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Axalimogene filolisbac for cervical cancer – beyond first line treatment

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LAY SUMMARY

Cervical cancer develops in a woman's cervix (the lower part of the womb, also called the neck of the womb). It mainly affects sexually active women aged between 30 and 45 years. Most cases of cervical cancer are caused by the human papilloma virus (HPV). 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. The 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 include bleeding from the vagina at times other than the usual periods. Symptoms of advanced cancer depend on where the cancer has spread to. Cervical cancer was the 14th most common cancer among females in the UK.

Axalimogene filolisbac is a type of cancer vaccine being developed as immunotherapy that attacks HPV-associated cancers such as cervical cancers. It works by alerting the body's immune system to the presence of cancer, stimulating the body's natural defenses to attack the cancer. Axalimogene filolisbac is given intravenously and is being developed for the treatment of persistent, recurrent, or metastatic, squamous or non-squamous cell cervical cancer in patients who progress beyond first-line therapy. If licensed, Axalimogene filolisbac will offer a new treatment option for this patient group.

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TARGET GROUP

Cervical cancer (persistent, recurrent, or metastatic, squamous or non-squamous cell carcinoma) – beyond fist line treatment

TECHNOLOGY

DESCRIPTION

Axalimogene filolisbac (ADXS11-001) is a targeted Listeria monocytogenes (*Lm*)-based investigational immunotherapy that attacks the human papillomavirus (HPV)-associated cancers by altering a live strain of *Lm* bacteria to generate cancer-fighting T-cells against cancer antigens while neutralizing the tumour's natural protection that guard the tumour microenvironment from immunologic attack.[1]

In the phase II clinical trial (NCT01266460) on patients with persistent or recurrent cervical cancer, patients receive live-attenuated *Lm* cancer vaccine, axalimogene filolisbac, intravenously (IV) over 30 minutes on day 1. Courses are repeated every 28 days in the absence of disease progression or unacceptable toxicity.[2]

Axalimogene filolisbac is classified by the EMA as an advanced therapy medicinal product (ATMP) for the treatment of cervical cancer.[1, 3]

Axalimogene filolisbac does not currently have Marketing Authorisation in the UK for any indication.[4]

Axalimogene filolisbac is in phase III stage of development for high risk locally advanced cervical cancer and phase II for head and neck cancer and for anal cancer.[5]

INNOVATION and/or ADVANTAGES

Axalimogene filolisbac is the only known cancer immunotherapy agent shown in preclinical studies to alert the body's immune system to the presence of cancer, diminish that cancer's natural defense mechanisms and then rally the body's killer T cells to attack the cancer.[5] Axalimogene filolisbac is based on a technology that utilizes live attenuated *Lm* bioengineered to secrete antigen/adjuvant fusion proteins. These *Lm*-based strains are believed to be a significant advancement in immunotherapy as they integrate multiple functions into a single immunotherapy, and are designed to access and direct antigen presenting cells to stimulate anti-tumour T-cell immunity, activate the immune system with the equivalent of multiple adjuvants and simultaneously reduce tumour protection in the tumour microenvironment to enable the T cells to eliminate tumours.[1]

If licensed, axalimogene filolisbac will offer an additional treatment option for patients with persistent, recurrent, or metastatic, squamous or non-squamous cell cervical cancer despite receiving a treatment.

DEVELOPER

Advaxis, Inc.

REGULATORY INFORMATION/ MARKETING PLANS

Axalimogene filolisbac is a designated orphan drug in the USA for the treatment of Stage II to IV invasive cervical carcinoma in April 2014.[6]

Axalimogene filolisbac was designated as a Fast Track product for high-risk locally advanced cervical cancer patients by the FDA in July 2016.[7]

As of February 2018, the company has submitted a conditional Marketing Authorization Application (MAA) to the European Medicines Agency (EMA) for axalimogene filolisbac for the treatment of adult women who progress beyond first-line therapy of persistent, recurrent or metastatic carcinoma of the cervix.[1]

PATIENT GROUP

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 the ectocervix. Inside of the cervix, there are glandular cells that produce mucus. This is called the endocervix. The skin-like cells of the ectocervix can become cancerous, leading to a squamous cell cervical cancer. This is the most common type of cervical cancer. The glandular cells of the endocervix can also become cancerous, leading to an adenocarcinoma of the cervix.[8]

Advanced cervical cancer means that a cancer that began in the cervix has spread to another part of the body. This is also called metastatic cancer.[9] Recurrent cervical cancer occurs when the cancer is detected months or years after the completion of an initial cancer treatment regimen. The recurrence of cervical cancer may be a local recurrence, which is contained to the cervix region. A metastatic recurrence occurs when the cancer has spreads to other organs, such as the kidney, bladder or lymph nodes. [10]

