A Phase 1 Open-label, Multicenter Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Anti-tumor Activity of HBM4003 in Subjects with Advanced Solid Tumors

Published: 08-09-2021
Last updated: 05-04-2024

Part 1: Dose-Escalation Stage (not in The Netherlands)Primary objective:* Safety and tolerability of HBM4003Secondary objectives:* Preliminary anti-tumor activities of HBM4003 in advanced solid tumors* Pharmacokinetics (PK) of HBM4003Other...

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

Summary

ID

NL-OMON50321

Source
ToetsingOnline

Brief title
HBM4003.1

Condition

- Hepatobiliary neoplasms malignant and unspecified
- Miscellaneous and site unspecified neoplasms benign

Synonym
Advanced and/or growing cancers

Research involving
Human

Sponsors and support

Primary sponsor: Harbour BioMed
Source(s) of monetary or material Support: Farmaceutisch bedrijf: Harbour BioMed

Intervention

Keyword: Phase I, Solid tumors

Outcome measures

Primary outcome

Part 2: Dose-Expansion Stage

Primary endpoints:

* Objective response rate defined as the proportion of subjects with best

overall response of CR or PR per RECIST 1.1.

Secondary outcome

Part 2: Dose-Expansion Stage

Secondary endpoints:

* Objective response rate defined as the proportion of subjects with best

overall response of CR or PR per iRECIST (for melanoma and RCC) mRECIST (For

HCC).

* Duration of objective response based on RECIST 1.1 and iRECIST (for melanoma

and RCC) or mRECIST (For HCC).

* Disease control rate per RECIST1.1, defined as the proportion of subjects

with a best overall response of CR, PR, or SD.

* Duration of disease control per RECIST1.1, defined as the time from the data

of start of treatment to the date of disease progression or death for subjects

who had CR or PR or SD during treatment.

* Maximal tumor shrinkage, defined as the greatest tumor shrinkage achieved at any follow-up assessment.

Other measurements:

* Progression free survival, defined as the time from first dosing to the first occurrence of disease progression as determined by the Investigator using RECIST 1.1 or death from any cause, whichever occurs first.

* Overall survival defined as the time from first dosing to death.

* Adverse events (AEs) according to Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 (including vital signs, physical examinations, and abnormal laboratory parameters).

* PK characteristics of HBM4003.

* Effects of covariates on PK through popPK approach, if data permit, and the results will be reported separately.

* Anti-drug antibodies, not limited to neutralizing antibody.

* Peripheral cellular biomarkers (ICOS+CD4+ T cells, CD8+ T cells, FcRIII expression, Ki67+CD4+ T cells, Treg cells), cytokine biomarkers (IL-2, IL-6, IL-8, IL-10, IFN- *, TNF-*), and tissue biomarkers (Treg cells, Teff cells, myeloid-derived suppressor cells [MDSCs], tumor associated macrophages [TAMs]).

* The relationships between cellular (or tumor) biomarkers and efficacy as well as safety, if data permit.

* The relationships between the exposure of HBM4003 and efficacy as well as safety, if data permit and the results will be reported separately.

Study description

Background summary

Previous research showed that cancers are recognized by our immune system. Under some circumstances, our immune system may control or even eliminate tumors. CTLA-4 plays a critical role in the negative control of our immune response. Inhibition of CTLA-4 by treatment with antibodies against CTLA-4 has become standard of care to treat many cancer types.

Currently, Ipilimumab is the only anti-CTLA-4 antibody on the market with approval for treatment of advanced melanoma. Higher doses of Ipilimumab are efficient, but the dosing is limited because of the occurrence of life-threatening adverse events. Recent studies suggested new approaches for the development of next generation anti-CTLA-4 antibodies which are more efficient and therefore expected to be less toxic and thus safer.

HBM4003 is one of these next generation anti-CTLA-4 antibodies. HBM4003 has been tested in animal studies involving mice and monkeys and results show the compound is safe. This is the first time HBM4003 will be studied in humans.

The purpose of this study is to determine whether the new medical product HBM4003 (a fully human anti-CTLA-4 monoclonal human heavy-chain antibody) is safe and HBM4003*s anti-tumor activity in the treatment of metastatic or unresectable melanoma, hepatocellular carcinoma (HCC), and renal cell carcinoma (RCC).

