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HEALTH TECHNOLOGY BRIEFING
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Bintrafusp alfa for advanced, unresectable cervical cancer

NIHRIO ID	28878	**NICE ID**	10630
Developer/Company	GlaxoSmithKline UK Ltd	**UKPS ID**	Not available

Licensing and market availability plans	Currently in phase II clinical trials

SUMMARY

Bintrafusp alfa is in clinical development for the treatment of advanced, unresectable, or metastatic cervical cancer. Cervical cancer can be defined as advanced or metastatic when originates in the cervix and spreads to various other parts of the body. If cervical cancer is recurrent, metastatic or persistent, there are limited treatment options, with treatments usually aiming to alleviate symptoms and improve quality of life.

Bintrafusp alfa is a type of protein called an antibody, which can bind to a cancer-causing protein. Therefore, it activates the natural killer (NK) cell to attack the cancer cells. Bintrafusp alfa is administered by intravenous infusion (injection into the vein). If licensed, bintrafusp alfa would offer an additional treatment option for patients with advanced, unresectable and/or metastatic cervical cancer.

PROPOSED INDICATION

For the treatment of women with advanced, unresectable and/or metastatic cervical cancer.[1]

TECHNOLOGY

DESCRIPTION

Bintrafusp alfa (M7824, MSB0011359C) is a bifunctional fusion protein that is composed of an anti-programmed death ligand 1 (PD-L1) human monoclonal antibody called avelumab, which has potential immune and antineoplastic checkpoint modulating activities as it is bound to the soluble extracellular domain of human transforming growth factor beta (TGFbeta) receptor type II (TGFbetaRII). Once administered, the avelumab moiety binds to PD-L1 while the TGFbetaRII moiety of bintrafusp alfa is also binds to and neutralises TGFbeta simultaneously. This increases cytotoxic T-lymphocyte (CTL) and natural killer (NK) cell, and prevents PD-L1 and TGFbeta mediated signaling. This inhibits tumour cell proliferation in susceptible tumour cells. PD-L1 and TGFbeta are both upregulated in certain types of cancers. The over expression of PD-L1 and TGFbeta is associated with an increase immune surveillance evasion and is a contributor to poor prognosis.[2]

Bintrafusp alfa is currently in phase II clinical development for the treatment of female patients with advanced unresectable and/or metastatic cervical cancer. In phase II clinical trial (NCT04246489), participants will receive 1200 milligrams (mg) bintrafusp alfa intravenously once every 2 weeks until confirmed disease progression, death, unacceptable toxicity and study withdrawal.[1]

INNOVATION AND/OR ADVANTAGES

Bintrafusp alfa is a potentially first in-class bifunctional fusion protein intervention.[3] In preliminary clinical studies, bintrafusp alfa has displayed anti-tumour activity both in combination with chemotherapy and as a monotherapy. Due to the mechanism of action of bintrafusp alfa, it can potentially offer a targeted approach to addressing causal pathophysiology of cancers that are deemed as difficult to treat.[4] In a phase I clinical trial (NCT02517398) bintrafusp alfa conveyed a manageable safety profile and clinical activity in previously treated cervical cancer patients.[5,6]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Bintrafusp alfa does not currently have Marketing Authorisation in the EU/UK for any indication.

Bintrafusp alfa is in phase II and phase III clinical development for the treatment of various types of cancers including: biliary tract cancer, thymoma and thymic carcinoma, and non-small cell lung cancer.[7]

PATIENT GROUP

DISEASE BACKGROUND

The cervix is the lower region of the womb, and is also known as the neck of the womb. The ectocervix is a layer of skin-like cells that cover the outer surface of the cervix. Inside of the cervix, there are glandular cells that mucus called endocervix. These glandular cells can become cancerous leading to adenocarcinoma of the cervix while the skin-like cells of the ectocervix can also become cancerous which leads to squamous cell cervical cancer. This form is the most common variation of cervical cancer.[8] The human papillomavirus (HPV) infection (HPV16 and HPV18), herpes, immune system deficiency, age, smoking status, use of oral contraceptives, socioeconomic factors, and exposure to diethylstilbesterol are the main risk factors associated with cervical cancer.[9] The most common sign and symptoms of cervical cancer include light bleeding between or following periods, blood spots, menstrual bleeding that is longer and heavier than usual, increased vaginal discharge, bleeding (after

intercourse, douching, or a pelvic examination), pain during sexual intercourse, bleeding after menopause and unexplained, persistent pelvic and/or back pain.[10]

Advanced cervical cancer is a cancer that originated in the cervix and has since spread to various other parts of the body. Advanced cervical cancer can also mean the cancer has come back after previous treatment also known as recurrence.[11] 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.[12] Unresectable cancer can be defined as a tumour or cancer that cannot be removed completely by surgery. There are many reasons why a tumour can be unresectable including the location of the tumour, the size of the tumour or the spread of the cancer, also known as metastases.[13] A metastatic cancer occurs when the cancer has spread to other organs, such as the bladder, kidney, or lymph nodes. This occurs 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.[12] Persistent cancer is when despite treatment given to the patient, a tumour has remained or when a second tumour has been diagnosed within three months after therapy was completed for the original tumour.[14]

