A Phase 1b/2 Open-Label Trial of Tisotumab Vedotin (HuMax®-TFADC) Monotherapy and in Combination with Other Agents in Subjects with Recurrent or Stage IVB Cervical Cancer

Published: 12-12-2018
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This study has been transitioned to CTIS with ID 2023-508832-68-00 check the CTIS register for the current data. Dose escalation: To establish the MTD and RP2D of tisotumab vedotin in combination in subjects with cervical cancer Dose expansion:...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Reproductive neoplasms female malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON52957

Source
ToetsingOnline

Brief title
GCT1015-05

Condition

- Reproductive neoplasms female malignant and unspecified

Synonym
Cervical Cancer, Cervical Carconoma

Research involving
Human

Sponsors and support

Primary sponsor: Genmab
Source(s) of monetary or material Support: Pharmaceutical industry

Intervention

Keyword: Cervical Cancer, Monotherapy and in combination, Phase 2, Tisotumab Vedotin (HuMax® TF ADC)

Outcome measures

Primary outcome

Dose escalation: Incidences of DLTs, AEs, SAEs, infusion-related AEs, CTCAE

grade >= 3 AEs, and AEs related to trial treatment during the trial Dose

expansion: Objective Response Rate (ORR) per Response Evaluation Criteria in

Solid Tumors (RECIST) v 1.1

Secondary outcome

• Adverse events (AEs) and evaluation of safety laboratory parameters.

• Objective Response Rate (ORR) per RECIST v1.1 (only dose escalation)

• Duration of Response (DOR) per RECIST v1.1.

• Time to Response (TTR) per RECIST v1.1.

• Progression free survival (PFS) per RECIST v1.1.

• Overall Survival (OS)

• PK-concentrations and anti-drug antibodies (ADA) associated with tisotumab

vedotin in combination.

Study description

Background summary

The investigational medicinal product, tisotumab vedotin, is an antibody-drug conjugate (ADC) composed of a human monoclonal immunoglobulin G1 (subtype *) targeting tissue factor (TF) conjugated via a protease cleavable valine citrulline linker to the drug monomethyl auristatin E (MMAE), a dolastatin 10 analog.
Dolastatins and auristatins belong to a class of chemotherapies that act as microtubule disrupting agents.
Tisotumab vedotin efficiently and specifically binds to TF. TF has a central physiological role in initiation of the coagulation cascade and is upregulated during oncological transformation and expressed on the membrane of neoplastic cells as well as on tumor-associated endothelial cells.
Upon binding to TF, tisotumab vedotin is rapidly internalized into tumor cells where it
undergoes lysosomal degradation resulting in release of the cytotoxic payload.
Tumor cell death occurs due to MMAE-mediated disruption of microtubules in TF-positive tumor cell and in neighboring tumor cells through *bystander* cytotoxicity.
Tisotumab vedotin targets TF-expressing tumors through intracellular delivery of the potent and clinically validated agent MMAE. TF is expressed in a wide variety of tumors including the gynecological cancers of the ovary and cervix, genito-urethral tumors, squamous cell carcinoma of the head and neck, lung cancers, tumors in the gastrointestinal tract, breast cancer, malignant melanoma and pancreatic cancer. TF is expressed on the membrane of neoplastic cells as well as on tumor-associated endothelial cells. Furthermore, expression of TF on tumor cells has been associated with negative overall survival or disease-free survival as described in several indications, including ovarian and bladder cancer.
High differential levels of TF expression have been observed in multiple cancers including cervical cancer; as such tisotumab vedotin is an attractive candidate as an anti-cancer therapy in cervical cancer.

Study objective

This study has been transitioned to CTIS with ID 2023-508832-68-00 check the CTIS register for the current data.

Dose escalation: To establish the MTD and RP2D of tisotumab vedotin in combination in subjects with cervical cancer
Dose expansion: Evaluate the antitumor activity of tisotumab vedotin monotherapy and in
combination in subjects with cervical cancer

Study design

This is an open label, multi-center trial of tisotumab vedotin monotherapy and in combination with bevacizumab, pembrolizumab, or carboplatin in subjects with

recurrent or stage IVB cervical cancer.
The trial will be conducted in two parts: dose escalation followed by dose expansion.