Study objective

Part 1: Dose-Escalation Stage (not in The Netherlands)
Primary objective:
* Safety and tolerability of HBM4003
Secondary objectives:
* Preliminary anti-tumor activities of HBM4003 in advanced solid tumors
* Pharmacokinetics (PK) of HBM4003
Other objectives:
* Immunogenicity of HBM4003
* Exploratory biomarkers

Part 2: Dose-Expansion Stage (in The Netherlands)
Primary objective:
* Preliminary anti-tumor activities of HBM4003 in metastatic or unresectable melanoma, HCC, and RCC
Secondary objective:
* Safety of HBM4003 in metastatic or unresectable melanoma, HCC and RCC
Other objectives:

* Immunogenicity of HBM4003
* To evaluate the PK characteristics of HBM4003 based on population PK (PopPK) modeling
* Exploratory biomarkers

Study design

This study has 2 parts: a dose-escalation stage (Part 1) in subjects with advanced solid tumors, followed by dose-expansion cohorts (Part 2) of subjects with metastatic or unresectable melanoma, HCC and RCC. Only part 2 will be performed in The Netherlands.

Part 2: Dose-Expansion Stage
Part 2 will begin once the recommended phase 2 dose (RP2D) and/or maximum tolerated dose (MTD) is established. Based on clinical safety, efficacy and PK/PD data, subjects with metastatic or unresectable melanoma, HCC and RCC will be treated at the RP2D dose regimen until subject death, disease progression, occurrence of unacceptable toxicity, withdrawal of consent by the subject, subject is lost to follow-up, or the sponsor terminates the study, whichever comes first.

In the case of dose-finding for molecularly targeted agents (MTAs), the dose-finding strategy should not only focus on safety endpoints, but also on determining an optimal biologically active dose. There may be more than on RP2D to be expanded in one or more selected tumor types in Part 2 (metastatic or unresectable melanoma, HCC or RCC) to further determine the optimal active dose. This will only be initiated following endorsement by the SRC.

Intervention

The investigational medicinal product for this study is HBM4003. The study drug HBM4003 will be given by intravenous infusion. Every administration will take at least 90 minutes to complete.

The patient will receive the study drug with a three weekly dosing frequency and a maximum of 6 cycles of treatment. Each cycle will last for 21 days and treatment will be given on Day 1 of each cycle.

Study burden and risks

There is an unmet need for cancer treatments with a better safety and toxicity profile. The subjects of the current study need to visit the study sites many times to undergo assessments and for infusion of the study drug HBM4003. Although HBM4003 is a fully humanized antibody engineered to reduce immunogenicity, potential for infusion reaction and immune responses may occur when HBM4003 is given intravenously. As such, any infusion reactions will be

graded accordingly, and appropriate preventative and/or suggestive corrective action implemented.

Harbour BioMed has identified diarrhoea as an important identified risk and based upon the mechanism of action of HBM4003, immune-mediated AEs (irAEs) and infusion related reactions are identified as important potential risks for HBM4003. As of 31 Aug 2020, five of 13 patients (38.5%) were observed diarrhoea (Grade *3) in clinical trial. Among the 13 patients, three AEs of diarrhoea (Grade*3), three AEs of colitis (Grade=2), and three AEs of rash(Grade*2)were reported as immune related.

Overall, the non-clinical data suggest that treatment with HBM4003 may be beneficial for subjects with advanced solid tumors, including subjects who have failed or do not tolerate other CTLA-4 antibodies and/or with a high tumor infiltration Treg cell level. The efficacy and safety profile of other anti-CTLA-4 monoclonal antibodies, including ipilimumab and tremelimumab, is well studied and documented. The safety profile and irAE profile with HBM4003 is expected to be manageable. Given the unmet medical need of these subjects and potential efficacy offered by this next generation anti-CTLA4 monoclonal antibody, there is a definite case for benefit to subjects with acceptable risk.

