FraminGHam

on multiple myeloma

Isatuximab, lenalidomide, bortezomib, and dexamethasone induction therapy fortransplant-eligible newly diagnosed multiple myeloma: final part 1 analysis of the GMMG-HD7 trial

Journal of Clinical Oncology, 2025 April 10; 43(11):1279–88

Patient-reported outcomes following ciltacabtagene autoleucel or standard of carein patients with lenalidomide-refractory multiple myeloma (CARTITUDE-4): results from a randomised, open-label, phase 3 trial

The Lancet Haematology, 2025 January; 12(1):e45–56

Ixazomib as consolidation and maintenance versus observation in patients with relapsed multiple myeloma eligible for salvage autologous stem-cell transplantation (Myeloma XII [ACCoRD]): interim analysis of a multicentre, open-label, randomised, phase 3 trial

The Lancet Haematology, 2024 November; 11(11):e816–29

Mechanisms of resistance against T-cell engaging bispecific antibodies in multiple myeloma: implications for novel treatment strategies

The Lancet Haematology, 2024 September; 11(9):e693–707

ISSUE 3, 2025

CURRENT TITLES

Framingham *on amyloidosis*

Framingham *on atherosclerosis*

Framingham *on benign haematology*

Framingham *on cystic fibrosis*

Framingham *on diabetes*

Framingham *on endocrinology*

Framingham *on gastroenterology*

Framingham *on gynaecology*

Framingham *on haematological malignancies*

Framingham *on infectious diseases*

Framingham *on lung cancer*

Framingham *on neurology*

Framingham *on respiratory diseases / asthma*

Framingham *on systemic fungal infections*

and many more...

OUR PURPOSE

The Framingham series of publications is designed to meet clinical specialists' need for a reliable guide to the most important articles appearing in their field.

Each issue presents an authoritative selection from the recently published literature, with the emphasis on evidence-based medicine. Articles are recommended for inclusion by Framingham's editorial office and an advisory board headed by key opinion leaders in the relevant clinical area.

Framingham's team of medical writers prepares original abstracts of these articles, in a structured format that presents the main points at a glance. Our aim is to convey the essence of each article in a concise but readable style.

Issues are published every three to six months.

DISCLAIMER

The abstracts in this publication are prepared with care to reflect the views expressed by the author or authors of the original source material. These views are not necessarily those of the publisher. While every care is taken to avoid errors, these cannot always be avoided; readers are advised to independently validate any data and recommendations contained herein before acting on this information. The publisher disclaims any responsibility or liability for the accuracy of such information.

Framingham

Editor
Catherine Harris Booth

Consulting Editor
Niels van de Donk, MD PhD
Professor of Haematology,
Cancer Center Amsterdam,
Amsterdam UMC,
Location VU University Medical Center,
Amsterdam, the Netherlands

Medical Writers (this issue)
Milena Braga-Basaria
Derek Collett
David Newton

Art Design
Jan van Halm

Layout and Printing
Drukmeesters,
Zwijndrecht, the Netherlands

Publishing Director
Evelien Enter

Publisher
Waldemar H.G. Dobrowolski

Framingham bv
Postbus 1593
1200 BN Hilversum
The Netherlands
www.framinghampublishers.com

Framingham *on multiple myeloma*
is published by the support of
Sanofi AB
Stockholm, Sweden
MAT-BE-2501125 - v1.0 10/2025

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 April 10; 43(11):1279–88

AUTHORS: Mai EK, Bertsch U, Pozek E, et al., for the German-Speaking Myeloma Multicenter Group (GMMG) HD7 Investigators
CENTRE FOR CORRESPONDENCE: Heidelberg Myeloma Center, Department of Internal Medicine V, Heidelberg University Hospital and Medical Faculty Heidelberg, Heidelberg University, Heidelberg, Germany

BACKGROUND & AIM: The addition of a CD38 monoclonal antibody to triplet therapy has been shown to improve efficacy in patients with newly diagnosed multiple myeloma (NDMM). Isatuximab is an IgG1 monoclonal antibody targeting CD38, and its combination with lenalidomide, bortezomib and dexamethasone (RVd) is approved for transplant-ineligible patients with NDMM. In the initial analysis of the GMMG-HD7 trial in patients eligible for transplant, 18 weeks of induction with isatuximab plus RVd (Isa-RVd) (without posttransplant consolidation) was associated with an improved rate of minimal residual disease (MRD)-negativity over RVd alone. The aim of the current analysis was to investigate additional prespecified outcomes among GMMG-HD7 participants.

STUDY DESIGN: Multicentre, randomized, open-label, active-controlled, phase 3 trial.

ENDPOINTS: Complete response rate; MRD-negativity; progression-free survival (PFS).

