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Health Technology Briefing
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Isatuximab with bortezomib, lenalidomide, and dexamethasone for treating patients with newly diagnosed multiple myeloma who are eligible for autologous stem cell transplant

Company/Developer	Sanofi

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 36889	NICE ID: Not available	UKPS ID: 668193

Licensing and Market Availability Plans

Currently in phase III clinical trials.

Summary

Isatuximab in combination with lenalidomide, bortezomib and dexamethasone is in development for the treatment of newly diagnosed multiple myeloma (MM) in patients who are eligible for autologous stem cell transplant (ASCT). ASCT uses the patient's own stem cells harvested from the bone marrow and collected from the blood. MM is a type of blood cancer that develops from plasma cells in the bone marrow. Relapse (the return of disease after a period of improvement) is common in patients with MM, indicating a need for new treatment approaches.

Isatuximab is a monoclonal antibody (a type of protein with an attachment site) that targets a specific protein known as the CD38 receptor. CD38 is found in high levels at MM cells. Isatuximab binding to the CD38 receptors leads to the killing of cancerous cells through a variety of mechanisms. If approved, isatuximab in combination with lenalidomide, bortezomib and dexamethasone will offer an additional treatment option for adult patients with newly diagnosed MM who are eligible for ASCT.

This briefing reflects the evidence available at the time of writing and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information. A version of the briefing was sent to the company for a factual accuracy check. The company was available to comment.

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Proposed Indication

Treatment of adult patients with newly diagnosed multiple myeloma (MM) who are eligible for autologous stem cell transplantation (ASCT).[a]

Technology

Description

Isatuximab (SARCLISA) is an IgG1-derived monoclonal antibody that binds to a specific extracellular epitope of CD38 receptor. CD38 is a transmembrane glycoprotein that is highly expressed on MM cells.[1] Upon binding to CD38-expressing MM cells, isatuximab is thought to induct tumour cell killing via fragment crystallisable-dependent mechanisms, including antibody-dependent cellular cytotoxicity, antibody-dependent cellular phagocytosis, and complement-dependent cytotoxicity, as well as via direct fragment-crystallisable independent mechanisms.[2]

Isatuximab in combination with bortezomib, lenalidomide and dexamethasone is in clinical development for the treatment of adult patients with newly diagnosed MM who are eligible for ASCT. In the first part of the phase III clinical trial (NCT03617731), participants are randomly assigned to undergo an induction phase with isatuximab -bortezomib-lenalidomide-dexamethasone (Isa-VRd) or VRd. In the experimental arm, they receive 10 mg/kg isatuximab IV multiple times during cycle 1, and less frequently in cycles 2 and 3. Additionally, they take 25 mg oral lenalidomide, 1.3 mg/m² bortezomib SC, and 20 mg oral dexamethasone on various days throughout the three 42-day cycles. All patients subsequently proceeded to intensification therapy, stem cell mobilisation and ASCT. During the second part of the trial, the maintenance phase, participants underwent a second randomisation to receive maintenance therapy with either lenalidomide alone or isatuximab and lenalidomide for up to 3 years. They received 10 mg/kg isatuximab IV on several days in cycle 1, less frequently in cycles 2 and 3, and once per cycle from cycles 4-39. They also take 25 mg oral lenalidomide daily in cycles 1-3 and 15 mg daily in cycles 4-39, with each cycle lasting 28 days.[3]

Key Innovation

Despite advances in treatment, MM remains largely incurable, indicating the need for the development of more effective therapeutic strategies.[4] Anti-CD38 antibodies including isatuximab have led to unprecedented outcomes when combined with standard-of-care regimens. Paralleling this expansion in therapeutic options, minimal residual disease (MRD) negativity has emerged as a response target.[5] MRD can be defined as the persistence of myeloma cells below the threshold of detection when using conventional morphologic methods.[6] MRD negativity is associated with longer remissions and potentially longer rates of survival for certain blood cancers, including MM.[7] Anti-CD38 monoclonal antibodies such as isatuximab represent the first immunotherapeutic approach in MM.[8] In patients with newly diagnosed MM, quadruplet regimens, consisting of a CD38 monoclonal antibody with a proteasome inhibitor, immunomodulatory agent, and steroids, have shown increased efficacy over triplet therapies.[9,10] If licenced, isatuximab in combination with lenalidomide, bortezomib and dexamethasone will offer an additional treatment option for adult patients with newly diagnosed MM who are eligible for ASCT.

