FraminGHam

on multiple myeloma | rare diseases

Elotuzumab plus pomalidomide and dexamethasone for relapsed/refractory multiple myeloma: final overall survival analysis from the randomized phase II ELOQUENT-3 trial

Journal of Clinical Oncology, 2023 January 20; 41(3):568–78

Isatuximab plus carfilzomib and dexamethasone in relapsed multiple myeloma patients with high-risk cytogenetics: IKEMA subgroup analysis

European Journal of Haematology, 2022 November; 109(5):504–12

Long-term follow-up of patients treated with caplacizumab and safety and efficacy of repeat caplacizumab use: post-HERCULES study

Journal of Thrombosis and Haemostasis, 2022 December; 20(12):2810–22

Early cytopenias and infections after standard of care idecabtagene vicleucel in relapsed or refractory multiple myeloma

Blood Advances, 2022 December 27; 6(24):6109–19

Chromosome 1q21 aberrations identify ultra high-risk myeloma with prognostic and clinical implications

American Journal of Hematology, 2022 September; 97(9):1142–9

Impact of comorbidities on health-related quality of life in nontransplant eligible patients with newly diagnosed multiple myeloma

HemaSphere, 2022 June 21; 6(7):e744

Quality of life, psychological distress, and prognostic perceptions in caregivers of patients with multiple myeloma

Blood Advances, 2022 September 13; 6(17):4967–74

and more...

ISSUE 2, 2023

CURRENT TITLES

Framingham *on anaesthesiology and surgery*

Framingham *on atherosclerosis*

Framingham *on cystic fibrosis*

Framingham *on dermatology*

Framingham *on endocrinology*

Framingham *on gastroenterology*

Framingham *on gynaecology*

Framingham *on lung cancer*

Framingham *on neurology*

Framingham *on osteoporosis*

Framingham *on ovarian cancer*

Framingham *on respiratory diseases*

Framingham *on systemic fungal infections*

Framingham *on urology*

and many more...

OUR PURPOSE

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

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

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

Issues are published every three to six months.

DISCLAIMER

Framingham

Editor
Catherine Booth

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

Medical Writers (this issue)
Milena Braga-Basaria
Derek Collett
Kathy Croom
Jane Grills
Gill Gummer
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 | rare diseases* is supported by
Sanofi AB
Stockholm, Sweden
MAT-DK-2200539 (ver.2.0) 02 2023

ELOTUZUMAB PLUS POMALIDOMIDE AND DEXAMETHASONE FOR RELAPSED/REFRACTORY MULTIPLE MYELOMA:

FINAL OVERALL SURVIVAL ANALYSIS FROM THE RANDOMIZED PHASE II ELOQUENT-3 TRIAL

Journal of Clinical Oncology, 2023 January 20; 41(3):568–78

AUTHORS: Dimopoulos MA, Dytfeld D, Grosicki S, Moreau P, Takezako N, Hori M, Leleu X, LeBlanc R, Suzuki K, Raab MS, Richardson PG, Popa McKiver M, Jou YM, Yao D, Das P, San-Miguel J
CENTRE FOR CORRESPONDENCE: National and Kapodistrian University of Athens School of Medicine, Alexandra Hospital, Athens, Greece

BACKGROUND & AIM: The initial analysis from the ELOQUENT-3 trial found that treatment with pomalidomide/dexamethasone (Pd) plus elotuzumab (EPd) improved progression-free survival over Pd alone in participants with relapsed/refractory multiple myeloma (RRMM). The aim of this paper was to report the final overall survival (OS) results from ELOQUENT-3.

STUDY DESIGN: Multicentre, randomized, controlled, open-label, phase 2 study.