METHOD: Patients aged 18–70 years with NDMM who required systemic treatment and who were eligible for autologous haematopoietic stem-cell transplantation (ASCT) were randomized to three 6-week cycles of induction therapy with Isa-RVd (n=331) or RVd (n=329). Following single or tandem ASCT, participants underwent a second randomization to maintenance therapy with lenalidomide alone or lenalidomide plus isatuximab. This paper reports updated results from first random assignment to posttransplant.

RESULTS: Complete response and MRD-negativity rates were both significantly higher among patients randomized to induction therapy with Isa-RVd versus RVd (Table). PFS was also significantly longer in the Isa-RVd group (hazard ratio 0.70, 95% confidence interval 0.52–0.95; p=0.0184), and this was not affected by maintenance therapy group. A preplanned analysis designed to account for the second randomization confirmed a PFS benefit for Isa-RVd plus lenalidomide maintenance over RVd plus lenalidomide, with an estimated 4-year PFS rate of 74% versus 64% (p=0.016).

CONCLUSION: In transplant-eligible patients with NDMM, adding isatuximab to RVd for 18-week induction therapy prior to ASCT was associated with significantly deeper responses and a significant and clinically meaningful improvement in PFS, regardless of subsequent maintenance therapy.

Response rates and MRD-negativity after ASCT according to induction therapy

	Isa-RVd	RVd	Odds ratio (95% CI)	*p*-value
Complete response, %	43.5	34.0	1.49 (1.08–2.07)	0.013
MRD-negativity, %	66.2	47.7	2.13 (1.56–2.92)	<0.0001
Complete response and MRD-negativity, %	38.1	25.8	1.76 (1.25–2.50)	0.001

https://doi.org/10.1200/JCO-24-02266

PATIENT-REPORTED OUTCOMES FOLLOWING CILTACABTAGENE AUTOLEUCEL OR STANDARD OF CARE IN PATIENTS WITH LENALIDOMIDE-REFRACTORY MULTIPLE MYELOMA (CARTITUDE-4):

RESULTS FROM A RANDOMISED, OPEN-LABEL, PHASE 3 TRIAL

The Lancet Haematology, 2025 January; 12(1):e45–56

AUTHORS: Mina R, Mylin AK, Yokoyama H, Magen H, Alsdorf W, Minnema MC, Shune L, Isufi I, Harrison SJ, Shah UA, Schecter JM, Vogel M, Lendvai N, Gries KS, Katz EG, Slaughter A, Lonardi C, Gilbert J, Li Q, Deraedt W, Filho OC, Patel N, Florendo E, Karlin L, Weisel K
CENTRE FOR CORRESPONDENCE: AOU Città della Salute e della Scienza di Torino, Turin, Italy

BACKGROUND & AIM: Patients with multiple myeloma often have decreased health-related quality of life (HRQoL), and it is important to consider HRQoL alongside clinical benefits when making treatment decisions. Ciltacabtagene autoleucel (cilta-cel) is a dual-binding, B-cell maturation antigen-directed chimeric antigen receptor T-cell therapy that is approved for treating lenalidomide-refractory relapsed or refractory multiple myeloma. The aim of this analysis was to understand the effects of cilta-cel on HRQoL and disease-related symptoms.

STUDY DESIGN: Randomized, open-label, phase 3 study.

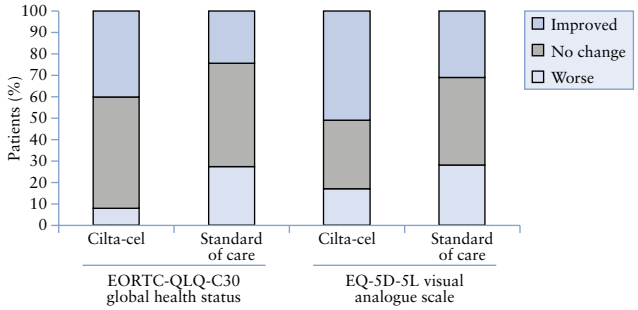
ENDPOINTS: Time to symptom worsening; change from baseline in HRQoL scores.

METHOD: Patients with lenalidomide-refractory relapsed or refractory multiple myeloma with one to three previous lines of therapy were randomized to receive cilta-cel (n=208) or standard of care (n=211). Time to symptom worsening was assessed using the Multiple Myeloma Symptom and Impact Questionnaire (MySIm-Q), and HRQoL using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) and the EQ-5D-5L questionnaire.