Cancer of the cervix often has no symptoms in its early stages. The most common symptom of cervical cancer is bleeding from the vagina at times other than the periods. The bleeding can occur between periods, during or after sex, or at any time after menopause.[11,12] Symptoms of advanced cancer depend on where the cancer has spread to. They might include tiredness and feeling unwell, griping pain in the abdomen, feeling bloated, constipation, vomiting large amounts.[13] Signs and symptoms of distant cervical cancer recurrence may include weight loss, fatigue, back pain, leg pain or swelling, leakage of urine from the vagina, and bone pain that does not go away.[10]

There are certain factors that increase the risk for cervical cancer. These include age (it mainly affects sexually active women aged between 30 and 45 years), human papilloma virus (HPV) mainly HPV 16 and HPV 18 that are responsible for about 70% of cervical cancer cases, human immunodeficiency virus (HIV), sexually transmitted infections, smoking tobacco, taking contraceptive pills, having children especially if having the first child before the age of 17, family history, and family history.[12,14] Having cervical cancer can cause emotional impacts. Also treatment of cervical cancer can cause

physical problems such as tiredness, early menopause, physical changes that might affect relationships and sex life, and lymphedema.[15,16]

CLINICAL NEED and BURDEN OF DISEASE

In the UK, cervical cancer was the 14th most common cancer among females, with around 3,100 new cases in 2015. Age standardised incidence rate in 2015 in the UK was 9.6 per 100,000 and in England was 9.2 per 100,000. It accounted for 2% of all new cancer cases in females in the UK (2015). Highest incidence rates in the UK were among females aged 25 to 29 (2013-2015). Incidence rates for cervical cancer are projected to rise by 43% in the UK between 2014 and 2035, to 17 cases per 100,000 females by 2035.[17,18] In England in 2016, there were 2,594 registrations of newly diagnosed cases of malignant neoplasm cervix uteri (ICD-10 code C53).[19]

There are around 870 cervical cancer deaths in the UK every year, that is, more than 2 people every day (2014-2016). Cervical cancer was the 19th most common cause of cancer death among females, with around 850 deaths in 2016. Mortality rates for cervical cancer in the UK were highest in females aged 85 to 89 (2014-2016).[17] In England and Wales in 2016, there were 725 deaths with malignant neoplasm of cervix uteri (ICD-10 code C53) recorded as the underlying cause.[20] Mortality rates for cervical cancer are projected to fall by 7% in the UK between 2014 and 2035, to 3 deaths per 100,000 females by 2035.[17]

About five in 100 of women diagnosed at the late stage cervical cancer survive for five years or more. Five-year relative survival for cervical cancer in women is below the European average in England, Wales.[17] The latest published survival statistics for cervical cancer (2016, patients diagnosed in 2011-2015 in England) report age-standardised 1-year survival rate of 80.9% and age-standardised 5-year survival rate of 61.3%.[21]

In England in 2016/2017 there were 8,839 hospital admissions with a primary diagnosis of malignant neoplasm of cervix uteri (ICD-10 code C53) resulting in 14,422 bed days and 5,703 day cases.[22]

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal guidance. Topotecan for the treatment of recurrent and stage IVB cervical cancer (TA183). October 2009.
- NICE guideline. Suspected cancer: recognition and referral (NG12). June 2015.
- NICE interventional procedure guidance. High dose rate brachytherapy for carcinoma of the cervix (IPG160). March 2006.

NHS ENGLAND and POLICY 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 for Medical Oncology. Cervical cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. 2017.[23]
- NHS Clinical Knowledge Summary. Cervical cancer and HPV. 2014.[24]
- 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.[25]
- World Health Organization. Comprehensive Cervical Cancer Control, a guide to essential practice. 2014.[26]
- International Federation of Gynaecology & Obstetrics. Global guidance for cervical cancer prevention and control. 2009.[27]

CURRENT TREATMENT OPTIONS

Advanced cases of cervical cancer are usually treated using a combination of chemotherapy and radiotherapy.[12] Radiotherapy can be delivered externally – a machine beams high-energy waves into the pelvis to destroy cancerous cells or internally (brachytherapy) – a radioactive implant is placed next to the tumour inside the vagina.[28]

Regarding drug treatment, the National Institute for Health and Care Excellence (NICE) recommends Topotecan for the treatment of recurrent and stage IVB cervical cancer as follows:[29]

- Topotecan in combination with cisplatin is recommended as a treatment option for women with recurrent or stage IVB cervical cancer 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.[30]