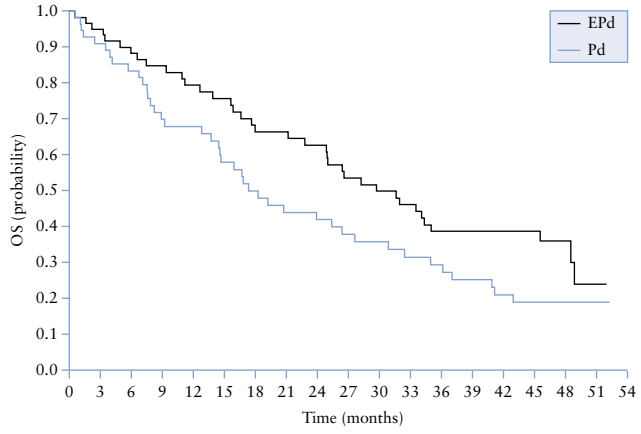
ENDPOINT: OS (secondary outcome of ELOQUENT-3).

METHOD: Adults with RRMM that was refractory to at least two lines of therapy including lenalidomide and a proteasome inhibitor were randomized to receive EPd (*n*=60) or Pd (*n*=57). Treatment was administered in 28-day cycles. Participants in the EPd group received elotuzumab (10 mg/kg intravenously) once daily on days 1, 8, 15 and 22 in cycles 1 and 2, and 20 mg/kg once daily on day 1 of each cycle thereafter. Pomalidomide (4 mg orally) was given once daily on days 1–21 of each cycle and dexamethasone (40/20 mg orally in those aged ≤75/>75 years) once weekly. On the days of elotuzumab administration, participants in the EPd group received both oral (28/8 mg) and intravenous (8 mg) dexamethasone.

RESULTS: At data cut-off after a minimum follow-up of 45 months, 61.7% of participants in the EPd group and 74.5% in the Pd group had died, most commonly because of disease progression (EPd 41.7%, Pd 49.1%). Median OS was significantly longer with EPd versus Pd, at 29.8 versus 17.4 months (hazard ratio 0.59, 95% confidence interval 0.37–0.93; *p*=0.0217; figure). OS rates were higher with EPd versus Pd at all time points, at 79% versus 68% at 1 year, 63% versus 44% at 2 years and 39% versus 29% at 3 years. There were no new safety concerns.

CONCLUSION: In people with RRMM previously treated with lenalidomide and a proteasome inhibitor, a statistically significant improvement in OS was demonstrated with EPd versus Pd.

Kaplan–Meier curve of OS



https://doi.org/10.1200/JCO.21.02815

PERSPECTIVES ON THE RISK-STRATIFIED TREATMENT OF MULTIPLE MYELOMA

Blood Cancer Discovery, 2022 July 6; 3(4):273–84

AUTHORS: Davies FE, Pawlyn C, Usmani SZ, San-Miguel JF, Einsele H, Boyle EM, Corre J, Auclair D, Cho HJ, Lonial S, Sonneveld P, Stewart AK, Bergsagel PL, Kaiser MF, Weisel K, Keats JJ, Mikhael JR, Morgan KE, Ghobrial IM, Orlowski RZ, Landgren CO, Gay F, Caers J, Chng WJ, Chari A, Walker BA, Kumar SK, Costa LJ, Anderson KC, Morgan GJ
CENTRE FOR CORRESPONDENCE: Clinical Myeloma Program, NYU Langone Perlmutter Cancer Center, New York, New York, USA

BACKGROUND & AIMS: Improved treatments for multiple myeloma (MM) have led to better outcomes in some but not all individuals. Many people – especially those with high-risk disease (table) – do not respond to treatment, or experience disease relapse and rapid progression. Improvements in diagnosis and a move towards a personalized risk-stratified approach based on the use of clinical and biochemical parameters and tumour-acquired genetic variants could help improve the survival of people with high-risk disease. The aims of this article were to discuss how outcomes may be improved in this population, and to provide recommendations for the design of clinical trials in high-risk MM.

ARTICLE TYPE: Review.

