Health Technology Briefing
October 2023

Isatuximab induction therapy with bortezomib, lenalidomide and dexamethasone for previously untreated multiple myeloma

Company/Developer	Sanofi

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 34858	NICE ID: Not Available	UKPS ID: 654401

Licensing and Market Availability Plans

Currently in phase III clinical trials.

Summary

Isatuximab in addition to bortezomib, lenalidomide and dexamethasone is currently in clinical development as an induction therapy option for patients with newly diagnosed multiple myeloma (MM) who are eligible for autologous stem cell transplant (ASCT). MM is a type of bone marrow cancer that often affects several areas of the body. MM has premalignant or asymptomatic stages, but if people progress to active myeloma disease, this leads to a range of problems. It is often diagnosed after a routine blood or urine test, or admission as an emergency in hospital. 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 treatment of MM remains complex and challenging given the high incidence of disease relapse and resistance to treatments, creating a strong demand for novel treatment options.

Isatuximab is a monoclonal antibody that targets CD38, a protein expressed predominantly on MM cells. Isatuximab utilises a dual approach of directly attacking the tumour cells and activating the immune system against the tumour cells as well.Isatuximab is given intravenously. If licensed, 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 eligible for ASCT.

Proposed Indication

Induction therapy for adult patients with untreated multiple myeloma (MM) who are eligible for autologous stem cell transplant.[1,2]

Technology

Description

Isatuximab (SAR650984) is a monoclonal antibody with multi-modal action for killing tumour cells via direct tumour targeting and immune cell engagement.[3] It specifically targets the transmembrane receptor and ectoenzyme CD38, a protein highly expressed on haematological malignant cells, including those in multiple myeloma (MM). Upon binding to CD38-expressing MM cells, isatuximab is thought to induce tumour cell killing via fragment crystallizable (Fc)-dependent mechanisms, including antibody-dependent cellular cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP), and complement-dependent cytotoxicity (CDC), as well as via direct Fc-independent mechanisms.[4] CD38 receptor-mediated signalling produces a variety of downstream effects, and has variable signalling impact depending on several factors. It has a role in T-cell activation mediated by the downstream activation of nuclear factor kB.[5] Furthermore, CD38 has dual functions as an ectoenzyme and as a surface receptor that promotes migratory phenotypes and signalling cascades responsible for the activation and proliferation of various immune cells.[6]

Isatuximab is currently in clinical development in combination with the international standard of care triplet regimen of bortezomib, lenalidomide and dexamethasone (VRd) in patients with untreated newly diagnosed MM who are eligible for stem cell transplant. In the phase III trial (NCT03617731), patients with newly diagnosed and transplant eligible MM who were in experimental arm IB were treated with 3 cycles Lenalidomide Bortezomib/Dexamethasone (VRd) + Isatuximab (lenalidomide 25 mg/d p.o. d1 - 14 and d22 - 35; bortezomib 1.3 mg/m2 s.c. d1, 4, 8, 11, 22, 25, 29, 32;dexamethasone p.o. 20 mg/d d1-2, 4-5, 8-9, 11-12, 15, 22-23, 25-26, 29-30, 32-33). Isatuximab (10 mg/kg i.v. C1: d 1, 8, 15, 22, 29; C2-3: d 1, 15, 29). Treatment repeats every 42 days (d43 = cycle 2 d1). Standard intensification: For all patients, stem cells are mobilized by GMMG Standard protocols (CAD: cyclophosphamide, doxorubicin, dexamethasone) and G-CSF (Granulocyte-Colony Stimulating Factor). At least $7.5x10^6$ CD34+ cells/kg body weight are harvested. High dose treatment (melphalan 200mg/m², HDT) followed by autologous stem cell transplantation (ASCT) is started 4 - 6 weeks after CAD. For patients not in CR after HDT1, a second HDT is performed within 3 months.[1]

Key Innovation

Despite therapeutic advances in the treatment of MM, 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.[7] Isatuximab is a novel humanised monoclonal antibody that binds to a specific extracellular epitope of CD38 receptor, which is widely expressed on plasma cells, and kills myeloma cells via multimodal mechanisms including ADCC, ADCP, CDC, and immune cell depletion or inhibition of immunosuppressive cells.[8,9] The combination of the proteasome inhibitor bortezomib with lenalidomide and dexamethasone has shown significant efficacy compared to lenalidomide and dexamethasone in patients with newly diagnosed myeloma.[10] The addition of isatuximab may potentially improve efficacy thus helping prolong progression free survival in patients with newly diagnosed myeloma.[11] If licensed, isatuximab in combination with bortezomib, lenalidomide and

dexamethasone will offer an additional treatment option for patients with newly diagnosed MM who are eligible for ASCT.

Regulatory & Development Status

Isatuximab currently has Marketing Authorisation in the EU/UK for:[12]

- in combination with pomalidomide and dexamethasone, for the treatment of adult patients with relapsed and refractory multiple myeloma who have received at least two prior therapies including lenalidomide and a proteasome inhibitor and have demonstrated disease progression on the last therapy.
- in combination with carfilzomib and dexamethasone, for the treatment of adult patients with multiple myeloma who have received at least one prior therapy.

