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HEALTH TECHNOLOGY BRIEFING
FEBRUARY 2021

Isatuximab in addition to bortezomib, lenalidomide and dexamethasone for newly diagnosed transplant-ineligible multiple myeloma – first line

NIHRIO ID	23795	**NICE ID**	10244
Developer/Company	Sanofi	**UKPS ID**	650337

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

SUMMARY

Isatuximab in addition to bortezomib, lenalidomide and dexamethasone is currently in clinical development as a first-line therapy option for patients with newly diagnosed multiple myeloma (MM) who are not eligible for autologous stem cell transplant (ASCT). MM may or may not be symptomatic in the early stages, but eventually leads to a range of problems. It is often diagnosed after a routine blood or urine test. The symptoms of myeloma may include: bone pain, bone fractures and spinal cord compression, anaemia, repeated infections, raised calcium levels in the blood, and kidney function impairment. The current first-line treatment option is high dose combination chemotherapy followed ASCT for which some patients may be ineligible.

Isatuximab is an anti-CD38 monoclonal antibody with a multi-modal action for killing tumor cells via direct tumor targeting and immune cell engagement. On review and approval, isatuximab in addition to standard combination chemotherapy treatment with bortezomib, lenalidomide and dexamethasone will offer an additional first-line treatment option for patients with newly diagnosed MM who are not eligible for ASCT.

PROPOSED INDICATION

Adult patients with newly diagnosed multiple myeloma who are not eligible for autologous stem cell transplant.[a]

TECHNOLOGY

DESCRIPTION

Isatuximab (SAR650984) is an anti-CD38 monoclonal antibody with multi-modal action for killing tumor cells via direct tumor targeting and immune cell engagement.[1] CD38 is a type 2 transmembrane protein expressed on both hematopoietic and non-hematopoietic tissues, with the highest density being on plasma cells and germinal center B cells. CD38 functions as a receptor involved in the transmission of activation and proliferation signals, as well as an ectoenzyme that has a role in calcium signaling and cell survival.[2] CD38 receptor-mediated signaling produces a variety of downstream effects, and has variable signaling impact depending on several factors. It has a role in T-cell activation mediated by the downstream activation of nuclear factor kB.[3]

Isatuximab is currently being evaluated in multiple ongoing phase III clinical trials in combination with current standard treatments for patients with both relapsed or refractory and treatment-naïve multiple myeloma (MM).[4] In the first line setting, isatuximab is being evaluated in combination with the standard of care triplet regimen of bortezomib, lenalidomide and dexamethasone (VRd) in two ongoing trials.[4,5] The phase III IMROZ trial (NCT03319667) randomised 475 patients with newly diagnosed MM to receive either induction treatment with 4×6 week cycles with IV isatuximab+subcutaneous bortezomib+oral lenalidomide+IV or oral dexamethasone followed by continuous treatment with 4-week cycles with IV isatuximab+oral lenalidomide+IV or oral dexamethasone, or a control regimen of induction with VRd followed by continuous treatment with lenalidomide+oral dexamethasone (Rd).[4]

INNOVATION AND/OR ADVANTAGES

Despite therapeutic advances in the treatment of multiple myeloma, the disease remains incurable with patients becoming refractory to both lenalidomide and proteosome inhibitors and having a poor prognosis with an estimated median overall survival of only 15 months.[6]

Isatuximab is a novel humanised monoclonal antibody that binds selectively to CD38, which is widely expressed on plasma cells, and kills myeloma cells via multimodal mechanisms including antibody-dependent cellular cytoxicity, antibody-dependent cellular phagocytosis, complement-dependent cellular cytotoxicity, and immune cell depletion or inhibition of immunosuppressive cells. Additionally, isatuximab, similar to other CD38 antibodies, modulates the NADase enzymatic activity of CD38. However, isatuximab differentiates itself from other CD38 Mabs in its ability to induce direct apoptosis without cross-linking, and in its binding epitope.[6]

The combination of the proteasome inhibitor bortezomib with lenalidomide and dexamethasone has shown significant efficacy in patients with newly diagnosed myeloma.[7] The addition of isatuximab may potentially provide a deeper response thus helping prolong progression free survival in patients with newly diagnosed myeloma.[5]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

[a] Information provided by Sanofi on UK PharmaScan

Isatuximab in addition to bortezomib, lenalidomide and dexamethasone does not currently have Marketing Authorisation in the EU/UK for any indication.