Intervention

Dose Escalation:
Arm A - Tisotumab vedotin once every 3 weeks (1Q3W) + Bevacizumab 7.5 mg/kg 1Q3W OR 15 mg/kg 1Q3W (Subjects who have progressed during or after standard of care therapy or are intolerant or ineligible to receive standard of care treatments).
Arm B - Tisotumab vedotin 1Q3W + Pembrolizumab 200 mg 1Q3W (Subjects who have progressed during or after standard of care therapy or are intolerant or ineligible to receive standard of care treatments).
Arm C - Tisotumab vedotin 1Q3W + Carboplatin AUC 5 1Q3W (Subjects who have progressed during or after standard of care therapy or are intolerant or ineligible to receive standard of care treatments).
Dose Expansion:
Arm D - Tisotumab vedotin at the Recommended Phase 2 Dose (RP2D) 1Q3W + Carboplatin AUC 5 1Q3W (Subjects that have not received prior systemic therapy for recurrent or stage IVB disease).
Arm E - Tisotumab vedotin at the RP2D 1Q3W + Pembrolizumab 200 mg 1Q3W (Subjects that have not received prior systemic therapy for recurrent or stage IVB disease).
Arm F - Tisotumab vedotin at the RP2D 1Q3W + Pembrolizumab 200 mg 1Q3W (Subjects who have progressed on or after standard of care treatments).
Arm G - Tisotumab vedotin monotherapy (0.9 mg/kg on Days 1, 8 and 15 of every 28-day cycle [3Q4W]) in cervical cancer subjects who have progressed on or after at least one but no more than two prior systemic therapies for their recurrent or stage IVB cervical cancer.
Arm H - Either the 4 drug (quadruplet) regimen (pembrolizumab, bevacizumab, carboplatin and tisotumab vedotin) or the 3 drug (triplet) regimen (pembrolizumab, carboplatin and tisotumab vedotin). The dosages will be as follows:
• Pembrolizumab 200 mg
• Bevacizumab (if assigned) 15mg/kg
• Carboplatin 5AUC
• Tisotumab vedotin 2.0 mg/kg
Up to 30 subjects might be recruited for each expansion arm.

Study burden and risks

Data from GEN701 cohort expansion demonstrates substantial efficacy of tisotumab vedotin in subjects with recurrent or metastatic cervical cancer along with a manageable safety profile. The safety profile of tisotumab vedotin in the cervical cohort was comparable to the profile observed

for other indications.

Contacts

Public
Genmab

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DK
Scientific
Genmab

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

- Must have squamous, adenosquamous, or adenocarcinoma of the cervix and progressed on or after standard of care treatments or are ineligible or intolerant to standard of care for recurrent or stage IVB cervical cancer. (Arms A, B and C only).
- Must have squamous, adenosquamous, or adenocarcinoma of the cervix and must not have received prior systemic therapy for recurrent or stage IVB cervical cancer (Arms D, E and H only).
- Must have squamous, adenosquamous, or adenocarcinoma of the cervix and progressed on or after at least one but no more than two prior systemic

therapies for recurrent or stage IVB cervical cancer (Arm F and G only).
- Have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
- Is not pregnant, breastfeeding, or expecting to conceive children within the projected duration of the trial and for at least 6 months after the last trial treatment administration. A WOCBP must agree to use adequate contraception during and for 6 months after the last dose of trial treatment administration (all arms).
- Must sign an informed consent form (ICF) indicating the trial subject understands the purpose of and procedures required for the trial and are willing to participate in the trial (All Arms).

Exclusion criteria

- Has clinically relevant bilateral hydronephrosis which cannot be alleviated by ureteral stents or percutaneous drainage. (All Arms)
- Has clinical signs or symptoms of gastrointestinal obstruction and requires parenteral hydration and/or nutrition. Post-operative obstructions within 4 weeks of abdominal surgery are permitted. (All Arms)
- Has clinically significant bleeding issues or risks (All arms)
- Prior history (within 3 months) or current evidence of hemoptysis (1/2 teaspoon or more) (Arm A only)
- Recent (within 4 weeks of first dose of trial treatment) clinically significant gastrointestinal or vaginal bleeding requiring PRBC transfusion (Arm A only)
- Recent (within 4 weeks of first dose of trial treatment) evidence of wound healing complications that require medical intervention (Arm A only)
- Has active ocular surface disease at baseline. Subjects with prior history of cicatricial conjunctivitis are ineligible (All Arms).

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	10-04-2020
Enrollment:	10
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Avastin
Generic name:	BEVACIZUMAB
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	CARBOPLATIN
Generic name:	CARBOPLATIN
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Keytruda
Generic name:	PEMBROLIZUMAB
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Tisotumab vedotin
Generic name:	Tisotumab vedotin

Ethics review

Approved WMO Date:	12-12-2018
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-04-2019
Application type:	First submission
Review commission:	METC Amsterdam UMC

Approved WMO Date:	24-04-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-05-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-07-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	01-10-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-11-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-02-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-04-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-04-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	27-11-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO	

Date:	08-12-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-01-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-01-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-03-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-05-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-07-2023
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:	02-10-2023
Application type:	Amendment
Review commission:	MEC Academisch Medisch Centrum (Amsterdam) Kamer G4-214

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Approved WMO Date:	05-12-2023
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:	19-01-2024
Application type:	Amendment
Review commission:	MEC Academisch Medisch Centrum (Amsterdam) Kamer G4-214 Postbus 22660 1100 DD Amsterdam 020 566 7389 mecamc@amsterdamumc.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
EU-CTR	CTIS2023-508832-68-00
EudraCT	EUCTR2017-004758-40-NL
CCMO	NL66166.018.18