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HEALTH TECHNOLOGY BRIEFING
MAY 2019

^{131}I-omburtamab for neuroblastoma with central nervous system or leptomeningeal metastasis in paediatric patients

NIHRIO ID	15011	**NICE ID**	10173
Developer/Company	Y-mAbs Therapeutics Inc.	**UKPS ID**	NA

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

*COMMERCIAL IN CONFIDENCE

SUMMARY

^{131}I-omburtamab is a medicinal product that is being developed for the treatment of children with advanced neuroblastoma that has spread to membranes lining the brain and spinal cord ('leptomeningeal metastasis'). Neuroblastoma is a rare cancer that mostly affects babies and young children. It develops from specialised nerve cells (neuroblasts) in the foetus that do not become mature nerve cells. Instead, they continue to grow and divide becoming cancerous. When neuroblastoma spreads to the brain and spinal cord, the prognosis is poor and there are limited treatment options.

^{131}I-omburtamab is a monoclonal antibody that binds to the surface of neuroblastoma cells. It is linked to radioactive iodine (iodine-131) that produces low-level radiation with a short range, a type of treatment known as radioimmunotherapy. As such, ^{131}I-omburtamab delivers precision radiation to the cancer cells. This radiation from the iodine damages the DNA of the cancer cells which shrinks the tumour and therefore controls the disease. ^{131}I-omburtamab is given by injection into cerebrospinal fluid. If licensed, ^{131}I-omburtamab may offer a treatment option for children with neuroblastoma which has spread to the central nervous system or brain.

PROPOSED INDICATION

Paediatric patients with neuroblastoma that have relapsed in the central nervous system (CNS) or in the meninges (leptomeningeal).[1]

TECHNOLOGY

DESCRIPTION

Omburtamab (burtomab; omburtamab I-131; 131I-8H9; 131I-mu8H9) is Iodine (131I) murine immunoglobulin G1 (IgG1) monoclonal antibody. It consists of an antibody that has been designed to recognise and attach to a protein called CD276, which is present in large amounts on the surface of neuroblastoma cells but is not in normal tissue. This antibody is linked to radioactive iodine (iodine-131) that emits radiation with a short range. The medicine is given into the fluid that surrounds the brain and spinal cord, enabling it to reach disease that has spread into the nervous system. When the medicine attaches to cancer cells, radiation from the iodine damages their DNA, resulting in death of the cell. This helps shrink the tumour and control the disease.[2]

^{131}I-omburtamab is currently in development for neuroblastoma with relapse in the CNS or in the meninges (leptomeningeal) in paediatric patients. In the phase II/III clinical trial (NCT03275402), ^{131}I-omburtamab is administered by intracerebroventricular injection. One ^{131}I-omburtamab treatment cycle takes 5 weeks and includes a dosimetry dose, a treatment dose, an observation period and post-treatment evaluations. The treatment cycle of ^{131}I-omburtamab consists of two doses; 2mCi at week 1 and 50mCi at week 2. Following safety checks at week 6, eligible patients received a second treatment cycle.[1]

INNOVATION AND/OR ADVANTAGES

Currently there are limited approved drugs to treat neuroblastoma which has spread to the brain.[3] ^{131}I-omburtamab targets the cancer cells with precision, while largely sparing the surrounding brain tissues from damage which is especially important for paediatric patients.[3] More significantly however, is the improvement in overall survival. Data from the German Childhood Cancer Registry for patients with metastatic neuroblastoma to the CNS found the median overall survival was 4.7 months (1990-2010). This can be compared to patients treated with ^{131}I-omburtamab in the phase 1 trial whose overall survival was 47 months.[4]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

^{131}I-omburtamab does not currently have Marketing Authorisation in the EU/UK for any indication.

^{131}I-omburtamab has the following regulatory designations/awards:

- An orphan drug in the EU in February 2017 for the treatment of neuroblastoma.[2]
- An orphan drug in the USA in August 2016 for the treatment of neuroblastoma.[5]
- A breakthrough therapy by the US FDA in 2017 for the treatment of paediatric patients with relapsed or refractory neuroblastoma with central nervous system or leptomeningeal metastasis.[6]
- A rare paediatric disease designation in the US in July 2016 for the treatment of neuroblastoma.[a,4]

[a] Information provided by Y-mAbs Therapeutics Inc.