RESULTS: At a median follow-up of 15.9 months (interquartile range 12.4–17.8 months), the median time to sustained multiple myeloma symptom worsening was 23.7 months in the cilta-cel group versus 18.9 months in the standard-of-care group (hazard ratio 0.42, 95% confidence interval 0.26–0.68; nominal p=0.0003). HRQoL improved over time in the cilta-cel group but remained near baseline in the standard-of-care group, with 12-month least-squares mean changes from baseline of +10.1 versus –1.5 points for EORTC QLQ-C30 global health status and +8.0 versus +1.4 points on the EQ-5D-5L visual analogue scale, and more patients treated with cilta-cel experiencing improved scores (Figure).

CONCLUSION: Among patients with lenalidomide-refractory relapsed or refractory multiple myeloma, cilta-cel improved HRQoL and delayed symptom worsening compared with standard of care.

Proportion of patients with a clinically meaningful change from baseline to month 12 in EORTC QLQ-C30 global health status (≥10-point difference) and the EQ-5D-5L visual analogue scale (≥7-point difference)



https://doi.org/10.1016/S2352-3026(24)00320-X

IXAZOMIB AS CONSOLIDATION AND MAINTENANCE VERSUS OBSERVATION IN PATIENTS WITH RELAPSED MULTIPLE MYELOMA ELIGIBLE FOR SALVAGE AUTOLOGOUS STEM-CELL TRANSPLANTATION (MYELOMA XII [ACCORD]): INTERIM ANALYSIS OF A MULTICENTRE, OPEN-LABEL, RANDOMISED, PHASE 3 TRIAL

The Lancet Haematology, 2024 November; 11(11):e816–29

AUTHORS: Cook G, Ashcroft AJ, Senior E, Olivier C, Hockaday A, Richards J, Cavenagh JD, Snowden JA, Drayson MT, de Tute R, Roberts L, Owen RG, Yong K, Garg M, Boyd K, Sati H, Gillson S, Cook M, Cairns DA, Parrish C, for the United Kingdom Myeloma Research Alliance
CENTRE FOR CORRESPONDENCE: Leeds Cancer Research UK Clinical Trials Unit, Leeds Institute of Clinical Trials Research, University of Leeds, Leeds, UK

BACKGROUND & AIM: There is no prospective evidence on whether consolidation and maintenance strategies improve the outcomes of patients with multiple myeloma (MM) following salvage autologous haematopoietic stem-cell transplantation (HSCT). Ixazomib is an oral second-generation proteasome inhibitor that has shown efficacy as a maintenance treatment following first-line autologous HSCT. The aim of this study was to investigate the efficacy of an ixazomib-containing consolidation and maintenance strategy following salvage autologous HSCT in patients with MM.

STUDY DESIGN: Interim analysis of a multicentre, open-label, randomized, controlled, phase 3 trial.

ENDPOINTS: Primary: progression-free survival (PFS). Secondary: overall survival; safety.

METHOD: Adults with relapsed MM who required treatment for first progressive disease at least 12 months after first autologous HSCT were initially randomized to receive either conventional autologous HSCT with melphalan or augmented autologous HSCT with melphalan plus ixazomib. This report concerns the second randomization, in which patients were assigned to consolidation with ixazomib, thalidomide and dexamethasone, followed by maintenance with ixazomib alone (*n*=103) until disease progression or intolerance, or observation (*n*=103).

RESULTS: Over a median follow-up of 27 months (interquartile range 13–38 months), median PFS was 20 months in the consolidation and maintenance group versus 13 months in the observation group (hazard ratio 0.55, 95% confidence interval 0.39–0.78; *p*=0.0006). The benefit of consolidation and maintenance on PFS was observed in most subgroups, with no effect of age, disease stage or previous proteasome inhibitor exposure. Median overall survival was not reached in either group and the 2-year overall survival rate was 91.1% in the consolidation and maintenance group and 92.0% in the observation group (HR 0.48, 95% CI 0.21–1.09). Serious adverse events occurred in 32% and 7% of patients, respectively. In the consolidation and maintenance group, the most common any-grade adverse events were peripheral sensory neuropathy (57%), fatigue (45%) and upper respiratory tract infection (45%), and the most common grade 3 or worse adverse events were upper respiratory tract infection (8%) and thrombocytopenia (5%); there were no treatment-related deaths.

CONCLUSION: At this interim analysis, patients with MM who received consolidation and maintenance treatment with an ixazomib-containing regimen following salvage autologous HSCT had superior PFS to those managed with observation.

https://doi.org/10.1016/S2352-3026(24)00249-7

MECHANISMS OF RESISTANCE AGAINST T-CELL ENGAGING BISPECIFIC ANTIBODIES IN MULTIPLE MYELOMA:

IMPLICATIONS FOR NOVEL TREATMENT STRATEGIES

The Lancet Haematology, 2024 September; 11(9):e693–707

AUTHORS: van de Donk NW, Chari A, Mateos MV
CENTRES: Department of Hematology, Amsterdam University Medical Center, Vrije Universiteit Amsterdam; Cancer Center Amsterdam, Cancer Biology and Immunology, Amsterdam, the Netherlands; Helen Diller Family Comprehensive Cancer Center, University of California San Francisco, San Francisco, California, USA; Instituto de Investigación Biomédica de Salamanca, Centro de Investigación del Cáncer, Centro de Investigación Biomédica en Red Cáncer, University Hospital of Salamanca, Salamanca, Spain

BACKGROUND & AIM: T-cell redirecting bispecific antibodies can be effective in treating multiple myeloma (MM), and work by simultaneously binding to antigens on MM cells and to CD3 on T cells. Currently approved agents include teclistamab and elranatamab (which target B-cell maturation antigen) and talquetamab (which targets G-protein-coupled receptor, class C, group 5, member D or GPRC5D), while others are in development. However, not all patients respond to this approach and most ultimately relapse because of acquired resistance, the mechanisms of which involve tumour-related features, T-cell characteristics and the immunosuppressive tumour microenvironment. The aim of this article was to review mechanisms of resistance against bispecific antibodies in MM.

ARTICLE TYPE: Expert review.

FINDINGS: Tumour-related features that can result in resistance to bispecific antibodies include low expression of the target antigen. In this case, higher antitumour activity might be achieved by using a bispecific antibody with two binding sites on the same antigen (e.g. alnuctamab, which targets B-cell maturation antigen and CD3) or by combining therapy with an agent that increases expression levels (e.g. ɣ-secretase inhibitors). Another potential mechanism of resistance is antigen loss, which can be caused by various genomic events. This may be prevented by using a trispecific antibody or two bispecific antigens to target two tumour-associated antigens. Other tumour-related factors include a high tumour burden and the expression of T-cell inhibitory ligands.

Reductions in T-cell numbers and function are seen in MM, and may be aggravated by continuous treatment with bispecific antibodies, leading to chronic T-cell stimulation and ultimately T-cell exhaustion. There are several potential strategies to overcome this, including using combination therapy, alternative bispecific antibody formats or new approaches to administration. In particular, antitumour activity could be improved by targeting inhibitory pathways (e.g. by immune checkpoint blockade) or costimulatory pathways.

Finally, the presence of immune suppressor cells and bone marrow stromal cells in the tumour microenvironment can contribute to resistance. Regulatory T cells and granulocytic myeloid-derived suppressor cells can impair the cytotoxic effects and proliferative ability of T cells, while bone marrow stromal cells impair the activity of cytotoxic agents and immunotherapies. One potential therapeutic strategy is to coadminister bispecific antibodies with CD38-targeting antibodies to remove $CD38^+$ immune suppressor cells, and thereby increase T-cell numbers and T-cell activity.

CONCLUSION: Improved knowledge of the mechanisms contributing to resistance to bispecific antibodies in MM can suggest therapeutic strategies to overcome these.