Contacts

Public
Harbour BioMed

Broadway 1
Cambridge 02142
US
Scientific
Harbour BioMed

Broadway 1
Cambridge 02142
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

1. Subject with HBV negative will be allowed.
a. If the subject has positive HBsAg, he/she should receive appropriate antiviral therapy for hepatitis B virus (HBV) according to institutional standard of care and HBV DNA level must be < 2000 UI/ml.
b. Negative HBsAb and positive HBcAb (past HBV), HBV DNA level must be <2000 UI/ml and the patient should be monitored for viral re-activation during the study.
2. Subject with positive HCV-Ab should be tested HCV-RNA and could be enrolled if HCVRNA titer is negative and should be monitored during the study.
3. Must have at least one measurable lesion at baseline based on Response Evaluation Criteria in Solid Tumors (RECIST) 1.1.
4. Must undergo tumor biopsy or provide archived tumor samples at screening.
5. Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1.
6. Adequate organ and bone marrow function, defined as:
a. Absolute neutrophil count *1×109/L, hemoglobin *9 g/dL, and platelet count *50×109/L.
b. Adequate liver function defined as
* AST and ALT *2.5×upper limit of normal (ULN) and total bilirubin (TBIL) *1.5×ULN;
* For subjects with liver metastases, ALT and AST * 5×ULN and TBIL * 2×ULN;
* For subjects with Gilbert syndrome, TBIL * 2×ULN.
c. Adequate renal function defined as creatinine clearance rate * 45mL/min according to Cockcroft-Gault.
7. Subjects of reproductive potential must be willing to use adequate contraception during the course of the study and through 3 months after the last dose of HBM4003.
a. Females of childbearing potential may participate, providing they meet the following conditions:
* Agree to practice abstinence; and If heterosexually active, agree to use at least 2 highly effective contraceptive methods (oral, injectable, or implantable hormonal contraceptive; tubal ligation; intra-uterine device; barrier contraceptive with spermicide; or vasectomized partner) throughout the study, and for 3 months following the last dose of IP; and
* Have a negative serum pregnancy test (sensitivity of at least 25 mIU/mL) within 7 days prior to starting study therapy (note that the screening serum pregnancy test can be used as the test prior to starting study therapy if it is performed within the 7-day timeframe).
b. Or must be a female of non-childbearing potential, defined as:

* Postmenopausal (i.e., *1 year without any menses) prior to Screening Visit, or
* Documented surgically sterile (*1 month prior to Screening Visit).
c. Male subjects with a female partner of childbearing potential must agree to practice
* Abstinence or to the use of a physician-approved contraceptive method throughout the course of the study and avoid fathering a child during the course of the study and for 3 months following the last dose of IP.
8. Life expectancy of*12 weeks (as determined by the investigator which could be estimated according to the tumor burden, general conditions and function of the organs of the patient)

Part 2 (Dose-Expansion Stage):
Male or female subject aged *18 years at the time of screening who has signed the ICF prior to the initiation of any study-specific procedures and are willing and able to comply with scheduled visits and other requirements of the study.
Melanoma Cohort:
a. Histologically confirmed metastatic or unresectable melanoma that progressed during or after treatment with a PD-1 inhibitor
b. Must have received BRAF inhibitor with/without a MEK inhibitor if positive with BRAF V600-activating mutation and in addition to anti-PD-1 inhibitor
HCC Cohort:
a. Histologically confirmed metastatic or unresectable HCC;
b. Child-Pugh Score of 6 points or less (A5-A6);
c. Progressed on or after previous anti-PD-1 treatment, with or without other synchronous or sequential systemic treatments (including anti-VEGFR TKI, anti-VEGF/VEGFR monoclonal antibody or chemotherapy, etc).
RCC Cohort:
a. Histologically confirmed metastatic or unresectable renal cell cancer (including both clear cell and non-clear histology);
b. Subjects with clear cell RCC must have failed at least 1 anti-VEGFR TKI treatment and/or anti-PD(L)1 treatment;
c. For subjects with non-clear cell RCC (e.g. PRCC), treatment naive is permitted.

Exclusion criteria

1. History of severe or not under well controlled allergic diseases, history of severe drug allergy, or are known to be allergic to macromolecular protein preparations or any component of HBM4003
2. Subject receiving the following anti-cancer medications or investigational drugs will be excluded:
a. Cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) antibody or any CTLA-4 bispecific antibody before the first dose of HBM4003;
b. Programmed cell death protein 1 (PD-1)/Programmed cell death protein ligand

