First-in-human, open-label, dose-escalation trial with expansion cohorts to evaluate safety of Axl-specific antibody-drug conjugate (enapotamab vedotin, HuMax®-AXL-ADC) in patients with solid tumors.

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4.1 Primary Objective• To determine the MTD and to establish the safety profile of enapotamab vedotin in a mixed population of patients with specified solid tumors. 4.2 Secondary Objectives• To evaluate the safety laboratory parameters of enapotamab...

Ethical review	Approved WMO
Status	Pending
Health condition type	Miscellaneous and site unspecified neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON48742

Source
ToetsingOnline

Brief title
First-in-human, trial of enapotamab vedotin in patients with solid tumours.

Condition

- Miscellaneous and site unspecified neoplasms malignant and unspecified

Synonym
Patients with solid tumors

Research involving
Human

Sponsors and support

Primary sponsor: Genmab
Source(s) of monetary or material Support: Genmab A/S

Intervention

Keyword: enapotamab vedotin, GCT1021-01

Outcome measures

Primary outcome

• To determine the MTD and to establish the safety profile of enapotamab vedotin in a mixed population of patients with specified solid tumors.

Secondary outcome

• To evaluate the safety laboratory parameters of enapotamab vedotin in a mixed population of patients with specified solid tumors.

• To establish the PK profile and evaluate immunogenicity of enapotamab vedotin after single and multiple infusions.

• To evaluate the antitumor activity of enapotamab vedotin in a mixed population of patients with specified solid tumors.

• To evaluate Axl expression in tumor biopsies from a mixed population of patients with specified solid tumors.

Study description

Background summary

Axl (also named Ark, Ufo, Tyro 7) is a transmembrane receptor tyrosine kinase. Human Axl consists of 894 amino acids and is a single chain glycoprotein.

Together with Tyro-3 and Mer, Axl forms the TAM family of receptor tyrosine kinases, which is characterized by two immunoglobulin-like domains (Ig1 and Ig2) and two fibronectin type III domains (FN1 and FN2) in the extracellular domain. Furthermore, these receptors have an intracellular tyrosine kinase domain that is activated upon ligand stimulation. Growth arrest-specific 6 (Gas6) is the physiological ligand of Axl that binds to the Axl Ig1- and Ig2-domains, resulting in activation of the intracellular kinase domain. Generally, Axl is expressed in various tumor types. Axl expression is thought to functionally contribute to tumor development. Enhanced tumor cell motility, adherence and migration, epithelial-to-mesenchymal transition, angiogenesis and resistance to targeted therapy and chemotherapy have been linked to Axl expression. Gas6, the physiological ligand of Axl, is also expressed in some cancers, potentially contributing to Axl activation through an Axl-Gas6 autocrine loop4.

enapotamab vedotin is a human IgG1 antibody that is generated by conjugation of an Axl specific antibody with the microtubule disrupting agent monomethyl auristatin E (MMAE) through the protease cleavable valine-citrulline (vc) linker5-7. Enapotamab vedotin binds to the Ig1 domain of Axl and does not compete with Gas6 for receptor binding. This is particularly relevant in tumors that co-express Axl and Gas6, in which enapotamab vedotin is still able to bind in the presence of Gas68.

The dominant mechanism of action for enapotamab vedotin is tumor cell killing by MMAE mediated interference with cell division. Upon binding of enapotamab vedotin to Axl expressed on the cell surface of tumor cells, the complex is rapidly internalized and targeted to the lysosomes. Proteolytic cleavage of the vc peptide linker in the lysosomes subsequently releases MMAE from the complex. Free MMAE can diffuse within the cell where it directly binds to microtubules and inhibits tubulin polymerization. Thereby MMAE interferes with proper assembly of the mitotic spindle during cell division resulting in cell cycle arrest and eventually cell death. Tubulin inhibitors primarily induce cytotoxicity in proliferating cells and not in quiescent cells. Therefore, proliferating tumor cells are preferentially targeted over normal cells, which are generally quiescent. Due to its membrane permeability, MMAE can also cause a bystander effect, e.g. cell death of proliferating Axl negative tumor cells that surround Axl positive tumor cells5.