PATIENT GROUP

DISEASE BACKGROUND

Neuroblastoma is a rare type of cancer that mostly affects babies and young children. It develops from specialised nerve cells (neuroblasts) in the foetus that do not become mature nerve cells. Instead, they continue to grow and divide. Neuroblastoma most commonly occurs in one of the adrenal glands situated above the kidneys, or in the nerve tissue that runs alongside the spinal cord in the neck, chest, tummy or pelvis. It can spread to other organs such as the bone marrow, bone, lymph nodes, liver, skin and CNS.[7] In very few cases, the tendency to get this type of cancer can be passed down from a parent to a child (called the familial type). However, most cases of neuroblastoma (98%) are not inherited (called the sporadic type).[8]

The symptoms of neuroblastoma vary depending on where the cancer is and whether it has spread. The early symptoms can be vague and hard to spot, and can easily be mistaken for those of more common childhood conditions. Symptoms can include a swollen or painful tummy (sometimes in association with constipation and difficulty passing urine), breathlessness and difficulty swallowing, a lump in the neck, blueish lumps in the skin and bruising (particularly around the eyes), weakness in the legs and unsteady walk, fatigue, loss of energy, pale skin, loss of appetite and weight loss, bone pain, a limp and general irritability and rarely, jerky eye and muscle movements.[7]

Metastasis is said to occur when neuroblastoma has spread to a different part of the body from where it started. Metastasis are present in up to 50% of patients with neuroblastoma at the time of diagnosis.[9] Despite the high frequency of dissemination to the bones and bone marrow of the cranium in children both at presentation and recurrence, spread to the CNS has been rare, including either brain parenchyma or leptomeningeal involvement.[9] Leptomeningeal metastases (LM) occur when cancer spreads to the membranes lining the brain and spinal cord,[10] and occurs in approximately 5% of all patients with cancer.[11]

CLINICAL NEED AND BURDEN OF DISEASE

The majority of neuroblastomas are diagnosed in children younger than 5 years old, and nearly all patients are diagnosed by the time they are 10 years old. The median age at diagnosis is around 18 months.[12] Neuroblastoma and other peripheral nervous cell tumours account for 6% of childhood cancer registrations in the UK.[13] In 2015, according to data provided by the Office of National Statistics, 80 children aged 0 to 14 years received a diagnosis of neuroblastoma.[14] Neuroblastoma is slightly more common in boys than in girls, by a ratio of 6:5.[15] It is one of the most difficult childhood cancers to cure with UK and Ireland 5-year survival of 64.7% for cases diagnosed during 2005–2007.[16]

Metastatic disease is found in > 50% of children at the time of diagnosis and confers a poor prognosis. The frequency of haematogenous spread to bone, bone marrow, and liver at the time of diagnosis contrasts strikingly with the rarity of metastases to the CNS.[17] Neuroblastoma metastatic to the CNS and leptomeningealis is associated with significant mortality (median survival < 6 months, < 10% survival at 36 months).[11]

Relapsed or refractory neuroblastoma is extremely difficult to cure. The median time to relapse is around 1.5 years from diagnosis. Up to 20% of patients with high risk disease will have primary refractory disease, and nearly 60% of patients who complete therapy will relapse.[18-21] Overall survival after relapse depends on risk stratification, with International Neuroblastoma Staging System (INSS) stage 4 patients having an overall survival rate of 2%.[22]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Management of CNS/LM neuroblastoma should be handled by a team of specialists including a paediatric oncologist, cancer surgeon, and radiation oncologist.[21] The optimum therapy for relapsed CNS/LM neuroblastoma is not clearly defined, due in large part to the lack of randomized studies.[23]

There are no established curative treatment options for many patients with refractory or relapsed neuroblastoma. The goal of treatment in these patients historically have not been curative, but rather to prolong survival and minimise the toxicities of additional therapy.[24] However, the discovery of new tumour targets and the development of novel antibody- and cell-mediated immunotherapy agents have led to a large number of clinical trials for children with relapsed neuroblastoma, and additional clinical trials using molecular and genetic tumour profiling to target tumour-specific aberrations are ongoing.[24]

CURRENT TREATMENT OPTIONS

Currently there are limited approved drugs to treat neuroblastoma which has spread to the brain.[3] According to a Children's Cancer and Leukaemia Group report in 2015, the proposed treatment pathway for UK patients with neuroblastoma that have a CNS relapse was outlined as:[23]

- Neurosurgical resection of CNS disease;
- Craniospinal radiotherapy (21Gy in 1.5Gy fractions);
- Temozolomide ± irinoteca;
- Patients with CR/VGPR (complete response/very good partial response) who have not previously received myeloablative chemotherapy could then proceed to MAT (Myeloablative Therapy - busulfan/melphalan), followed by systemic immunotherapy with anti-GD2 for patients who have not already received this, plus oral cis-retinoic acid.

