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on multiple myeloma | rare diseases

Second revision of the International Staging System (R2-ISS) for overall survival in multiple myeloma: a European Myeloma Network (EMN) report within the HARMONY project

Journal of Clinical Oncology, 2022 October 10; 40(29):3406–18

Addition of elotuzumab to lenalidomide and dexamethasone for patients with newly diagnosed, transplantation ineligible multiple myeloma (ELOQUENT-1): an open-label, multicentre, randomised, phase 3 trial

The Lancet Haematology, 2022 June; 9(6):e403–14

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Journal of Clinical Oncology, 2022 September 20; 40(27):3132–50

Novel management and screening approaches for haematological complications of Gaucher's disease

Journal of Blood Medicine, 2021 December 7; 12:1045–56

Primary outcomes by 1q21+ status for isatuximab-treated patients with relapsed/refractory multiple myeloma: subgroup analyses from ICARIA-MM and IKEMA

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Prevalence of monoclonal gammopathies and clinical outcomes in a high-risk US population screened by mass spectrometry: a multicentre cohort study

The Lancet Haematology, 2022 May; 9(5):e340–9

LocoMMotion: a prospective, non-interventional, multinational study of real-life current standards of care in patients with relapsed and/or refractory multiple myeloma

Leukemia, 2022 May; 36(5):1371–6

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SECOND REVISION OF THE INTERNATIONAL STAGING SYSTEM (R2-ISS) FOR OVERALL SURVIVAL IN MULTIPLE MYELOMA:

A EUROPEAN MYELOMA NETWORK (EMN) REPORT WITHIN THE HARMONY PROJECT

Journal of Clinical Oncology, 2022 October 10; 40(29):3406–18

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BACKGROUND & AIM: Survival outcomes vary among people with newly diagnosed multiple myeloma (NDMM) according to their risk level. Approximately 60% of those with NDMM have intermediate-risk disease according to the Revised International Staging System (R-ISS). The aim of this study was to update the R-ISS by analysing the additive value of each individual myeloma risk feature.

STUDY DESIGN: Pooled data analysis.

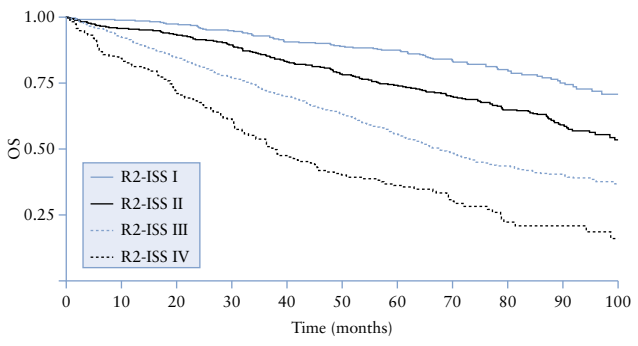
ENDPOINTS: Primary: overall survival (OS). Progression-free survival (PFS) was a secondary endpoint.

METHOD: Individual data were collected from 10,843 people with NDMM enrolled in 16 clinical trials. The top risk features predicting PFS and OS were identified in a training set (*n*=7072), including chromosome 1q gain/amplification. These were used to develop an additive risk scoring system for survival outcomes in multiple myeloma, termed the Second Revision of the ISS (R2-ISS). The R2-ISS was then validated using patient-level data from a separate validation cohort (*n*=3771).

RESULTS: ISS stage, del(17p), lactate dehydrogenase, t(4;14) and 1q+ had the highest impact on PFS and OS in the training set; these variables were simultaneously present in 2226 individuals. A value was assigned to each risk feature according to its impact on OS (ISS-III 1.5 points, ISS-II 1 point, del[17p] 1 point, high lactate dehydrogenase 1 point and 1q+ 0.5 points) and an additive score was generated for each person. Four risk groups were identified according to an individual's overall R2-ISS score: low (R2-ISS I, 19.2%, 0 points), low–intermediate (II, 30.8%, 0.5–1 points), intermediate–high (III, 41.2%, 1.5–2.5 points) and high (IV, 8.8%, 3–5 points). Median OS for these groups, respectively, was not reached, 109.2 months, 68.5 months and 37.9 months (figure); median PFS was 68, 45.5, 30.2 and 19.9 months. Differences between the R2-ISS groups were statistically significant. The prognostic value of the R2-ISS was confirmed in the independent validation set.

CONCLUSION: A revised ISS system, R2-ISS, was developed to improve the risk stratification of people with NDMM.

OS in individuals with NDMM stratified according to the R2-ISS (training set)



https://doi.org/10.1200/JCO.21.02614

ADDITION OF ELOTUZUMAB TO LENALIDOMIDE AND DEXAMETHASONE FOR PATIENTS WITH NEWLY DIAGNOSED, TRANSPLANTATION INELIGIBLE MULTIPLE MYELOMA (ELOQUENT-1):

AN OPEN-LABEL, MULTICENTRE, RANDOMISED, PHASE 3 TRIAL

The Lancet Haematology, 2022 June; 9(6):e403–14

AUTHORS: Dimopoulos MA, Richardson PG, Bahlis NJ, Grosicki S, Cavo M, Beksaç M, Legieć W, Liberati AM, Goldschmidt H, Belch A, Magen H, Larocca A, Laubach JP, Petrucci MT, Reece D, White D, Mateos MV, Špička I, Lazaroiu M, Berdeja J, Kaufman JL, Jou YM, Ganetsky A, Popa McKiver M, Lonial S, Weisel K; for the ELOQUENT-1 investigators
CENTRE FOR CORRESPONDENCE: National and Kapodistrian University of Athens School of Medicine, Athens, Greece

BACKGROUND & AIM: Effective first-line therapies are particularly critical for people with multiple myeloma who are ineligible for haematopoietic stem-cell transplantation (HSCT). Elotuzumab is a humanized monoclonal antibody that, when added to lenalidomide plus dexamethasone – the standard of care (SoC) in this setting – has been reported to reduce the risk of disease progression or death by 30% in people with relapsed/refractory multiple myeloma. The aim of this study was to evaluate this combination in people with previously untreated, newly diagnosed multiple myeloma (NDMM) who are ineligible for HSCT.

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

ENDPOINTS: Primary: progression-free survival. Secondary: overall response rate; overall survival; safety.

METHOD: Adults with NDMM were randomized to receive SoC (lenalidomide + dexamethasone) with or without elotuzumab (n=374 in each arm). Elotuzumab was given intravenously at a dose of 10 mg/kg on days 1, 8, 15 and 22 during cycles 1 and 2 and on days 1 and 15 during cycles 3–18, and then at a dose of 20 mg/kg on day 1 of subsequent cycles.

