A Randomized, Open-Label, Phase 3 Trial of Tisotumab Vedotin vs Investigator*s Choice Chemotherapy in Second- or Third-Line Recurrent or Metastatic Cervical Cancer

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The purpose of this study is to demonstrate improvement in clinical efficacy of tisotumab vedotin compared to chemotherapy in participants with second- or third-line (2L-3L) cervical cancer (Overall Survival-OS)

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Miscellaneous and site unspecified neoplasms benign
Study type	Interventional

Summary

ID

NL-OMON51118

Source
ToetsingOnline

Brief title
SGNTV-003

Condition

- Miscellaneous and site unspecified neoplasms benign

Synonym
Recurrent Cervical Cancer; Cancer of the cervix that has come back or spread to other parts of the body

Research involving
Human

Sponsors and support

Primary sponsor: Seagen
Source(s) of monetary or material Support: Seagen Inc.

Intervention

Keyword: Cervical Cancer, Metastatic, Recurrent

Outcome measures

Primary outcome

Demonstrate improvement in clinical efficacy of tisotumab vedotin compared to chemotherapy in participants with second- or third-line (2L-3L) cervical cancer (Overall Survival-OS)

Secondary outcome

1. Assess improvement in clinical efficacy of tisotumab vedotin compared to chemotherapy (Progression-free survival-PFS)

2. Demonstrate improvement in antitumor activity of tisotumab vedotin compared to chemotherapy (Objective Response Rate - ORR)

3. Assess the antitumor response of tisotumab vedotin and chemotherapy (Time-to-response - TTR) and (Duration of response - DOR)

4. Evaluate the safety and tolerability of tisotumab vedotin

5. Assess health-related quality of life (HRQOL)

Study description

Background summary

For the vast majority of patients diagnosed with recurrent/metastatic cervical cancer (r/mCC), platinum-based chemotherapy regimens were the 1L standard of care for many years. More recently, a systemic combination therapy of bevacizumab with either cisplatin+paclitaxel or paclitaxel+topotecan was established as the standard of care for 1L treatment of patients with persistent, r/mCC based on the Gynecologic Oncology Group (GOG) 240 trial. The addition of bevacizumab to chemotherapy was associated with an increased incidence of hypertension of grade 2 or higher (25% vs. 2%), thromboembolic events of grade 3 or higher (8% vs. 1%), and gastrointestinal fistulas of grade 3 or higher (3% vs. 0%). This regimen is the standard of care for the 1L treatment of r/mCC for patients who are eligible to receive bevacizumab.

Treatment options after the 1L are limited, and no standard of care therapies have been identified.

Tisotumab vedotin binds to TF-expressing tumor cells, followed by internalization of the ADC-TF complex, and the local release of MMAE via proteolytic cleavage. MMAE disrupts the microtubule network of actively dividing cells, leading to cell cycle arrest and apoptotic cell death. Released MMAE can diffuse out of the cell into the tumor microenvironment and enter neighboring cells by passive diffusion. If the neighboring cell is undergoing active cell division, then MMAE can once again induce cell cycle arrest and apoptotic death-a process called bystander cytotoxicity-independent of the neighboring cell*s TF expression level. The direct cytotoxicity of Tisotumab vedotin may be augmented by the immune-mediated tumor cell killing effects of antibody-dependent cell-mediated cytotoxicity, antibody-dependent cellular phagocytosis, and immunogenic cell death clinic. Finally, in vivo anti-tumor activity of tisotumab vedotin was demonstrated in multiple tumor types in mouse efficacy models implanted with cell line-derived and patient-derived tumor xenografts.

Study objective

The purpose of this study is to demonstrate improvement in clinical efficacy of tisotumab vedotin compared to chemotherapy in participants with second- or third-line (2L-3L) cervical cancer (Overall Survival-OS)

Study design

This is an open-label, randomized (1:1), global, phase 3 study of tisotumab

vedotin versus investigator*s choice of chemotherapy in participants with r/mCC who have received 1 or 2 prior lines of systemic therapy for their recurrent or metastatic disease. Eligible participants will be randomized to either tisotumab vedotin 2.0 mg/kg Q3W or investigator*s choice of chemotherapy (See protocol section 4.3).

