FraminGHam

on multiple myeloma

Supportive care in myeloma –
when treating the clone alone is not enough

Hematology, ASH Education Program, 2024 December 6; 2024(1):569–81

Bortezomib before and after high-dose therapy
in transplant-eligible patients with newly diagnosed
multiple myeloma:
long-term overall survival after more than 10 years
of follow-up from the phase III
HOVON-65/GMMG-HD4 trial

HemaSphere, 2024 November 20; 8(11):e70052

Isatuximab plus bortezomib, lenalidomide,
and dexamethasone for transplant-ineligible
newly diagnosed multiple myeloma patients:
a frailty subgroup analysis of the IMROZ trial

Haematologica, 2025 March 20; Epub ahead of print

Daratumumab or active monitoring
for high-risk smoldering multiple myeloma

The New England Journal of Medicine, 2025 May 8; 392(18):1777–88

ISSUE 1, 2025

CURRENT TITLES

Framingham *on amyloidosis*

Framingham *on atherosclerosis*

Framingham *on benign haematology*

Framingham *on chronic lymphocytic leukaemia*

Framingham *on cystic fibrosis*

Framingham *on dermatology*

Framingham *on diabetes*

Framingham *on endocrinology*

Framingham *on gastroenterology*

Framingham *on gynaecology*

Framingham *on haematological malignancies*

Framingham *on HIV/AIDS*

Framingham *on infectious diseases*

Framingham *on lung cancer*

Framingham *on menopause*

Framingham *on neurology*

Framingham *on respiratory diseases / asthma*

Framingham *on systemic fungal infections*

and many more...

DISCLAIMER

ADVISORY BOARD

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.

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)
Lorraine Law
Kathy Longley
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-2500647 (ver. 1) Jun 2025

SUPPORTIVE CARE IN MYELOMA – WHEN TREATING THE CLONE ALONE IS NOT ENOUGH

Hematology, ASH Education Program, 2024 December 6; 2024(1):569–81

AUTHORS: Zweegman S, van de Donk NW
CENTRE: Department of Hematology, Amsterdam University Medical Center, Universiteit van Amsterdam, Cancer Center Amsterdam, Amsterdam, the Netherlands

BACKGROUND & AIM: While the overall survival of patients with multiple myeloma (MM) has improved thanks to the introduction of effective therapies, treatment-related adverse events mean there has not been an accompanying improvement in quality of life. It is therefore crucial to optimize supportive care in order to maximize patients' outcomes. The aim of this article was to review aspects of supportive care in MM.

ARTICLE TYPE: Expert review.

FINDINGS: Myeloma-related bone disease affects most patients with MM during the course of their disease, and current options for its prevention mainly involve using bisphosphonates to inhibit osteoclast activity. The International Myeloma Working Group (IMWG) recommends that all patients with MM should receive bisphosphonates regardless of the presence of bone disease, as they are associated with fewer pathological fractures and skeletal-related events, and less pain. Zoledronate is the preferred option, with pamidronate and denosumab as alternatives.

The risk of venous thromboembolism is increased in patients with MM, and particularly in those treated with immunomodulatory drugs. The IMWG therefore recommends risk-adapted prophylaxis for all patients receiving therapy, with aspirin for patients at low risk and low-molecular-weight heparin for those at high risk. New tools have been introduced that may help refine risk stratification and aid the choice of anticoagulant regimen in individual patients, and direct oral anticoagulants may be an option for long-term use.

MM therapies targeting GPRC5D (G-protein-coupled receptor, class C, group 5, member D) can cause on-target, off-tumour effects involving the skin, nails and mouth. Evidence suggests that there are fewer such effects with GPRC5D-targeted chimeric antigen receptor T-cell therapy than with bispecific antibodies. While these events are common, they are manageable and do not usually require discontinuation of therapy. There is scope for investigating different dosing schedules to minimize toxicity.

The risk of infections is increased in patients with MM, whose immune system is compromised by both the disease itself and the use of immunomodulatory drugs. The IMWG recommends using prophylactic Ig replacement therapy in patients with serum Ig concentrations of less than 400 mg/dL and in those with severe recurrent infections. Other measures are needed for individuals on T-cell-redirecting therapies, and these are discussed.