RESULTS: Overall, 90% and 91% of participants in the elotuzumab and SoC groups, respectively, discontinued treatment owing mainly to disease progression, adverse events unrelated to study drug or study drug toxicity. After a median follow-up of 70.6 months (interquartile range 35.1–79.2 months), median progression-free survival was similar in both groups, at 31.4 months in the elotuzumab arm and 29.5 months in the SoC arm (hazard ratio 0.93, 95.71% confidence interval 0.77–1.12; p=0.44). There was also no difference between the two groups in the overall response rate (83% with elotuzumab versus 79% with SoC; odds ratio 1.26, 95% CI 0.87–1.82; p=0.22) or median overall survival (60.4 versus 57.6 months, respectively; HR 0.99, 95% CI 0.82–1.19; p=0.89). The most common grade 3–4 treatment-related adverse event was neutropenia (17% with elotuzumab and 21% with SoC). Study drug toxicity was reported as the cause of death in 1% of participants in each group.

CONCLUSION: In HSCT-ineligible people with previously untreated NDMM, adding elotuzumab to lenalidomide plus dexamethasone did not significantly improve progression-free or overall survival.

https://doi.org/10.1016/S2352-3026(22)00103-X

CIRCULATING TUMOR CELLS FOR THE STAGING OF PATIENTS WITH NEWLY DIAGNOSED TRANSPLANT-ELIGIBLE MULTIPLE MYELOMA

Journal of Clinical Oncology, 2022 September 20; 40(27):3151–61

AUTHORS: Garcés JJ, Cedena MT, Puig N, Burgos L, Perez JJ, Cordon L, Flores-Montero J, Sanoja-Flores L, Calasanz MJ, Ortiol A, Blanchard MJ, Rios R, Martin J, Martínez-Martinez R, Bargay J, Sureda A, de la Rubia J, Hernandez MT, Rodriguez-Otero P, de la Cruz J, Orfao A, Mateos MV, Martinez-Lopez J, Lahuerta JJ, Rosiñol L, Blade J, San-Miguel JF, Paiva B
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BACKGROUND & AIM: Multiple myeloma is diagnosed using conventional cytology to quantify the clonal expansion of plasma cells in the bone marrow. However, bone marrow infiltration can be patchy, which limits the prognostic value of this procedure. The use of peripheral blood biopsies could provide a more minimally invasive and comprehensive quantification of tumour burden in multiple myeloma. Circulating tumour cell (CTC) numbers in peripheral blood may be a biomarker of the spread of active disease, and quantifying CTCs could provide information on both tumour burden and the dissemination rate. The aim of this study was to examine the clinical significance of CTCs and define optimal cut-offs by which to stratify transplant-eligible individuals with newly diagnosed multiple myeloma (NDMM).

STUDY DESIGN: Prospective assessment of participants in two clinical trials.

ENDPOINTS: Level of CTCs in peripheral blood; ability to predict progression-free survival (PFS).

METHOD: CTCs were measured in the peripheral blood of 374 individuals with NDMM. CTCs in peripheral blood at diagnosis and measurable residual disease (MRD) in bone marrow were assessed using next-generation flow cytometry. Plasma cells in bone marrow aspirates were determined by morphology and flow cytometry. The predictive performance of CTC levels was assessed using multivariable Cox regression models.

RESULTS: CTCs were detected in 344 participants (92%), at a median level of 0.017% (range 0.0002–16%). In multivariable analysis including peripheral blood CTC levels and bone marrow plasma cells, only CTCs were independently prognostic of PFS (hazard ratio 1.1, 95% confidence interval 1.0–1.2; p=0.01). In multivariable analysis including International Staging System stage, lactate dehydrogenase levels and cytogenetic abnormalities, a CTC cut-off of 0.01% was independently prognostic of PFS (HR 2.02, 95% CI 1.3–3.1; p=0.001). At a median follow-up of 5 years, 90% of participants with undetectable CTCs remained progression-free irrespective of complete remission and MRD status. In all other participants with detectable CTCs, only those who gained MRD negativity had a statistically significant increase in PFS ($p \leq 0.045$ in all subgroups).

CONCLUSION: In individuals with NDMM, peripheral blood CTC levels at diagnosis were identified as a risk factor for PFS.

https://doi.org/10.1200/JCO.21.01365

HIGH LEVELS OF CIRCULATING TUMOR PLASMA CELLS AS A KEY HALLMARK OF AGGRESSIVE DISEASE IN TRANSPLANT-ELIGIBLE PATIENTS WITH NEWLY DIAGNOSED MULTIPLE MYELOMA

Journal of Clinical Oncology, 2022 September 20; 40(27):3120–31

AUTHORS: Bertamini L, Oliva S, Rota-Scalabrini D, et al.
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BACKGROUND & AIMS: High levels of circulating tumour plasma cells (CTC-high) are an indicator of aggressive disease in multiple myeloma and may have important prognostic value. The aims of this study were to confirm the prognostic impact of CTC-high and to identify a possible cut-off value to help with predicting survival in the context of concomitant risk factors and minimal residual disease (MRD).

STUDY DESIGN: Multicentre, randomized, phase 2 clinical trial.

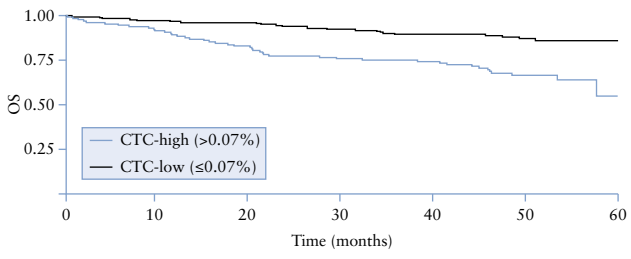
ENDPOINT: Impact of CTC levels on progression-free survival (PFS) and overall survival (OS).

METHOD: The study included adults younger than 65 years (n=401) with newly diagnosed multiple myeloma who were eligible for autologous stem-cell transplantation. The presence of CTC was prospectively evaluated at diagnosis using two-tube single-platform flow cytometry (sensitivity 4×10^{-5}). The impact of different CTC levels was tested using univariate and multivariate Cox proportional hazards analysis for PFS, adjusted for established risk factors (International Staging System score, lactate dehydrogenase level and cytogenetic abnormalities) and depth of response (MRD-negative versus -positive). A prognostic cut-off value that maximized the Harrell's C-statistic was selected.