[a] Information provided by Sanofi

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Regulatory & Development Status

Isatuximab currently has Marketing Authorisation in the EU/UK as follows:[1]

- In combination with pomalidomide and dexamethasone, for the treatment of adult patients with relapsed and refractory MM 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 MM who have received at least one prior therapy
- In combination with bortezomib, lenalidomide, and dexamethasone, for the treatment of adult patients with newly diagnosed MM who are ineligible for ASCT

Isatuximab is in phase III/II clinical development for:[11]

- Relapsed/refractory (RRMM) in combination with novel agents
- Smouldering MM
- Leukemia
- AL amyloidosis (combination)
- Lymphoid malignancy

Patient Group

Disease Area and Clinical Need

Multiple myeloma, also known as myeloma, is a type of blood cancer that develops from plasma cells in the bone marrow.[12,13] The exact cause of MM is unknown, however it is more common in men, adults over 60, black people, and people with a family history of monoclonal gammopathy of unknown significance (MGUS) or MM.[12] MM damages the bones and affects the production of healthy blood cells, and often affects several areas of the body, such as the spine, skull, pelvis and ribs.[12] MM may not cause any symptoms in the early stages, but eventually leads to a wide range of problems including bone pain, bone fractures and spinal cord compression, anaemia, repeated infections, raised calcium levels in the blood, unusual bleeding, thickened blood, and kidney problems.[14] Treatment can often help to control the condition for several years, but most cases of MM cannot be cured.[12] An ASCT is a common standard of care treatment option at diagnosis for MM.[15] An ASCT uses the patient's own stem cells harvested from the bone marrow and collected from the blood.[16] After ASCT, patients often receive a maintenance therapy.[15] Maintenance therapy is treatment that is given to help keep cancer from coming back after it has disappeared following the initial therapy.[17] ASCT can often help patients live longer and keep the MM in remission longer than drug treatments alone.[15]

MM is the 19th most common cancer in the UK, accounting for 2% of all new cancer cases (2017-2019).[18] The age standardised incidence rate of MM in England is 12.8 and 7.9 per 100,000 amongst males and females respectively.[19] In England (2023-24), there were 167,351 finished consultant episodes (FCEs) and 161,752 admissions for MM (ICD-10 code C90.0), which resulted in 154,272 day cases and 99,531 FCE bed days.[20] In England (2020), there were 2,731 males and 1,982 females diagnosed with MM.[21] For patients diagnosed between 2013 and 2017, followed up to 2018, the 1-year and 5-year age-standardised survival rates were 82.7% and 52.3% respectively.[22]

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Recommended Treatment Options
NICE recommends the following as induction treatment options for newly diagnosed MM: • Daratumumab plus bortezomib, thalidomide and dexamethasone as induction and consolidation treatment for untreated MM in adults, when an ASCT is suitable[23] • Bortezomib in combination with dexamethasone, or with dexamethasone and thalidomide, for the induction treatment of adults with previously untreated MM, who are eligible for high-dose chemotherapy with haematopoietic stem cell transplantation[24] NICE recommends lenalidomide as a maintenance treatment after an ASCT for newly diagnosed MM in adults, only if the dosage schedule is 10 mg per day on days 1 to 21 of a 28-day cycle.[25]

