Innovation Observatory

NHS National Institute for Health Research

EVIDENCE BRIEFING
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Pegargiminase in addition to pemetrexed and cisplatin for advanced malignant pleural mesothelioma – first line

NIHRIO ID	6383	**NICE ID**	10058
Developer/Company	Polaris Pharmaceuticals Inc	**UKPS ID**	Not available

Licensing and market availability plans	Currently in phase III clinical trials

SUMMARY

Pegargiminase is a medicinal product currently being developed to be given in addition to pemetrexed and cisplatin for the treatment of advanced malignant pleural mesothelioma. Malignant pleural mesothelioma is rare a type of cancer that affects the outer linings of the lungs and the internal chest wall. Mesothelioma is often diagnosed at an advanced stage. Malignant pleural mesotheliomas are most often surgically unresectable, and they respond poorly to current chemotherapy and radiation therapy.

Pegargiminase is administered by intramuscular injection and works by depleting the external supply of an amino acid called arginine. External supply of arginine is critical for the survival of mesothelioma cell lines that are deficient with an enzyme called ASS1. Depletion of external supply of arginine will lead to death of cancer cells that are arginine-dependent while leaving the patient's normal cells unharmed and may block the growth of cancer cells that need arginine to grow. If licensed, pegargiminase in addition to pemetrexed and cisplatin will offer a new first line treatment option for patients with advanced malignant pleural mesothelioma with low ASS1 expression.

PROPOSED INDICATION

Malignant pleural mesothelioma (advanced; low argininosuccinate synthetase 1 expression) – first line.[1]

TECHNOLOGY

DESCRIPTION

Pegargiminase (ADI-PEG 20), pegylated arginine deiminase, is an enzyme which degrades the amino acid arginine.[1,2] Exogenous supply of arginine is critical for the survival of mesothelioma cell lines that display loss of the urea cycle and also of arginine biosynthetic enzyme argininosuccinate synthetase 1 (ASS1) – a tumour suppressor. Loss of the tumor suppressor ASS1 in mesothelioma cell lines, due partly to epigenetic silencing, was observed in 63% of archival mesotheliomas by immunohistochemical analysis, warranting therapeutic stratification of an arginine–depleting agent..[3] Pegargiminase is designed to deplete the external supply of arginine, which causes arginine-dependent cancer cells to die while leaving the patient's normal cells unharmed. Multiple cancers have been reported to have a high degree of arginine dependency.[4] Pegargiminase is produced by genetically modified bacteria and is modified by a process called 'pegylation', meaning that it has been attached to a chemical called polyethylene glycol, which is expected to prolong the time needed to remove the medicine from the body.[5]

Pegargiminase is being developed to be given with pemetrexed and cisplatin for the treatment of advanced malignant pleural mesothelioma patients with low ASS1 expression.[1,2] In the phase II/III clinical trial (NCT02709512), pegargiminase, in addition to the standard of care treatment (pemetrexed and cisplatin), is given at a weekly dose of 36 mg/m^2 by intramuscular (IM) injection.[1]

INNOVATION AND/OR ADVANTAGES

It has been hypothesised that exogenous arginine is required for the survival of ASS1-deficient mesothelioma.[3] Evidence suggest that pegargiminase might be of significant benefit for patients with malignant mesothelioma because early clinical studies showed that it might improve the outcome of patients with this condition when used with standard treatment for malignant mesothelioma.[5] For example, a phase II clinical trial (NCT01279967)[6] showed improvement in progression free survival (PFS) in patients with ASS1-deficient mesothelioma who were treated with pegargiminase.[3]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

- Pegargiminase does not currently have Marketing Authorisation in the EU/UK for any indication.
- Pegargiminase as part of combination therapy is in phase II trials for:[7]
  - Unresectable hepatocellular carcinoma
  - Soft tissue sarcoma
- Pegargiminase is a designated orphan drug in the EU in January 2015 for the treatment of malignant mesothelioma.[5]
- Pegargiminase is a designated orphan drug in the USA in July 2014 for the treatment of mesothelioma.[8]