1 (PD-L1)/Programmed cell death protein ligand 2 (PD-L2)-directed antibody within 8 weeks of first dose of HBM4003
c. Cancer vaccines within 3 months prior to first dose of HBM4003
d. Live vaccine within 4 weeks prior to first dose of HBM4003
e. Any other anti-cancer therapy within 2 weeks prior to first dose of HBM4003
3. Not yet recovered from surgery or (immune-related) toxicity related with previous treatment
* Subject who has had major surgical procedure(s) within 28 days prior to the first dose of HBM4003, or not yet recovered from a previous surgical procedure
4. Failed to recover from any immune-related toxicity from prior cancer therapy to * Grade 1 prior to screening for this study
5. Concomitant medication or treatment
a. Any concurrent chemotherapy, radiotherapy, immunotherapy, or biological therapy for cancer treatment. Concurrent use of hormones on a stable dose for non-cancer related conditions is acceptable. Androgen deprivation therapy for advanced prostate cancers is acceptable. Local treatment of isolated non-target lesions for palliative intent is acceptable
b. Any traditional anti-tumor herbal medications (for example, semen coicis and glaucescent fissistigma root are considered to have anti-tumor effect according to the Traditional Chinese Medicine Pharmacopoeia of Chinese Pharmacopoeia);
c. Receipt of red blood cells or platelets infusion, granulocyte colony stimulating factor (G-CSF) or granulocyte monocyte colony stimulating factor (GM-CSF) within 1 week of the first dose of IP
d. Received treatment with corticosteroids or other immunosuppressive medications within 2 weeks before the first dose of HBM4003
6. Have concomitant diseases that may affect the treatment efficacy and safety evaluation
a. Known brain metastases or other central nervous system metastases that are either symptomatic or untreated that require concurrent treatment, inclusive of but not limited to surgery, radiation, and/or corticosteroids. Subjects with previously treated brain metastases may participate provided they are clinically stable for at least 4 weeks prior to study entry, have no evidence of new or enlarging metastases, and are on a stable dose of steroids of total daily dose of <1.5 mg/kg of dexamethasone
b. Active infection that requires treatment with antibiotics within 14 days prior to first dose of HBM4003
c. Known history of infection with human immunodeficiency virus or known AIDS
d. autoimmune disease, including but not limited to inflammatory bowel disease, autoimmune hepatitis, Guillain-Barré syndrome, demyelinating lesions, extensive dermatitis, immune-related interstitial pneumonia or Grave*s disease requiring antithyroid drugs
e. Known primary immunodeficiency
f. Clinically significant gastrointestinal disorders
g. Have received allogeneic organ transplantation or allogeneic hematopoietic stem cell transplantation or have received autologous hematopoietic stem cell transplantation within 3 months prior to the first dose
h. Subjects with medically confirmed autoimmune coeliac disease are to be

excluded
7. Subjects with clinically significant congenital or acquired cardiovascular disease cardiovascular diseases
a. Electrocardiogram abnormalities that the Investigator believes the study will pose an additional risk to the subject
b. Symptomatic congestive heart failure
c. Myocardial infarction within 3 months prior to the first dose of HBM4003
d. Uncontrolled hypertension, defined as an average systolic blood pressure * 160 mmHg or an average DBP * 100 mmHg
e. Unstable angina pectoris
f. Severe uncontrolled ventricular arrhythmia
8. History of other uncured or history of other malignancies
9. Pregnant or breastfeeding women
10. Any condition in the opinion of the Investigator would interfere with evaluation of HBM4003
11. Have experienced immune-related GI adverse events on any prior immunotherapy or toxicity that led to permanent discontinuation of prior immunotherapy
12. Severe cirrhosis, hepatic atrophy or portal hypertension
13. Imaging studies indicated that the main portal vein tumor embolus is more than 1/2 of the lumen, or inferior vena cava tumor embolus or heart involvement.
14. Any clinically significant pleural effusion, pericardial effusion or ascites that cannot be controlled with continuous draining or other methods at screening
15. Any history of hepatic encephalopathy (greater than or equal to Grade 2) within 12 months prior to enrolment or require medications to prevent or control encephalopathy.
16. Subjects weighing < 30 kg
17. Active or prior documented GI bleeding within 12 months

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	7
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	HBM4003
Generic name:	HBM4003

Ethics review

Approved WMO Date:	08-09-2021
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	13-12-2021
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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	EUCTR2021-003997-29-NL
ClinicalTrials.gov	NCT04135261
CCMO	NL78893.078.21