https://doi.org/10.1016/S2352-3026(24)00186-8

Compulsory information: SARCLISA (isatuximab) 20mg/mL concentrate for solution for infusion. Please refer to the Summary of Product Characteristics (SPC) before prescribing. Presentations: Each vial contains 100 mg of isatuximab in 5 mL of concentrate or contains 500 mg of isatuximab in 25 mL of concentrate. *Excipient with known effect:* This medicine contains 0.2 mg of polysorbate 80 in each mL of isatuximab concentrate for solution for infusion, which is equivalent to 0.1 mg/kg of body weight. Polysorbates may cause allergic reactions. **Indication:** SARCLISA is indicated: in combination with pomalidomide and dexamethasone, for the treatment of adult patients with relapsed and refractory multiple myeloma (MM) who have received at least two prior therapies including lenalidomide and a proteasome inhibitor (PI) 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 and in combination with bortezomib, lenalidomide, and dexamethasone, for the treatment of adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplantation, and in combination with bortezomib, lenalidomide, and dexamethasone, for the induction treatment of adult patients with newly diagnosed multiple myeloma who are eligible for autologous stem cell transplant. **Dosage and Administration*:** SARCLISA should be administered by a healthcare professional, in an environment where resuscitation facilities are available. *Premedication, with the following medicinal products, should be administered 15-60 minutes prior to starting a SARCLISA infusion:* Dexamethasone 40 mg oral or intravenous (IV) (or 20 mg oral or IV for patients ≥75 years of age) when administered in combination with isatuximab and pomalidomide. Dexamethasone 20 mg (IV on the days of isatuximab and/or carfilzomib infusions, and oral on the other days): when administered in combination with isatuximab and carfilzomib. Dexamethasone 20 mg (intravenous on the days of isatuximab infusion, and oral on the other days): when administered in combination with isatuximab, bortezomib, and lenalidomide. Montelukast 10 mg oral (or equivalent), at least at cycle 1. Acetaminophen 650 mg to 1000 mg oral (or equivalent). H2 antagonists (ranitidine 50 mg IV or equivalent [e.g., cimetidine]), or oral proton pump inhibitors (e.g., omeprazole, esomeprazole). Diphenhydramine 25 mg to 50 mg IV or oral (or equivalent [e.g., cetirizine, promethazine, dexchlorpheniramine]). The IV use is preferred for diphenhydramine for at least the first 4 infusions. The above recommended dose of dexamethasone (oral or IV) corresponds to the total dose to be administered only once before the infusion, as part of the premedication and the backbone treatment, before isatuximab and pomalidomide, before isatuximab and carfilzomib administration, and before isatuximab, bortezomib, and lenalidomide administration. Patients who do not experience an infusion reaction upon their first 4 administrations of SARCLISA may have their need for subsequent premedication reconsidered. *Management of neutropenia:* The use of colony-stimulating factors (e.g. G-CSF) should be considered to mitigate the risk of neutropenia. In the event of grade 3 or grade 4 neutropenia or febrile neutropenia and/or neutropenic infection, SARCLISA administration should be delayed or omitted until recovery. *Prevention of infection:* Antibacterial and antiviral prophylaxis (such as herpes zoster prophylaxis) can be considered during treatment. *Posology:* The recommended dose of SARCLISA is 10 mg/kg body weight administered as an intravenous infusion in combination with pomalidomide and dexamethasone (Isa-Pd) or in combination with carfilzomib and dexamethasone (Isa-Kd), or in combination with bortezomib, lenalidomide, and dexamethasone (Isa-VRd). SARCLISA dosing schedule for Isa-Pd or Isa-Kd: *Cycle 1:* Dosing on days 1, 8, 15 and 22 (weekly). *Cycle 2 and beyond:* Dosing on days 1, 15 (every 2 weeks). Each treatment cycle consists of a 28-day period. Treatment is repeated until disease progression or unacceptable toxicity. SARCLISA dosing schedule for Isa-VRd in patients who are ineligible for autologous stem cell transplant (ASCT) (IMROZ) *Cycle 1:* Dosing on days 1, 8, 15, 22 and 29 (weekly). *Cycles 2 to 4:* Dosing on days 1, 15, and 29 (every 2 weeks). *Cycles 5 to 17: Dosing on days 1 and 15 (every 2 weeks). Cycle 18 and beyond: Dosing on day 1 (every 4 weeks).* Treatment is repeated until disease progression or unacceptable toxicity. For other medicinal products that are administered with SARCLISA, refer to the respective current summary of product characteristics. SARCLISA dosing schedule for Isa-VRd in patients who are eligible for ASCT (GMMG-HD7) *Induction treatment: Cycle 1:* Dosing on days 1, 8, 15, 22 and 29 (weekly). *Cycles 2 to 3:* Dosing on days 1, 15, and 29 (every 2 weeks). Stop for intensification treatment (high dose chemotherapy and ASCT) followed by SOC maintenance treatment. *Missed dose:* The administration schedule must be carefully followed. If a planned dose of SARCLISA is missed, administer the dose as soon as possible and adjust the treatment schedule, accordingly, maintaining the treatment interval. *Dose adjustments:* No dose reduction of SARCLISA is recommended. Administration adjustments should be made if patients experience infusion reactions or in case of Grade 3 or 4 neutropenia, or febrile neutropenia and/or neutropenic infection. *Infusion rates:* please refer to full SmPC. **Special Populations:** *Elderly:* no dose adjustment is recommended. *Patients with renal impairment:* No dose adjustment is recommended in patients with mild to severe renal impairment including end-stage renal disease. *Patients with hepatic impairment:* No dose adjustment is recommended in patients with mild hepatic impairment. Data in patients with moderate and severe hepatic impairment are limited, but there is no evidence to suggest that dose adjustment is required in these patients. *Paediatric population (<18 years old):* Outside its authorized indications, SARCLISA has been studied in children aged 28 days to less than 18 years of age with relapsed or refractory acute lymphoblastic or myeloid