Isatuximab in combination with lenalidomide and dexamethasone is in phase 3 clinical trials for high-risk smoldering multiple myeloma and, isatuximab in combination with pomalidomide and dexamethasone, for relapsed and/or refractory multiple myeloma.[8] Isatuximab is also in phase 2 clinical development for monoclonal gammopathy (MGUS), and amyloidosis.[9]

PATIENT GROUP

DISEASE BACKGROUND

Multiple myeloma , also known as myeloma, is a type of bone marrow cancer. Bone marrow is the spongy tissue at the centre of some bones that produces the body's blood cells.[10] It's called MM as the cancer often affects several areas of the body, such as the spine, skull, pelvis and ribs.[10]

The exact cause of myeloma is not yet fully understood. It is known that myeloma develops when genetic 'errors' occur within the DNA of a plasma cell, but it is not currently known why these errors arise. Although it is not currently known what causes myeloma, researchers have identified some risk factors. These risk factors are defined as anything that increases a person's chances of getting myeloma. The risk of myeloma increases as people get older and myeloma is slightly more common in men than women, and in black populations than in white or Asian populations. It is generally now accepted that all myeloma patients have had Monoclonal Gammopathy of Undetermined Significance (MGUS) first, whether it was identified or not.[11]

There are also thought to be multiple environmental factors which may increase the risk of developing myeloma. These include exposure to certain types of industrial and agricultural chemicals, exposure to high doses of radiation, viruses and a weakened immune system. However, in the majority of cases, the causes of myeloma are likely to be unknown and unique to each individual patient.[11]

MM may not cause any symptoms in the early stages but eventually leads to a wide range of problems. It is often diagnosed after a routine blood test or, sometimes, a urine test. Patients with myeloma report significant impairment in health-related quality of life[12], with such symptoms as: bone pain, bone fractures and spinal cord compression, anaemia, repeated infections, raised calcium levels in the blood, unusual bleeding, thickened blood and kidney problems.[13]

CLINICAL NEED AND BURDEN OF DISEASE

Myeloma is the 19th most common cancer in the UK, accounting for 2% of all new cancer cases (2016). In females in the UK, it is the 18th most common cancer (1% of all new female cancer cases) and in males in the UK, myeloma is the 16th most common cancer (2% of all new male cancer cases).[14] In England, in 2017 there were 5,034 newly diagnosed cases of MM and malignant plasma cell neoplasms (ICD-10: C90). Most cases are reported for people aged 70-74.[15] In the UK, by 2035 the European age-standardised mortality rate for myeloma is projected to be 4.92 per 100,000 persons (equivalent to 3,850 deaths).[16]

In England in 2018-19 there were 142,827 finished consultant episodes and 137,870 hospital admissions with a primary diagnosis of MM (ICD-10 code C90.0), resulting in 89,190 bed days and 126,115 day cases.[17] During the years 2013-2017 in England, 82.7% patients diagnosed with MM survived their disease for 1-year (age-standardised), and 52.3% survived for 5 years.[18]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Not everyone diagnosed with myeloma needs immediate treatment – for example, the condition may not be causing any problems. This is sometimes referred to as asymptomatic or smouldering myeloma. The initial treatment for multiple myeloma may be either: non-intensive – for older or less fit patients (this is more common); intensive – for younger or fitter patients. Both non-intensive and intensive treatments involve taking a combination of anti-myeloma medicines. But intensive treatment involves higher doses and is followed by a stem cell transplant.[19]

CURRENT TREATMENT OPTIONS

For the first-line treatment of transplant ineligible MM patients NICE recommends:[20]

- Thalidomide in combination with an alkylating agent and a corticosteroid for patients whom a high-dose chemotherapy with stem cell transplantation is considered inappropriate
- Bortezomib in combination with an alkylating agent and a corticosteroid for patients whom a high dose chemotherapy with stem cell transplantation is considered inappropriate and the person is unable to tolerate or has contraindications to thalidomide.
- Lenalidomide plus dexamethasone is recommended as an option for previously untreated MM in adults who are not eligible for a stem cell transplant, only if:
    - thalidomide is contraindicated (including for pre-existing conditions that it may aggravate) or
    - the person cannot tolerate thalidomide, and
    - the company provides lenalidomide according to the commercial arrangement.