Unconjugated HuMax-AXL, was unable to induce in vitro cytotoxicity, and did not inhibit tumor growth in xenograft models. However, enapotamab vedotin was internalized after target binding, which is required for the cytotoxic function of tubulin-inhibitor-based anti-drug conjugate (ADCs). Cytotoxic payloads were conjugated to Axl antibodies to test their anti-tumor activity in mouse xenograft models. Enapotamab vedotin was selected from the panel as the clinical candidate, since it demonstrated the most potent anti-tumor activity in vivo. Furthermore, anti-tumor efficacy of enapotamab vedotin was shown in xenograft models derived from various tumor indications.

For more comprehensive information regarding enapotamab vedotin, refer to the current version of the Investigator's Brochure for enapotamab vedotin

Study objective

4.1 Primary Objective
• To determine the MTD and to establish the safety profile of enapotamab vedotin in a mixed population of patients with specified solid tumors.
4.2 Secondary Objectives
• To evaluate the safety laboratory parameters of enapotamab vedotin in a mixed population of patients with specified solid tumors.
• To establish the PK profile and evaluate immunogenicity of enapotamab vedotin after single and multiple infusions.
• To evaluate the antitumor activity of enapotamab vedotin in a mixed population of patients with specified solid tumors.
• To evaluate Axl expression in tumor biopsies from a mixed population of patients with specified solid tumors.
4.3 Exploratory Objective
• To explore biomarkers predictive of response and resistance to enapotamab vedotin.
4.4 Primary Endpoints
• Dose Limiting Toxicities (DLTs).
• Adverse events AEs: incidences of AEs, serious adverse events (SAEs), infusion-related AEs >= grade 3 AEs, and AEs related to Investigational Medicinal Product (IMP) during

Study design

The trial consists of a dose-escalation part with 2 arms (part I) and a dose expansion part (part II).
Part I of this trial is a FIH, open-label, dose-escalation, safety trial of Axl-specific antibody drug conjugate (ADC) enapotamab vedotin in a mixed patient population with solid tumors to determine the MTD and the safety profile of enapotamab vedotin.
Part I of this trial includes two arms for identification of the most optimal dosing regimen:
• 1Q3W: Dosing once every 3 weeks.
o There is broad experience with 1Q3W dosing of ADCs9 and brentuximab vedotin has received market authorization using this schedule (see Investigator*s Brochure).
• 3Q4W: Weekly dosing for 3 weeks followed by one treatment-free week.
o Since enapotamab vedotin is expected to have a half-life in the range of 0.94 - 1.37 days a more frequent dosing schedule may improve the therapeutic window.
The less frequent dosing-arm (1Q3W) is designed as a Modified Bayesian Continuous Reassessment Method (mCRM) incorporating Escalation With Overdose Control (EWOC). This design is considered appropriate as the Bayesian mCRM in general better estimates the MTD with less bias and more precision than a classic 3+3 design10. A comprehensive comparison of the Continual Reassessment Method (CRM) to the standard 3+3 dose escalation scheme in phase I dose-finding

studies has been described by Iasonos et. al10.
The properties of MMAE-based ADCs have been studied comprehensively and based on the overview provided by Deslandes9 (in particular Table 1 of the article), an U.S. Food and Drug Administration (FDA) analysis of ADCs11, in combination with sponsor*s own development experience with tisotumab vedotin (HuMax-TF-ADC) it is assumed that the MTD will be between 1.8 mg/kg - 2.5 mg/kg for the 1Q3W dose schedule.
The design provides flexibility in terms of cohort sizes (allowed to vary in CRM but not in classic 3+3 design).
In contrast, the more frequent dosing-arm (3Q4W) will be conducted as a classic 3+3 design as it consists of fewer dose-levels 5-6 and will include fewer patients (15-36, 17 expected as compared to 28 in the 1Q3W-arm). The CRM would need at least ~20-25 patients in order to work properly10.
The 3Q4W-arm will follow the 1Q3W-arm. Decisions in this arm will be supplemented by information from the 1Q3W-arm which at all times will have exposed patients at higher dose-levels than the 3Q4W-arm.
The aim of the expansion part is to provide further data on the safety, tolerability, pharmacokinetic (PK) and anti tumor activity of the selected dose.