PATIENT GROUP

DISEASE BACKGROUND

Mesothelioma (malignant mesothelioma) is a form of cancer that affects the mesothelium (the lining that covers the outer surface of some of the body's organs). Mesothelioma that affects the pleura (outer lining of the lungs and internal chest wall) is called pleural mesothelioma. Pleural mesothelioma is the most common form of mesothelioma.[9,10,11] Mesothelioma is also grouped according to how the cells look under a microscope. These are epithelioid, biphasic, sacromatoid, and desmoplastic.[12] Immunohistochemical analysis of archival mesotheliomas has shown that almost two-third of mesothelioma cell lines lack tumour suppressor ASS1 due partly to epigenetic silencing.[3]

Mesothelioma is almost always caused by exposure to asbestos.[10] Current evidence suggests that around 85% of all mesotheliomas that occur in males are attributable to asbestos exposures that occurred in occupational settings. The long latency period (i.e. the time between initial exposure to asbestos and the manifestation of the disease) is typically at least 30 years, which means that most mesothelioma deaths occurring today are a result of past exposures that occurred because of the widespread industrial use of asbestos during 1950-1980.[13]

Pleural mesothelioma causes the pleura to thicken. This thickening of the pleura may begin to press onto the lungs or attach to the inside of the chest wall. In either case the expansion of the lung becomes progressively restricted by the tumour. Fluid, sometimes several litres, can collect between the two layers of the pleura; this affects the lungs ability to expand and causes the person to feel breathless. This is known as a pleural effusion.[9] Symptoms of pleural mesothelioma include chest pain, shortness of breath, fatigue, fever and sweating, a persistent cough, loss of appetite and unexplained weight loss, and swollen fingertips.[9,10]

Mesothelioma is often diagnosed at an advanced stage.[10] Different systems have been established for staging mesothelioma. The staging system most commonly used in the UK for pleural mesothelioma is called the International Mesothelioma Interest Group (IMIG) system. Stage 1 is the earliest stage and stage 4 is the most advanced stage where the cancer cannot be removed by surgery because it has spread to distant organs or tissues or invaded deeply into tissues close to the pleura.[9,12]

CLINICAL NEED AND BURDEN OF DISEASE

Due to the short average survival time following a diagnosis of mesothelioma, incidence and mortality data are more reliable than prevalence data in depicting trends. In 2012, an estimated 5,400 people were living with mesothelioma in the UK.[14] The worldwide incidence of the disease continues to increase; in Western Europe, more than 5,000 new cases per year are estimated to occur, with more than a quarter of a million deaths expected to occur over the next 40 years.[15]

The number of patients diagnosed in 2014 with malignant pleural mesotheliomas (MPM) in England was 2,179 with a median age of 75 years. MPM predominantly affects men – 83.4% of patients were male compared with 16.6% female. In 2014, there were 1,818 men diagnosed with MPM compared with 361 women.[16]

There were 2,595 mesothelioma deaths (2,197 males; 398 females) in Great Britain in 2016, broadly similar to the previous four years. The latest projections suggest that there will continue to be around 2,500 deaths per year for the rest of this current decade before annual numbers begin to decline. The continuing increase in annual mesothelioma deaths in recent years has been driven mainly by deaths among those aged 70 and above.[13] In 2014, the percentage of patients surviving to 3 months after diagnosis was 79.4%; and patients surviving to 1 year after diagnosis was 43.1% (The survival of patients vary by network).[16]

In 2014, 36.5% (795 cases) of MPM patients received chemotherapy.[16] The population eligible to receive pegargiminase in addition to pemetrexed and cisplatin could not be estimated from available published resources.