PLACE OF TECHNOLOGY

If licensed, isatuximab in combination with bortezomib, lenalidomide and dexamethasone will offer an additional first-line treatment option for patients with newly diagnosed multiple myeloma who are not eligible for SCT.

CLINICAL TRIAL INFORMATION

Trial	**IMROZ; NCT03319667, 2017-002238-21;** A Phase 3 Randomized, Open-label, Multicenter Study Assessing the Clinical Benefit of Isatuximab (SAR650984) in Combination With Bortezomib (Velcade®), Lenalidomide (Revlimid®) and Dexamethasone Versus Bortezomib, Lenalidomide and Dexamethasone in Patients With Newly Diagnosed Multiple Myeloma (NDMM) Not Eligible for Transplant **Phase III** – active, not recruiting **Locations:** EU (not incl. UK), USA and other countries **Primary completion date**: December 2022
Trial design	Randomised, open-label, parallel assignment, outcomes assessor blinded
Population	N=475 (actual enrolment); patients with newly diagnosed NDMM not eligible for transplant; aged 18 to 80 years.
Intervention(s)	• Isatuximab: Intravenous • Bortezomib: Intravenous/subcutaneous • Lenalidomide: Oral

	• Dexamethasone: Oral/intravenous • Acetaminophen (paracetamol) or equivalent: oral • Ranitidine or equivalent: Intravenuous • Diphenhydramine or equivalent: Intravenuous
Comparator(s)	• Bortezomib: Intravenous/subcutaneous • Lenalidomide: Oral • Dexamethasone: Oral/intravenous
Outcome(s)	Progression free survival (PFS) [Time frame: up to approximately 60 months after the first patient in (FPI) or scheduled assessment]
Results (efficacy)	-
Results (safety)	-

ESTIMATED COST

The NHS indicative price for isatuximab is:[21]

- Sarclisa 100mg/5ml concentrate for solution for infusion vials £506.94 (Hospital only)
- Sarclisa 500mg/25ml concentrate for solution for infusion vials £2534.69 (Hospital only).

The NHS indicative price for bortezomib is:[22]

- Bortezomib 3.5mg/1.4ml solution for injection vials £495.55 and powder for solution for injection: £217.82 (1mg), £544.56 (2.5mg) and £762.38 (3.5mg).

The NHS indicative price for lenalidomide is:[23]

- £3,426.00 for 21x2.5 mg capsules, £3,570.00 for 21x5 mg capsules, £3,675.00 for 21x7.5 mg capsules, £3,780.00 for 21x10 mg capsules, £3,969.00 for 21x15 mg capsules, £4,168.50 for 21x20 mg capsules and £4,368.00 for 21x25 mg capsules.

The NHS indicatice price for dexamethasone is:[24]

- Neofordex tablets a pack of 10 x 40 £200.00.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Daratumumab in combination for untreated multiple myeloma when stem cell transplant is unsuitable ID1492 (TA10441). Expected date of issue to be confirmed.
- NICE technology appraisal. Lenalidomide plus dexamethasone for previously untreated multiple myeloma [TA587]. June 2019
- NICE technology appraisal. Bortezomib and thalidomide for the first-line treatment of multiple myeloma (TA228). July 2011.
- NICE guideline. Myeloma: diagnosis and management (NG35). October 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.

OTHER GUIDANCE

- The Society for Immunotherapy of Cancer consensus statement on immunotherapy for the treatment of multiple myeloma. July 2020.[4]
- NCCN Guidelines. Insights: Multiple Myeloma, Version 3. 2018.[25]
  European Society of Medical Oncology (ESMO). Clinical Practice Guidelines for diagnosis, treatment and follow-up: Multiple myeloma. 2017.[26]

ADDITIONAL INFORMATION

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NB: This briefing presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.