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HEALTH TECHNOLOGY BRIEFING JULY 2020

Oportuzumab monatox for non-muscle invasive bladder cancer - second line

NIHRIO ID	8019	**NICE ID**	10009
Developer/Company	Sesen Bio Inc.	**UKPS ID**	Not available

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

SUMMARY

Oportuzumab monatox is in clinical development for the treatment of patients with non-muscle invasive bladder cancer (NMIBC), specifically high-grade (Ta or any T1) papillary disease who were unresponsive to prior treatment with Bacillus Calmette-Guerin (BCG) with or without interferon. Bladder cancer starts in the inner lining of the bladder and the most common symptom is passing blood in urine. NMIBC is an early bladder cancer and is the most common type. This type of cancer if often found on small sections of tissue and can spread to connective tissue that separates the lining of the bladder from the muscles beneath, but does not involve the bladder wall muscle. NMIBC is a very prevalent cancer that can progress to become incurable high-grade NMIBC means the cancer is more likely to grow, spread quickly and to come back after initial treatment. Current standard of care include bladder removal or radical cystectomy which has significant impact on patients quality of life (QoL).

Oportuzumab monatox is given by catheter directly into the bladder. It works by binding to a protein called epithelial cell adhesion molecule (EpCAM) on the surface of epithelial cells and some types of cancer cells. It targets and kills EpCAM positive cells tumour cells programmed cell death. If licensed, oportuzumab monatox will provide an additional treatment option for patients with NMIBC, specifically high-grade (Ta or any T1) papillary disease who were unresponsive to prior treatment with BCG.

PROPOSED INDICATION

Treatment of adult patients with non-muscle invasive bladder cancer (NMIBC), specifically high grade (Ta or any T1) papillary disease who were unresponsive to prior treatment with Bacillus Calmette-Guerin (BCG).[1]

TECHNOLOGY

DESCRIPTION

Oportuzumab monatox (Vicinium) is a fusion protein immunotoxin consisting of a humanized, single-chain monoclonal antibody fragment specific for the EpCAM conjugated with a truncated form of pseudomonas exotoxin A with potential antineoplastic activity. Oportuzumab monatox binds to Ep-CAM-positive tumour cells, thereby delivering the pseudomonas exotoxin A moiety specifically; the pseudomonas exotoxin A moiety then inactivates elongation factor 2 (EF-2) through ADP ribosylation, resulting in inhibition of protein synthesis in target cells.[2]

Oportuzumab monatox is currently in clinical development for the treatment of adult patients with NMIBC In the phase III clinical trial (NCT02449239), patients received 30 mg of oportuzumab monatox in 50 mL of saline administered twice weekly (BIW) for 6 weeks followed by once weekly for 6 weeks, for a total of 12 weeks for induction. For maintenance patients received 30 mg of oportuzumab monatox in 50 mL of saline administered once weekly every other week for up to 104 weeks.[1]

INNOVATION AND/OR ADVANTAGES

NMIBC is a very prevalent cancer that can progress to become incurable. The usual treatment for patients who relapse or become refractory to BCG, the standard of care, is to complete bladder removal or radical cystectomy. Removing the bladder is potentially morbid and complex surgery with potential for side effects that can drastically reduce patient's quality of life.[3] For patients unable or unwilling to undergo cystectomy, treatment options are limited.[1]

In phase I and II studies oportuzumab monatox demonstrated excellent safety profile and meaningful clinical activity as assessed by the complete response (CR) at 3 months of 29-40% in patients with NMIBC.[4] Further initial data from the phase III trial confirm the safety and efficacy of oportuzumab monatox and demonstrate that EpCAM, the molecular target of oportuzumab monatox, is nearly ubiquitously expressed in high-grade NMIBC. The novel mechanism of oportuzumab monatox coupled with the promising clinical benefit may provide an important alternative to existing therapies, including radical cystectomy.[5]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Oportuzumab monatox does not currently have Marketing Authorisation in the EU/UK for any indication.