Intervention

Not applicable

Study burden and risks

Although there is no clinical experience with enapotamab vedotin as this is a first-in-human (FIH) trial, while there is substantial experience with MMAE-based ADCs as described in Investigator*s Brochure (IB), the following notable observations in the toxicology studies with enapotamab vedotin pointing to potential risks in human should be kept in mind.
• During infusion of enapotamab vedotin in non-clinical toxicology studies in cynomolgus monkeys, infusion-related reactions with swelling of the eye lids, decreased muscle tone, labored breathing, or brief loss of consciousness was observed during the second treatment in 2 out of a total of 30 monkeys treated with enapotamab vedotin (1Q3W x 3). Infusion-related clinical signs did not occur or were milder during the third infusion in the monkeys when the infusion time was prolonged from 30 to 60 min. Infusion-related reactions have also been observed with related ADC compounds using MMAE as the toxin. Patients should be monitored closely during infusion of enapotamab vedotin.
• Bone marrow suppression has been observed in non-clinical studies of enapotamab vedotin and this adverse effect is expected during treatment with MMAE-ADCs and is a common adverse finding for other MMAE-ADCs. Low neutrophil count with increased risk of infections as well as anemia, lymphocytopenia and thrombocytopenia might occur and hematological parameters should be monitored during treatment.

• Enapotamab vedotin caused dose-related, reversible changes in the male reproductive system (reduced sperm motility, lower testes and epididymides weights, and degenerative changes in the sperm-producing epithelium in testes). As risk mitigation, it is recommended that fertile males consider having semen specimen obtained for storage for potential future conception.
• MMAE is metabolized mainly via the CYP3A4 pathway and is capable of inhibiting human CYP3A4/5 enzymatic activity in vitro at concentrations that may be achieved during clinical treatment and is a substrate for P-gp. Patients who are receiving strong CYP3A4 or P-gp inhibitors concomitantly with enapotamab vedotin should be closely monitored for adverse reactions.
Peripheral neuropathy has been observed frequently in patients receiving MMAE-ADCs. Pausing of dosing or dose adjustment of enapotamab vedotinin case of neuropathy is required (please refer to Section 7.3.2).
Important potential and newly identified risks for enapotamab vedotin include constipation. In particular, events of constipation (<= Grade 3), some of them leading to hospitalization, have been observed. The use of prophylactic concomitant medication to avoid and manage constipation is described in Section 7.4.1.

Please refer to the IMPD Risk benefit assessment for the benefit-risk of enapotamab vedotin.

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

Patients with advanced and/or metastatic cancer:
- who have failed available standard treatments or
- who are not candidates for standard therapy., Patients must have measurable disease according to Response
Evaluation Criteria In Solid Tumors (RECIST) version 1.1.
Have an acceptable renal, liver, and hematological function., All patients must provide a tumor tissue sample (Formalin Fixed Paraffin Embedded (FFPE) blocks / slides) from archival tissue or fresh biopsy collected before Cycle 1, Day 1, preferably derived from advanced disease stage., Age >= 18 years., Have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1., Life expectancy of at least 3 months., Patients, both females and males, of childbearing/reproductive potential must agree to use adequate contraception during and for 6 months after the last infusion of enapotamab vedotin., Patients must provide a signed informed consent form.