RESULTS: Participants were followed for a median of 50 months (interquartile range 45–54 months). An optimal CTC cut-off of 0.07% (approximately 5 cells/μL) was established (C-index 0.64). Multivariate analysis revealed that participants with CTC-high had significantly shorter PFS than those with CTC-low (hazard ratio 2.11, 95% confidence interval 1.49–2.97, p<0.001); the 4-year PFS rate was 38% versus 69%, respectively. OS was also significantly shorter among participants with CTC-high versus CTC-low (HR 2.61, 95% CI 1.49–4.56; p<0.001), with a 4-year OS rate of 68% versus 92% (figure). The only factor that reduced the negative impact of CTC-high was reaching MRD negativity (interaction p=0.039).

CONCLUSIONS: In individuals with newly diagnosed multiple myeloma, a CTC level above an optimal cut-off level of 0.07% was identified as an independent high-risk factor for aggressive disease. MRD negativity was the most important factor influencing the negative prognostic impact of CTC.

Kaplan–Meier estimates of OS in participants with CTC-high versus -low



https://doi.org/10.1200/JCO.21.01393

IDENTIFICATION OF HIGH-RISK MULTIPLE MYELOMA WITH A PLASMA CELL LEUKEMIA-LIKE TRANSCRIPTOMIC PROFILE

Journal of Clinical Oncology, 2022 September 20; 40(27):3132–50

AUTHORS: Hofste Op Bruinink D, Kuiper R, van Duin M, Cupedo T, van der Velden VH, Hoogenboezem R, van der Holt B, Beverloo HB, Valent ET, Vermeulen M, Gay F, Broijl A, Avet-Loiseau H, Munshi NC, Musto P, Moreau P, Zweegman S, van de Donk NW, Sonneveld P
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BACKGROUND & AIMS: People with primary plasma cell leukaemia (pPCL) – a high-risk, aggressive subtype of multiple myeloma – can be distinguished from those with newly diagnosed multiple myeloma (NDMM) by the presence of a circulating tumour cell (CTC) level of 20% or higher. However, some individuals with NDMM without such high CTC levels experience an aggressive disease course similar to that seen in pPCL. Molecular determinants of this PCL-like disease remain to be determined. The aims of this study were to define a transcriptomic classifier for PCL-like disease, and to evaluate its prognostic value in the context of conventional high-risk markers in people with NDMM.

STUDY DESIGN: Diagnostic study.

ENDPOINTS: Development and validation of a transcriptomic classifier for PCL-like disease; prognostic value of PCL-like status for progression-free and overall survival.

METHOD: Baseline CTC levels, tumour burden and tumour transcriptomics were obtained from 154 individuals with NDMM and 29 with pPCL. Genes associated with high CTC levels were ranked using linear regression, and the optimal number to distinguish NDMM from pPCL was determined using a 'leave one out' cross-validation analysis. A cut-off for PCL-like disease was established by selecting the minimal PCL-like score to detect all pPCL tumours. The prognostic value of the PCL-like score was assessed in an independent cohort of 2139 individuals with NDMM.

RESULTS: High CTC levels were associated with the expression of 1700 genes, irrespective of tumour burden (false discovery rate <0.05). Of these, 54 genes were used to generate a PCL-like score. A PCL-like score cut-off of 3.55 or higher demonstrated a sensitivity of 93% to identify pPCL. Overall, 10% of NDMM tumours were classified as PCL-like. PCL-like multiple myeloma was similar transcriptionally and cytogenetically to pPCL, but had both a lower CTC level (median 3.0% versus 35%, $p<0.0001$) and tumour burden (median 36% versus 71%, $p=0.045$). Multivariate analyses including Revised International Staging System stage, age and treatment confirmed the significant prognostic value of PCL-like status versus intramedullary multiple myeloma (PCL-like score <3.55) for both progression-free survival (hazard ratio 1.64, 95% confidence interval 1.30–2.07; $p<0.0001$) and overall survival (HR 1.89, 95% CI 1.42–2.50; $p<0.0001$).

CONCLUSIONS: A molecular classifier representing PCL-like disease was developed and validated. This classifier was able to identify a PCL-like transcriptome in a subgroup of individuals with NDMM who did not meet the diagnostic criteria for pPCL.

https://doi.org/10.1200/JCO.21.01217

HOW I TREAT IMMUNE-MEDIATED THROMBOTIC THROMBOCYTOPENIC PURPURA AFTER HOSPITAL DISCHARGE

Blood, 2022 August 4; 140(5):438–44

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BACKGROUND & AIMS: Immune-mediated thrombotic thrombocytopenic purpura (iTTP) is increasingly being recognized as a chronic disease that is associated with a risk of relapse and long-term complications, including cardiovascular and cognitive problems. Treatments for iTTP include plasma exchange, high-dose glucocorticoids, rituximab and caplacizumab. The aims of this article were to review the risk factors for exacerbation, relapse and long-term complications in people with iTTP, and to discuss a strategy for monitoring individuals after hospital discharge.

ARTICLE TYPE: Expert review.

FINDINGS: Clinical exacerbation of iTTP has been defined as recurrent thrombocytopenia (<150×10^9/L), with or without clinical evidence of new or progressive ischaemic organ injury, within 30 days of stopping plasma exchange or anti-von Willebrand factor therapy, with no alternative explanation for thrombocytopenia. The evidence suggests that risk factors for exacerbation might include specific demographics and ADAMTS13 activity, and several studies have shown that persistently low ADAMTS13 levels (or high anti-ADAMTS13 immunoglobulin) are associated with a higher risk. Caplacizumab is the only treatment clearly shown to reduce exacerbation rates, although there are questions over its cost-effectiveness.

Around half of those with iTTP who are not treated with rituximab experience relapse within 5 years of diagnosis. It is therefore important to monitor individuals following remission, including regularly measuring ADAMTS13 activity. Previous relapse, severely deficient ADAMTS13 activity in remission and anti-ADAMTS13 autoantibodies during remission have all been associated with an increased risk of iTTP relapse, but other factors are also involved, including the presence of ultra-large circulating von Willebrand factor multimers. A model including these factors has been developed that might improve the prediction of relapse over ADAMTS13 activity alone, but its clinical application needs more research. Several studies have reported that pre-emptive rituximab can prevent relapse, and there is also some evidence for cyclosporine and splenectomy.

iTTP is associated with several long-term complications, including hypertension, myocardial infarction, cerebrovascular accident, neurocognitive injury, headaches, depression and posttraumatic stress disorder. Preventative strategies include addressing modifiable cardiovascular risk factors and referring to a cardiologist for a baseline evaluation and assessment of cardiovascular risk. In addition, people with signs or symptoms of mood or cognitive issues can be referred for neurocognitive testing.