leukaemia but efficacy has not been established. **Contraindications:** Hypersensitivity to the active substance or to any of its excipients. **Precautions and Warnings*:** *Traceability:* In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded. *Infusion reactions (IRs):* Infusion reactions, mostly mild or moderate, have been observed in 38.2% of patients treated with SARCLISA in ICARIA-MM, in 45.8% of patients treated with Isa-Kd in IKEMA, and in 24.0% of patients treated with Isa-VRd in IMROZ. In ICARIA-MM, all infusion reactions started during the first SARCLISA infusion and resolved on the same day in 98% of the infusions. The most common symptoms of an infusion reaction included dyspnoea, cough, chills and nausea. The most common severe signs and symptoms included hypertension, dyspnoea, and bronchospasm. In IKEMA, the infusion reactions occurred on the infusion day in 99.2% of episodes. In patients treated with Isa-Kd, 94.4% of those experiencing an infusion reaction experienced it during the first cycle of treatment. All infusion reactions resolved. The most common symptoms of an infusion reaction included cough, dyspnoea, nasal congestion, vomiting and nausea. The most common severe signs and symptoms included hypertension and dyspnoea. In IMROZ, the infusion reactions started on the infusion day in all patients, mostly during the first SARCLISA infusion, and resolved the same day in 97.3% of patients. All infusion reactions resolved. The most common symptoms of an infusion reaction included dyspnoea and chills. The most common severe sign and symptom was hypertension. However, serious infusion reactions including severe anaphylactic reactions have also been observed after SARCLISA administration. To decrease the risk and severity of infusion reactions, patients should be pre-medicated prior to SARCLISA infusion with acetaminophen, diphenhydramine or equivalent; dexamethasone is to be used as both premedication and anti-myeloma treatment. Vital signs should be frequently monitored during the entire SARCLISA infusion. When required, interrupt SARCLISA infusion and provide appropriate medical and supportive measures. In case symptoms do not improve to grade ≤1 after interruption of SARCLISA infusion, persist or worsen despite appropriate medicinal products, require hospitalization or are life-threatening, permanently discontinue SARCLISA and institute appropriate management. *Neutropenia*: Neutropenia was reported as a laboratory abnormality in: 96.1 % of Isa-Pd patients; 54.8% of Isa-Kd patients; and 87.5% of Isa-VRd patients. Neutropenia was reported as an adverse reaction in: 46.7 % of Isa-Pd patients; 4.5 % of Isa-Kd patients; and 30% of Isa-VRd patients. Grade 3-4 neutropenia reported as a laboratory abnormality in: 84.9 % of Isa-Pd patients and as an adverse reaction in 45.4 % of Isa-Pd patients; as a laboratory abnormality in 19.2 % of Isa-Kd patients (with 17.5 % Grade 3 and 1.7 % Grade 4) and as an adverse reaction in 4.0 % of Isa-Kd patients; and as a laboratory abnormality in 54.4% of Isa-VRd patients (with 35.7% Grade 3 and 18.6% Grade 4) and as an adverse reaction in 30% of Isa-VRd patients. Neutropenic complications have been observed in: 30.3 % of Isa-Pd patients (including 11.8 % of febrile neutropenia and 25.0 % of neutropenic infections); 2.8 % of Isa-Kd patients (including 1.1 % of febrile neutropenia and 1.7 % of neutropenic infections); and 12.5% of patients (including 2.3% of febrile neutropenia and 10.6% of neutropenic infection). Complete blood cell counts should be monitored periodically during treatment. Patients with neutropenia should be monitored for signs of infection. No dose reductions of SARCLISA are recommended. SARCLISA dose delays and the use of colony-stimulating factors (e.g. G-CSF) should be considered to mitigate the risk of neutropenia. *Infection:* A higher incidence of infections, including grade ≥ 3 infections, mainly pneumonia, upper respiratory tract infection and bronchitis, occurred with SARCLISA. Patients receiving SARCLISA should be closely monitored for signs of infection and appropriate standard therapy instituted. Antibacterial and antiviral prophylaxis (such as herpes zoster prophylaxis) according to treatment guidelines should be considered during treatment. *Second primary malignancies (SPMs)*: In ICARIA-MM, second primary malignancies (SPMs) were reported at a median follow-up time of 52.44 months in 10 patients (6.6%) treated with Isa-Pd and in 3 patients (2%) treated with Pd. SPM were skin cancer in 6 patients treated with Isa-Pd and in 3 patients treated with Pd, solid tumours other than skin cancer in 3 patients treated with Isa-Pd (one patient also had a skin cancer), and haematological malignancy (myelodysplastic syndrome) in 1 patient treated with Isa-Pd. Patients continued treatment after resection of the new malignancy, except two patients treated with Isa-Pd. One patient developed metastatic melanoma and the other developed myelodysplastic syndrome. In IKEMA study, at a median follow-up time of 56.61 months, SPMs were reported in 18 patients (10.2%) treated with Isa-Kd and in 10 patients (8.2%) treated with Kd. SPMs were skin cancers in 13 patients (7.3%) treated with Isa-Kd and in 4 patients (3.3%) treated with Kd, were solid tumours other than skin cancer in 7 patients (4.0%) treated with Isa-Kd and in 6 patients (4.9%) treated with Kd, and haematological malignancy (acute myeloid leukaemia) in 1 patient (0.8%) in the Kd group. For 1 patient (0.6%) in the Isa-Kd group, the aetiology of the SPM was unknown. Two patients (1.1%) in the Isa-Kd group and one patient (0.8%) in the Kd group had both skin cancer and solid tumours other than skin cancer. Patients with skin cancer continued treatment after resection of the skin cancer. Solid tumours other than skin cancer were diagnosed within 3 months after treatment initiation in 3 patients (1.7%) treated with Isa-Kd and in 2 patients (1.6%) treated with Kd. In IMROZ study, at a median follow-up time of 59.73 months, SPMs were reported in 42 patients (16.0%) treated with Isa-VRd (0.041 events per patient-year) and in 16 patients (8.8%) treated with VRd (0.026 events per patient-year). SPMs were