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(s):** Germany **Study completion date (estimated):** March 2027
Trial Design	Randomised, parallel assignment, open label
Population	N=662; aged 18 to 70 years; diagnosis of untreated MM requiring systemic therapy; eligible for high dose therapy and autologous stem cell transplantation.
Intervention(s)	**Arm IB:** Isa-RVd (isatuximab (IV) + lenalidomide (oral); bortezomib (SC); dexamethasone (oral)) **Arm IIB (maintenance):** lenalidomide (oral) + isatuximab (IV)
Comparator(s)	**Arm IA:** RVd (lenalidomide (oral); bortezomib (SC); dexamethasone (oral)) **Arm IIA (maintenance):** lenalidomide (oral)
Outcome(s)	Primary outcome measures: • MRD negativity after induction treatment (comparison of arms IA and IB) [time frame: 18 weeks after start of study treatment] • Progression free survival after second randomisation (arms IIA and IIB) [time frame: time from 2. randomisation to progression or death from any cause, whichever comes first, censored after three years of maintenance therapy] See trial record for full list of other outcomes.
Results (efficacy)	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).[26] As of 31st January 2024, Isa-RVd induction therapy significantly prolonged progression-free survival compared with RVd regardless of maintenance therapy (hazard ratio, 0.70 [95% CI, 0.52 to 0.95]; P = .0184.[9]
Results (safety)	Between 23rd October 2018 and 22nd September 2020, at least one grade 3 or 4 adverse event occurred in 208 (63%) of 330 patients in the isatuximab group

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	versus 199 (61%) of 328 patients in the control group. 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.[26]

Estimated Cost

- Isatuximab is already marketed in the UK; a 100mg vial (20mg/mL) costs £506.94.[27]
- Lenalidomide is already marketed in the UK; a pack of 21 x 25mg capsules costs £4,368.00.[28]
- Bortezomib is already marketed in the UK; a 3.5mg vial (1.4mg/mL) costs £495.55.[29]
- Dexamethasone is already marketed in the UK; a pack of 10x20mg soluble tablets costs £20.00.[30]

Relevant Guidance

NICE Guidance

- NICE technology appraisal awaiting development. Isatuximab in combination as induction therapy for untreated multiple myeloma when an autologous stem cell transplant is suitable (TA11465). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Ixazomib citrate for maintenance treatment of untreated multiple myeloma after autologous stem cell transplant (TA10843). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Daratumumab with bortezomib, lenalidomide and dexamethasone for untreated multiple myeloma when an autologous stem cell transplant is suitable (TA11254). Expected date of issue to be confirmed.
- NICE technology appraisal. Daratumumab in combination for untreated multiple myeloma when a stem cell transplant is suitable (TA763). February 2022.
- NICE technology appraisal. Lenalidomide maintenance treatment after an autologous stem cell transplant for newly diagnosed multiple myeloma (TA680). March 2021.
- 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. Clinical Commissioning Policy: Second allogeneic haematopoietic stem cell transplant for relapsed disease (all ages). 2017. 16068/P.
- NHS England. Clinical Commissioning Policy: Haematopoietic Stem Cell Transplantation (HSCT) (All Ages): Revised. 2015. B04/Pa.
- 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. 2013/14 NHS Standard Contract for Haematopoietic Stem Cell Transplantation (Adult). B04/S/a.

Other Guidance

- National Comprehensive Cancer Network (NCCN). Guidelines Insights: Multiple Myeloma, Version 1.2025. 2025. [31]

Copyright © National Institute for Health and Care Research Innovation Observatory, The University of Newcastle upon Tyne.

- European Society for Medical Oncology (ESMO). Multiple myeloma: EHA-ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. 2021.[32]
- International Myeloma Working Group (IMWG). Treatment of relapsed and refractory multiple myeloma: recommendations from the International Myeloma Working Group. 2021.[33]
- British Society of Haematology (BSH). Guidelines for screening and management of late and long-term consequences of myeloma and its treatment. 2017.[34]

Additional Information

References

1 Electronic Medicines Compendium (emc). *SARCLISA 20 mg/mL concentrate for solution for infusion*. 2025. Available from: https://www.medicines.org.uk/emc/product/14817/smpc [Accessed 02 Apr 2025].

2 Zhu C, Song Z, Wang A, Srinivasan S, Yang G, Greco R, et al. Isatuximab Acts Through Fc-Dependent, Independent, and Direct Pathways to Kill Multiple Myeloma Cells. *Frontiers in Immunology*. 2020;11. Available from: https://doi.org/10.3389/fimmu.2020.01771.

3 Clinicaltrials.gov. *Trial on the Effect of Isatuximab to Lenalidomide/Bortezomib/ Dexamethasone (RVd) Induction and Lenalidomide Maintenance in Patients With Newly Diagnosed Myeloma (GMMG HD7)*. *Trial ID: NCT03617731*. 2018. Status: Active, not recruiting. Available from: https://clinicaltrials.gov/study/NCT03617731 [Accessed 02 Apr 2025].

