NIHR | Innovation Observatory

HEALTH TECHNOLOGY BRIEFING
JULY 2020

LN-145 for recurrent, metastatic or persistent cervical carcinoma

NIHRIO ID	28113	**NICE ID**	10432
Developer/Company	Iovance Biotherapeutics	**UKPS ID**	Not available

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

SUMMARY

LN-145 is in development for the treatment of recurrent, metastatic or persistent cervical cancer. Recurrent cancer is when the cancer returns months or years after the original treatment; persistent cancer is when the tumour does not respond to treatment or a second tumour develops despite the completion of treatment. Metastatic cancer is when the tumour has spread outside the original tumour site, to other areas 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.

LN-145 is composed of T-cells (a type of immune cell) that are collected from the patient and grown to large numbers in the laboratory. They are then administered intravenously into the patient alongside IL-2 (a protein that activates T-cells), in order to encourage them to recognise and destroy the tumour. Therefore, if licensed, LN-145 would offer an additional treatment option to patients with recurrent, metastatic or persistent cervical cancer, who currently have limited treatment options.

PROPOSED INDICATION

Treatment of recurrent, metastatic or persistent cervical carcinoma.[1]

TECHNOLOGY

DESCRIPTION

LN-145 is a proprietary preparation of autologous tumour infiltrating lymphocytes (TIL). The autologous TIL are isolated from an autologous tumour sample and expanded *ex vivo* in the presence of interleukin-2 (IL-2). Upon infusion of LN-145 into the patient, lymphocytes within the product recognise and kill the patient's tumour cells.[2]

In a phase II clinical trial (NCT03108495), patients were administered LN-145 after non-myeloablative (NMA) lymphodepletion.[1] Immediately following LN-145 infusion, patients received up to 6 doses of IL-2 to support growth and activation of the infused TIL.[3]

INNOVATION AND/OR ADVANTAGES

TIL are derived from a patient's own immune cells called lymphocytes, and specifically the T lymphocytes that have localised to the tumour and therefore can recognise and potentially kill the patient's own cancer cells. LN-145 is derived through isolation and expansion of a patient's own naturally occurring TIL from a sample of tumour removed from the patient. Then, when administered, TIL target and infiltrate cancer in the patient and attack the cancer in greater number.[3]

In the phase II clinical trial, NCT03108495, LN-145 resulted in a 44% objective response rate in previously treated cervical cancer patients with acceptable safety profile. LN-145 therefore offers patients a viable therapeutic option.[4]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

LN-145 is not licensed in the EU/UK for any indication.

In April 2018, the US Food and Drug Administration (FDA) granted orphan drug designation to LN-145 for the treatment of cervical cancer with a tumour size of greater than 2 cm in diameter.[5,6]

In February 2019 the FDA granted LN-145 fast track designation for the treatment of patients with recurrent, metastatic, or persistent cervical cancer who have progressed while on or after chemotherapy.[7] In May 2019, the FDA granted breakthrough therapy designation to LN-145 to treat advanced cervical cancer.[8]

LN-145 is also in phase II clinical trials for:[9]

- Squamous cell carcinoma of the head and neck
- Non-small cell lung cancer

PATIENT GROUP

DISEASE BACKGROUND

Cervical cancer is the abnormal growth of cells in the lining of the cervix (the lower part of the womb). The cancer can occur in the endocervix (skin-like cells on the outer surface) leading to adenocarcinoma or in the ectocervix (mucosal cells) leading to squamous cell cervical cancer – the most common type of cervical cancer.[10]

The early stages of cervical cancer are symptomless, therefore screening is encouraged in women over 25 years, in order to detect cancer in the early stages. In later stage cancers, symptoms include unusual vaginal bleeding (after sex, between periods or after the menopause), dyspareunia (pain or discomfort during sex), vaginal discharge and/or pelvic pain.[11]

The greatest risk factor for cervical cancer is being positive for the human papilloma virus (HPV), with 70% of cervical cancers being caused by HPV16 and HPV18. Women are also at higher risk of developing cervical cancer if they are positive for human immunodeficiency virus (HIV) or other sexually transmitted diseases such as chlamydia; if they are on a prescription of the contraceptive pill; if they have had children at a young age (<25 years old); if they have a family history of the disease or have had previous cancers such as cancer of the vagina, vulva kidney or urinary tract.[12]

When diagnosed, cervical cancer is staged from I to IV:[13]

- Stage I – cancer is contained within the neck of the womb (cervix)
- Stage II – the cancer has spread outside of the cervix into the surrounding tissue
- Stage III – the cancer has spread outside the cervix into the structures around it
- Stage IV – the cancer has spread to the bladder, rectum or further away