Bortezomib currently has Marketing Authorisation in the EU/UK for:[13]

- as monotherapy or in combination with pegylated liposomal doxorubicin or dexamethasone is indicated for the treatment of adult patients with progressive multiple myeloma who have received at least 1 prior therapy and who have already undergone or are unsuitable for haematopoietic stem cell transplantation.
- in combination with melphalan and prednisone is indicated for the treatment of adult patients with previously untreated multiple myeloma who are not eligible for high-dose chemotherapy with haematopoietic stem cell transplantation
- in combination with dexamethasone, or with dexamethasone and thalidomide, is indicated for the induction treatment of adult patients with previously untreated multiple myeloma who are eligible for high-dose chemotherapy with haematopoietic stem cell transplantation.
- in combination with rituximab, cyclophosphamide, doxorubicin and prednisone is indicated for the treatment of adult patients with previously untreated mantle cell lymphoma who are unsuitable for haematopoietic stem cell transplantation.

Lenalidomide currently has Marketing Authorisation in the EU/UK for:[14]

- as monotherapy is indicated for the maintenance treatment of adult patients with newly diagnosed multiple myeloma who have undergone autologous stem cell transplantation.
- as combination therapy with dexamethasone, or bortezomib and dexamethasone, or melphalan and prednisone is indicated for the treatment of adult patients with previously untreated multiple myeloma who are not eligible for transplant.
- in combination with dexamethasone is indicated for the treatment of multiple myeloma in adult patients who have received at least one prior therapy.
- as monotherapy is indicated for the treatment of adult patients with transfusion-dependent anaemia due to low- or intermediate-1-risk myelodysplastic syndromes associated with an isolated deletion 5q cytogenetic abnormality when other therapeutic options are insufficient or inadequate.
- as monotherapy is indicated for the treatment of adult patients with relapsed or refractory mantle cell lymphoma
- in combination with rituximab (anti-CD20 antibody) is indicated for the treatment of adult patients with previously treated follicular lymphoma (Grade 1 – 3a).

Dexamethasone currently has Marketing Authorisation in the EU/UK for:[15]

- It is indicated in a wide variety of disorders amenable to glucocorticoid therapy, as well as an adjunct in the control of cerebral oedema.
- Is indicated in the treatment of coronavirus disease 2019 (COVID-19) in adult and adolescent patients (aged 12 years and older with body weight at least 40 kg) who require supplemental oxygen therapy.

Patient Group

Disease Area and Clinical Need

Multiple myeloma (MM), 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. It is called MM as the cancer often affects several areas of the body, such as the spine, skull, pelvis and ribs.[16] Early in MM, there might be no symptoms. Eventually MM can cause symptoms, including bone pain (especially in the spine, ribs or hips), nausea, constipation, loss of appetite, and mental fogginess or confusion.[17] 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. However, researchers have identified some risk factors that may increase 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 the earliest premalignant stage of Monoclonal Gammopathy of Undetermined Significance (MGUS) first, whether it was identified or not. 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.[18]

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).[19] In the UK, there are around 6,000 new cases, and around 3,100 myeloma deaths every year (2016-2018). Furthermore, it is predicted that almost 1 in 3 (29.1%) people diagnosed with myeloma in England survive their disease for ten years or more (2013-2017).[20] In England in 2022-23 there were 155,822 finished consultant episodes and 150,740 hospital admissions with a primary diagnosis of MM (ICD-10 code C900), resulting in 99,552 bed days and 142,557 day cases.[21]

Recommended Treatment Options

NICE guidelines currently recommend the following treatments for people with newly diagnosed multiple myeloma and are transplant eligible:[22-24]

- Daratumumab in combination with bortezomib, thalidomide and dexamethasone as induction and consolidation treatment for untreated multiple myeloma in adults, when an autologous stem cell transplant is suitable.
- Bortezomib in combination with dexamethasone, or with dexamethasone and thalidomide for induction therapy before high-dose chemotherapy and ASCT

Clinical Trial Information

Trial	NCT03617731; A Randomized Phase III Trial Assessing the Benefit of the Addition of Isatuximab to Lenalidomide / Bortezomib / Dexamethasone (RVd) Induction and Lenalidomide Maintenance in Patients With Newly Diagnosed Multiple Myeloma **Phase III:** Active, not recruiting **Location:** Germany **Primary completion date:** May 2025