CONCLUSION: Supportive care is essential for patients with MM to reduce skeletal-related events, prevent venous thromboembolism, optimize T-cell-redirected therapy and avoid infections.

https://doi.org/10.1182/hematology.2024000579

BORTEZOMIB BEFORE AND AFTER HIGH-DOSE THERAPY IN TRANSPLANT-ELIGIBLE PATIENTS WITH NEWLY DIAGNOSED MULTIPLE MYELOMA:

LONG-TERM OVERALL SURVIVAL AFTER MORE THAN 10 YEARS OF FOLLOW-UP FROM THE PHASE III HOVON-65/GMMG-HD4 TRIAL

HemaSphere, 2024 November 20; 8(11):e70052

AUTHORS: Mai EK, Nogai A, Lokhorst HM, van der Holt B, Zweegman S, Weisel KC, Croockewit S, Jauch A, Hillengass J, Stevens-Kroef M, Raab MS, Broijl A, Bos GM, Brossart P, Ypma P, Hanoun C, Bertsch U, Hielscher T, Salwender HJ, Scheid C, Goldschmidt H, Sonneveld P
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 introduction of proteasome inhibitors, immunomodulatory drugs and monoclonal antibodies has improved the life expectancy of patients with multiple myeloma, and multidrug combinations have been associated with increased progression-free survival and depth of response. However, it is not clear whether these benefits lead to improved long-term overall survival (OS). The aim of this study was to assess the long-term OS of patients with multiple myeloma receiving high-dose, multidrug therapy, with or without bortezomib.

STUDY DESIGN: Investigator-sponsored, multicentre, randomized, open-label, phase 3 trial.

ENDPOINT: OS.

METHOD: The HOVON-65/GMMG-HD4 trial included 827 patients with newly diagnosed, symptomatic multiple myeloma from 75 centres in the Netherlands, Belgium and Germany. One group of participants was randomized to receive induction therapy with vincristine, adriamycin and dexamethasone (VAD), followed by high-dose chemotherapy with melphalan and autologous stem-cell transplantation (ASCT) and then maintenance therapy with thalidomide. The second group received induction therapy with bortezomib, adriamycin and dexamethasone (PAD), followed by ASCT and maintenance therapy with bortezomib. Progression-free survival results after a median follow-up of 96 months have been reported previously, and the current paper reports final long-term OS data.

RESULTS: A total of 508 patients (61%) died. The median follow-up of those still alive, including 78 patients lost to follow-up (n=319), was 11.4 years (interquartile range 10.2–12.3 years). The 12-year OS rate was 32% in the VAD group and 36% in the PAD group, with no significant difference between the two on either univariable Cox regression analysis (hazard ratio 0.87, 95% confidence interval 0.73–1.04; p=0.12) or using a stratified log-rank test (p=0.15). However, PAD was associated with improved OS in patients with International Staging System stage 3 disease (HR 0.66, 95% CI 0.45–0.97), 13q14 deletion (HR 0.68, 95% CI 0.51–0.90) or renal impairment (HR 0.31, 95% CI 0.16–0.57). Multivariable Cox regression analysis found that PAD was significantly associated with an OS benefit (HR 0.84, 95% CI 0.70–1.00; p=0.048).

CONCLUSIONS: More than 30% of patients survived for 12 years or longer, with a small OS improvement seen when combining high-dose chemotherapy with bortezomib versus vincristine. OS was significantly improved with PAD versus VAD in subgroups of patients with stage 3 disease, 13q14 deletion or renal impairment.

https://doi.org/10.1002/hem3.70052

ISATUXIMAB PLUS BORTEZOMIB, LENALIDOMIDE, AND DEXAMETHASONE FOR TRANSPLANT-INELIGIBLE NEWLY DIAGNOSED MULTIPLE MYELOMA PATIENTS:

A FRAILTY SUBGROUP ANALYSIS OF THE IMROZ TRIAL

Haematologica, 2025 March 20; Epub ahead of print

AUTHORS: Manier S, Dimopoulos MA, Leleu XP, Moreau P, Cavo M, Goldschmidt H, Orlowski RZ, Tron M, Tekle C, Brégeault MF, Shafer AT, Beksac M, Facon T
CENTRE FOR CORRESPONDENCE: Department of Hematology, University Hospital Center of Lille, Lille, France

BACKGROUND & AIM: In the phase 3 IMROZ study, the addition of isatuximab to bortezomib, lenalidomide and dexamethasone (Isa-VRd) was associated with significantly improved progression-free survival (PFS) versus bortezomib, lenalidomide and dexamethasone alone (VRd) in transplant-ineligible patients aged 80 years or younger with newly diagnosed multiple myeloma (NDMM). Frail patients do not tolerate myeloma treatment regimens as well as fit patients and have worse outcomes. As such, the aim of this subgroup analysis of the IMROZ data was to investigate the efficacy of Isa-VRd followed by Isa-Rd versus VRd followed by Rd according to patient frailty.

STUDY DESIGN: Post hoc subgroup analysis of an international, open-label, phase 3 study.