Persistent cancer is when there is continued evidence of the original tumour in the form of symptoms or morphological features, or if a second tumour is diagnosed within three months after therapy was completed for the original tumour. Metastatic cancer is when the cancer has spread outside of the cervix to regions of the body away from the cervix such as the lungs. [13-15]

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, or a metastatic recurrence, which 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.[13,15]

CLINICAL NEED AND BURDEN OF DISEASE

In the UK in 2017, cervical cancer was the 14th most common cancer accounting for 2% of all new cancers cases in females.[16] 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.[17] European age-standardised incidence rates for cervical cancer are projected to rise by approximately 43% in the UK between 2014 and 2035, from 12 to 17 cases per 100,000 by 2035.[18]

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.[19]

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.[20] 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.[18]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Treatment of cervical cancer is based on several factors including the type and stage of the cancer, as well as the possible side effects of the treatment. In addition, in advanced cancer, where the cancer has spread, patients may opt for treatments that reduce symptoms.[21-23]

Depending on the stage of cervical cancer, treatment options may include surgery, chemotherapy and radiotherapy together (chemoradiotherapy), radiotherapy, and chemotherapy.[21]

Advanced cervical cancer is treated with chemotherapy, with or without radiotherapy. Surgery is also sometimes used. In patients with recurrent cancer, pelvic exenteration (removal of the cervix, vagina, womb, ovaries, bladder and rectum) is offered.[21]

Surgical resection or radiotherapy may potentially be curative for selected women with locally recurrent disease, however, in the majority of cases this will not be feasible. Thus, women with recurrent and metastatic cervical cancer have limited systemic treatment options.[24]

CURRENT TREATMENT OPTIONS

In the UK, chemotherapy is offered to patients with metastatic or recurrent cervical cancers. These include:[25]

- Cisplatin
- Carboplatin
- Paclitaxel (Taxol)
- Paclitaxel-carboplatin
- Topotecan (Hycamtin, postactasol)
- Carboplatin-etoposide

NICE recommends topotecan in combination with cisplatin for women with recurrent or stage IVb cervical cancer if they have not previously received cisplatin.[26] Bevacizumab, in combination with paclitaxel and cisplatin or, alternatively, paclitaxel and topotecan in patients who cannot receive platinum therapy, is indicated for the treatment of adult patients with persistent, recurrent, or metastatic carcinoma of the cervix.[27]

PLACE OF TECHNOLOGY

If licensed, LN-145 would offer an additional treatment option for patients with recurrent, metastatic or persistent cervical carcinoma.[1]

CLINICAL TRIAL SUMMARY INFORMATION

Trial	NCT03108495, 2016-003447-11

	A Phase 2, Multicenter Study to Evaluate the Efficacy and Safety Using Autologous Tumour Infiltrating Lymphocytes (LN-145) in Patients With Recurrent, Metastatic or Persistent Cervical Carcinoma **Phase II - recruiting** **Locations:** Europe (including the UK) and the US **Estimated primary completion date:** December 2021
Trial design	Non-randomised, single group assignment, open label
Population	- N = 138 (planned) - Patients with recurrent, metastatic or persistent cervical carcinoma, with or without a prior line of therapy that included pembrolizumab - Females ages 18 years and older
Intervention(s)	- Post-NMA lymphodepletion, patients are infused with their autologous TIL (LN-145) followed by IL-2 administration
Comparator(s)	No comparator
Outcome(s)	Primary outcomes; - Objective response rate [Time frame: up to 6 months] - Efficacy and adverse events [Time frame: up to 60 months] For full list of outcomes, see trial record
Results (efficacy)	LN-145 resulted in 44% objective response rate in previously treated cervical cancer patients[4]
Results (safety)	LN-145 demonstrated an acceptable safety and efficacy profile[4]

ESTIMATED COST

The cost of LN-145 is not yet known.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE Guidance. Tisotumab vedotin for treating recurrent or metastatic cervical cancer after systemic therapy [GID-TA10620]. Date TBC.
- 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 Complex Gynaecology: Specialist Gynaecological Cancers. E10/S/f

- NHS England. 2013/14 NHS Standard Contract for Cancer: Radiotherapy (All Ages). B01/S/a

OTHER GUIDANCE

- British Gynaecological Cancer Society. Cervical Cancer Guidelines: Recommendations for Practice. 2020.[28]
- European Society Medical Oncology. Cervical cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. 2017.[29]
- NHS Clinical Knowledge Summary. Cervical cancer and HPV. 2017.[30]
- World Health Organisation. Comprehensive Cervical Cancer Control, a guide to essential practice. 2014.[31]
- 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.[32]
- International Federation of Gynaecology & Obstetrics. Global guidance for cervical cancer prevention and control. 2009.[33]

ADDITIONAL INFORMATION

Iovance Biotherapeutics Inc did not enter information about this technology onto the UK PharmaScan database; the primary source of information for UK horizon scanning organisations on new medicines in development. As a result, the NIHR Innovation Observatory has had to obtain data from other sources. UK PharmaScan is an essential tool to support effective NHS forward planning; allowing more effective decision making and faster uptake of innovative new medicines for patients who could benefit. We urge pharmaceutical companies to use UK PharmaScan so that we can be assured of up-to-date, accurate and comprehensive information on new medicines.