CONCLUSION: The authors present a post-hospital discharge follow-up schedule to monitor for iTTP exacerbations and discontinuing caplacizumab, and for long-term follow-up to predict the risk of relapse and development of long-term complications.

https://doi.org/10.1182/blood.2021014514

NOVEL MANAGEMENT AND SCREENING APPROACHES FOR HAEMATOLOGICAL COMPLICATIONS OF GAUCHER'S DISEASE

Journal of Blood Medicine, 2021 December 7; 12:1045–56

AUTHORS: Giraldo P, Andrade-Campos M
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BACKGROUND & AIM: Gaucher disease is a multisystem disease, but particularly affects the haematopoietic system as it targets monocyte-macrophages. The aim of this review was to summarize the haematological manifestations and complications associated with Gaucher disease, and the implications for diagnosis and management.

TYPE OF ARTICLE: Systematic review.

FINDINGS: A literature search identified 129 papers about the diagnosis and follow-up of Gaucher disease that included haematological manifestations. Papers covering different populations confirmed that haematological manifestations such as thrombocytopenia and splenomegaly are seen in almost all individuals with Gaucher disease type 1. Anaemia and hepatomegaly are also common. There is, however, considerable variability in haematological manifestations and their severity among individuals.

Diagnostic strategies that incorporate haematological parameters alongside a minimum of clinical suspicion are more cost-effective than other strategies. Haematological parameters are reliable and easily accessible measurements that can be included as part of scoring systems for assessing disease and evaluating treatment outcomes. The biomarkers chitotriosidase, sphingolipid and glucosylsphingosine can be helpful for diagnosis and follow-up.

Bleeding is also a frequent manifestation in Gaucher disease. It is often secondary to thrombocytopenia, but can also be caused by coagulation factor abnormalities or platelet abnormalities. It is important to screen for coagulation disorders in any individual for whom surgery is planned and in pregnancy; the evaluation should include platelet counts and haemostatic function tests.

The treatment of Gaucher disease is aimed at improving haematological parameters, and reducing visceral volumes and bone marrow infiltration. Haematological alterations can be reversed in more than 90% of individuals treated with enzyme replacement or substrate reduction therapy. However, current treatments do not reverse the underlying inflammatory process.

Long-term complications of Gaucher disease include an increased risk of haematological malignancy, particularly B-cell and plasma cell malignancies. Persistent immune alterations, such as polyclonal and monoclonal gammopathies, may also develop. Further research is needed to fully understand these long-term risks.

CONCLUSION: Haematological manifestations are a universal feature of Gaucher disease, and the assessment of haematological parameters is important for diagnosing and managing the disease.

https://doi.org/10.2147/JBM.S279756

TRIPLET THERAPY, TRANSPLANTATION AND MAINTENANCE UNTIL PROGRESSION IN MYELOMA

The New England Journal of Medicine, 2022 July 14; 387(2):132–47

AUTHORS: Richardson PG, Jacobus SJ, Weller EA, et al.; for the DETERMINATION Investigators
CENTRE FOR CORRESPONDENCE: Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, Massachusetts, USA

BACKGROUND & AIM: A previous study indicated that people with newly diagnosed multiple myeloma (NDMM) who are given triplet therapy with lenalidomide, bortezomib and dexamethasone (RVD), followed by lenalidomide maintenance therapy, experience increased progression-free survival benefit but no overall survival benefit with the addition of autologous stem-cell transplantation (ASCT) to their treatment plan. The aim of this study was to further investigate the effects of adding ASCT to RVD plus lenalidomide maintenance in people with NDMM.

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

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

METHOD: Adults aged up to 65 years with symptomatic NDMM received one cycle of RVD. Participants in the RVD-alone group then received two additional RVD cycles plus stem-cell mobilization followed by five additional RVD cycles (n=357), while those in the transplantation group received high-dose melphalan plus ASCT and, on recovery, two additional RVD cycles (n=365). Participants in both groups received lenalidomide maintenance therapy until disease progression or unacceptable side effects.

RESULTS: At a median follow-up of 76.0 months, median progression-free survival was significantly longer in the transplantation group versus the RVD-alone group, at 67.5 versus 46.2 months (hazard ratio 1.53, 95% confidence interval 1.23–1.91; p<0.001). The median duration of response was 56.4 versus 38.9 months, respectively (HR 1.45, 95% CI 1.09–1.93). However, there was no difference in overall survival between the two groups, with an estimated 5-year overall survival rate of 79.2% in the RVD-alone group and 80.7% in the transplantation group (HR 1.10, 95% CI 0.73–1.65; p>0.99). There were also no significant differences between the groups in the percentages of participants with either a partial or complete response or better. Fewer participants in the RVD-alone versus the transplantation group experienced grade 3 or worse treatment-related adverse events (78.2% versus 94.2%) and grade 3 or worse treatment-related haematological adverse events (60.5% versus 89.9%; p<0.001).

CONCLUSION: Among adults with NDMM, RVD plus ASCT was associated with significantly longer progression-free survival than RVD alone, but with no improvement in overall survival.

https://doi.org/10.1056/NEJMoa2204925

ISATUXIMAB PLUS CARFILZOMIB AND DEXAMETHASONE VERSUS CARFILZOMIB AND DEXAMETHASONE IN ELDERLY PATIENTS WITH RELAPSED MULTIPLE MYELOMA:

IKEMA SUBGROUP ANALYSIS

Hematological Oncology, 2022 December; 40(5):1020–29

AUTHORS: Facon T, Moreau P, Martin TG, Spicka I, Oriol A, Koh Y, Lim A, Mikala G, Rosiñol L, Yağci M, Cavo M, Yong K, Risse ML, Asset G, Schwab S, Martinez G
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BACKGROUND & AIM: In the IKEMA trial, the addition of the anti-CD38 antibody isatuximab to carfilzomib plus dexamethasone (Kd) significantly improved progression-free survival (PFS) compared with Kd alone in people with relapsed multiple myeloma (MM). The aim of this IKEMA subgroup analysis was to investigate the efficacy and safety of this combination according to participant age.

STUDY DESIGN: Subgroup analysis of a prospective, randomized, open-label, active-controlled, phase 3 clinical trial.