ENDPOINTS: Primary: PFS. Key secondary endpoints included rates of complete response or better and minimal residual disease (MRD)-negativity in those with a complete response or better.

METHOD: IMROZ randomized patients aged 80 years or younger with transplant-ineligible NDMM to receive Isa-VRd followed by Isa-Rd (n=265) or VRd followed by Rd (n=181). The simplified International Myeloma Working Group frailty score was used to classify patients at baseline as frail (score ≥2) or non-frail (score 0/1), and analyses of the endpoints were performed according to frailty status. MRD was assessed using next-generation sequencing of bone marrow samples from patients with a complete response or better at a threshold of 10^{-5}.

RESULTS: Overall, 26.7% of patients were classified as frail (69 receiving Isa-VRd and 50 receiving VRd) and 72.0% as non-frail (193 and 128, respectively). After a median follow-up of 59.7 months, PFS was significantly improved with Isa-VRd versus VRd in both non-frail patients (not reached versus 59.70 months; hazard ratio 0.615, 95% confidence interval 0.419–0.903, p=0.0131) and frail patients (not reached versus 28.91 months; HR 0.518, 95% CI 0.294–0.912, p=0.0227). Both frail and non-frail subgroups had higher rates of complete response or better with Isa-VRd versus VRd. In these patients, MRD-negativity was seen in significantly more frail patients treated with Isa-VRd versus VRd (46.4% versus 20.0%; odds ratio 3.459, 95% CI 1.495–8.006, p=0.0030). Definitive discontinuation rates due to treatment-emergent adverse events were similar in both treatment arms regardless of frailty status.

CONCLUSION: Compared with VRd alone, combination therapy with Isa-VRd resulted in significantly improved PFS and deep response rates regardless of frailty status in patients with transplant-ineligible NDMM.

https://doi.org/10.3324/haematol.2024.287200

DARATUMUMAB OR ACTIVE MONITORING FOR HIGH-RISK SMOLDERING MULTIPLE MYELOMA

The New England Journal of Medicine, 2025 May 8; 392(18):1777–88

AUTHORS: Dimopoulos MA, Voorhees PM, Schjesvold F, et al., for the AQUILA Investigators
CENTRE FOR CORRESPONDENCE: Alexandra General Hospital, National and Kapodistrian University of Athens, Athens, Greece

BACKGROUND & AIM: There are no approved treatments for patients with smouldering multiple myeloma (MM) who are at high risk of progressing to active MM. Daratumumab is an anti-CD38 monoclonal antibody that is used to treat MM, and a phase 2 study has reported activity of daratumumab monotherapy in patients with intermediate- or high-risk smouldering MM. The aim of this study was to investigate whether daratumumab delays progression to active disease in patients with high-risk smouldering MM.

STUDY DESIGN: Open-label, multicentre, randomized, phase 3 trial.

ENDPOINTS: Primary: progression-free survival. Secondary endpoints included overall survival, response rate and safety.

METHOD: Adults with smouldering MM who were at high risk for progression to active MM were randomized to receive subcutaneous daratumumab (1800 mg every week in cycles 1 and 2, every 2 weeks in cycles 3–6 and every 4 weeks thereafter; *n*=194) or active monitoring (*n*=196). Treatment was continued for 39 cycles or 36 months, or until disease progression.

RESULTS: At a median follow-up of 65.2 months (range 0–76.6 months), progression to active disease or death had occurred in 34.5% of patients in the daratumumab group versus 50.5% in the active-monitoring group (hazard ratio 0.49, 95% confidence interval 0.36–0.67; $p<0.001$), with a 5-year progression-free survival rate of 63.1% versus 40.8%, respectively. The 5-year overall survival rate was also better with daratumumab, at 93.0% versus 86.9% in the active-monitoring group (HR 0.52, 95% CI 0.27–0.98). A total of 17 patients (8.8%) in the daratumumab group had a complete response or better versus none in the active-monitoring group, with a very good partial response or better in 58 (29.9%) versus two (1.0%) patients, respectively. Overall, 40.4% of patients in the daratumumab group and 30.1% in the active-monitoring group had grade 3/4 adverse events, the most common of which was hypertension (5.7% and 4.6%, respectively). Adverse events led to treatment discontinuation in 11 patients (5.7%) in the daratumumab group and to death in two patients (1.0%; COVID-19 and COVID-19-related pneumonia), but there were no new safety concerns.

CONCLUSIONS: Daratumumab monotherapy was associated with a significantly lower risk of progression to active MM or death compared with active monitoring among patients with high-risk smouldering MM, and higher overall survival. There were no new safety concerns.

https://doi.org/10.1056/NEJMoa2409029

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.