Exclusion criteria

Acute deep vein thrombosis or clinically relevant pulmonary embolism, not stable for at least 4 weeks prior to first enapotamab vedotin administration., Have clinically significant cardiac disease, including:
- Onset of unstable angina within 6 months of signing the ICF.
- Acute myocardial infarction within 6 months of the signing the ICF., Known congestive heart failure (Grade III or IV as classified by the New York Heart Association); and/ or a known decreased cardiac ejection fraction of < 45% and/or baseline QT interval as corrected by Fridericia*s formula (QTcF) > 480 msec or uncontrolled atrial fibrillation., Uncontrolled hypertension defined as systolic blood pressure >=160 mmHg and/or diastolic blood pressure >=100 mmHg, despite optimal medical management., Have received granulocyte colony stimulating factor (G-CSF) or granulocyte/macrophage colony stimulating factor support three weeks prior to first enapotamab vedotin administration., Have received a cumulative dose of corticosteroid >= 150 mg prednisone (or equivalent doses of corticosteroids) within two weeks before the first enapotamab vedotin administration. , History of >= grade 3 allergic reactions to monoclonal antibody therapy as well as known or suspected allergy or intolerance to any agent given in the course of this trial., Major surgery within 4 weeks before

first enapotamab vedotin administration., Any history of intracerebral arteriovenous malformation, cerebral aneurysm, brain metastases or stroke., Any anticancer therapy including; small molecules, immunotherapy, chemotherapy monoclonal antibodies or any other experimental drug within 5 half-lives but maximum 4 weeks before first infusion. Accepted exceptions are bisphosphonates, denosumab and gonadotropin-releasing hormone agonist or antagonist, which can be continued throughout the trial., Any prior therapy with a conjugated or unconjugated auristatin derivative/vinca-binding site targeting payload. (Previous treatment with vinca alkaloids is allowed in line with inclusion criterion #1.), Radiotherapy within 14 days prior to first enapotamab vedotin administration. (Palliative radiotherapy will be allowed)., Known past or current malignancy other than inclusion diagnosis, except for:
- Cervical carcinoma of Stage 1B or less.
- Non-invasive basal cell or squamous cell skin carcinoma.
- Non-invasive, superficial bladder cancer.
- Prostate cancer with a current PSA level < 0.1 ng/mL.
- Breast cancer in BRCA1 or BRCA2 positive ovarian cancer patients.
- Any curable cancer with a complete response (CR) of > 2 years duration., Melanoma patients with an LDH >= 3 x ULN, Ongoing significant, uncontrolled medical condition including:
- Serious, non-healing wound, skin ulcer (of any grade), or bone fracture., Presence of >= grade 2 peripheral neuropathy., Clinically significant active viral, bacterial or fungal infection requiring:
- I.v. treatment with anti-infective therapy that has been administered less than two weeks prior to first dose, or
- Oral treatment with anti-infective therapy that has been administered less than one week prior to first dose.
- Prophylactic anti-infective therapy, which is given without clinical symptomatic is allowed (e.g. antibiotic prophylaxis prior to dental extraction, etc.).
Known human immunodeficiency virus seropositivity., Known history / positive serology for hepatitis B (unless immune due to vaccination or resolved natural infection or unless passive immunization due to immunoglobulin therapy):, Known positive serology for hepatitis C (unless due to immunoglobulin therapy)., Substance abuse, medical, psychological or social conditions that may interfere with the patient's participation in the trial or evaluation of the trial result., History of organ allograft (except for corneal transplant) or autologous or allogeneic bone marrow transplant, or stem cell rescue within 3 months prior to the first dose of enapotamab vedotin., Body weight < 40 kg., Women who are pregnant or breast feeding.

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	02-04-2018
Enrollment:	42
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	enapotamab vedotin
Generic name:	enapotamab vedotin

Ethics review

Approved WMO Date:	07-03-2018
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	19-07-2018
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	13-11-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	14-12-2018

Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	11-01-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	15-02-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	29-07-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	11-09-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	10-12-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	16-12-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	15-01-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	23-01-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	11-03-2020

Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	12-03-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	12-10-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	15-10-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	14-07-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	12-08-2021
Application type:	Amendment
Review commission:	METC NedMec

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	EUCTR2016-002243-42-NL
ClinicalTrials.gov	NCT02988817
CCMO	NL64490.031.18