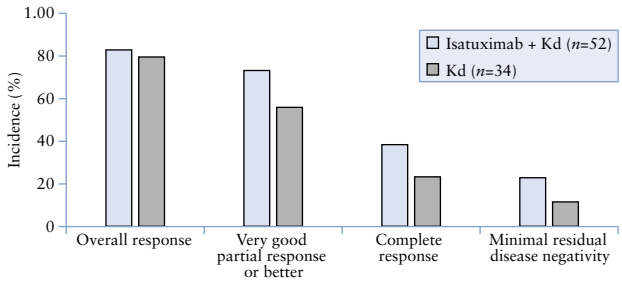
ENDPOINTS: Primary: PFS. Secondary: depth of response; safety.

METHOD: In the IKEMA study, participants with relapsed MM following one to three previous treatments were randomized to receive either isatuximab plus Kd (*n*=179) or Kd alone (*n*=123). Isatuximab was given intravenously at a dose of 10 mg/kg every week for 4 weeks and then every 2 weeks. The current analysis looked at efficacy among elderly (age ≥70 years; *n*=86) and younger (age <70 years; *n*=216) participants.

RESULTS: Compared with Kd alone, the addition of isatuximab significantly improved PFS among both elderly (hazard ratio 0.36, 95% confidence interval 0.18–0.75) and younger participants (HR 0.61, 95% CI 0.38–0.97). In addition, isatuximab plus Kd was associated with a greater depth of response (figure). Although the incidence of grade 3 or worse treatment-emergent adverse events (TEAEs) was higher with isatuximab plus Kd versus Kd alone among both elderly (90.2% versus 76.5%) and younger participants (71.4% versus 63.6%), the incidence of serious TEAEs was similar in both arms (72.5% versus 70.6% and 54.0% versus 52.3%, respectively). The most common grade 3 or worse TEAEs among both elderly and younger participants were hypertension and pneumonia, with similar incidences in both arms. Definitive discontinuation of treatment owing to TEAEs was less frequent with isatuximab plus Kd than Kd in both elderly and younger participants (11.8% versus 23.5% and 7.1% versus 10.2%, respectively).

CONCLUSION: In participants with relapsed MM, isatuximab plus Kd had a manageable safety profile and improved PFS in both elderly (≥70 years) and younger individuals.

Depth of response in the elderly group (age ≥70 years)



https://doi.org/10.1002/hon.3038

PRIMARY OUTCOMES BY 1Q21+ STATUS FOR ISATUXIMAB-TREATED PATIENTS WITH RELAPSED/REFRACTORY MULTIPLE MYELOMA:

SUBGROUP ANALYSES FROM ICARIA-MM AND IKEMA

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BACKGROUND & AIM: Gain or amplification of 1q21 (1q21+) is found in approximately 40% of people with multiple myeloma at diagnosis, and the severity of this abnormality increases with disease progression. In the phase 3 ICARIA-MM and IKEMA studies, the addition of isatuximab to pomalidomide–dexamethasone or carfilzomib–dexamethasone increased progression-free survival (PFS) in participants with relapsed/refractory multiple myeloma, and subgroup analyses indicated a potential benefit among those with 1q21+. The aim of the current study was to investigate the effects of isatuximab in four groups of participants from ICARIA-MM and IKEMA, based on 1q21+ status and the presence of high-risk chromosomal abnormalities (HRCA).

STUDY DESIGN: Subgroup analysis of two randomized, open-label, phase 3 trials.

ENDPOINTS: Primary: PFS. Secondary endpoints included overall survival and the overall response rate.

METHOD: This analysis included 241 ICARIA-MM and 265 IKEMA participants in whom cytogenetic risk was assessable. Participants had relapsed/refractory multiple myeloma and were treated with pomalidomide–dexamethasone or carfilzomib–dexamethasone, with or without the addition of isatuximab. The presence of 1q21+ was evaluated using CD138+ plasma cells, and four subgroups of participants were examined: 1q21+ (≥3 copies with or without HRCA), isolated 1q21+ (≥3 copies without HRCA), gain(1q21) (3 copies with or without HRCA) and amp(1q21) (≥4 copies with or without HRCA). Analyses were performed using an unstratified Cox regression model.

RESULTS: Adding isatuximab to pomalidomide–dexamethasone was associated with a significant improvement in median PFS among participants with 1q21+ (9.5 versus 3.8 months; hazard ratio 0.40, 95% confidence interval 0.25–0.63), as well as a numerical improvement in median overall survival (21.3 versus 13.9 months; HR 0.72, 95% CI 0.48–1.07). There was a clear benefit of adding isatuximab among all subgroups of participants, regardless of HRCA. Adding isatuximab to carfilzomib–dexamethasone was again associated with a significant improvement in median PFS (not reached versus 16.2 months; HR 0.57, 95% CI 0.33–0.98). There were also benefits in other participant 1q21 subgroups.

CONCLUSION: Adding isatuximab to the standard-of-care backbone therapy improved the outcomes of participants with relapsed/refractory multiple myeloma with gain or amplification of 1q21.

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PREVALENCE OF MONOCLONAL GAMMOPATHIES AND CLINICAL OUTCOMES IN A HIGH-RISK US POPULATION SCREENED BY MASS SPECTROMETRY:

A MULTICENTRE COHORT STUDY

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BACKGROUND & AIM: Monoclonal gammopathy of undetermined significance (MGUS) is a premalignant clonal expansion of plasma cells that has a 1% yearly risk of progression to multiple myeloma. Previous studies evaluating the prevalence of MGUS were based mainly on serum protein electrophoresis and immunofixation electrophoresis, which have limited sensitivity in detecting lower-level monoclonal gammopathies. Furthermore, most of these studies were performed in majority White populations, while the prevalence of MGUS is known to be much higher in Black individuals. The aim of this study was to evaluate the prevalence and clinical implications of monoclonal gammopathies screened by quantitative mass spectrometry in individuals at high risk for multiple myeloma on the basis of Black race and family history of haematological malignancy.

STUDY DESIGN: Cohort study.

ENDPOINT: Detection of monoclonal gammopathy.

METHOD: Serum samples from 7622 individuals were screened and quantified for monoclonal gammopathies using quantitative matrix-assisted laser desorption ionization–time of flight (MALDI-TOF) mass spectrometry and EXENT-iQ software. Overall, 6305 participants (83%) had high-risk features for multiple myeloma (i.e. Black race or family history of haematological malignancies). M-protein concentrations at the monoclonal gammopathy of indeterminate potential (MGIP) level (<0.2 g/L) were confirmed by liquid chromatography–mass spectrometry testing.