4 Dima D, Jiang D, Singh DJ, Hasipek M, Shah HS, Ullah F, et al. Multiple Myeloma Therapy: Emerging Trends and Challenges. *Cancers*. 2022;14(17):4082. https://www.mdpi.com/2072-6694/14/17/4082.

5 ASH News Daily. *The IsKia Trial: Diving Into Deeper Responses for Multiple Myeloma*. Available from: https://ashpublications.org/ashnewsdaily/news/7641/The-IsKia-Trial-Diving-Into-Deeper-Responses-for [Accessed 08 Apr 2025].

6 Caroni F, Sammartano V, Pacelli P, Sicuranza A, Malchiodi M, Dragomir A, et al. Minimal Residual Disease Significance in Multiple Myeloma Patients Treated with Anti-CD38 Monoclonal Antibodies. *Pharmaceuticals*. 2025;18(2):159. https://www.mdpi.com/1424-8247/18/2/159.

7 Leukemia & Lymphoma Society. *Minimal Residual Disease (MRD)* Available from: https://www.lls.org/sites/default/files/National/USA/Pdf/Publications/FS35_MRD_Final_2019.pdf [Accessed 08 Apr 2025].

8 Gozzetti A, Ciofini S, Simoncelli M, Santoni A, Pacelli P, Raspadori D, Bocchia M. Anti CD38 monoclonal antibodies for multiple myeloma treatment. *Hum Vaccin Immunother*. 2022;18(5):2052658. Available from: https://doi.org/10.1080/21645515.2022.2052658.

9 Mai EK, Bertsch U, Pozek E, Fenk R, Besemer B, Hanoun C, et al. Isatuximab, Lenalidomide, Bortezomib, and Dexamethasone Induction Therapy for Transplant-Eligible Newly Diagnosed Multiple Myeloma: Final Part 1 Analysis of the GMMG-HD7 Trial. *Journal of Clinical Oncology*. 2025;43(11):1279-88. Available from: https://doi.org/10.1200/jco-24-02266.

10 Channar A, Naqvi SAA, Khan MA, Bibi A, Saxena A, Tripathi N, et al. Quadruplet therapy for transplant-eligible newly diagnosed multiple myeloma (TENDMM): A systematic review and

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meta-analysis. *Journal of Clinical Oncology*. 2024;42(16_suppl):e19534-e. Available from: https://doi.org/10.1200/JCO.2024.42.16_suppl.e19534.

11 Clinicaltrials.gov. *Search Results*. Available from: https://clinicaltrials.gov/search?intr=Isatuximab%20&spons=Sanofi&aggFilters=phase:2%203 [Accessed 01 Apr 2025].

12 NHS. *Overview: Multiple myeloma*. 2021. Available from: https://www.nhs.uk/conditions/multiple-myeloma/ [Accessed 01 Apr 2025].

13 Cancer Research UK. *What is myeloma?* 2023. Available from: https://www.cancerresearchuk.org/about-cancer/myeloma/about [Accessed 01 Apr 2025].

14 NHS. *Symptoms: Multiple myeloma*. 2021. Available from: https://www.nhs.uk/conditions/multiple-myeloma/symptoms/ [Accessed 01 Apr 2025].

15 American Cancer Society. *Stem Cell Transplant for Multiple Myeloma*. 2025. Available from: https://www.cancer.org/cancer/types/multiple-myeloma/treating/stem-cell-transplant.html [Accessed 08 Apr 2025].

16 Cancer Research UK. *Stem cell transplant for myeloma*. 2023. Available from: https://www.cancerresearchuk.org/about-cancer/myeloma/treatment/intensive-treatment [Accessed 08 Apr 2025].

17 National Cancer Institute. *Maintenance therapy*. Available from: https://www.cancer.gov/publications/dictionaries/cancer-terms/def/maintenance-therapy [Accessed 08 Apr 2025].

18 Cancer Research UK. *Myeloma statistics*. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/myeloma#heading-Zero [Accessed 01 Apr 2025].

