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HEALTH TECHNOLOGY BRIEFING FEBRUARY 2020

Naxitamab in combination with granulocyte-macrophage colony stimulation factor for relapsed/refractory high-risk neuroblastoma

NIHRIO ID	20601	**NICE ID**	10208
Developer/Company	Y-mAbs Therapeutics	**UKPS ID**	Not available

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

SUMMARY

Naxitamab in combination with granulocyte macrophage colony stimulation (GM-CSF) is in clinical development for the treatment of patients with relapsed/refractory high risk neuroblastoma. 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. Relapsed or refractory high risk neuroblastoma has significant effect on children, young people and their families and carers. Existing treatments and procedures for neuroblastoma are painful and debilitating, with severe and long-lasting side effects.

Naxitamab is a type of protein that has been designed to recognise and attach to a specific structure called GD2 that is present in high amounts on the surface of neuroblastoma cells, but not normal cells. Naxitamab attaches to the neuroblastoma cells and activates the immune system, which then kills the cancer cells. If licensed, naxitamab in combination with GM-CSF may provide a treatment option for patients with relapsed/refractory high-risk neuroblastoma.

PROPOSED INDICATION

Second-line treatment of patients with relapsed/refractory high-risk neuroblastoma.[1,2, a]

TECHNOLOGY

DESCRIPTION

Naxitamab (hu3F8) is a monoclonal antibody that has been designed to recognise and attach to a specific structure called GD2 that is present in high amounts on the surface of neuroblastoma cells, but not normal cells. When the medicine attaches to the neuroblastoma cells, it is expected to make them a target for the body's immune system (the body's natural defences), which then kills the cancer cells.[3]

Naxitamab in combination with GM-CSF is currently in clinical development for the treatment of patients with relapsed/refractory high-risk neuroblastoma. In the phase II clinical trial (NCT03363373) patients were administered at 3mg/kg/day on days 1,3 and 5 totalling 9mg/kg per cycle.[2]

INNOVATION AND/OR ADVANTAGES

Naxitamab has the highest binding affinity to the GD2 tumour target than any other antibody in clinical development.[4,5] In particular, its modest toxicity allows for doses 2.5 times greater than existing GD-2 targeting antibody therapies. Naxitamab also has a significantly shorter infusion time (approximately 30 minutes compared to 10-20 hours for other GD2 targeting antibody-based therapies) and the ability to be administered in an outpatient setting (compared to hospitalisation stays of four days or longer for other GD2 targeting antibody-based therapies).[6]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

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

- Naxitamab was granted orphan designation in the EU in November 2018 for the treatment of neuroblastoma.[3]
- Naxitamab, in combination with GM-CSF, received a breakthrough therapy designation by the FDA for high-risk neuroblastoma in August 2018.[7]

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 and skin.[8] High-risk neuroblastom is harder to cure and is more likely to become resistant to standard therapies or come (recur) after initially successful treatment.[9]

[a] Information provided by Y-mAbs Therapeutics

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).[9] In some cases, the neuroblastoma can return after treatment. This is known as relapsed neuroblastoma. If the tumour does not resolve with treatment, it is known as refractory neuroblastoma.[10]

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, bluish 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.[8]

CLINICAL NEED AND BURDEN OF DISEASE

The majority of neuroblastomas are diagnosed in children younger than 5 years old. Around 100 children are diagnosed with neuroblastoma each year in the UK.[11] The median age at diagnosis is around 15 months.[12] Neuroblastoma and other peripheral nervous cell tumours account 6% of childhood cancer registrations in the UK.[13] Neuroblastoma rarely occurs in adults, and less than 10% of the cases in patients older than 10 years.[14]

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 will have primary refractory disease, and nearly 60% of patients who complete therapy will relapse.[15-18]

In 2015, 80 children aged 0-14 years were diagnosed with neuroblastoma.[19] Neuroblastoma is more common in boys than in girls, by a ratio of 6:5.[20] It is one of the most difficult childhood cancers to cure.[21] In the UK, 5-year survival was 71% for cases diagnosed during 2011-2015.[13]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

