A Dose-Escalation and Expansion Study of the Safety and Pharmacokinetics of XB002 as Single-Agent and Combination Therapy in Subjects with Inoperable Locally Advanced or Metastatic Solid Tumors

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This study has been transitioned to CTIS with ID 2023-508267-69-00 check the CTIS register for the current data. Cohort-Expansion Stage (Single-Agent and Combination Therapy Cohorts):Primary:• To evaluate the preliminary efficacy of XB002 when...

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

Summary

ID

NL-OMON56126

Source
ToetsingOnline

Brief title
Study of XB002 in Subjects With Solid Tumors (JEWEL-101)

Condition

- Other condition

Synonym
advanced cancer, metastatic cancer

Health condition

Inoperable Locally Advanced or Metastatic Solid Tumors

Research involving
Human

Sponsors and support

Primary sponsor: Exelixis, Inc., Kanika Asija
Source(s) of monetary or material Support: Exelixis;Inc.

Intervention

Keyword: Inoperable Locally Advanced or Metastatic Solid Tumors, Phase 1, XB002

Outcome measures

Primary outcome

Cohort-Expansion Stage (Single-Agent and Combination Therapy Cohorts):

To evaluate preliminary efficacy of XB002 when administered alone and in combination therapy by determining the ORR per RECIST 1.1 (or other applicable response criteria, eg, RANO or PCWG3 criteria) as assessed by the Investigator.

Secondary outcome

• To evaluate the safety and tolerability of XB002 when administered alone and in combination therapy

• To further evaluate the PK of XB002 (antibody conjugated to payload), total antibody (unconjugated and conjugated antibody), and free payload following IV administration alone and in combination therapy

• To assess the immunogenicity of XB002

• To evaluate the anti-tumor activity of XB002 alone and in combination therapy as measured by DOR and PFS per RECIST 1.1 (or other applicable response criteria, eg, RANO or PCWG3 criteria) as assessed by the Investigator

• To evaluate the anti-tumor activity of XB002 alone and in combination therapy

as measured by ORR, DOR, and PFS per RECIST 1.1 (or other applicable response

criteria, eg, RANO or PCWG3 criteria) as assessed by a BIRC for selected cohorts

• To evaluate overall survival

• To evaluate changes in tumor markers from baseline for selected tumor

indications

Study description

Background summary

See protocol page 57 (1. Background and Rationale)

Study objective

This study has been transitioned to CTIS with ID 2023-508267-69-00 check the CTIS register for the current data.

Cohort-Expansion Stage (Single-Agent and Combination Therapy Cohorts):
Primary:
• To evaluate the preliminary efficacy of XB002 when administered alone and in combination therapy by determining the ORR per RECIST 1.1 (or other applicable response criteria, eg, RANO or PCWG3 criteria) as assessed by the Investigator
Additional:
• To evaluate the safety and tolerability of XB002 when administered alone and in combination therapy
• To further evaluate the PK of XB002 (antibody conjugated to payload), total antibody (unconjugated and conjugated antibody), and free payload following IV administration alone and in combination therapy
• To assess the immunogenicity of XB002
• To evaluate the anti-tumor activity of XB002 alone and in combination therapy as measured by DOR and PFS per RECIST 1.1 (or other applicable response criteria, eg, RANO or PCWG3 criteria) as assessed by the Investigator
• To evaluate the anti-tumor activity of XB002 alone and in combination therapy as measured by ORR, DOR, and PFS per RECIST 1.1 (or other applicable response criteria, eg, RANO or PCWG3 criteria) as assessed by a Blinded Independent Radiology Committee (BIRC) for selected cohorts
• To evaluate overall survival
• To evaluate changes in tumor markers from baseline for selected tumor indications
Exploratory:

• To assess the effects of XB002 on tumor and blood biomarkers
• To evaluate the exposure of nivolumab or bevacizumab in combination with XB002
• To assess the immunogenicity of nivolumab or bevacizumab in combination with XB002
• To evaluate the association between TF expression and efficacy outcomes
• To evaluate the safety, tolerability, and anti-tumor activity of XB002 when administered alone at the RD and RD-low doses in SCCHN, NSCLC, EOC, and cervical cancer
• To evaluate patient-reported outcomes and the impact of ocular symptoms on vision-related function