FINDINGS: Recommendations for improving outcomes in people with high-risk MM include optimizing both diagnosis (including risk stratification) and treatment (using the most appropriate therapy from the current therapeutic armamentarium). Current MM staging systems lack sensitivity and specificity for risk stratification. Newer technologies that may be able to enhance the ability to detect high-risk disease include gene-expression profiling, whole-exome sequencing, whole-genome sequencing, and the use of targeted panels and imaging analysis.

There is a need for clinical trials in individuals with high-risk MM and for phase 2/3 studies looking at risk stratification in such populations. Participants should be selected using an agreed set of cytogenetic, interphase FISH, mutational and expression-based markers. The efficacy endpoints traditionally used in MM clinical trials – progression-free and overall survival – remain appropriate, but the reporting of these and other outcomes (e.g. response rates and timings, and safety) needs to be standardized to allow better comparison of results across trials. The timing of sample collection and analysis of samples also need to be standardized so that the impact of therapy on biologically distinct segments of MM contributing to high-risk disease can be determined.

CONCLUSION: Accurate risk stratification could help improve the outcomes of individuals with high-risk MM.

Features of high-risk MM

Clinical	Extramedullary disease Large focal lesions Plasma cell leukaemia Primary refractoriness to treatment
Laboratory and genetic	Revised International Staging System score Cytogenetic features • t(4;14) • t(14;16) • t(14;20) • gain(1q) • TP53 deletion/mutation High-risk gene-expression profile
Functional	Relapse in 12–18 months after an initial response to therapy
Novel	Microenvironment features on single-cell analysis and advanced imaging

https://doi.org/10.1158/2643-3230.BCD-21-0205

TECLISTAMAB IN RELAPSED OR REFRACTORY MULTIPLE MYELOMA

The New England Journal of Medicine, 2022 August 11; 387(6):495–505

AUTHORS: Moreau P, Garfall AL, van de Donk NW, et al.
CENTRE FOR CORRESPONDENCE: Hematology Clinic, University Hospital Hôtel-Dieu, Nantes, France

BACKGROUND & AIM: Treatment options for people with multiple myeloma who progress despite standard therapy with immunomodulatory agents, proteasome inhibitors and anti-CD38 antibodies are limited and their prognosis is poor. Teclistamab is a T-cell-redirecting, bispecific antibody that targets both CD3 expressed on the surface of T cells and B-cell maturation antigen expressed on the surface of myeloma cells, which results in the lysis of myeloma cells expressing this antigen. In phase 1 of the multicohort Study of Teclistamab in Participants with Relapsed or Refractory Multiple Myeloma (MajesTEC-1), teclistamab produced responses in participants with relapsed or refractory multiple myeloma. The aim of this paper was to report the efficacy and safety results of the pivotal phase 1–2 part of MajesTEC-1.

STUDY DESIGN: Open-label, phase 1–2 study.

ENDPOINTS: Overall response; response duration; progression-free survival; measurable residual disease (MRD); adverse events.

METHOD: The study involved 165 participants with relapsed or refractory multiple myeloma who had previously received at least three lines of therapy, including an immunomodulatory drug, proteasome inhibitor and anti-CD38 antibody. All received teclistamab, 1.5 mg/kg per week subcutaneously, following step-up doses of 0.06 and 0.3 mg/kg. An overall response was defined as a partial response or better and MRD was assessed by next-generation sequencing of DNA from bone marrow aspirates.

RESULTS: After a median follow-up of 14.1 months (range 0.3–24.4 months), the overall response rate was 63.0% (104/165) and 26.7% (44/165) of participants were MRD-negative. Among the 39.4% (65/165) of participants who had a complete response or better, 46% (30/65) were MRD-negative. The median response duration was 18.4 months and median progression-free survival was 11.3 months. The most common adverse events of any grade were cytokine release syndrome (72.1% of participants), neutropenia (70.9%), anaemia (52.1%) and thrombocytopenia (40.0%). Moreover, grade 3 or 4 events were observed for these four conditions in 0.6%, 64.2%, 37.0% and 21.2% of participants, respectively. Neurotoxic events, including immune effector cell-associated neurotoxicity syndrome, were seen in 14.5% of participants and were mainly grade 1/2.