There are no established treatment options for many patients with relapsed or refractory neuroblastoma but treatment is usually chemotherapy, radiotherapy, stem cell transplant, surgery and isotretinoin.[22] The goal of treatment in these patients historically have not been curative, but rather to prolong survival and minimise the toxicities of additional therapy.[23] Patients in the high-risk category are initially treated with multi-agent chemotherapy, surgery and radiotherapy, followed by consolidation therapy with high-dose chemotherapy and autologous stem cell transplant. Radiotherapy may also be given after cell transplant.[24]

CURRENT TREATMENT OPTIONS

Currently NICE recommends the following treatment for patients with neuroblastoma:[22]

- Dinutuximab beta is recommended as an option for treating high-risk neuroblastoma in patients aged 12 months and over whose disease has at least partially responded to induction chemotherapy, followed by myeloablative therapy and stem cell transplant if:
    - They have not already had anti-GD2 immunotherapy

PLACE OF TECHNOLOGY

If licensed, naxitamab in combination with GM-CSF will offer a treatment option for patients with relapsed/refractory high-risk neuroblastoma.

CLINICAL TRIAL INFORMATION

Trial	NCT03363373, EudraCT 2017-001829-40; A Pivotal Phase 2 Trial of Antibody Naxitamab (hu3F8) and Granulocyte-Macrophage Colony Stimulating Factor (GM-CSF) in High-Risk Neuroblastoma Patients With Primary Refractory Disease or Incomplete Response to Salvage Treatment in Bone and/or Bone Marrow **Phase II - ongoing** **Location(s): EU (incl UK), USA, Canada and Hong Kong**
Trial design	Single group assignment, open label
Population	N=95 (planned) to be included for having 85 evaluable patients; aged ≥ 1 year; high-risk neuroblastoma patients with either primary refractory disease or incomplete response to salvage therapy in bone and/or bone marrow[b]
Intervention(s)	Naxitamab + GM-CSF • Naxitamab is administered at 3 mg/kg/day on days 1, 3, and 5 totalling 9 mg/kg per cycle
Comparator(s)	No comparator
Outcome(s)	• Response rate during naxitamab treatment • Progression free survival[b]
Results (efficacy)	-
Results (safety)	-

Trial	NCT01757626; Phase I/II Study of Combination Therapy of Antibody Hu3F8 With Granulocyte- Macrophage Colony Stimulating Factor (GM-CSF) in Patients With Relapsed/Refractory High-Risk Neuroblastoma. **Phase I/II - ongoing** **Location: USA**
Trial design	Non-randomised, single group assignment, open-label
Population	Interim Analysis 117 as safety population; aged ≥ 1 year
Intervention(s)	Naxitamab + GM-CSF
Comparator(s)	No comparator

[b] Information provided by Y-mAbs Therapeutics

Outcome(s)	• Maximum tolerated dosage [Time frame: 1 year] • Assess the toxicity [Time frame: 1 year] • ORR (centralised independently reviewed according to latest INRC) for all patients with evaluable disease at baseline[c]
Results (efficacy)	-
Results (safety)	-

ESTIMATED COST

The cost of naxitamab is not yet known.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal 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). B17/S/a.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Radiotherapy (All Ages). B01/S/a.
- NHS England. Clinical Commissioning Policy: Haematopoietic Stem Cell Transplantation. NHSCB/ B04/P/a. April 2013.

OTHER GUIDANCE

- NICE Clinical knowledge summary. Childhood cancers-recognition and referral. November 2016.[25]
- Children's cancer and leukaemia group (CCLG). Options for the treatment of patients with relapsed/progressive high-risk neuroblastoma. March 2015.[26]

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 upto-date, accurate and comprehensive information on new medicines.

[c] Information provided by Y-mAbs Therapeutics

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