REFERENCES

1 Clinicaltrials.gov. *Study of LN-145, Autologous Tumor Infiltrating Lymphocytes in the Treatment of Patients With Cervical Carcinoma.* Available from: https://clinicaltrials.gov/ct2/show/NCT03108495 [Accessed 29 Jun 2020].

2 National Cancer Institute. *Autologous tumor infiltrating lymphocytes LN-145.* Available from: https://www.cancer.gov/publications/dictionaries/cancer-drug/def/autologous-tumor-infiltrating-lymphocytes-ln-145 [Accessed 29 Jun 2020].

3 Iovance Biotherapeutics. *Immunotherapy For Recurrent, Metastatic Or Persistent Cervical Carcinoma.* Available from: https://www.iovance.com/clinical/c-145-04-cervical-carcinoma/ [Accessed 29 Jun 2020].

4 Jazaeri, A., Zsiros E., Navroze R., Artz A., Edwards R., Wenham R., et al. *Safety and efficacy of adoptive cell transfer using autologous tumor infiltrating lymphocytes (LN-145) for treatment of recurrent, metastatic, or persistent cervical carcinoma.* Journal of Clinical Oncology. 2019;37:2538-. Available from: https://ascopubs.org/doi/abs/10.1200/JCO.2019.37.15_suppl.2538

5 BioSpace. *Updated: Iovance Continues Path in Developing TIL Treatments for Solid Tumors.* Available from: https://www.biospace.com/article/iovance-continues-path-in-developing-til-treatments-for-solid-tumors/ [Accessed 29 Jun 2020].

6 US Food and Drug Administration. *Search Orphan Drug Designations and Approvals: autologous tumor infiltrating lymphocytes (TIL).* Available from: https://www.accessdata.fda.gov/scripts/opdlisting/oopd/detailedIndex.cfm?cfgridkey=20176015 [Accessed 23 Jul 2020].

7 Intrado GlobeNewswire. *Iovance Biotherapeutics was Granted Fast Track Designation for LN-145 for Cervical Cancer.* Available from: https://www.globenewswire.com/news-