CLINICAL NEED AND BURDEN OF DISEASE

In the UK cervical cancer was the 14th most common cancer accounting for 2% of all new cancers cases in females in 2017.[15] Between 2013-17 there were 12,849 women diagnosed with cervical cancer in England. The age-standardised 1-year and 5-year survival were 81.1% and 61.4% respectively.[16] The European age-standardised incidence rates for cervical cancer are projected to rise in the UK by approximately 43% between 2014 and 2035.[17]

In England (2019-20) there were 9,451 finished consultant episodes (FCE) of patients with a main diagnosis of malignant neoplasm of cervix uteri (ICD-10 code C53). Of these FCE there were 5,613 day cases and 14,491 bed days.[18] In England and Wales in 2017, there were 730 deaths with malignant neoplasm of cervix uteri recorded as the underlying cause.[19]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

The type of cervical cancer treatment offered to patients can depend on several factors including the type and stage of the cancer, possible side effects and patient's preference and overall health. Depending on the stage of cervical cancer, treatment options may include surgery, a combination of chemotherapy and radiotherapy (chemoradiotherapy), radiotherapy, and chemotherapy.[20] In patients with recurrent cancer, pelvic exenteration (removal of the cervix, vagina, womb, ovaries, bladder and rectum) is offered. Advanced cervical cancer (stage 2B, 3 and 4A) is commonly treated with chemoradiotherapy whereas, for cervical cancer that are metastatic and have spread further into the body such as to the lungs (stage 4B or metastatic cancer), chemotherapy, radiotherapy and other medicines to help with symptoms are used as treatment options.[20] Surgical resection or radiotherapy may potentially be curative for selected women with locally recurrent or metastatic disease, however in the majority of cases this option is not be feasible. Women with unresectable and metastatic cervical cancer have limited systemic treatment options.[21]

CURRENT TREATMENT OPTIONS

For patients with stage 4B and recurrent cervical cancer NICE recommends topotecan with cisplatin is recommended 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 4B cervical cancer, should have the option to continue their therapy until they and their clinicians consider it appropriate to stop.[22]

PLACE OF TECHNOLOGY

If licensed, bintrafusp alfa will offer an additional treatment option for patients with advanced unresectable and/or metastatic cervical cancer.

CLINICAL TRIAL INFORMATION

Trial	NCT04246489; 2019-003583-40; A Phase II, Multicenter, Open Label Study of Bintrafusp Alfa (M7824) Monotherapy in Participants With Advanced, Unresectable Cervical Cancer With Disease Progression During or After Platinum-Containing Chemotherapy **Trail phase:** Phase II **Location(s):** EU, USA and other countries **Primary completion date:** December 2021
Trial design	Multicentre, open Label, and single group assignment
Population	n= 146 (actual); aged 18 and older adult females with advanced unresectable and/or metastatic cervical cancer (squamous cell carcinoma, adenocarcinoma, adenosquamous cell carcinoma) with disease progression during or after the prior platinum-containing chemotherapy; must have measurable disease, and must provide a tumour tissue sample, either from archival tissue or newly obtained core or excisional biopsy. If the participant received local therapy (For example: radiation therapy or chemoradiotherapy) after the archival tissue was taken, a new biopsy will be required; who have Eastern Cooperative Oncology Group (ECOG) PS of 0 to 1; have a life expectancy greater than or equals to (>=) 12 weeks as judged by the Investigator; Adequate haematological, hepatic and renal function as defined in the protocol.
Intervention(s)	Participants will receive 1200 mg of bintrafusp alfa, intravenously once every 2 weeks.
Comparator(s)	-
Outcome(s)	Confirmed Objective Response (OR) According to Response Evaluation Criteria in Solid Tumours (RECIST Version 1.1) as Evaluated by Independent Review Committee [Time Frame: Time from first treatment to planned final assessment at approximately 2 years] See trial record for full list of other outcomes
Results (efficacy)	-

Results (safety)	-

ESTIMATED COST

The cost of bintrafusp alfa is not yet known.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal guidance in development. Pembrolizumab with chemotherapy for treating recurrent, persistent or metastatic cervical cancer (TA10669). May 2022
- NICE technology appraisal guidance in development. LN-145 for treating recurrent, persistent or metastatic cervical cancer (TA10728). Expected date of issue to be confirmed.
- NICE technology appraisal guidance in development. Tisotumab vedotin for treating recurrent or metastatic cervical cancer after systemic therapy (TA10620). Expected date of issue to be confirmed.
- 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

- NHS Clinical Knowledge Summary. Cervical cancer and HPV. May 2021[23]
- British Gynaecological Cancer Society. Cervical cancer guidelines: Recommendations for practice. September 2020[24]
- European Society Medical Oncology. Cervical cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. July 2017[25]
- World Health Organisation. Comprehensive cervical cancer control, a guide to essential practice (Second edition). December 2014[26]

ADDITIONAL INFORMATION

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