National Institute for Health Research

NIHR Innovation Observatory
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Listeria monocytogenes vaccine for unresectable malignant plural mesothelioma

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LAY SUMMARY

Malignant pleural mesothelioma is a type of cancer of the lungs caused mostly by exposure to asbestos. When asbestos fibres are inhaled, they can cause tumours to grow in the pleura, the thin membrane of cells (mesothelium) that line the lungs and chest wall. The disease is five times more common in men than women, and occurs between the ages of 60 and 79 years because there is typically a time lag of decades between asbestos exposure and when the disease occurs. It is often diagnosed at an advanced stage and the prognosis is usually poor. People with malignant pleural mesothelioma often have symptoms and respiratory problems such as breathlessness, cough, and fluid on the lungs, as well as chest pain. As the disease progresses, more general symptoms such as tiredness, excessive sweating, weight loss, loss of appetite and difficulty in swallowing become common.

Listeria monocytogenes vaccine is under development for patients who have progressive disease, have had previous chemotherapy and for whom surgery is unsuitable. In current treatment pathways the aim is often symptom management rather than tumour removal, so this drug represents a novel treatment approach for patients who are unsuitable for surgery. The drug aims to help to improve symptoms and has the potential to be well-tolerated by many patients.

TARGET GROUP

Pleural mesothelioma in adults (unresectable, malignant); in combination with standard-of-care chemotherapy or pembrolizumab.

TECHNOLOGY

DESCRIPTION

Listeria monocytogenes vaccine (ANZ-207; CRS-207) is a recombinant listeria-based cancer vaccine, which acts by enhancing tumour-specific T cell and anti-tumour responses. It targets the tumour-associated antigen mesothelin, a tumour differentiation antigen which is overexpressed in many epithelial-derived cancers, including malignant mesotheliomas. Listeria monocytogenes vaccine is designed to be administered in combination with chemotherapy or a humanised antibody in patients who are unsuitable for surgery.[1,2]

In a phase II clinical trial, listeria monocytogenes vaccine and pembrolizumab were administered in 3-week cycles. For cycle 1, subjects received pembrolizumab (200 mg) by intravenous infusion (IV) over 30 minutes on day 1 and listeria monocytogenes vaccine (starting dose 1 × 109 colony-forming units [CFU]), administered IV over 1 hour on day 2. After 4 cycles, subjects continue to receive pembrolizumab on day 1 at each treatment cycle (every three weeks), and listeria monocytogenes vaccine is administered once every 6 weeks. Treatment cycles continued for up to 24 months.[1]

Listeria monocytogenes vaccine does not currently have Marketing Authorisation in the EU for any indication.

Listeria monocytogenes vaccine is in phase II development for the following indications:[1]

- Ovarian cancer
- Fallopian tube cancer
- Oesophageal cancer
- Andenocarcinoma of the gastro-oesophageal junction
- Gastric cancer
- Solid tumour
- Peritoneal cancer
- Metastatic adenocarcinoma of the pancreas

INNOVATION and/or ADVANTAGES

If licensed, listeria monocytogenes vaccine will offer an additional treatment option for patients with unresectable malignant pleural mesothelioma. Because the aim of current treatment in patients whose disease is unsuitable for surgery is often symptom management rather than tumour removal, the drug represents a novel treatment approach. The developers, Aduro BioTech, state that the platform upon which the vaccine is based (LADD - Live, Attenuated Double-Deleted Listeria) is well-tolerated and has a good safety profile, allowing for combination with checkpoint inhibitors, chemotherapy or other treatment regimens. It is not neutralised by the patient's immune system, therefore allowing for repeat administration and sustained enhancement of tumour antigen-specific T cell immunity. Finally, it can be manufactured through a relatively simple and cost-effective process.[2]

DEVELOPER

Aduro BioTech Inc.

AVAILABILITY, LAUNCH or MARKETING

Listeria monocytogenes vaccine is a designated orphan drug in the EU/USA for malignant pleural mesothelioma.[3]

The drug is in phase II of development.

PATIENT GROUP

BACKGROUND

Malignant pleural mesothelioma is a cancer caused mostly (in 90% of cases) by exposure to asbestos, and it accounts for approximately 80–90% of all mesothelioma cases.[4] When asbestos fibres are inhaled, they can cause tumours to grow in the pleura, the thin membrane of cells (mesothelium) that line the lungs and chest wall.[5] The condition is significantly more common in men, with a male to female ratio of 5:1. People with mesothelioma usually present with the disease between the ages of 60 and 79 years.[6]

Most people with malignant pleural mesothelioma present with chest pain and dyspnoea and have pleural effusions evident on examination. Fatigue, profuse sweating, weight loss, anorexia and difficulty in swallowing become common as the disease progresses. Presentation and diagnosis often occur at an advanced stage and the prognosis for most patients is extremely poor (6-12 months), with a median survival time of about 1 year.[4]