Intervention

Not applicable

Study burden and risks

For the Investigational product - Tisotumab Vedotin, Subjects should come to the study center every 21 days for infusion administration and blood draw controls. every 6 weeks a CT scan should be made to monitor tumor development. The administered medication also has a chance of side effects as described in detail in the test subject information. In view of the prognosis for this group of subjects and the group that has already been extensively treated, the burden in relation to the expected outcome is acceptable.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

1.Age >=18 years , or considered an adult by local regulations, at time of consent.

Has recurrent or metastatic cervical cancer with squamous cell, adenocarcinoma, or adenosquamous histology and:

Has experienced disease progression during or after treatment with a standard of care systemic chemotherapy doublet, or platinum-based therapy (if eligible), defined as either:
paclitaxel+cisplatin+bevacizumab, or + anti-PD-(L)1 agent
paclitaxel+carboplatin+bevacizumab, or + anti-PD-(L)1 agent
paclitaxel+topotecan/nogitecan+bevacizumab + anti-PD-(L)1 agent

2. Has ECOG performance status of 0 or 1 prior to randomization.

3. Has life expectancy of at least 3 months.

4. Has a negative serum pregnancy test for participants of reproductive potential. Participants that are postmenopausal, permanently sterilized or previously subjected to bilateral oophorectomy, bilateral salpingectomy and/or hysterectomy can be considered as not having reproductive potential (refer to Section 10.4 of protocol).

5. Participants of reproductive potential must agree to use adequate contraception during and for 6 months after the last study treatment administration. Adequate contraception is defined as highly effective methods of contraception (refer to Section 10.4 of protocol). Two highly effective methods of contraception must be used in countries where this is required.

6. Must agree not to breastfeed or donate ova, starting at the time of informed consent and continuing through 6 months after receiving the last dose of study drug administration

7. Where required by local health authorities, has negative serology for hepatitis B surface antigen (HBsAg)/HBV DNA, or hepatitis C antibody (HCVAb) or RNA. Active hepatitis C is defined by a known positive HCVAb result and known quantitative HCV RNA results greater than the lower limits of detection of the assay.

8. Must be able to provide tumor tissue. The most recent archival tumor biopsy is preferred if collected within the last 2 years. If an archival tumor biopsy less than 2 years old is not available, a fresh tumor biopsy will be collected before initiation of study treatment, if clinically feasible. If a fresh biopsy cannot be collected, the most recent archival tumor sample may be submitted, even if obtained more than 2 years prior to participant enrollment.

9. Must be willing and able to adhere to the prohibitions and restrictions specified in this protocol.

10. Measurable disease according to RECIST v1.1 as assessed by the investigator

11. Must demonstrate acceptable screening laboratory values (please refer to protocol pg. 32)

Exclusion criteria

1. Has primary neuroendocrine, lymphoid, sarcomatoid, or other histologies not mentioned in inclusion criterion 3 (refer to Section 5.1 of protocol).

2. Has clinically significant bleeding issues or risks:
- Known past or current coagulation defects leading to an increased risk of bleeding
- Diffuse alveolar hemorrhage from vasculitis
- Known bleeding diathesis
- Ongoing major bleeding (i.e. participant requires a transfusion of >2 platelet concentrates within 14 days of the first dose of the study treatment)
- Trauma with increased risk of life-threatening bleeding
- History of severe head trauma or intracranial surgery within 8 weeks of study entry.

3. Has cardiovascular issues or risks:
- Clinically significant cardiac disease, including unstable angina or acute myocardial infarction, 6 months prior to screening
- Any medical history of congestive heart failure (grade III or IV as classified by the New York Heart Association)
- Any medical history of decreased ejection fraction of <45%
- A marked baseline prolongation of QT/QTc interval (e.g., repeated demonstration of a QTc interval >450 msec)
- A complete left bundle branch block (defined as QRS interval >=120 msec in left bundle branch block form) or an incomplete left bundle branch block

4. Central nervous system (CNS): any history of intracerebral arteriovenous malformation, cerebral aneurysm, or stroke (transient ischemic attack >1 month prior to screening is allowed).