In August 2018, oportuzumab monatox was granted Fast Track designation by US FDA for the treatment of BCG-unresponsive high-grade NMIBC.[6]

PATIENT GROUP

DISEASE BACKGROUND

Bladder cancer is cancer that starts in the inner lining of the bladder.[7] Bladder cancer can be classified by how far it has spread. If the cancerous cells are contained inside the inner lining of the bladder, it is described as non-muscle-invasive, early or superficial (i.e. NMIBC). This is the most common type of bladder cancer.[8,9] Early bladder cancer usually appears as small growths, shaped like mushrooms, which grow out of the bladder lining. This is called papillary bladder cancer. These growths can be surgically removed and they may never come back. However, some types of NMIBC are more likely to come back, including carcinoma in situ (CIS) and high-grade (T1) tumours, both of which can grow quickly. CIS are flat cancers that do not grow out of the bladder wall, but the cancer cells look very abnormal; this is known as high-grade cancer. High-grade T1 tumours are superficial cancers that have grown from the bladder lining into a layer underneath, called the lamina propria.[9,10] High grade means the cancer is more likely to grow, spread and come back after treatment.[11]

Bladder cancer is caused by changes to the cells of the bladder. It is often linked with exposure to certain chemicals, but the exact cause is not always known.[12] There are certain factors that can increase the risk for bladder cancer. These include smoking, exposure to chemicals such as arylamines and polycyclic aromatic hydrocarbons, exposure to water disinfection chemicals such as chlorine and trihalomethanes, treatment for some other cancers, other medical conditions such as diabetes and spinal cord injury, bladder infections and chronic bladder irritation, diet and alcohol intake, previous bladder cancer, and family history.[13]

The most common symptom of bladder cancer is blood in urine that is usually painless. Less common symptoms of bladder cancer include a need to urinate on a more frequent basis, sudden urges to urinate, and a burning sensation when passing urine.[14]

A diagnosis of bladder cancer, and some treatments for the condition, can have a significant impact on a patient's life.[15] NMIBC patients have significantly lower QoL compared with the general population, especially in fatigue, physical and role functioning and mental health.[16]

CLINICAL NEED AND BURDEN OF DISEASE

In 2017, bladder cancer was the 11th most common cancer in the UK, accounting for 3% of all new cancer cases.[17] In England in 2017, there were 8,686 new registrations for malignant neoplasm of bladder (ICD-10 code C67) and the direct age standardised rate per 100,000 population was 27.6 among males and 8.2 among females.[18] Using the 2018/19 England mid-year adult population estimates, this equates to 5,945 new cases in males and 1,843 new cases in females.[19]

The European-standardised incidence rate of bladder cancer in the UK is projected to decrease by 2035 from 20.44 per 100,000 in 2014 (equating to 10,057 observed cases) to 13.43 per 100,000 (equating to 10,386 projected cases).[20]

In England in 2018-2019, there were 73,789 finished consultant episodes (FCEs) for malignant neoplasm of the bladder as primary diagnosis (ICD-10 code C67) and 69,198 admissions resulting in 100,777 bed days and 41,236 day cases. Approximately 75% of these consultant episodes were for male patients.[21]

In 2017 in England and Wales, there were 5,014 deaths (3,441 male and 1,573 female) recorded with malignant neoplasm of bladder as the cause (ICD-10 code C67).[22] Between 2013 and 2017 in England, the 1-year and 5-year age-standardised net cancer survival rates for

stage were 95.3% and 79.4% respectively.[23] The European-standardised mortality rate of bladder cancer in the UK is projected to decrease by 2035 from 10.91 per 100,000 in 2014 to 9.39 per 100,000.[20]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Bladder cancer is treated by a multidisciplinary team that may include an urologist, a clinical oncologist, a pathologist, and a radiologist. The recommended treatment plan for NMIBC depends on the risk of the cancer returning or spreading beyond the lining of the bladder. This risk is calculated using a series of factors, including the number of tumours present in the bladder, whether the tumours are larger than 3 cm (1 inch) in diameter, whether the patient has had bladder cancer before, and the grade of the cancer cells.[24] People with high-risk NMIBC have transurethral resection of a bladder tumour (TURBT) operation to remove the cancer from the bladder lining (TURBT procedure may be performed during the first cystoscopy, when tissue samples are taken for testing). Patients should be offered a second TURBT, within 6 weeks of the initial investigation. A CT scan or an MRI scan may also be required.[24,25]