CLINICAL NEED and BURDEN OF DISEASE

The incidence of malignant pleural mesothelioma in men in the UK is 3.4 per 100,000;[7] this is increasing and is expected to peak in the 2020's because there is a lag of 20-50 years between exposure and disease, and asbestos was banned in the UK in 1999.[5]

The one year survival rate is 38%, and five year survival is 10%.[8] In England and Wales in 2015, 2,305 people died of all kinds of mesothelioma (ICD-10 code C45.0).[9] Hospital admissions data for England in 2015-2016 recorded 5,118 hospital admissions and 6,042 finished consultant episodes for pleural mesothelioma.[10]

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal. Pemetrexed for the treatment of malignant pleural mesothelioma (TA135). January 2008.
- NICE technology appraisal. Bevacizumab for untreated malignant pleural mesothelioma (ID1183), in development [GID-TA10197]. Suspended July 2017, company has advised they will not be pursuing a licensing application.

- NICE technology appraisal. NGR-TNF for previously treated advanced malignant pleural mesothelioma (ID655), in development [GID-TA10183]. Suspended July 2017, company has advised they will not be pursuing a licensing application.

NHS ENGLAND and POLICY GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Cancer: Malignant Mesothelioma (Adult). B10/S/a.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Adult). B15/S/a.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Radiotherapy (All Ages). B01/S/a.

OTHER GUIDANCE

Baas P, Fennell D, Kerr KM, Van Schil PE, Haas RL, Peters S. Malignant pleural mesothelioma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of oncology. 2015 28;26(suppl_5):v31-9.[7]

CURRENT TREATMENT OPTIONS

There is no standard treatment pathway for malignant pleural mesothelioma in England and Wales. Clinical management is multimodal and a patient may receive a combination of treatments (surgery, chemotherapy and/or radiotherapy), although surgery is not indicated for the majority of patients and the aim of treatment is often active symptom control rather than removal of the tumour. Pemetrexed in combination with cisplatin is the only chemotherapy regimen that is currently licensed for this indication, and is recommended by NICE as a treatment option only in people who have a World Health Organization (WHO) performance status of 0 or 1, who are considered to have advanced disease, and for whom surgical resection is considered inappropriate.[6] A variety of combination and single-agent regimens such as the mitomycin C, vinblastine and cisplatin combination (MVP) or vinorelbine are also used.[6] European Society for Medical Oncology (ESMO) clinical practice guidelines recommend doublet chemotherapy with pemetrexed or raltitrexed and cisplatin. Personalised therapy is warranted, but in its infancy. Radiotherapy can be used as part of a multimodality treatment or for palliation but there is no good evidence about its effectiveness.[7]

EFFICACY and SAFETY

Trial	NCT03175172; ADU-CL-13; KEYNOTE KN-701; NCI-2017-01124; CDR789579; CRS-207 plus pembrolizumab; phase II
Sponsor	Aduro BioTech Inc.
Status	Ongoing
Source of Information	Trial registry[11]
Location	USA
Design	Uncontrolled
Participants	n=35 (planned); aged 18 years and over; malignant pleural mesothelioma; previously treated; progressive disease; no more than 2 prior lines of anti-cancer therapy, one of which must have included pemetrexed and a platinum

Schedule	Patients receive CRS-207 and pembrolizumab in 3-week cycles. In cycle 1, patients receive 200 mg IV pembrolizumab over 30 minutes on day 1 and CRS-207 (starting dose 1×10^9 colony-forming units [CFU]), administered IV over 1 hour on day 2. After 4 cycles, patients continue to receive pembrolizumab on day 1 at each treatment cycle (every 3 weeks); CRS-207 is administered once every 6 weeks. Treatment cycles continue for up to 24 months as long as there is adequate safety and potential for clinical benefit.
Follow-up	Active treatment cycles for up to 24 mths; follow up 18 mths
Primary Outcomes	Objective response rate
Secondary Outcomes	Disease control rate Progression free survival Improvement in pulmonary function (FVC) Overall survival
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Estimated December 2018

ESTIMATED COST and IMPACT

COST

The cost of listeria monocytogenes vaccine 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

INFORMATION FROM

No information was received from Aduro BioTech.

Aduro BioTech 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

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[2] Aduro BioTech. *Attacking cancer on multiple fronts: cancer immunotherapy*. Available from: http://www.aduro.com/technology/immunotherapy/ [Accessed 5 September 2017].

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[6] National Institute for Health and Care Excellence. *Pemetrexed for the treatment of malignant pleural mesothelioma (TA135)*. January 2008.

[7] Baas P, Fennell D, Kerr KM, Van Schil PE, Haas RL, Peters S. Malignant pleural mesothelioma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of Oncology*. 2015 28;26(suppl_5):v31-9

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[11] ClinicalTrials.gov. *Evaluation of CRS-207 with pembrolizumab in previously treated MPM - NCT03175172.* Available from: https://www.clinicaltrials.gov/ct2/show/NCT03175172?term=NCT03175172&rank=1 [Accessed 5 September 2017]. Last updated August 2017.