CONCLUSIONS: In people with relapsed or refractory multiple myeloma who had received at least three previous lines of therapy, teclistamab was associated with an overall response rate of 63% and a median response duration of 18.4 months. Toxic effects consistent with T-cell redirection were mostly low grade.

https://doi.org/10.1056/NEJMoa2203478

ISATUXIMAB PLUS CARFILZOMIB AND DEXAMETHASONE IN RELAPSED MULTIPLE MYELOMA PATIENTS WITH HIGH-RISK CYTOGENETICS:

IKEMA SUBGROUP ANALYSIS

European Journal of Haematology, 2022 November; 109(5):504–12

AUTHORS: Spicka I, Moreau P, Martin TG, Facon T, Martinez G, Oriol A, Koh Y, Lim A, Mikala G, Rosiñol L, Yağci M, Cavo M, Risse ML, Asset G, Macé S, van de Velde H, Yong K
CENTRE FOR CORRESPONDENCE: 1st Department of Medicine – Department of Hematology, First Faculty of Medicine, Charles University and General Hospital, Prague, Czech Republic

BACKGROUND & AIM: The presence of the high-risk chromosomal abnormalities t(4;14), del(17p) and t(14;16) is a negative prognostic factor in people with multiple myeloma (MM). In the phase 3 IKEMA study, the addition of the monoclonal antibody isatuximab to carfilzomib and dexamethasone (Isa-Kd) significantly improved progression-free survival (PFS) compared with carfilzomib and dexamethasone alone (Kd) in participants with relapsed MM. The aim of this subgroup analysis was to examine the efficacy and safety of Isa-Kd in IKEMA participants with high-risk cytogenetics.

STUDY DESIGN: Subgroup analysis of a multicentre, randomized, controlled, parallel-group, open-label phase 3 study.

ENDPOINTS: Primary: PFS. Secondary endpoints included minimal residual disease (MRD) negativity, very good partial response or better (≥VGPR) rate, complete response rate and safety.

METHOD: Data from participants with relapsed MM and abnormalities in at least one of del(17p) (50% cut-off), t(4;14) or t(14;16) (30% cut-off) were extracted from the IKEMA study database, and study outcomes were analysed for this subgroup.

RESULTS: Overall, 23.5% (*n*=42/179) and 25.2% (*n*=31/123) of IKEMA participants treated with Isa-Kd and Kd, respectively, had at least one high-risk chromosomal abnormality. In these participants, treatment with Isa-Kd versus Kd improved PFS, at a median of not reached versus 18.201 months (hazard ratio 0.724, 95% confidence interval 0.361–1.451). Further analysis showed that improved PFS was more pronounced in participants with t(4;14) (median PFS not reached with Isa-Kd versus 11.138 months with Kd; HR 0.549, 95% CI 0.232–1.301) compared with del(17p) (median PFS not reached versus 19.154 months; HR 0.837, 95% CI 0.281–2.496). Similarly, an improved depth of response (similar to that seen in standard-risk participants) with Isa-Kd was seen only in participants with t(4;14). Compared with participants treated with Kd alone, these participants had improved rates of ≥VGPR (72.7% versus 50.0%), MRD negativity (31.8% versus 25.0%) and complete response (36.4% versus 20.0%). No separate efficacy analyses were conducted in participants with t(14;16) because of small participant numbers. Grade 3 or worse treatment-emergent adverse events were more common with Isa-Kd than Kd (85.7% versus 63.3%) among participants with high-risk cytogenetics, but the incidence of serious events was similar in the two arms (64.3% versus 66.7%).