release/2019/02/26/1742262/0/en/Iovance-Biotherapeutics-was-Granted-Fast-Track-Designation-for-LN-145-for-Cervical-Cancer.html [Accessed 29 Jun 2020].
8 National Cancer Institute. *FDA grants breakthrough therapy designation of new TIL therapy for advanced cervical cancer*. Available from: https://ccr.cancer.gov/news/article/fda-grants-breakthrough-therapy-designation-of-new-til-therapy-for-advanced-cervical-cancer [Accessed 29 Jun 2020].
9 Clinicaltrials.gov. *Search result: LN-145, phase 2, 3* Available from: https://clinicaltrials.gov/ct2/results?term=LN-145&age_v=&gndr=&type=&rslt=&phase=1&phase=2&Search=Apply [Accessed 07 Jul 2020].
10 Cancer Research UK. *What is cervical cancer?* Available from: https://www.cancerresearchuk.org/about-cancer/cervical-cancer/about [Accessed 29 Jun 2020].
11 Cancer Research UK. *Cervical cancer - Symptoms*. Available from: https://www.cancerresearchuk.org/about-cancer/cervical-cancer/symptoms [Accessed 29 Jun 2020].
12 Cancer Research UK. *Cervical cancer - Risks and causes*. Available from: https://www.cancerresearchuk.org/about-cancer/cervical-cancer/risks-causes [Accessed
13 Cancer Research UK. *Cervical cancer - Stages, types and grades*. Available from: https://www.cancerresearchuk.org/about-cancer/cervical-cancer/stages-types-grades [Accessed 29 Jun 2020].
14 Yueh, B., Feinstein A., Weaver E., CSasaki C., Concato J. *Prognostic Staging System for Recurrent, Persistent, and Second Primary Cancers of the Oral Cavity and Oropharynx*. Otolaryngology - Head and Neck Surgery. 1998;124(9):975-81. Available from: https://jamanetwork.com/journals/jamaotolaryngology/fullarticle/220885#:~:text=Tumors%20were%20also%20classified%20as,for%20at%20least%203%20months.
15 Cancer Treatment Centres of America. *Cervical cancer stages*. Available from: https://www.cancercenter.com/cancer-types/cervical-cancer/stages [Accessed 29 Jun 2020].
16 Cancer Research UK. *Cervical cancer statistics*. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/cervical-cancer#heading-Zero [Accessed 29 Jun 2020].
17 Office for National Statistics. *Cancer registration statistics, England*. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancerregistrationstatisticscancerregistrationstatisticsengland [Accessed 29 Jun 2020].
18 Cancer Research UK. *Cancer incidence for all cancers combined*. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/incidence/all-cancers-combined#heading-Three [Accessed 29 Jun 2020].
19 NHS Digital. *Hospital Admitted Patient Care Activity 2018-19*. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2018-19 [Accessed 29 Jun 2020].
20 Office for National Statistics. *Death registrations summary tables - England and Wales*. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/datasets/deathregistrationssummarytablesenglandandwalesreferencetables [Accessed 29 Jun 2020].
21 NHS. *Treatment - Cervical cancer*. Available from: https://www.nhs.uk/conditions/cervical-cancer/treatment/ [Accessed 29 Jun 2020].
22 Cancer Research UK. *Cervical cancer - Making decisions about treatment for advanced cancer*. Available from: https://www.cancerresearchuk.org/about-cancer/cervical-cancer/advanced/treatment/making-decisions-about-treatment [Accessed 25 Jun 2020].
23 Cancer Research UK. *Cervical cancer - Treatment for advanced cancer*. Available from: https://www.cancerresearchuk.org/about-cancer/cervical-cancer/advanced/treatment [Accessed 25 Jun 2020].
24 Boussios, S., Seraj E., Zarkavelis G., Petrakis D., Kollas A., Kafantari A., et al. *Management of patients with recurrent/advanced cervical cancer beyond first line platinum regimens: Where do we stand? A literature review*. Critical Reviews in Oncology/Hematology. 2016 2016/12/01/;108:164-74. Available from: https://doi.org/10.1016/j.critrevonc.2016.11.006 http://www.sciencedirect.com/science/article/pii/S1040842816303213 29 Jun 2020
25 Cancer Research UK. *Cervical Cancer - Chemotherapy drugs*. Available from: https://www.cancerresearchuk.org/about-cancer/cervical-cancer/treatment/chemotherapy/drugs [Accessed 20 Jun 2020].

26 National Institute for Health Care Excellence. *Cervical cancer - Treatment and Management*. 2018. Available from: https://pathways.nice.org.uk/pathways/cervical-cancer/treatment-and-management-of-cervical-cancer [Accessed 25 Jun 2020].
27 Electonic Medicines Consortium. *Avastin 25mg/ml concentrate for solution for infusion*. Available from: https://www.medicines.org.uk/emc/medicine/15748/SPC/Avastin+25mg+ml+concentrate+for+solution+for+infusion/#INDICATIONS [Accessed 23 Jul 2020].
28 British Gynaecological Cancer Society (BGCS). *British Gynaecological Cancer Society (BGCS) Cervical Cancer Guidelines: Recommendations for Practice* Last Update Date: Available from: https://www.bgcs.org.uk/professionals/guidelines-for-recent-publications/ [Accessed 29 Jun 2020].
29 Marth, C., Landoni F., Mahner S., McCormack M., Gonzalez-Martin A., Colombo N. *Cervical Cancer: ESMO Clincal Practice Guidelines*. 2017. Available from: https://www.esmo.org/guidelines/gynaecological-cancers/cervical-cancer [Accessed 20 Jun 2020].
30 National Institute for Health Care Excellence. *Cervical Cancer and HPV*. 2017. Available from: https://cks.nice.org.uk/cervical-cancer-and-hpv#!topicSummary [Accessed 25 Jun 2020].
31 World Health Organisation. *Comprehensive Cervical Cancer Control: A guide to essential practice*. 2014. Available from: https://www.who.int/reproductivehealth/publications/cancers/cervical-cancer-guide/en/ [Accessed 25 Jun 2020].
32 Saslow, D., Solomon, D., Lawson, H. W., Killackey, M., Kulasingam, S. L., Cain, J., Garcia, F. A.,, al. E. *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*. CA: a cancer journal for clinicians. 2012;62(3):147-72. Available from: https://academic.oup.com/ajcp/article/137/4/516/1760450
33 International Federation of Gynecology and Obstetrics. *Global Guidance For Cervical Cancer Prevention and Control*. 2009. Available from: https://www.figo.org/committee-gynecologic-oncology [Accessed 25 Jun 2020].

NB: This briefing presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.