The treatment option for patients with high-risk NMIBC includes either a course of BCG treatment (using a variant of the BCG vaccine), or an operation to remove the bladder (cystectomy). If BCG treatment does not work, or the side effects are too strong, the patient will be referred back to a specialist urology team. The patient should be offered regular follow-ups.[24]

The patient can have the growths removed with cystoscopy again if stage Ta or T1 bladder cancer comes back (relapses) after treatment. Biopsies are usually taken to check that the cancer is still at an early stage. If it is, the patient usually has chemotherapy or BCG treatment into the bladder. Then they go back to having regular cystoscopies to check the bladder. The patient may need more intensive treatment if the cancer is grade 3, at a more advanced stage than before, or CIS that has come back after treatment into the bladder.[25]

CURRENT TREATMENT OPTIONS

Currently, there are no NICE recommended medicines for the treatment of adult patients with NMIBC, specifically high-grade (Ta or any T1) papillary disease who were unresponsive to prior treatment with BCG.

PLACE OF TECHNOLOGY

If licensed, oportuzumab monatox will provide a treatment option for adult patients with non-muscle invasive bladder cancer (NMIBC), specifically high grade (Ta or any T1) papillary disease who were unresponsive to prior treatment with BCG.[1]

CLINICAL TRIAL INFORMATION

Trial	NCT02449239; Open-Label, multicenter, phase 3 study to evaluate the efficacy and tolerability of intravesical vicinium in subjects with non muscle-invasive carcinoma in situ and/or high-grade papillary disease of the bladder treated with BCG

	Phase III- Ongoing **Location(s):** USA and Canada Primary completion date: December 2020
Trial design	Single group assignment, open label
Population	N= 134; non-invasive urothelial carcinoma (transitional cell carcinoma) of the bladder; CIS (with or without papillary disease); grade t1 papillary disease; high-grade Ta papillary disease
Intervention(s)	Vicinium • Induction - 30 mg of vicinium in 50 mL of saline administered twice weekly (BIW) for 6 weeks followed by once weekly for 6 weeks, for a total of 12 weeks • Maintenance - 30 mg of vicinium in 50 mL of saline administered once weekly every other week for up to 104 weeks
Comparator(s)	No comparator
Outcome(s)	Complete response rate (CR) (Time frame: Up to 24 months) See trial record for full list of other outcomes.
Results (efficacy)	The 3-month CR rate across the CIS cohorts with BCG-refractory disease within 12 months of the last BCG was 42%. In an additional cohort of 34 evaluable subjects with recurrent papillary-only NMIBC, the 3-month recurrence-free rate was 68%. By immunohistochemistry > 95% of screening NMIBC samples expressed EpCAM, the target of oportuzumab monatox. The intensity of EpCAM expression did not appear to correlate with response.[26]
Results (safety)	Oportuzumab monatox was well tolerated: 46% of subjects had adverse events related to study drug, the most common being dysuria (12%), UTI or pollakiuria (10%) and hematuria (7%). Three treatment-related SAEs included renal failure (grade 5) with cholestatic hepatitis (grade 4) in one subject and recovered acute kidney injury (grade 3) in another.[26]

ESTIMATED COST

The cost of oportuzumab monatox is not yet know.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE guideline. Bladder cancer: diagnosis and management (NG2). February 2015.
- NICE quality standard. Bladder cancer (QS106). December 2015.
- NICE interventional procedure guidance in development. Transurethral laser ablation for non-muscle invasive bladder cancer (GID-IPG10100). Expected date of issue to be confirmed.

- NICE interventional procedure guidance in development. Electrically-stimulated intravesical chemotherapy for non-muscle invasive bladder cancer (IPG638). January 2019.
- NICE interventional procedure guidance. Intravesical microwave hyperthermia and chemotherapy for non-muscle-invasive bladder cancer (IPG628). September 2018.

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: Radiotherapy (All Ages). B01/S/a.
- NHS England. Clinical Commissioning Policy: Robotic Assisted Surgery for Bladder Cancer. July 2016. 16033/P

OTHER GUIDANCE

- NHS England. Guidelines for the Management of Bladder Cancer. 2016.[27]
- European Society for Medical Oncology (ESMO). Bladder cancer: ESMO Practice Guidelines for diagnosis, treatment and follow-up. 2014.[28]

ADDITIONAL INFORMATION

Sesen Bio 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.

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