Study design

This is a Phase 1, open-label, multicenter, dose-escalation and expansion study evaluating the safety, tolerability, PK, pharmacodynamics, and clinical antitumor activity of XB002 administered IV q3w alone and in combination with nivolumab or bevacizumab to subjects with advanced solid tumors. This study consists of Dose-Escalation and Cohort-Expansion Stages for the evaluation of XB002 as monotherapy and in combination with nivolumab or bevacizumab. First, the safety and PK of XB002 monotherapy will be evaluated in the Single-Agent Dose-Escalation Stage. In this stage, subjects with advanced solid tumors will be treated with XB002 in dose-escalation cohorts using the i3+3 design (Liu et al 2020).
Dose-escalation steps of XB002 will be tailored by monitoring safety and PK data. The safety and PK of XB002 combination therapy will be evaluated in the Combination Therapy Cohort-Expansion Stage for nivolumab or bevacizumab. A Cohort Review Committee (described in Section 3.7.1) will determine the MTD and the RD of XB002 from both Dose Escalation Stages (single-agent XB002 and in combination with nivolumab or bevacizumab) for use in the corresponding Cohort-Expansion Stages. After the RD of XB002 has been identified in the Dose-Escalation Stage, safety and efficacy of XB002, both as a single-agent and in combination with nivolumab or bevacizumab may be further evaluated in the Cohort-Expansion Stage. The opening or closing of each Expansion Cohort will be determined by the Sponsor. The TA TF+ cohort may be opened at selected sites and/or countries.
Subjects in the Dose-Escalation Stage will provide available archival tumor tissue during the screening period (if archival tissue is not available, fresh tumor biopsy material can be provided if the biopsy can be safely performed per investigator discretion). Subjects in the Cohort-Expansion Stage are required to provide tissue samples (archival or fresh biopsy tumor tissue) during the screening period. Fresh tumor biopsy during the screening period should not be performed for the TA TF+ cohort. Subjects in both stages may also provide tumor tissue from a fresh biopsy optionally during the treatment period. All subjects will receive XB002 as a single 30-minute IV infusion q3w. Subjects will continue treatment until a discontinuation criterion is met. After the last follow-up visit subjects will be followed every 12 weeks to obtain information on subsequent anticancer therapy and survival.

Note: XB002 plus bevacizumab combination therapy was terminated in light of recent safety data reviewed as of 20 Dec 2023.

Intervention

XB002 Injection Drug Product will be administered IV over approximately 30 minutes (see Table 11) every three weeks (q3w). Dosing of XB002 will be based on actual body weight (mg/kg). For subjects with a body weight > 100 kg, the maximum total dose will be calculated based on 100 kg body weight. Standard institutional dose rounding rules can be applied. If not available, rounding should be based on the nearest milligram.
Nivolumab will be administered in the clinic at a dose of 360 mg as an IV infusion over approximately 30 minutes q3w for a maximum of 2 years. Nivolumab should be administered prior to XB002. The time in between infusions is expected to be at least 30 minutes (from the end of the nivolumab infusion to the start of the XB002 infusion). The initial infusions of nivolumab and XB002 will be given without premedication for potential IRRs. Premedication for IRRs is allowed after the initial infusions. No bolus or IV push of nivolumab is allowed.

Study burden and risks

Effects of XB002 in Animals:
In studies in animals done to understand possible XB002 side effects, XB002 caused changes in the eye and eyelids, including changes in the conjunctiva and cornea. Symptoms at higher doses included swelling around the eye, eyelid swelling, eye discharge, eye redness, dry eye, ulceration (ulcer), inflammation and changes which might result in blurry vision. In addition, inflammation was seen in lungs, and dry and/or red skin. In some animals, particularly at high doses, the eye symptoms persisted within 6 weeks after the last treatment, though longer term recovery was not assessed and improvement may occur with time.

Effects of XB002 in Humans
There is limited experience with XB002 in humans, so the risks are not completely known. As of 21 December 2023, a total of 109 patients have been dosed in the Dose Escalation and Cohort Expansion stages of the study and received XB002 alone or in combination therapy at various dosages (up to 2.5 mg/kg). To date, the following side effects have been stablished for XB002:

Very common (may affect more than 1 in 10 people)
• Inflammation of the membranes protecting your eye (conjunctiva)
• Protein loss in the urine

Common (may affect up to 1 in 10 people)
• Nephrotic syndrome, a kidney disease which results in protein loss in the

urine, low protein levels in the blood and fluid collection in your body (eg in the ankles off the legs). This disease may cause kidney injury and may require hospitalization. It also may increase the risk of infections and may lead to blood clotting problems (thromboses). The observation of this disease led to a XB002 dose reduction to 1.75 mg/kg maximally. In light of this, it is very important that frequent urine samples are collected and analyzed.