skin cancers in 22 patients (8.4%) treated with Isa-VRd and in 7 patients (3.9%) treated with VRd, were solid tumours other than skin cancer in 17 patients (6.5%) treated with Isa-VRd and in 7 patients (3.9%) treated with VRd, and haematological malignancy in 3 patients (1.1%) treated with Isa-VRd and in 2 patients (1.1%) treated with VRd. Patients with SPM of skin cancer continued treatment after resection of the skin cancer, except one patient in each treatment group. SPMs with fatal outcome were reported in 6 patients (2.3%) treated with Isa-VRd (neuroendocrine carcinoma of the skin, malignant melanoma, squamous cell carcinoma of skin, squamous cell carcinoma of lung, colorectal cancer, and rectal adenocarcinoma) and in 2 patients (1.1%) treated with VRd (metastases to peritoneum and adenocarcinoma of colon). The overall incidence of SPMs in all the SARCLISA-exposed patients is 4,3%. Physicians should carefully evaluate patients before and during treatment as per IMWG guidelines for occurrence of SPM and initiate treatment as indicated. *Tumour lysis syndrome:* Cases of tumour lysis syndrome (TLS) have been reported in patients who received isatuximab. Patients should be monitored closely and appropriate precautions taken. *Interference with Serological Testing (indirect antiglobulin test):* SARCLISA administration may result in a false positive indirect antiglobulin test (indirect Coombs test). This interference with the indirect Coombs test may persist for at least 6 months after the last infusion of SARCLISA. To avoid potential problems with Red Blood Cell transfusion, patients being treated with SARCLISA should have blood type and screen tests performed prior to the first SARCLISA infusion. Phenotyping may be considered prior to starting SARCLISA treatment as per local practice. If treatment with SARCLISA has already started, the blood bank should be informed that the patient is receiving SARCLISA and SARCLISA interference with blood compatibility testing can be resolved using dithiothreitol (DTT)-treated RBCs. If an emergency transfusion is required, non-cross-matched ABO/RhD-compatible RBCs can be given as per local blood bank practices. *Interference with determination of complete response:* SARCLISA can interfere with both serum protein electrophoresis (SPE) and immunofixation (IFE) assays used for the clinical monitoring of endogenous M-protein. Interference can impact the accuracy of the determination of complete response in some patients with IgG kappa myeloma protein. ***Interactions**:* *Interference with serological testing:* Because CD38 protein is expressed on the surface of red blood cells, SARCLISA may interfere with blood bank serologic tests with potential false positive reactions in indirect antiglobulin tests (indirect Coombs tests), antibody detection (screening) tests, antibody identification panels, and antihuman globulin (AHG) crossmatches in patients treated with SARCLISA. *Interference with Serum Protein Electrophoresis and Immunofixation Tests:* SARCLISA may be incidentally detected by serum protein electrophoresis (SPE) and immunofixation (IFE) assays used for the monitoring of M-protein and could interfere with accurate response classification based on International Myeloma Working Group (IMWG) criteria. ***Fertility, pregnancy and lactation**:* Women of childbearing potential treated with SARCLISA should use effective contraception during treatment and for at least 5 months after cessation of treatment. There are no available data on isatuximab use in pregnant women. Immunoglobulin G1 monoclonal antibodies are known to cross the placenta after the first trimester of pregnancy. The use of SARCLISA in pregnant women is not recommended. It is unknown whether isatuximab is excreted in human milk. Human IgGs are known to be excreted in breast milk during the first few days after birth, which is decreasing to low concentrations soon afterwards; however, a risk to the breast-fed infant cannot be excluded during this short period just after birth. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from isatuximab therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman. No human and animal data are available to determine potential effects of isatuximab on fertility in males and females. **Adverse Reactions*:** In ICARIA-MM (Isa-Pd): *Very common:* Decreased appetite, neutropenia, thrombocytopenia, infusion reactions, pneumonia*, upper respiratory tract infection, diarrhoea, bronchitis, dyspnoea, nausea, vomiting. *Common:* Weight decreased, atrial fibrillation, skin cancers, Solid tumour (non-skin cancer), herpes zoster, febrile neutropenia, anaemia. *Uncommon:* Anaphylactic reaction, haematology malignancy. In IKEMA (Isa-Kd): *Very common:* Infusion reactions, hypertension, diarrhoea, upper respiratory tract infection, pneumonia*, fatigue, dyspnoea, bronchitis, cough, vomiting. *Common:* anaemia, neutropenia, thrombocytopenia, skin cancers, solid tumours other than skin cancers, herpes zoster. Uncommon: Anaphylactic reaction**. Not known: Lymphopenia. In IMROZ (Isa-VRd): Very common: pneumonia, upper respiratory tract infection, bronchitis, COVID-19, neutropenia, thrombocytopenia, dyspnoea, diarrhoea, nausea, vomiting, infusion reaction, decreased appetite, Common: febrile neutropenia, anaemia, herpes zoster, skin cancer, solid tumour (non-skin cancer), atrial fibrillation, weight decreased. Uncommon: haematology malignancy, anaphylactic reaction**. Not known lymphopenia. In GMMG-HD7 (Isa-VRd): Very common: Neutropenia, infusion reactions. Common: Pneumonia, anaemia, thrombocytopenia, lymphopenia, neutrophil count decreased. Uncommon: Anaphylactic reaction**, solid tumours (non-skin cancers). **These adverse events also occurred as serious adverse events. ***Prescribers should consult the SPC in relation to other adverse reactions.* **Marketing Authorisation Holder:** Sanofi Winthrop Industries, 82 avenue Raspail, 94250 Gentilly, France. Date of last revision of SmPC: 18.07.2025 Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu. Before prescribing the product always refer to your full local prescribing information as this information may vary from country to country.