RESULTS: Monoclonal gammopathy was detected in 36% (*n*=2740) of the overall screened cohort. Mass-spectrometry MGUS was detected in 10% (*n*=755) of the cohort and MGIP in 26% (*n*=1952). The prevalence of MGUS among high-risk individuals was 36% (*n*=2269/6305). The prevalence of MGUS among high-risk individuals aged 50 years or older was 6% (*n*=101/1714) using serum protein electrophoresis with immunofixation electrophoresis and 43% (*n*=1788/4207) using mass spectrometry. The prevalence of both MGIP and mass-spectrometry MGUS increased with age, and the prevalence of mass-spectrometry MGUS was significantly higher in men versus women (*p*=0.0002). Having any mass-spectrometry–detected monoclonal gammopathy was associated with increased all-cause mortality (hazard ratio 1.55, 95% confidence interval 1.16–2.08; *p*=0.0035). All monoclonal gammopathies were associated with an increased chance of comorbidities.

CONCLUSIONS: Individuals at high risk for multiple myeloma, defined by self-reported Black race and family history of haematological malignancy, were found to have a high prevalence of monoclonal gammopathies, including age-associated MGIP.

https://doi.org/10.1016/S2352-3026(22)00069-2

LOCOMMOTION: A PROSPECTIVE, NON-INTERVENTIONAL, MULTINATIONAL STUDY OF REAL-LIFE CURRENT STANDARDS OF CARE IN PATIENTS WITH RELAPSED AND/OR REFRACTORY MULTIPLE MYELOMA

Leukemia, 2022 May; 36(5):1371–6

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BACKGROUND & AIM: Although advances in medical treatment have improved survival for people with multiple myeloma, the condition remains incurable and most individuals will eventually progress through treatment with proteasome inhibitors, immunomodulatory drugs and anti-CD38 monoclonal antibodies. It is unclear how such heavily pretreated, triple-class–exposed individuals are managed in the real-world, and what outcomes they can expect. The aim of this study was therefore to investigate the management and outcomes of this population in everyday clinical practice.

STUDY DESIGN: Ongoing, multinational, prospective, non-interventional study.

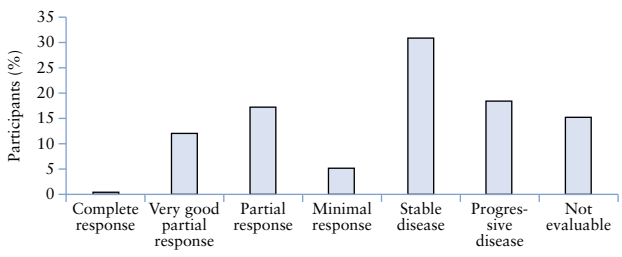
ENDPOINTS: Primary: overall response rate. Secondary endpoints included progression-free and overall survival. Safety was also assessed.

METHOD: Adults with relapsed/refractory multiple myeloma (RRMM) who had received at least three prior lines of therapy or were double-refractory to a proteasome inhibitor and immunomodulatory drug were recruited from 63 European and 13 US sites between August 2019 and October 2020 (n=248). Participants were treated with standard-of-care (SoC) therapies (i.e. non-experimental therapies used in local clinical practice to treat adults with RRMM) and followed for survival and subsequent treatments.

RESULTS: At a median follow-up of 11.01 months (range 0.1–19.2 months), participants had received a median of 4.0 (range 1–20) lines of SoC therapy and were treated for a median of 3.9 months (range <1.0–18.0 months). The overall response rate was 29.8% (figure). Overall, 92 unique SoC treatment regimens were used, and 160 participants (64.5%) received combinations of at least three drugs. The most frequently used proteasome inhibitors, immunomodulatory drugs and anti-CD38 monoclonal antibodies were carfilzomib (25.4%), pomalidomide (29.8%) and daratumumab (9.3%), respectively. Median progression-free and overall survival were 4.6 and 12.4 months, respectively. Treatment-emergent adverse events were reported in 83.5% of participants (grade 3/4 in 52.8%).

CONCLUSION: This population of heavily pretreated, triple-class–exposed participants with RRMM received 92 different SoC treatments, with poor outcomes.

Best response to SoC treatment



https://doi.org/10.1038/s41375-022-01531-2

Notes

Prescribing Information: CABLIVI (caplacizumab) ▼ 10 mg powder and solvent for solution for injection
Please refer to the Summary of Product Characteristics (SPC) before prescribing.