EFFICACY and SAFETY

Trial	**GOG-0265, NCT01266460, 18 years and older; axalimogene filolisbac; phase II extension**
Sponsor	Gynecologic Oncology Group (sponsor); Advaxis Inc, (collaborator)
Status	Ongoing
Source of Information	Trial registry;[2] presentation;[31] company website[5]
Location	USA
Design	Single group assignment, open label
Participants	n=67 (planned); n= 50 enrolled; aged 18 years and older; females; cervical cancer; persistent or recurrent; squamous or non-squamous cell carcinoma, adenosquamous carcinoma, or adenocarcinoma of the cervix with documented disease progression; must have measurable disease as defined by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1; must have a Gynecologic

	Oncology Group (GOG) performance status of 0 or 1; recovered from effects of recent surgery, radiotherapy, or chemotherapy; should be free of active infection requiring antibiotics; must have had one prior systemic chemotherapeutic regimen for management of advanced, metastatic, or recurrent carcinoma of the cervix.
Schedule	Patients receive live-attenuated Listeria monocytogenes cancer vaccine (Axalimogene filolisbac) IV over 30 minutes on day 1. Courses repeat every 28 days in the absence of disease progression or unacceptable toxicity.
Follow-up	Follow up: every 3 months for 2 years and then every 6 months for 3 years Treatment duration: 3 months.
Primary Outcomes	- Incidence of adverse effects as assessed by the Common Terminology Criteria for Adverse Events (CTCAE) version (v)4.0 [Time Frame: Up to 5 years] - Number of patients with dose-limiting toxicities, as assessed by CTCAE v 4.0 [Time Frame: 28 days] - Proportion of patients who survive for at least 12 months [Time Frame: 12 months]
Secondary Outcomes	- Distribution of overall survival [Time Frame: Time from study entry to time of death or the date of last contact, assessed up to 5 years] - Distribution of progression-free survival [Time Frame: Time from study entry to time of progression or death, whichever occurs first, assessed up to 5 years] - Proportion of patients who have objective tumour response (complete or partial) [Time Frame: Up to 5 years] - Changes in clinical immunology based upon serum [Time Frame: Baseline to up to 24 hours after dose 3]
Key Results	The final efficacy results demonstrated that 38% of patients (n = 19/50) with heavily pre-treated persistent or recurrent metastatic (squamous or non-squamous cell) carcinoma of the cervix (PRmCC) were alive 12 months following treatment with axalimogene filolisbac. The study protocol used a logistic model-based calculation to establish the expected 12-month survival rate. The model identified the key prognostic factors of age, race and performance status significantly related to survival from a database of approximately 500 patients with PRmCC who participated in 17 previous phase 2 studies conducted by the Gynecologic Oncology Group (GOG), now part of NRG Oncology. Using this model, the expected 12-month survival rate of patients enrolled in the study was calculated to be 24.5%. As a result, the 38% 12-month survival rate of patients treated with axalimogene filolisbac represents a 52% improvement over the expected survival rate and is the highest 12-month survival rate achieved to date in this setting. The probability of this survival improvement being detected by chance versus a true treatment effect was calculated to be 0.02. A compelling and ongoing complete response of 18.5 months was observed and the longest ongoing survival is 40.6 months.[5]
Adverse effects (AEs)	The safety profile was consistent with previous clinical experience. The most common grade 1 or grade 2 treatment-related adverse events (TRAEs) were hypotension and symptoms related to cytokine release (e.g., nausea, chills, fever). Eighteen out of 50 patients experienced a grade 3 TRAE and two out of

	50 patients experienced a grade 4 TRAE, which were hypotension and symptoms related to cytokine release.[5]
Expected reporting date	Study Primary completion date reported as October 2018

ESTIMATED COST and IMPACT

COST

The cost of axalimogene filolisbac is not yet known.

IMPACT – SPECULATIVE

IMPACT ON PATIENTS AND CARERS

☒ Reduced mortality/increased length of survival

☐ Reduced symptoms or disability

☐ Other

☐ No impact identified

IMPACT ON HEALTH and SOCIAL CARE SERVICES

☐ Increased use of existing services

☐ Decreased use of existing services

☐ Re-organisation of existing services

☐ Need for new services

☐ Other

☒ None identified

IMPACT ON COSTS and OTHER RESOURCE USE

☐ Increased drug treatment costs

☐ Reduced drug treatment costs

☐ Other increase in costs

☐ Other reduction in costs

☐ Other

☒ None identified

OTHER ISSUES

☐ Clinical uncertainty or other research question identified

☒ None identified

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