CONCLUSION: Isa-Kd improved outcomes among people with relapsed MM and the high-risk chromosomal abnormality t(4;14), with a manageable safety profile.

https://doi.org/10.1111/ejh.13835

ANTI-CD38 ANTIBODY THERAPY FOR PATIENTS WITH RELAPSED/REFRACTORY MULTIPLE MYELOMA:

DIFFERENTIAL MECHANISMS OF ACTION AND RECENT CLINICAL TRIAL OUTCOMES

Annals of Hematology, 2022 October; 101(10):2123–37

AUTHORS: Leleu X, Martin T, Weisel K, Schjesvold F, Iida S, Malavasi F, Manier S, Min CK, Ocio EM, Pawlyn C, Perrot A, Quach H, Richter J, Spicka I, Yong K, Richardson PG
CENTRE FOR CORRESPONDENCE: Service d'Hematologie Et Therapie Cellulaire, CHU and CIC Inserm 1402, Poitiers Cedex, France

BACKGROUND & AIM: The transmembrane glycoprotein CD38 has important roles in regulating calcium signalling and in the migration of leukocytes to tumour microenvironments. Its high expression on multiple myeloma (MM) cells makes it an ideal therapeutic target. Two humanized monoclonal antibodies targeting CD38 – isatuximab and daratumumab – have demonstrated antimyeloma activity as monotherapy and combined with other agents, with manageable safety profiles. Both are approved for the treatment of people with relapsed and/or refractory MM (RRMM). Daratumumab is also approved for use in people with newly diagnosed MM and those with light-chain amyloidosis. The aim of this review was to compare the mechanisms of action of and the results of key clinical studies investigating isatuximab and daratumumab in people with RRMM.

ARTICLE TYPE: Expert review.

FINDINGS: The therapeutic effects of antibodies targeting CD38 are exerted via Fc-dependent immune mechanisms (antibody-dependent cellular cytotoxicity, complement-directed cytotoxicity and antibody-directed cellular phagocytosis) and direct effector mechanisms on MM cells (e.g. inhibition of CD38 enzymatic activity, direct apoptosis). However, the extent to which isatuximab and daratumumab effect each of these mechanisms differs, probably because the two antibodies bind to distinct, non-overlapping epitopes on the CD38 molecule. Further studies are required to elucidate how differences in the mechanisms of action of the two antibodies may translate into better clinical outcomes for people with MM.

In phase 3 clinical trials, both isatuximab and daratumumab in combination with either pomalidomide or carfilzomib (both plus dexamethasone) have substantially improved progression-free survival in people with RRMM. Isatuximab has also demonstrated efficacy in subgroups of people with renal impairment, soft-tissue plasmacytomas or 1q21 gain. To date, randomized head-to-head trials comparing the two agents are lacking. In addition, evidence for the use of isatuximab or daratumumab in people who have progressed following treatment with anti-CD38 mono- or combination therapy is limited.

Further clinical data from larger populations are required to inform the optimal anti-CD38 antibody therapeutic strategies in people with RRMM (e.g. the appropriate sequence of anti-CD38 antibody therapies and criteria for the optimal selection and timing of antibody therapy).

CONCLUSIONS: The anti-CD38 antibodies isatuximab and daratumumab exert similar antimyeloma activity through varying mechanisms of action in people with RRMM. Further studies are required to better define their role in the management of those with RRMM.

https://doi.org/10.1007/s00277-022-04917-5

AN INTEGRATED MULTIOMIC APPROACH AS AN EXCELLENT TOOL FOR THE DIAGNOSIS OF METABOLIC DISEASES:

OUR FIRST 3720 PATIENTS

European Journal of Human Genetics, 2022 September; 30(9):1029–35

AUTHORS: Almeida LS, Pereira C, Aanicai R, et al.
CENTRE FOR CORRESPONDENCE: CENTOGENE GmbH, Rostock, Germany

BACKGROUND & AIM: Inherited metabolic disorders (IMDs) comprise a large group of individually rare genetic diseases that disrupt the metabolic pathway. It is essential to recognize and to treat these diseases early in order to prevent neurological impairment or death, and there have been significant improvements in the diagnosis of IMDs over the last few years. The aim of this article was to present the authors' experience of using an integrated multiomic approach as a first-line diagnostic tool for people with a suspected IMD.