19 *Myeloma incidence statistics*. 2024. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/myeloma/incidence#heading-Zero [Accessed 01 Apr 2025].

20 NHS England. *Hospital Admitted Patient Care Activity, 2023-24*. 2024. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2023-24.

21 NHS England. *Cancer Registration Statistics, England 2020*. 2022. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/cancer-registration-statistics/england-2020.

22 Office for National Statistics. *Cancer survival in England - adults diagnosed*. 2019. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancersurvivalratescancersurvivalinenglandadultsdiagnosed [Accessed 08 Apr 2025].

23 National Institute for Health and Care Excellence (NICE). *Daratumumab in combination for untreated multiple myeloma when a stem cell transplant is suitable* (*TA763)*. Available from: https://www.nice.org.uk/guidance/ta763/chapter/1-Recommendations [Accessed 10 June 2025].

24 National institute for Health and Care Excellence (NICE). *Bortezomib for induction therapy in multiple myeloma before high-dose chemotherapy and autologous stem cell transplantation* (*TA311)*. Available from: https://www.nice.org.uk/guidance/ta311/chapter/1-Recommendations [Accessed 10 June 2025].

25 National Institute for Health and Care Excellence (NICE). *Lenalidomide maintenance treatment after an autologous stem cell transplant for newly diagnosed multiple myeloma* (*TA680)*. Available from: https://www.nice.org.uk/guidance/ta680 [Accessed 02 Apr 2025].

26 Goldschmidt H, Mai EK, Bertsch U, Fenk R, Nievergall E, Tichy D, et al. Addition of isatuximab to lenalidomide, bortezomib, and dexamethasone as induction therapy for newly diagnosed, transplantation-eligible patients with multiple myeloma (GMMG-HD7): part 1 of an open-

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label, multicentre, randomised, active-controlled, phase 3 trial. *Lancet Haematol*. 2022;9(11):e810-e21. Available from: https://doi.org/10.1016/s2352-3026(22)00263-0.

27 British National Formulary (BNF). *Isatuximab [Specialist drug] Medicinal forms*. Available from: https://bnf.nice.org.uk/drugs/isatuximab-specialist-drug/medicinal-forms/ [Accessed 02 Apr 2025].

28 British National Formulary (BNF). *Lenalidomide [Specialist drug] Medicinal forms*. Available from: https://bnf.nice.org.uk/drugs/lenalidomide-specialist-drug/medicinal-forms/ [Accessed 02 Apr 2025].

29 British National Formulary (BNF). *Bortezomib [Specialist drug] Medicinal forms*. Available from: https://bnf.nice.org.uk/drugs/bortezomib-specialist-drug/medicinal-forms/ [Accessed 02 Apr 2025].

30 British National Formulary (BNF). *Dexamethasone Medicinal forms*. Available from: https://bnf.nice.org.uk/drugs/dexamethasone/medicinal-forms/ [Accessed 02 Apr 2025].

31 Kumar SK, Callander NS, Adekola K, Anderson LD, Baljevic M, Baz R, et al. NCCN Guidelines® Insights: Multiple Myeloma, Version 1.2025. *J Natl Compr Canc Netw*. 2025;23(5):132-40. Available from: https://doi.org/10.6004/jnccn.2025.0023.

32 Dimopoulos MA, Moreau P, Terpos E, Mateos MV, Zweegman S, Cook G, et al. Multiple myeloma: EHA-ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up[†]. *Annals of Oncology*. 2021;32(3):309-22. Available from: https://doi.org/10.1016/j.annonc.2020.11.014.

33 Moreau P, Kumar SK, San Miguel J, Davies F, Zamagni E, Bahlis N, et al. Treatment of relapsed and refractory multiple myeloma: recommendations from the International Myeloma Working Group. *Lancet Oncol*. 2021;22(3):e105-e18. Available from: https://doi.org/10.1016/s1470-2045(20)30756-7.

34 Snowden JA, Greenfield DM, Bird JM, Boland E, Bowcock S, Fisher A, et al. Guidelines for screening and management of late and long-term consequences of myeloma and its treatment. *British Journal of Haematology*. 2017;176(6):888-907. Available from: https://doi.org/10.1111/bjh.14514.

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