***Presentations:** Each vial of powder contains 10 mg of caplacizumab*. Each pre-filled syringe of solvent contains 1 mL of water for injections.
*Indication: CABLIVI is indicated for the treatment of adults and adolescents of 12 years of age and older weighing at least 40 kg experiencing an episode of acquired thrombotic thrombocytopenic purpura (aTTP), in conjunction with plasma exchange and immunosuppression
***Dosage and Administration:** Treatment with CABLIVI should be initiated and supervised by physicians experienced in the management of patients with thrombotic microangiopathies. *Posology: First dose:* Intravenous injection of 10 mg of caplacizumab prior to plasma exchange. *Subsequent doses:* Daily subcutaneous administration of 10 mg of caplacizumab after completion of each plasma exchange for the duration of daily plasma exchange treatment, followed by daily subcutaneous injection of 10 mg of caplacizumab for 30 days after stopping daily plasma exchange treatment. If at the end of this period there is evidence of unresolved immunological disease, it is recommended to optimise the immunosupression regimen and continue daily subcutaneous administration of 10 mg of caplacizumab until the signs of underlying immunological disease are resolved (e.g. sustained normalisation of ADAMTS13 activity level). In the clinical development program, caplacizumab has been administered daily for up to 65 days *Missed dose:* If a dose of CABLIVI is missed, it can be administered within 12 hours. If more than 12 hours have passed since the dose was to have been given, the missed dose should NOT be administered and the next dose should be administered per the usual dosing schedule. *Dose adjustments:* No dose reduction of CABLIVI is recommended. ***Special Populations:** *Renal impairment:* No dose adjustment is necessary. *Hepatic impairment:* No dose adjustment is necessary. No data regarding the use of caplacizumab in patients with severe acute or chronic hepatic impairment are available. Use of Cablivi in this population requires a benefit/risk assessment and close clinical monitoring. *Elderly:* While experience with the use of caplacizumab in the elderly is limited, there is no evidence to suggest that dose adjustment or special precautions are needed for elderly patients. *Paediatric population*: The safety and efficacy of caplacizumab in the paediatric population have not been established in clinical trials. The posology of Cablivi in adolescents of 12 years of age and older weighing at least 40 kg is the same as in adults. No recommendations can be made on the posology of Cablivi for paediatric patients below 40 kg of body weight
***Contraindications:** Hypersensitivity to the active substance or to any of the 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. *Bleeding: Active clinically significant bleeding*: In case of active, clinically significant bleeding, treatment with Cablivi should be interrupted. If needed, the use of von Willebrand Factor concentrate could be considered to correct hemostasis. Cablivi should only be restarted upon the advice of a physician experienced in the management of thrombotic microangiopathies. *Increased risk of bleeding:* In the setting of concomitant use of oral anticoagulants or high dose heparin. Due to a potential increased risk of bleeding, initiation or continuation of treatment with oral anticoagulants or high dose heparin requires a benefit/risk assessment and close clinical monitoring. *In the setting of concomitant use of anti-platelet agents and / or low molecular weight heparin (LMWH):* While no increased risk of bleeding was observed in clinical trials, concomitant treatment with antiplatelet agents and / or LMWH requires a benefit/risk assessment and close clinical monitoring. *In patients with coagulopathies:* Due to a potential increased risk of bleeding, use of Cablivi in patients with underlying coagulopathies (e.g. hemophilia, other coagulation factor deficiencies) is to be accompanied by close clinical monitoring. *In patients undergoing surgery:* If a patient is to undergo elective surgery or a dental procedure, the patient should be advised to inform the physician or dentist that they are using Cablivi, and treatment should be stopped at least 7 days before the planned intervention. The patient should also notify the physician who supervises the treatment with Cablivi about the planned procedure. If emergency surgery is needed, the use of von Willebrand Factor concentrate could be considered to correct hemostasis.
****Interactions:*** No interaction studies evaluating use of caplacizumab with oral anticoagulants (e.g. vitamin K antagonists, direct oral anticoagulants [DOAC] such as thrombin inhibitors or factor Xa inhibitors) or high dose heparin have been performed.
Pregnancy, lactation and fertility: There are no data on the use of caplacizumab in pregnant women. As a precautionary measure, it is preferable to avoid the use of Cablivi during pregnancy. There are no data on the use of caplacizumab in breastfeeding women. It is unknown whether caplacizumab is excreted in human milk. A risk to the child cannot be excluded. A decision must be made whether to discontinue breastfeeding or to abstain/discontinue from therapy, taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman. The effects of caplacizumab on fertility in humans are unknown.
***Adverse Reactions:** The most frequent adverse reactions in clinical trials were epistaxis, headache and gingival bleeding. The most common serious adverse reaction was epistaxis. In clinical studies, bleeding events occurred in different body systems, independent of treatment duration. In the post marketing setting, cases of major bleeding, including life-threatening and fatal bleeding have been reported in patients receiving caplacizumab, mainly

in those using concomitant anti-platelet agents or anticoagulants. ***Prescribers should consult the SPC in relation to other adverse reactions.***

Marketing Authorisation Holder: Ablynx NV, Technologiepark 21, 9052 Zwijnaarde, Belgium.

Denmark:
Pakningsstørrelser: Enkelstyks pakning: 1 hætteglas med pulver, 1 fyldt injektionssprøjte med solvens, 1 hætteglasadapter, 1 hypodermisk kanyle, 2 alkoholservietter. Flerstyks pakning: 7 enkelstyks pakninger eller 7 hætteglas med pulver, 7 fyldte injektionssprøjter med solvens, 7 hætteglasadaptere, 7 hypodermiske kanyler og 14 alkoholservietter. For dagsaktuel pris se www.medicinpriser.dk. **Udlevering:** BEGR. **Tilskud:** Ikke tilskudsberettiget. **Indehaver af markedsføringstilladelsen:** Ablynx NV, Technologiepark 21, 9052 Zwijnaarde, Belgien. 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. Dato for reklamematerialet: 11.02.2023.

Finland:
Pakkaukset ja hinnat (TH ei alv, 15.10.2019): 1x1ml pakkaus (sis. 10 mg kaplasitsumabia): 4354,81 €; vmh+alv 5309,63 €. **Korvattavuus:** Sairaalavalmiste. Ei sv-korvattavuutta. Reseptilääke. Tutustu valmisteyhteenvetoon ennen lääkkeen määräämistä. **Myyntiluvan haltija:** Ablynx NV. **Markkinoija:** Sanofi Oy, www.sanofi.fi **Lisätiedot:** ks. valmisteyhteenveto.

Norway:
Reseptstatus: C **Pakninger/priser:** 1 sett (hettegl. + ferdigfylt sprøyte) varenummer 039371, Pris: 56 558,50
Refusjon: Nei
Lokal representant: sanofi-aventis Norge A/S, Prof. Kohts vei 5-17, 1325 Lysaker.
Fullstendig preparatomtale finnes på www.legemiddelsok.no

Sweden:
Prescription medication. Not reimbursed. B01AX07. The SmPC is available on www.fass.se. In Sweden Cablivi 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. Date for last SmPC review: June 2022

This medicinal product is subject to additional monitoring.

Compulsaroy 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.
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. Sarclisa is indicated in combination with carfilzomib and dexamethasone, for the treatment of adult patients with multiple myeloma who have received at least one prior therapy.
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; Paracetamol 650 mg to 1000 mg oral (or equivalent); Diphenhydramine 25 mg to 50 mg IV or oral (or equivalent [e.g., cetirizine, promethazine, dexchlorpheniramine]). The IV route 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 and before isatuximab and carfilzomib administration. Patients who do not experience an infusion reaction upon their first 4 administrations of SARCLISA may have their need for subsequent premedication reconsidered. *Managing 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 4 neutropenia, SARCLISA administration should be delayed until neutrophil count improves to at least 1.0×10^9/L. *Posology:* The recommended dose of SARCLISA is 10 mg/kg body weight administered as an IV infusion in combination with pomalidomide and dexamethasone