STUDY DESIGN: Observational cohort study.

ENDPOINT: IMD diagnosis.

METHOD: The study included 3720 individuals from 62 countries who were assessed using a next-generation sequencing panel that integrated genetic and biochemical testing. The panel included 206 genes with single-nucleotide and copy-number variant detection, followed by semiautomatic variant filtering and reflex biochemical testing. Selected variants were evaluated for their pathogenicity and causality, and classified as pathogenic, likely pathogenic, variant of uncertain significance, likely benign or benign. Reports were issued that took into account these findings, together with the individual's phenotype, clinical suspicion and other laboratory results. Reports were considered to be positive for individuals with pathogenic/likely pathogenic variants that explained their phenotype; unclear for individuals with a variant of uncertain significance compatible with the clinical phenotype; and negative for individuals with no relevant variant.

RESULTS: A genetic diagnosis was achieved in 1389 individuals (37% of the cohort). The diagnostic yield was highest for those from Asia (60%), followed by Africa (41%) and Latin America (29%). A total of 701 pathogenic/likely pathogenic unique single-nucleotide variants were identified, as well as 40 unique copy-number variants. The results of biochemical testing influenced the final diagnosis in 620 individuals and more than 120 different diseases were diagnosed, the most common of which were Gaucher disease, Niemann–Pick disease type A/B, phenylketonuria, mucopolysaccharidosis type I and Wilson disease.

CONCLUSION: Integrated genetic and biochemical testing influenced decisions on the clinical relevance of variants and had a diagnostic yield of 37%.

https://doi.org/10.1038/s41431-022-01119-5

LONG-TERM FOLLOW-UP OF PATIENTS TREATED WITH CAPLACIZUMAB AND SAFETY AND EFFICACY OF REPEAT CAPLACIZUMAB USE:

POST-HERCULES STUDY

Journal of Thrombosis and Haemostasis, 2022 December; 20(12):2810–22

AUTHORS: Scully M, de la Rubia J, Pavenski K, Metjian A, Knöbl P, Peyvandi F, Cataland S, Coppo P, Kremer Hovinga JA, Minkue Mi Edou J, De Passos Sousa R, Callewaert F, Gunawardena S, Lin J
CENTRE FOR CORRESPONDENCE: University College London Hospitals, London, UK

BACKGROUND & AIM: The efficacy of caplacizumab for the treatment of immune-mediated thrombotic thrombocytopenic purpura (iTTP) was demonstrated in the phase 3 HERCULES trial, which reported significant reductions in mortality, iTTP recurrence and thromboembolic events with caplacizumab compared with placebo, as well as a faster normalization of platelet count. Real-world studies have confirmed these results, but data are still lacking on the long-term outcomes of individuals treated with caplacizumab. The aim of this study was therefore to investigate the long-term safety and efficacy of caplacizumab in people with iTTP.

STUDY DESIGN: Prospective follow-up study.

ENDPOINTS: Safety; TTP-related events (TTP-related death, recurrence and major thromboembolic events).

METHOD: The study included 104 adults with iTTP who had participated in the HERCULES trial for 3 years, during which they had received caplacizumab (*n*=75) or placebo (*n*=29). Following HERCULES, they were followed-up twice a year for a further 3 years. Those experiencing iTTP recurrence (defined as recurrent thrombocytopenia requiring initiation of therapeutic plasma exchange) during this time could receive open-label caplacizumab with therapeutic plasma exchange and immunosuppressive therapy. Participants receiving caplacizumab were seen weekly throughout treatment, and adverse events were assessed over the whole study period and during recurrences.