Effects of Nivolumab in Humans:
Be aware of important symptoms of inflammation. Nivolumab acts on your immune system (the body*s own defense) and may cause inflammation in parts of your body. Inflammation may cause serious damage to your body and some inflammatory conditions may be life-threatening and need treatment or withdrawal of nivolumab.
The following side effects have been reported with nivolumab alone:
Very common (may affect more than 1 in 10 people)
• Infections of the upper respiratory airway
• A decreased number of red blood cells (which carry oxygen), white blood cells (which are important in fighting infection) or platelets (cells which help the blood to clot)
• High (hyperglycaemia) or low (hypoglycaemia) sugar levels in the blood
• Diarrhea (watery, lose or soft stools), vomiting, nausea, constipation, stomach pain
• Skin rash sometimes with itching
• Feeling tired or weak, fever, oedema (swelling)
• Decreased appetite
• Headache
• Shortness of breath (dyspnoea), cough
• Pain in the muscles, bones (musculoskeletal pain) and joints (arthralgia)

Please refer to the ICF for risks and discomforts associated with study procedures (Section 7).

Contacts

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US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Cytologically or histologically and radiologically confirmed solid tumor that is inoperable, locally advanced, metastatic, or recurrent.

2. Subjects in the Cohort-Expansion Stage must have measurable disease per RECIST 1.1 as determined by the investigator. Note: Measurable disease at screening is not required for the following subjects:
a. Subjects in the Dose-Escalation Stage.
b. Subjects with prostate cancer (Cohort I) without soft tissue disease (RECIST 1.1 assessments are not required for these subjects).
c. Subjects with primary brain tumors, such as glioblastoma (RECIST assessments are not required for these subjects).

3. Available archival tumor tissue collected no more than 3 years prior to consent, if possible. If archival tumor tissue is not available, a fresh tumor biopsy may be collected from subjects enrolled in the Dose-Escalation Stage and should be collected from subjects in the Cohort-Expansion Stage. Fresh tumor biopsy during the screening period should not be performed for the TA TF+ cohort. Specific requirements for tumor tissue samples are provided in the Laboratory Manual.

4. Recovery to baseline or <= Grade 1 severity (Common Terminology Criteria for Adverse Events version 5 [CTCAE v5]) from AEs, unless AEs are clinically nonsignificant (eg, alopecia) or stable (eg, peripheral neuropathy not limiting subjects* instrumental activities of daily life).

5. Age 18 years or older or meeting country definition of adult, whichever is older on the day of consent.

6. Eastern Cooperative Oncology Group (ECOG) Performance Status of 0-1

7. Adequate organ and marrow function, based upon meeting of laboratory criteria within 10 days before first dose of study treatment:
a. Absolute neutrophil count (ANC) >= 1500/mm3 (>= 1.5 GI/L) without granulocyte colony-stimulating factor (G-CSF) support within 2 weeks prior to screening laboratory sample collection.
b. Platelets >= 100,000/mm3 (>= 100 GI/L)] without transfusion within 2 weeks prior to screening laboratory sample collection.
c. Hemoglobin >= 9 g/dL (>= 90 g/L) without transfusion within 2 weeks prior to screening laboratory sample collection.
d. Activated partial thromboplastin time (aPTT) <= 1.2 × upper limit of normal (ULN) and prothrombin time (PT) <= × 1.2 ULN or International Normalized Ratio (INR) <= 1.3 without anticoagulation therapy (INR <= 3 if on stable oral coumarin-based anticoagulant).
e. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) <= 3 × ULN. Note: Subjects with hepatic metastases and ALT and AST > × 3 ULN may be allowed at the discretion of the Investigator.
f. Total bilirubin <= 1.5 × ULN (for subjects with known Gilbert*s disease, total bilirubin <= 3 × ULN).
g. Serum creatinine <= 1.5 × ULN or calculated creatinine clearance >= 45 mL/min (>= 0.75 mL/sec) using the Cockcroft-Gault equation
h. Urine protein creatinine ratio (UPCR) <= 1.0.

8. Capable of understanding and complying with the protocol requirements and must have signed the informed consent document.