5. Ophthalmological conditions: Active ocular surface disease or a history of cicatricial conjunctivitis or inflammatory conditions that predispose to cicatrizing conjunctivitis (e.g. Wagner syndrome, atopic keratoconjunctivitis, autoimmune disease affecting the eyes), ocular Stevens-Johnson syndrome or toxic epidermal necrolysis, mucus pemphigoid, and participants with penetrating ocular transplants are ineligible. Cataracts alone is not an exclusion criterion.

6. Other cancer: known past or current malignancy other than inclusion diagnosis. Exceptions are malignancies with a negligible risk of metastasis or death (e.g., 5year OS =90%) such as non-invasive basal cell or squamous cell skin carcinoma; non-invasive, superficial bladder cancer, and ductal carcinoma in situ.

7. Brain metastases are allowed if the following criteria are met: definitive therapy (eg, surgery or stereotactic brain radiotherapy) has been completed >8 weeks before the first dose of study treatment; no evidence of clinical or radiologic progression of the brain metastases; participant has completed perioperative corticosteroid therapy or steroid taper. NOTE: Chronic steroid therapy is acceptable provided that the dose is stable for 1 month prior to screening.

8. Surgery/Procedures: major surgery within 4 weeks or minor surgery within 7 days prior to the first study treatment administration.

9. Peripheral neuropathy grade > 2

10. Prior anti-cancer therapy:
- Any prior treatment with MMAE-derived drug.
- Radiotherapy within 21 days prior to the first administration of study treatment. Participants must have recovered from all clinically significant radiation-related toxicities. At least 42 days must have elapsed from the last administration of chemo radiotherapy.
- Small molecules, chemotherapy, immunotherapy, or monoclonal antibodies within 28 days prior to the first administration of study treatment.
- Currently participating in or has participated in a study of an investigational agent or device and received active treatment within 28 days prior to the first dose of study treatment.

11. Has known seropositivity of human immunodeficiency virus (HIV); known medical history of hepatitis B or C infection. Note: No testing for HIV, hepatitis B, or hepatitis C is required, unless mandated by local health authorities. Exceptions include latent or controlled HIV infection.

12. Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy (dose exceeding 10 mg daily of prednisone or equivalent) or any other form of immunosuppressive therapy within 7 days prior to the first dose of

tisotumab vedotin

13. Is pregnant or intends to conceive children within 6 months of ending study treatment

14. Known allergies, hypersensitivity, or intolerance to study treatment or its excipients (refer to the Investigator*s Brochure for further information on tisotumab vedotin)

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	06-12-2021
Enrollment:	32
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Alimta
Generic name:	Pemetrexed
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Gemzar

Generic name:	Gemcitabine
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	HuMax-TF
Generic name:	Tisotumab vedotin
Product type:	Medicine
Brand name:	Hycamtin
Generic name:	Topotecan
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Irinotecan
Generic name:	Camptosar
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	27-05-2021
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	27-08-2021
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-01-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-05-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-11-2022
Application type:	Amendment

Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-12-2022
Application type:	Amendment
Review commission:	MEC Academisch Medisch Centrum (Amsterdam) Kamer G4-214 Postbus 22660 1100 DD Amsterdam 020 566 7389 mecamc@amsterdamumc.nl
Approved WMO Date:	18-01-2023
Application type:	Amendment
Review commission:	MEC Academisch Medisch Centrum (Amsterdam) Kamer G4-214 Postbus 22660 1100 DD Amsterdam 020 566 7389 mecamc@amsterdamumc.nl
Approved WMO Date:	26-07-2023
Application type:	Amendment
Review commission:	MEC Academisch Medisch Centrum (Amsterdam) Kamer G4-214 Postbus 22660 1100 DD Amsterdam 020 566 7389

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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	EUCTR2019-001655-39-NL
CCMO	NL76637.018.21