RESULTS: Among all participants, the incidence of adverse events in the post-HERCULES study period was 91% among those who had received caplacizumab during HERCULES and 90% among those who had received placebo. The incidences of serious adverse events were 37% and 55%, respectively, while the incidences of TTP-related events were 8% and 38%, respectively. A total of 19 participants (15% of the caplacizumab-treated group and 28% of the placebo group) experienced one or more iTTP recurrences during the post-HERCULES study period, of whom 13 were treated with open-label caplacizumab. All first episodes of recurrence resolved or were resolving in participants who received caplacizumab, including nine participants who had repeat caplacizumab use. All six second recurrences (all treated with caplacizumab) also resolved. The safety profile of caplacizumab was similar to that reported in HERCULES.

CONCLUSION: These post-HERCULES study results support the long-term safety and efficacy of caplacizumab for iTTP, including its repeated use for recurrences.

https://doi.org/10.1111/jth.15892

EARLY CYTOPENIAS AND INFECTIONS AFTER STANDARD OF CARE IDECABTAGENE VICLEUCEL IN RELAPSED OR REFRACTORY MULTIPLE MYELOMA

Blood Advances, 2022 December 27; 6(24):6109–19

AUTHORS: Logue JM, Peres LC, Hashmi H, et al.
CENTRE FOR CORRESPONDENCE: Department of Blood and Marrow Transplant and Cellular Immunotherapy; H. Lee Moffitt Cancer Center and Research Institute, Tampa, Florida, USA

BACKGROUND & AIM: Idecabtagene vicleucel (ide-cel) is an autologous anti–B-cell maturation agent CAR-T cell therapy that is approved in the USA for the treatment of people with relapsed/refractory multiple myeloma (RRMM) after four lines of therapy. In the pivotal phase 2 KarMMa study, grade 3 or worse cytopenias and infections were common, most often within the first 8 weeks following infusion. The aim of this study was to characterize the early immune effects in people with RRMM receiving standard-of-care ide-cel in a real-world setting.

STUDY DESIGN: Retrospective analysis.

ENDPOINTS: Incidence of cytopenias and infections in the first 100 days after infusion.

METHOD: The study included data from adults with RRMM who received ide-cel at three US centres. Individuals underwent apheresis according to institutional standard-of-care procedures for ide-cel treatment. Fludarabine and cyclophosphamide lymphodepletion (LD) conditioning was carried out, followed by ide-cel infusion. Antibiotic prophylaxis was provided and supportive therapies to manage cytopenias were given as needed at the discretion of the treating physician.

RESULTS: Overall, 52 individuals with RRMM received LD conditioning treatment followed by ide-cel infusion and 47 had 90 days of follow-up. After ide-cel, 94% of individuals experienced grade 3 or worse cytopenia at day 7. Haematological parameters improved with time, but any grade 3 or worse cytopenia was still present in 65% of individuals at day 30 and in 40% at day 90. Within 100 days of ide-cel infusion, 54% of individuals developed an infection, with severe infections (grade ≥3) in 23%. Infections that developed within the first 30 days were typically bacterial (68%) and severe (50%); of those occurring later (days 31–100), 50% were bacterial and 42% were viral, and only 13% were severe. In univariate analysis, a high pre–CAR-T marrow myeloma burden (≥50%), circulating plasma cells at pre-LD and grade 3 or worse anaemia pre-LD were associated with grade 3 or worse cytopenia at days 30 and 90. The only significant risk factor for infections was a longer time from last bridging treatment to LD (median 29 versus 15 days).

CONCLUSIONS: Cytopenias and infections were found to be common following ide-cel treatment in people with RRMM. Infections within 30 days of treatment were typically bacterial and severe, while moderate viral infections were more prevalent after this point.