Netherlands:
L01FC02. U.R. Sarclisa wordt vergoed via add-on. Voor prijzen zie de Z-index taxe. Voor meer informatie zie de SmPC op http://www.geneesmiddeleninformatiebank.nl. Lokale vertegenwoordiger: Sanofi B.V. Paasheuvelweg 25, 1105 BP Amsterdam. Tel: +31 (0)20 2454000.

Belgium:
Prescription medication. Reimbursed. The SmPC is available on https://www.afmps.be/. In Belgium Sarclisa is provided by Sanofi Belgium NV, Leonardo Da Vincilaan 19 1831 Diegem, tel +32 27 10 54 00. For questions on our medicinal products, please contact: medical_info.belgium@sanofi.com.

Denmark:
Pakningsstørrelser: 1 htgl. koncentrat (5 ml) til infusionsvæske, opløsning (Vnr. 45 89 04). 1 htgl. koncentrat (25 ml) til infusionsvæske, opløsning (Vnr. 13 30 49). **For dagsaktuel pris** se www.medicinpriser.dk **Udlevering:** BEGR. **Tilskud:** Ikke tilskudsberettiget. **Indehaver af markedsføringstilladelsen**: Sanofi Winthrop Industrie, 82 avenue Raspail, 94250 Gentilly, France. De med * markerede afsnit er omskrevet/forkortet i forhold til det godkendte produktresumé. Produktresuméet kan vederlagsfrit rekvireres hos Sanofi A/S, Lyngbyvej 2, 2100 København Ø.

Norway:
Refusjon: H-resept: L01F C02. Refusjonsberettiget bruk: Isatuxsimab (Sarclisa) som kombinasjonsbehandling med karfilzomib og deksametason ved myelomatose, etter minst en tidligere behandling. Som kombinasjon med bortezomib og deksametason som førstelinjebehandling av voksne pasienter med nydiagnostisert myelomatose hvor autolog stamcelletransplantasjon ikke er aktuelt **Pakninger og priser:** 5 ml (hettegl.) kr 7908,50. 25 ml (hettegl.) kr 39397,30. **Reseptstatus: C Lokal representant:** sanofi-aventis Norge AS, Prof. Kohts vei 5-17, 1325 Lysaker. Tlf: +47 67 10 71 00. Fullstendig preparatomtale finnes på www.legemiddelsok.no/.

Sweden:
Prescription medication. Not reimbursed. L01FC02. The SmPC is available on www.fass.se. In Sweden Sarclisa is provided by Sanofi AB, Box 300 52, 104 25 Stockholm, tel +46 8 634 50 00. For questions on our medicinal products, please contact infoavd@sanofi.com.

Finland
Pakkaukset ja hinnat: Sarclisa TMH 100 mg 558,04 €, 500 mg 2790,18 € Reseptilääke, sairaalalääke. Huom. Tutustu valmisteyhteenvetoon ennen lääkkeen määräämistä. **Lisätiedot:** www.sanofi.fi.