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HEALTH TECHNOLOGY BRIEFING DECEMBER 2019

Tisotumab vedotin for recurrent or metastatic cervical cancer

NIHRIO ID	24328	**NICE ID**	10298
Developer/Company	Genmab A/S	**UKPS ID**	652609

Licensing and market availability plans	Currently in phase II clinical trials.

SUMMARY

Tisotumab vedotin is currently in clinical development for the treatment of patients with recurrent or metastatic cervical cancer who have received at least one prior systemic therapy. Cervical cancer develops in a woman's cervix (lower part of the womb). It mainly affects sexually active women aged between 30 and 45 years. Cervical cancer often has no symptoms in its early stages. Cervical cancer that has spread to another part of the body is called advanced or metastatic cancer. Cancer that returns after months or years of the completion of the initial treatment is called recurrent cancer. The most common symptom of cervical cancer includes bleeding from the vagina at times other than the usual periods. Despite the recent developments, the prognosis remains poor and systemic therapy options are needed for women with recurrent and metastatic cervical cancer.

Tisotumab vedotin is administered by intravenous infusion. It is an antibody-drug conjugate that binds to tissue factor (TF), a protein expressed on the cell surface of tumour cells. This then induces cancer cells death. If licenced tisotumab vedotin will offer a treatment option for adult females with recurrent or metastatic cervical cancer who have received at least one prior systemic therapy.

PROPOSED INDICATION

Treatment of patients with recurrent or metastatic cervical cancer who have received at least one prior systemic therapy.[a]

TECHNOLOGY

DESCRIPTION

Tisotumab vedotin (HuMax-TF-ADC) is an antibody-drug conjugate (ADC) targeted to tissue factor (TF), a protein involved in tumour signalling and angiogenesis.[1] It is composed of a fully human monoclonal antibody (mAb) that specifically binds to TF conjugated to the microtubule-disrupting agent monomethyl auristatin E (MMAE) via a protease-cleavable valine-citrulline linker.[2] TF is a transmembrane protein that is the main physiological initiator of coagulation and is involved in angiogenesis, cell adhesion, motility, and cell survival.[1]

Tisotumab vedotin is currently in clinical development for the treatment of adult patients with recurrent or metastatic cervical cancer who have received at least one prior systemic therapy. In the phase II clinical trial (NCT03438396) patients received tisotumab vedotin intravenously with a dose of 2.0 mg/kg every 3 weeks until progression or toxicity.[3]

INNOVATION AND/OR ADVANTAGES

Tisotumab vedotin is a first-in-human antibody-drug conjugate targeted to TF.[2] Tisotumab vedotin includes an antibody targeting TF conjugated with MMAE via a linker. Based on its high expression on many solid tumours and its rapid internalization, TF is considered a suitable target for antibody-drug conjugates. In pre-clinical trials, tisotumab vedotin has shown strong ability to bind to TF and inhibit tumour growth. Further in a phase IIa study, preliminary data demonstrated a manageable safety profile and encouraging efficacy (objective response rate (ORR) 37%) in relapsed, recurrent or metastatic cervical cancer.[4]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Tisotumab vedotin does not currently have Marketing Authorisation in the EU/UK for any indication.

Tisotumab is currently in phase II clinical development for various cancers including ovarian cancer, colorectal neoplasm, non-small-cell lung, exocrine pancreatic cancer and endometrium cancer etc.[5]

PATIENT GROUP

DISEASE BACKGROUND

The cervix is the lower part of the womb also called the neck of the womb. The cervix is covered with a layer of skin-like cells on its outer surface, called ectocervix. Inside of the cervix, there are glandular cells that produce mucus called endocervix. The skin-like cells of the ectocervix can become cancerous, leading to squamous cell cervical cancer. This is the

[a] Information provided by Genmab A/S on UK PharmaScan

most common type of cervical cancer. The glandular cells of the endocervix can also become cancerous, leading to adenocarcinoma of the cervix.[6]

Recurrent cervical cancer occurs when the cancer is detected months or years after the completion of an initial cancer treatment regimen, which may have included surgery, radiation therapy and or chemotherapy. The recurrence of cervical cancer may be a local recurrence, which is contained in the cervix region. A metastatic recurrence occurs when cancer has spread to other organs, such as the kidney, bladder or lymph nodes. This recurrence happens when the cervical cancer cells break off from the original tumour and travel to other parts of the body through the lymphatic or circulatory system.[7]

The main risk factors for cervical cancer include age, human papillomavirus (HPV) infection (HPV16 and HPV18), immune system deficiency, herpes, smoking status, socioeconomic factors, use of oral contraceptives and exposure to diethylstilbestrol (DES).[8]

The most common sign and symptoms of cervical cancer include blood spots or light bleeding between or following periods, menstrual bleeding that is longer and heavier than usual, bleeding after intercourse, douching, or a pelvic examination, increased vaginal discharge, pain during sexual intercourse, bleeding after menopause, and unexplained, persistent pelvic and/or back pain.[9]

CLINICAL NEED AND BURDEN OF DISEASE

In the UK in 2016, cervical cancer was the 14th most common cancer accounting for 2% of all new cancers cases in females.[10] In England in 2017, there were 2,591 registrations of newly diagnosed cases of malignant neoplasm of cervix uteri (ICD-10 code C53) and the direct age-standardised rate per 100,000 population was 9.4.[11] European age-standardised incidence rates for cervical cancer are projected to rise by approximately 43% in the UK between 2014 and 2035, 12 to 17 cases per 100,000 by 2035.[12]

In England, in 2018-19 there were 9,321 finished consultant episodes (FCEs) for malignant neoplasm of cervix uteri (ICD-10 code C53) and 8,702 admissions resulting in 14,033 bed days and 5,656 day cases.[13]