With the 20–50 year lag between exposure to asbestos and the development of MPM, estimates of the likely burden of disease suggest that numbers of cases in the UK are likely to peak between 2020 and 2025.[16]

PATIENT TREATMENT PATHWAY

PATIENT PATHWAY

If pleural mesothelioma is suspected, a number of different tests may need to be carried out, including an X-ray, a computerised tomography scan, fluid drainage, and thoracoscopy and pleural biopsy.[10, 17] Malignant pleural mesotheliomas are most often surgically unresectable, and they respond poorly to current chemotherapy and radiation therapy.[18]

There is no standard treatment pathway for MPM in England and Wales. The clinical management is multimodal and a patient may receive a combination of treatments. A multidisciplinary team will discuss the best treatment option. MPM is often found when it is advanced. Nearly all treatment aims to control MPM for as long as possible and keep symptoms under control (palliative care). The main treatment of advanced MPM is chemotherapy to help shrink the cancer. Radiotherapy may be used to shrink the cancer, slow down its growth, or control symptoms.[10,17]

The patient may also have treatment for their individual symptoms to help them feel as comfortable as possible. For example, regularly draining fluid from the chest may help the patient's breathing and strong painkillers may help relieve the pain. Sometimes, a procedure is carried out to stop the fluid coming back again by making the outside of the lungs stick to the inside of the chest (pleurodesis), or a tube is put in the chest to drain the fluid regularly at home.[10]

Given the symptom burden associated with a mesothelioma diagnosis, timely referral to specialist palliative care or a pain management is advisable (regional access may vary). Referral to centres offering access to cordotomy for pain management should correspondingly be considered.[16]

CURRENT TREATMENT OPTIONS

Pemetrexed is licensed in the UK for the treatment of unresectable MPM which has not previously been treated with chemotherapy (in combination with cisplatin).[19]

NICE recommends pemetrexed as a treatment option for malignant pleural mesothelioma only in people who have a World Health Organization performance status of 0 or 1, who are considered to have advanced disease and for whom surgical resection is considered inappropriate. Patients currently receiving pemetrexed who do not fall into the patient population as defined above should have the option to continue therapy until they and their clinicians consider it appropriate to stop.[20]

PLACE OF TECHNOLOGY

If licensed, pegargiminase in addition to pemetrexed and cisplatin will offer an additional first line treatment option for advanced malignant pleural mesothelioma with low ASS 1 expression.

CLINICAL TRIAL INFORMATION

Trial	ATOMIC, NCT02709512, POLARIS2015-003; pegargiminase vs placebo, both in combination with pemetrexed and cisplatin; phase II/III
Sponsor	Polaris Group
Status	Ongoing
Source of Information	Trial registry[1]
Location	UK, Italy, USA, Australia, and Taiwan
Design	Randomised, placebo-controlled, double-blind, parallel assignment
Participants	n= 386 (planned); aged 18 years and older; MPM; advanced; biphasic or sarcomatoid histology; measurable disease; naïve to prior chemotherapy or immunotherapy; Eastern Cooperative Oncology Group (ECOG) performance status of 0 – 1; predicted life expectancy of at least 12 weeks.
Schedule	Randomised to pegargiminase 36 mg/m^2 given weekly by IM injection over the course of study; or placebo 36 mg/m^2 given weekly by IM injection over the course of study; both in combination with pemetrexed 500 mg/m^2 every 3 weeks intravenously (IV) and cisplatin 75 mg/m^2 every 3 weeks IV.
Follow-up	Active treatment period: over the course of study Follow-up: approximately 18 months
Primary Outcomes	Response rate [time frame: approximately 18 months]
Secondary Outcomes	Progression free survival [time frame: approximately 18 months]
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Study completion date reported as June 2021

ESTIMATED COST

The cost of pegargiminase is not yet known.

ADDITIONAL INFORMATION

Polaris Pharmaceuticals, 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.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Bevacizumab for untreated malignant pleural mesothelioma (ID1183). Expected date of issue to be confirmed.
- NICE technology appraisal in development. NGR-TNF for previously treated advanced malignant pleural mesothelioma (ID655). Expected date of issue to be confirmed.
- NICE technology appraisal. Pemetrexed for the treatment of malignant pleural mesothelioma (TA135). January 2008.

NHS ENGLAND (POLICY/COMMISSIONING) 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

- Malignant pleural mesothelioma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up, 2015.[21]
- Guidelines of the European Respiratory Society and the European Society of Thoracic Surgeons for the management of malignant pleural mesothelioma, 2010.[22]

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