBA1412 be the MTD-1 identified in Part A.

Part C - Combination Therapy Expansion Phase
For the expansion phase of Part C, the dose will be the RP2D determined based on the safety, biomarker, and PK profiles.

Intervention

The IMP will be administered

Study burden and risks

KBA1412 is in phase 1 clinical development. No data is therefore available regarding the safety profile of this agent in humans. KBA1412 is currently not approved for the treatment of any human disease.

OTHER POTENTIAL STUDY PROCEDURAL RISKS NOT RELATED TO STUDY DRUG(S)
Blood samples
Blood sample collection can result in pain, bleeding, localized bruising, or thrombosis.
The risks of this infusion needle are infections, bleeding and slight discomfort and bruising at the injection site.

CT/MRI scans

You will be exposed to radiation when undergoing a CT scan. The additional radiation falls within the standards that apply in our country for this type of additional radiation burden. It is highly unlikely that a CT scan will cause any problems.
Some CT scans require you to have an injection of contrast liquid. There is a small risk of developing an allergic reaction to the contrast agent. This reaction can be mild (itching, skin rash, nausea) or serious (difficulty breathing or shock).
You may also undergo MRI scans of the brain and other areas, as applicable. An MRI scanner does not emit radiation, but it is a powerful magnet. Therefore, you cannot have an MRI scan if you have an electronic implant (e.g., a pacemaker, hearing aid, nerve stimulator, etc.) or if you have metal or magnetic implants (e.g., skin expander, blood vessel clips, stents)
Finally, you may experience claustrophobia in an MRI scanner as you will have to lie still in a narrow space for approximately 20 minutes.
You can always contact the study doctor if you have questions about this.

Bone scan
A radioactive imaging agent (radioactive means that it emits radiation or rays of energy or particles) will be injected in your veins. Injection will be done by an authorized trained person only and handled with appropriate safety measures to minimize radiation exposure during the injection. The amount of the radioactive imaging agent injected into your vein for the procedure is very small and it involves minimal risk.

ECG
During an ECG, your skin can react to the electrodes (suction caps) that are placed on your chest. This irritation usually disappears immediately after the electrodes have been removed.

MUGA/ECHO
During a MUGA scan of the heart, radioactive particles are injected in a liquid that adheres to the red blood cells. This allows the heart*s functioning to be imaged. Echocardiography of the heart uses ultrasound waves instead of radioactive substances.

Biopsies
In general, having a biopsy can cause pain, swelling, bleeding and/or infection at the site where the biopsy needle penetrates through your skin. There is also the possibility that having this procedure may shift some cells from the tumour into the surrounding tissues (tissues that come into contact with the biopsy needle). This means the tumour could spread to that particular area.

Contacts

Public
Kling Biotherapeutics B.V.

Meibergdreef 59 Meibergdreef 59
Amsterdam 1105 BA
NL
Scientific
Kling Biotherapeutics B.V.

Meibergdreef 59 Meibergdreef 59
Amsterdam 1105 BA
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

• Male or female patients aged >=18 years with histologically and/or cytologically confirmed locally advanced or metastatic solid tumors refractory to standard therapy or for whom no standard therapy is available.
• For Parts B and C, tumor types are initially restricted to melanoma, ovarian cancer, gastric cancer, and colorectal. Any additional tumor types may be added as defined by the SRC.
• For Parts B and C, patients for whom anti-PD-1 or anti-programmed cell death ligand 1 (anti-PD-L1) are the SOC should have progressed on these therapies before being eligible for enrollment in Parts B and C. Patients cannot have received more than one anti-PD-1 or anti-PD-L1 based regimen.
• Disease accessible for core needle biopsy both pre- and post-treatment with KBA1412.

Biopsies will be mandatory depending on feasibility of obtaining tissue.
• Measurable disease defined as: At least 1 lesion of >=10 mm in the longest diameter for a non lymph node or >=15 mm in the short-axis diameter for a lymph node that is serially measurable according to Response Evaluation Criteria in Solid Tumors for immunotherapy (iRECIST) using computerized tomography/magnetic resonance imaging (CT/MRI) and will not be used for on-study paired biopsies.
• Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0-1.
• Adequate hematologic function as defined by:
- Absolute neutrophil count >= 1500/µL.
- Platelet count >=175.000/µL.
- Hemoglobin >= 9.0 g/dL (transfusion and growth factor independent).
- Prothrombin time/international normalized ratio (PT/INR) and partial thromboplastin time (PTT) <=1.5 × upper limit of normal (ULN).

Exclusion criteria

• History of severe hypersensitivity reactions to other monoclonal antibodies.
• Prior treatment with:
- Any chemotherapy, anticancer small molecule therapy or investigational drug or device within 14 days or 5 half-lives (whichever is longer) prior to study treatment administration.
- Biological agents (including monoclonal antibodies) within 28 days prior to study treatment administration.
- Radiation, within 14 days prior to study treatment administration.
- Treatment with nitrosoureas or mitomycin C require a 42-day washout prior to study treatment administration.
- Anti-CD40 antibody or with FMS-like tyrosine kinase 3 ligand (FLT3L).
- KBA1412.
• Major surgery or significant traumatic injury within 4 weeks prior to study treatment administration.
• Excluding the primary tumor leading to enrollment in this study, any other active malignancy (except for definitively treated melanoma in-situ, basal or squamous cell carcinoma of the skin, or carcinoma in-situ of the bladder or cervix) within 24 months prior to study treatment administration.
• Primary central nervous system (CNS) malignancy.
Patients with stable CNS metastases post radiotherapy and no longer receiving corticosteroids prior to study treatment administration, may be considered for this study.
• Use of immunosuppressive medications within 4 weeks or systemic corticosteroids at doses exceeding 10 mg/ day (prednisone equivalent) within 2 weeks prior to study treatment administration.
• Active autoimmune disease that has required systemic treatment within 2 years prior to study treatment administration.
• Clinically significant cardiovascular disease, e.g., cerebral vascular accident/stroke or myocardial infarction, within 6 months prior to study

treatment administration, unstable angina, congestive heart failure (New York Heart Association [NYHA] Class >=III), or unstable cardiac arrhythmia requiring medication.
• History of a major bleeding event (requiring a blood transfusion of >2 units) not related to a tumor within 12 months prior to study treatment administration.
• History of clinically significant coagulation or platelet disorder or a history of being refractory to platelet transfusions within 12 months prior to study treatment administration.
• Receiving or requiring anticoagulation therapy or any drug or herbal supplements that affect platelet function, with exception of low-dose anticoagulation medications that are used to maintain the patency of a central IV catheter. Enrolment of a patient is allowed 2 weeks after stop of use of anticoagulation therapy or medications.

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	07-09-2022
Enrollment:	22
Type:	Actual

Medical products/devices used

Registration:	No
Product type:	Medicine
Brand name:	Not Applicable
Generic name:	Not Applicable

Ethics review

Approved WMO Date:	01-06-2022
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	19-10-2022
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	26-10-2022
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	30-11-2022
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	06-01-2023
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	08-02-2023
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)

	metc-ldd@lumc.nl
Approved WMO Date:	13-05-2023
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	21-06-2023
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	28-03-2024
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	15-04-2024
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	30-04-2024
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	31-05-2024
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)

metc-ldd@lumc.nl

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	EUCTR2021-006869-38-NL
ClinicalTrials.gov	NCT05501821
CCMO	NL80712.058.22