In England and Wales in 2017, there were 730 deaths with malignant neoplasm of cervix uteri (ICD-10 code C53) recorded as the underlying cause.[14] The age-standardised 1-year and 5-year survival for females diagnosed with cervical cancer in England in 2017 was 81.1% and 61.4% respectively.[15]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

The treatment of cervical cancer depends on several factors including the type and stage of cancer, possible side effects and patient's preference and overall health.[16] Depending on the stage of cervical cancer treatment options may include surgery, chemotherapy and radiotherapy together (chemoradiotherapy), radiotherapy, and chemotherapy.[17]

For advanced cervical cancer (stage 2b, 3 and 4A) is usually treated with chemoradiotherapy while for cervical cancer that spread further away in the body such as lungs (stage 4b or metastatic cancer) is treated with chemotherapy, radiotherapy and other medicines to help with symptoms.[17] Surgical resection or radiotherapy may potentially be curative for selected women with locally recurrent or metastatic disease, however in the majority of cases this will

not be feasible. Women with recurrent and metastatic cervical cancer have limited systemic treatment options.[18]

CURRENT TREATMENT OPTIONS

According to the current NICE treatment pathway for women with recurrent and stage 4B cervical cancer recommends topotecan with cisplatin as a treatment option only if they have not previously received cisplatin. Women who have previously received cisplatin and are currently being treated with topotecan in combination with cisplatin for recurrent and stage IVB cervical cancer should have the option to continue their therapy until they and their clinicians consider it appropriate to stop.[19]

PLACE OF TECHNOLOGY

If licensed, tisotumab vedotin will offer a treatment option for adult patients with recurrent or metastatic cervical cancer who have received at least one prior systemic therapy.

CLINICAL TRIAL INFORMATION

Trial	NCT03438396, **GCT1015-04;** females aged ≥ 18 years; phase II
Sponsor	Genmab
Status	Ongoing
Source of Information	Trial registry[3]
Location	EU (not UK) and USA
Design	Single group assignment, open label
Participants	N=102; aged 18 years and older: extra-pelvic metastatic or recurrent cervical cancer including squamous cell, adenocarcinoma histology who have experienced disease progressed on standard of care chemotherapy in combination with bevacizumab.
Schedule	Patients received tisotumab vedotin intravenously with a dose of 2.0 mg/kg every 3 weeks until progression or toxicity.
Follow-up	Up to 5 years[b]
Primary Outcomes	Confirmed objective response rate [Time frame: up to 2 years]
Secondary Outcomes	• Duration of response [Time frame: up to 2 years] • Progression free survival [Time frame: up to 2 years] • Overall survival [Time frame: up to 2 years]
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Estimated primary completion rate reported as of December 2019. Estimated study completion date reported as of April 2023.

Trial	NCT02001623, **GEN701**; adults aged ≥ 18 years; phase I/II
Sponsor	Genmab

[b] Information provided by Genmab

Status	Completed
Source of Information	Trial registry,[20] Publication[2]
Location	EU (incl UK) and USA
Design	Single group assignment, open label
Participants	N=195; aged 18 years and older: patients with relapsed, advanced and or/metastatic cancer who have failed available standard treatments or who are not candidates for standard therapy.
Schedule	Patients received tisotumab vedotin intravenously with a dose of 2.0 mg/kg every 3 weeks until progression or toxicity
Follow-up	28 months[c]
Primary Outcomes	Adverse events measured throughout the study from first treatment until end of trial (Time frame: after first treatment cycle (3 weeks) and at end of trial (an expected average of 6 months)
Secondary Outcomes	• PK profile of HuMax-TF-ADC after single and multiple infusions (Time frame: after first treatment cycles (3 weeks) and at end of trial (an expected average of 6 months) • Anti-tumour activity of HuMax-TF-ADC; tumour size (RECIST), PSA and/or CA-125 [Time frame: at end of trial (an expected average of 6 months)]
Key Results	Dose-limiting toxicities, including grade 3 type 2 diabetes mellitus, mucositis, and neutropenic fever, were seen at the 2·2 mg/kg dose; therefore, 2·0 mg/kg of tisotumab vedotin intravenously once every 3 weeks was established as the recommended phase 2 dose.
Adverse effects (AEs)	The most common adverse events of grade 3 or worse were fatigue (14 [10%] of 147 patients), anaemia (eight [5%]), abdominal pain (six [4%]), hypokalaemia (six [4%]), conjunctivitis (five 3%), hyponatraemia (five [3%]), and vomiting (five [3%]). 67 (46%) of 147 patients had a treatment-emergent serious adverse event. 39 (27%) of 147 patients had a treatment-emergent serious adverse event related to the study drug. Infusion-related reactions occurred in 17 (12%) of 147 patients.
Expected reporting date	Estimated primary completion rate reported as of April 2019. Estimated study completion date reported as of April 2019.

ESTIMATED COST

The cost of tisotumab vedotin is not known yet.

[c] Information provided by Genmab

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal guidance. Topotecan for the treatment of recurrent and stage IVB cervical cancer (TA183). October 2009.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Adult). B15/S/a.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Children, teenagers and Young Adults). B12/S/b.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Radiotherapy (All Ages). B01/S/a.

OTHER GUIDANCE

- European Society Medical Oncology. Cervical cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. 2017.[21]
- NHS Clinical Knowledge Summary. Cervical cancer and HPV. 2017.[22]
- World Health Organisation. Comprehensive Cervical Cancer Control, a guide to essential practice. 2014.[23]
- American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology Screening Guidelines for the prevention and Early Detection of Cervical Cancer. 2012.[24]
- International Federation of Gynaecology & Obstetrics. Global guidance for cervical cancer prevention and control. 2009.[25]

ADDITIONAL INFORMATION

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