PLACE OF TECHNOLOGY

If licensed, ^{131}I-omburtamab will offer a treatment option for paediatric patients with neuroblastoma with relapse in the CNS or in the meninges (leptomeningeal), who currently have limited effective therapies available.

CLINICAL TRIAL INFORMATION

Trial	NCT03275402; EudraCT 2017-001828-22; **children up to 18 years; ^{131}I-omburtamab; phase II/III**
Sponsor	Y-mAbs Therapeutics, Inc.
Status	Ongoing
Source of Information	Trial registry[1,25]
Location	EU (not UK) and USA
Design	Single group assignment, open label
Participants	n=32 (planned); aged up to 18 yrs; histologically confirmed diagnosis of neuroblastoma with relapse in the CNS or in the meninges (leptomeningeal); patients must be between the ages of birth and 18 yrs at the time of screening; patients must have a life expectancy of at least 3 months.

Schedule	^{131}I-omburtamab is administered by intracerebroventricular infusion. One treatment cycle of ^{131}I-omburtamab consists of 2 doses; 2mCi at week 1 and 50mCi at week 2). First cycle is initiated right after confirmation of eligibility at week 1. At week 6 the participant will be evaluated for safety and if eligible, receive a second cycle of ^{131}I-omburtamab.
Follow-up	Participants completing at least one treatment period will first enter a follow-up period through week 26 and thereafter the long-term follow-up where patients will be evaluated for up to 3 yrs post-omburtamab treatment after the trial is ended
Primary Outcomes	Overall survival rate [Time frame: 3 yrs]: Overall survival rate at 3 yrs after the first treatment dose of ^{131}I-omburtamab.
Secondary Outcomes	▪ Overall survival [Time frame: 3 yrs]: Overall survival at 3 yrs after the first treatment dose of ^{131}I-omburtamab. ▪ Objective response rate (ORR) [Time frame: 3 yrs]: ORR is defined and assessed as a combination of partial response and complete response as defined by the RANO criteria and CSF cytology. ▪ Objective response rate (ORR) [Time frame: 3 yrs]: ORR according to CSF cytology. ORR is defined and assessed as a combination of partial response and complete response. ▪ CNS progression free survival (PFS) [Time frame: 6 month]: CNS PFS will be assessed at 6 months after the first treatment dose of ^{131}I-omburtamab by comparing baseline radiological scans by MRI to radiological scans conducted 26 weeks after 131I-omburtamab treatment. ▪ Dosimetry of ^{131}I-omburtamab [Time frame: 2 weeks]: Whole-body, organ, blood, and CSF radiation dosimetry. ▪ Assessment of peak plasma concentration (Cmax) of ^{131}I-omburtamab [Time frame: Baseline, 30 minutes, 1 hr, 4 hrs, 1, 2, 3 and 7 days]: Cmax will be calculated and summarized with descriptive statistics. ▪ Assessment of residence time of ^{131}I-omburtamab [Time Frame: Baseline, 30 minutes, 1 hour, 4 hour, 1, 2, 3 and 7 days.]: Residence time will be calculated and summarized with descriptive statistics. ▪ Assessment of elimination half-life of ^{131}I-omburtamab [Time frame: Baseline, 30 minutes, 1 hr, 4 hrs, 1, 2, 3 and 7 days.]: Elimination half-life will be calculated and summarized with descriptive statistics. ▪ Safety of ^{131}I-omburtamab [Time frame: 3 years]: The frequency, type, and duration of treatment-emergent severe adverse events and serious adverse events, including clinically significant laboratory abnormalities. All adverse events will be graded according to CTCAE, version 4.0. ▪ Performance assessment [Time frame: 3 yrs]: Performance assessment to monitor gross changes in neurological function is performed at week 26 and subsequently every 6 months during trial period using Lansky (< 16 yrs) and Karnofsky (≥ 16 yrs).
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Estimated primary completion date December 2019. Estimated study completion date December 2022.

ESTIMATED COST

The cost of omburtamab is not yet known.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal guidance in development. Neuroblastoma (high-risk) - dinutuximab (maintenance, after therapy) (ID799). Expected date of issue to be confirmed.
- NICE technology guidance. Dinutuximab beta for treating neuroblastoma (TA538). August 2018.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- 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.
- NHS England. 2013/14 NHS Standard Contract for Paediatric Neurosurgery Services. E09/S/a
- NHS England. Clinical Commissioning Policy: Haematopoietic Stem Cell Transplantation. NHSCB/B04/P/a. April 2013.

OTHER GUIDANCE

ADDITIONAL INFORMATION

Y-mAbs Therapeutics 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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