Trial Design	Randomized, parallel assignment, open label
Population	N=662; adults ages 18 to 70 years old; confirmed diagnosis of untreated multiple myeloma requiring systemic therapy; patient is eligible for high dose therapy and autologous stem cell transplantation
Intervention(s)	Experimental: IB Patients in arm IB are treated with 3 cycles RVd (lenalidomide 25 mg/d p.o. d1 - 14 and d22 - 35; bortezomib 1.3 mg/m2 s.c. d1, 4, 8, 11, 22, 25, 29, 32; dexamethasone p.o. 20 mg/d d1-2, 4-5, 8-9, 11-12, 15, 22-23, 25-26, 29-30, 32-33) + Isatuximab (10 mg/kg i.v. C1: d 1, 8, 15, 22, 29; C2-3: d 1, 15, 29).Treatment repeats every 42 days (d43 = cycle 2 d1). Standard intensification: For all patients, stem cells are mobilized by GMMG (German-Speaking Myeloma Multicenter Group) Standard protocols (CAD: cyclophosphamide, doxorubicin, dexamethasone) and G-CSF. At least 7.5x106 CD34+ cells/kg body weight are harvested. High dose treatment (melphalan 200mg/m², HDT) followed by autologous stem cell transplantation (ASCT) is started 4 - 6 weeks after CAD. For patients not in CR after HDT1, a second HDT is performed within 3 months. Experimental: IIB maintenance treatment with Lenalidomide 10mg/d (increased to 15mg/d after 3 months) + Isatuximab (10 mg/kg; C1: d1, 8, 15, 22; C2-C3: d1 + 15; C4-39:d1, repeated every 28d). Within the trial, maintenance treatment is planned for up to 36 months or until progression if progression occurs first.
Comparator(s)	Active Comparator: IA 3 cycles RVd (lenalidomide 25 mg/d p.o. d1 - 14 and d22 - 35; bortezomib 1.3 mg/m2 s.c. d1, 4, 8, 11, 22, 25, 29, 32; dexamethasone p.o. 20 mg/d d1-2, 4-5, 8-9, 11-12, 15, 22-23, 25-26, 29-30, 32-33). Treatment repeats every 42 days (d43 = cycle 2 d1). Standard intensification: For all patients, stem cells are mobilized by GMMG Standard protocols (CAD: cyclophosphamide, doxorubicin, dexamethasone) and G-CSF. At least 7.5x106 CD34+ cells/kg body weight are harvested. High dose treatment (melphalan 200mg/m², HDT) followed by autologous stem cell transplantation (ASCT) is started 4 - 6 weeks after CAD. For patients not in CR after HDT1, a second HDT is performed within 3 months. Active Comparator: IIA maintenance treatment with Lenalidomide 10mg/d (increased to 15mg/d after 3 months) repeated every 28d. Maintenance treatment is planned for up to 36 months or until progression if progression occurs first.
Outcome(s)	Primary outcome(s): • MRD (minimal residual disease) negativity after induction Treatment (comparison of arms IA and IB) [time frame: 18 weeks after start of study treatment] • Progression Free Survival (PFS) after second randomization (arms IIA and IIB) [time frame: time from 2. randomization to progression or death from any cause whichever comes first, censored after three years of maintenance therapy]

	See trial record for full list of outcomes.
Results (efficacy)	Between Oct 23, 2018, and Sep 22, 2020, 660 patients were included in the ITT analysis (331 in the isatuximab group and 329 in the control group). 654 (99%) patients were White, two were African, one was Arabic, and three were Asian. 250 (38%) were women and 410 (62%) were men. The median age was 59 years (IQR 54–64). MRD negativity after induction therapy was reached in 166 (50%) patients in the isatuximab group versus 117 (36%) in the control group (OR 1·82 [95% CI 1·33–2·48]; p=0·00017). Median follow-up time from start to end of induction therapy was 125 days (IQR 125–131) versus 125 days (125–132).[2]
Results (safety)	At least one grade 3 or 4 adverse event occurred in 208 (63%) of 330 patients versus 199 (61%) of 328 patients. Neutropenia of grade 3 or 4 occurred in 77 (23%) versus 23 (7%) patients and infections of grade 3 or 4 occurred in 40 (12%) versus 32 (10%) patients. Among 12 deaths during induction therapy, one death due to septic shock in the isatuximab group and four deaths (one cardiac decompensation, one hepatic and renal failure, one cardiac arrest, and one drug-induced enteritis) in the control group were considered treatment-related.[2]

Estimated Cost

The estimated cost for isatuximab solution for infusion is:[25]

- £506.94 (Hospital only) for 100mg/5ml concentrate
- £2534.69 (Hospital only) for 500mg/25ml concentrate

The estimated cost for lenalidomide is:[26]

- £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
- £4,368.00 for 21x25 mg capsules

The estimated cost for dexamethasone solution for injection is:[27]

- £23.99 for 3.3mg/1ml and 3.8mg/1ml solution
- £24.44 for 6.6mg/2ml solution

The estimated cost for bortezomib is:[28]

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

Relevant Guidance

NICE Guidance

- NICE technology appraisal. Daratumumab in combination for untreated multiple myeloma when a stem cell transplant is suitable (TA763). February 2022.

- NICE technology appraisal. Bortezomib for induction therapy in multiple myeloma before high-dose chemotherapy and autologous stem cell transplantation (TA311). April 2014.
- 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

- NCCN Guidelines. Insights: Multiple Myeloma, Version 1. 2024.[29]
- Multiple myeloma: EHA-ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. 2021.[30]
- The Society for Immunotherapy of Cancer consensus statement on immunotherapy for the treatment of multiple myeloma. July 2020.[31]

Additional Information

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