9. Sexually active fertile subjects and their partners must agree to highly effective methods of contraception (defined in Appendix E) during the course of the study and for the following durations after the last dose of treatment (whichever is later).
• 7 months after the last dose of XB002 for women of childbearing potential (WOCBP) and 4 months after the last dose of XB002 for men.
• 5 months after the last dose of nivolumab for WOCBP.
• 6 months after the last dose of bevacizumab for WOCBP.
• Male subjects with female partners of childbearing potential must agree to use a condom until 4 months after the last dose of XB002.

10. Female subjects of childbearing potential must not be pregnant at screening. Female
subjects are considered to be of childbearing potential unless one of the following criteria
is met: permanent sterilization (hysterectomy, bilateral salpingectomy, or bilateral

oophorectomy) or documented postmenopausal status.

Exclusion criteria

1. Receipt of any tissue factor-targeting antibody drug conjugate or auristatin derivate-based antibody drug conjugate.
2. Receipt of any chemotherapy or anticancer antibody (eg, anti-VEGF mAb, antibody-drug conjugate, or PD-1/PD-L1 mAb) within 21 days (nitrosoureas or mitomycin within 42 days) before first dose of study treatment.
3. Receipt of any type of small molecule kinase inhibitor (including investigational kinase inhibitors) within 2 weeks before first dose of study treatment.
4. Receipt of any anticancer hormonal therapy within 2 weeks or within 5 half-lives of the agent, whichever is shorter, before first dose of study treatment. Note: Concomitant use of a luteinizing hormone-releasing hormone (LHRH) agonist (eg, leuprolide, goserelin) or antagonist (eg, relugolix) is permitted.
5. Radiation therapy within 2 weeks before first dose of study treatment. Subjects with clinically relevant ongoing complications (eg, radiation induced esophagitis or pneumonitis) from prior radiation therapy are not eligible. See inclusion criteria #4 for relevant details.
6. Known brain metastases or cranial epidural disease unless adequately treated with radiotherapy and/or surgery (including radiosurgery) and stable for at least 4 weeks before first dose of study treatment. Note: Eligible subjects must be neurologically asymptomatic and without corticosteroid treatment at the time of first dose of study treatment.
7. The subject has uncontrolled, significant intercurrent or recent illness.
8. Major surgery (eg, GI surgery, removal or biopsy of brain metastasis) within 4 weeks before first dose of study treatment. Minor surgery (eg, simple excision, tooth extraction, port placement) within 7 days before first dose unless discussed with and approved by the Sponsor. Complete wound healing from surgery must have occurred and any surgery related AEs must have resolved before the first dose. Subjects with clinically relevant ongoing complications from prior surgery are not eligible.
9. Corrected QT interval calculated by the Fridericia formula (QTcF) > 480 ms per electrocardiogram (ECG) within 4 weeks before first dose of study treatment (see Section 5.7.7 for Fridericia formula) Note: If a single ECG shows a QTcF with an absolute value > 480 ms, two additional ECGs at intervals of approximately 3 minutes must be performed within 30 minutes after the initial ECG, and the average of the three consecutive results for QTcF must be <= 480 ms for the subject to be eligible.
10. History of psychiatric illness likely to interfere with ability to comply with protocol requirements or give informed consent.
11. Pregnant or lactating females.
12. Previously identified allergy or hypersensitivity to components of the

study treatment formulations or history of severe infusion-related reactions (IRRs) to monoclonal antibodies.
13. Another unresolved malignancy or a malignancy that is considered to be cured within 2 years before first dose of study treatment. Note: Subjects with superficial non-melanoma skin cancers, or localized, low grade tumors deemed cured and not treated with systemic therapy, within 2 years before first dose of study treatment are eligible.

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	21-12-2023
Enrollment:	19
Type:	Actual

Medical products/devices used

Registration:	No
Product type:	Medicine
Brand name:	nivolumab
Generic name:	nivolumab
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	XB002
Generic name:	XB002

Ethics review

Approved WMO Date:	22-11-2022
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	28-06-2023
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	28-08-2023
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	25-09-2023
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	07-12-2023
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	22-01-2024
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	14-03-2024
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO	

Date:	12-04-2024
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

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
EU-CTR	CTIS2023-508267-69-00
EudraCT	EUCTR2021-006543-10-NL
ClinicalTrials.gov	NCT04925284
CCMO	NL81905.068.22