(Isa-Pd regimen) or in combination with carfilzomib and dexamethasone (Isa-Kd regimen). *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. For other medicinal products that are administered with SARCLISA, refer to the respective current summary of product characteristics. The administration schedule must be carefully followed. *Missed dose:* If a 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. *Infusion rates:* please refer to full SmPC.
Special Populations: *Elderly:* no dose adjustment is recommended. *Patients with mild to severe renal impairment:* no dose adjustment is recommended. *Patients with mild hepatic impairment:* no dose adjustment is recommended. 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):* No data available.
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:* Infusion reactions, mostly mild or moderate, have been observed in 38.2% of patients treated with SARCLISA in ICARIA-MM (Isa-Pd regimen), and in 45.8% of patients in the IKEMA trial (Isa-Kd regimen). 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 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. Serious infusion reactions including severe anaphylactic reactions have been observed after SARCLISA administration. 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 after interruption of SARCLISA infusion, persist or worsen despite appropriate treatment with medicinal products, require hospitalization or are life-threatening, permanently discontinue SARCLISA and institute appropriate management. *Neutropenia:* In patients receiving Isa-Pd, neutropenia occurred as a laboratory abnormality in 96.1% of patients and as an adverse reaction in 46.7% of patients, with Grade 3-4 neutropenia reported as a laboratory abnormality in 84.9% of patients and as an adverse reaction in 45.4% of patients. Neutropenic complications have been observed in 30.3% of patients, including 11.8% of febrile neutropenia and 25.0% of neutropenic infections. In patients treated with Isa-Kd, neutropenia occurred as a laboratory abnormality in 54.8% of patients and as an adverse reaction in 4.5% of patients, with Grade 3-4 neutropenia reported as a laboratory abnormality in 19.2% of patients (with 17.5% Grade 3 and 1.7% Grade 4) and as an adverse reaction in 4.0% of patients. Neutropenic complications have been observed in 2.8% of patients, including 1.1% of febrile neutropenia and 1.7% of neutropenic infections. Complete blood cell counts should be monitored periodically during treatment. Patients with neutropenia should be monitored for signs of infection. *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. Antibiotics and antiviral prophylaxis can be considered during treatment. *Second primary malignancies (SPMs):* In ICARIA-MM, SPMs were reported in 6 patients (3.9%) treated with Isa-Pd and in 1 patient (0.7%) treated with Pd, and included skin cancer in 4 patients treated with Isa-Pd and in 1 patient treated with Pd. Patients continued treatment after resection of the skin cancer. In IKEMA, SPMs were reported in 13 patients (7.3%) treated with Isa-Kd and in 6 patients (4.9%) treated with Kd. SPMs were skin cancers in 9 patients (5.1%) treated with Isa-Kd and in 3 patients (2.5%) treated with Kd, and were solid tumours other than skin cancer in 5 patients (2.8%) treated with Isa-Kd and in 4 patients (3.3%) treated with Kd. One patient (0.6%) 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. The overall incidence of SPMs in all the SARCLISA-exposed patients is 3.6%. 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). 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, an anti-CD38 antibody, 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:* Neutropenia, infusion reactions, pneumonia*, upper respiratory tract infection, diarrhoea, bronchitis, dyspnoea, nausea, febrile neutropenia*, vomiting. *Common:* Decreased appetite, weight decreased, atrial fibrillation, skin squamous cell carcinoma, Herpes Zoster. In IKEMA (Isa-Kd): *Very common:* Infusion reactions, hypertension, diarrhoea, upper respiratory tract infection, pneumonia*, fatigue, dyspnoea, bronchitis, cough, *Common:* Skin cancers, neutropenia, solid tumours other than skin cancers. *Uncommon:* Anaphylactic reaction*. *These adverse events also occurred as serious adverse events.
In IKEMA (Isa-Kd), Very common: Pneumonia, Upper respiratory tract infection, bronchitis, neutropenia, febrile neutropenia, dyspnoea, diarrhoea, nausea, vomiting, infusion reaction. *Common: Herpes zoster, skin squamous cell carcinoma, decreased appetite, atrial fibrillation, weight decreased. Uncommon: Anaphylactic reactions.
Prescribers should consult the SPC in relation to other adverse reactions.
Marketing Authorisation Holder: Sanofi-aventis groupe, 54 rue La Boétie, 75008 Paris, France.
Date of last revision of SmPC: December 2022

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, Frankrig. 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.
Version: 5. Dato for reklamematerialet: 21.02.2023

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

Norway:
Reseptstatus: C Pakninger og priser: Hetteglass 5 ml, vnr 458904, **Pris** 7 908,50/ Hetteglass 25 ml, vnr 133049, Pris 39 397,30. **Refusjon:** Beslutning fra Beslutningsforum avventes.
Lokal representant: sanofi-aventis Norge AS, Prof. Kohts vei 5-17, 1325 Lysaker.
Fullstendig preparatomtale finnes på www.legemiddelsok.no/

Sweden:
Prescription medication. Not reimbursed. L01XC38. 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.

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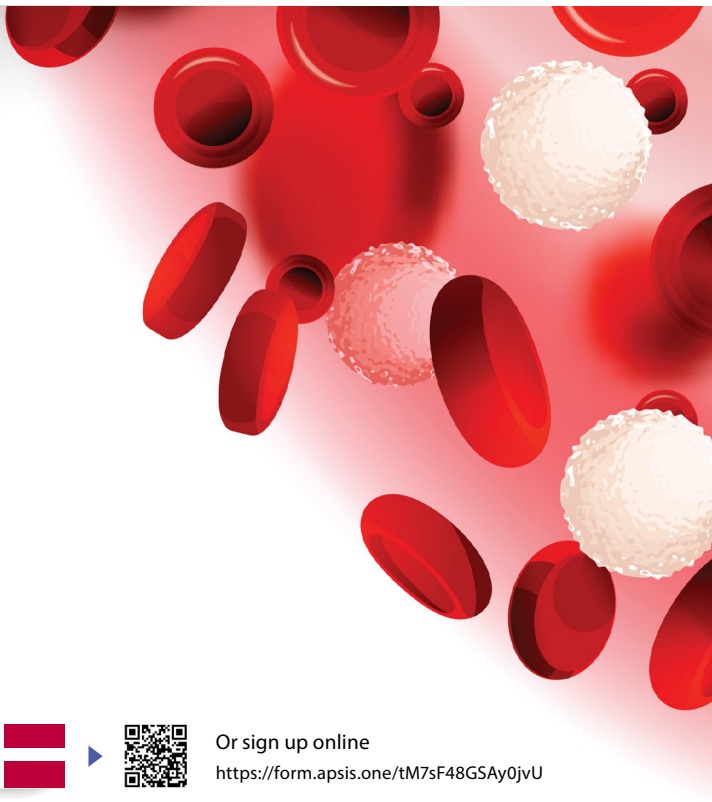

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to make a difference for patients with
hematological diseases.

We invest in a number of scientific and educational projects to support continuing education and to facilitate fast dissemination of relevant information. One of them is Framingham in Multiple Myeloma with the addition of Gauchers disease and aTTP.

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