https://doi.org/10.1182/bloodadvances.2022008320

CHROMOSOME 1Q21 ABERRATIONS IDENTIFY ULTRA HIGH-RISK MYELOMA WITH PROGNOSTIC AND CLINICAL IMPLICATIONS

American Journal of Hematology, 2022 September; 97(9):1142–9

AUTHORS: Kastritis E, Migkou M, Dalampira D, Gavriatopoulou M, Fotiou D, Roussou M, Kanellias N, Ntanasis-Stathopoulos I, Malandrakis P, Theodorakakou F, Sevastoudi A, Eleutherakis-Papaiakovou E, Triantafyllou T, Terpos E, Katodritou E, Dimopoulos MA
CENTRES: Department of Clinical Therapeutics, National and Kapodistrian University of Athens, School of Medicine, Athens; Department of Hematology, Theageneion Cancer Hospital, Thessaloniki, Greece

BACKGROUND & AIM: Gain/amplification of 1q21 (+1q21) is a common cytogenetic abnormality in people with multiple myeloma (MM), but its prognostic impact is unclear. The aim of this study was to further investigate the prognostic implications of +1q21 in individuals with newly diagnosed, symptomatic MM.

STUDY DESIGN: Retrospective cohort study.

ENDPOINTS: Presence of +1q21 and associations with survival.

METHOD: Data were analysed from 912 consecutive individuals with symptomatic MM who were diagnosed and treated in a single centre between 2004 and 2021. All individuals had been tested for +1q21 at diagnosis using standard FISH, with positivity defined as at least 20% of clonal cells harbouring +1q21. An independent cohort of 272 consecutive individuals from a second centre was used to validate the results.

RESULTS: At initial diagnosis, 249 participants (27.3%) had +1q21, of whom 150 (16.4%) had three copies and 99 (10.9%) had four or more copies. Individuals with +1q21 were older (p=0.026), more anaemic (p<0.001), and had lower platelet counts (p<0.001) and worse renal function (p=0.004) than those without +1q21. The presence of +1q21 was also associated with advanced International Staging System (ISS) stage (p=0.003), advanced Revised (R)-ISS stage (p<0.001) and the concurrent presence of t(4;14), t(14;16) and del13q cytogenetic aberrations (p<0.001, p=0.005 and p<0.001, respectively). Compared with individuals without +1q21, those with +1q21 had shorter median progression-free survival (PFS) (34 versus 20 months, p<0.001) and overall survival (OS) (75 versus 44 months, p<0.001). However, there was no additional prognostic impact of the 1q21 copy number. On multivariate analysis adjusted for R-ISS stage, age, treatment and use of high-dose melphalan, +1q21 was found to be an independent prognostic factor for both PFS (hazard ratio 1.503, 95% confidence interval 1.207–1.872; p<0.001) and OS (HR 1.410, 95% CI 1.092–1.821; p=0.008). Participants with R-ISS stage 3 and +1q21 were identified as a separate ultra-high-risk group, with OS of 16.6 months (versus 43 months for those with R-ISS stage 3 without +1q21; p=0.028). These findings were validated in the independent cohort.

CONCLUSIONS: In participants with newly diagnosed, symptomatic MM, the presence of +1q21 was associated with more advanced disease and worse PFS and OS. Participants with both R-ISS stage 3 disease and +1q21 constituted an ultra-high-risk group.

https://doi.org/10.1002/ajh.26639

IMPACT OF COMORBIDITIES ON HEALTH-RELATED QUALITY OF LIFE IN NONTRANSPLANT ELIGIBLE PATIENTS WITH NEWLY DIAGNOSED MULTIPLE MYELOMA

HemaSphere, 2022 June 21; 6(7):e744

AUTHORS: Bennink MC, Stege CA, Lissenberg-Witte BI, Oerlemans S, Seefat MR, Sonneveld P, Zweegman S
CENTRES FOR CORRESPONDENCE: Department of Haematology, Erasmus University Medical Center, Rotterdam, the Netherlands

BACKGROUND & AIM: The availability of novel therapies has led to notable improvements in the overall survival of people with multiple myeloma (MM). However, long-term treatment can result in adverse events that can negatively impact health-related quality of life (HRQoL). Although most people with MM are diagnosed when they are elderly (median age 70 years) and are therefore likely to have comorbidities, only limited data are available on the HRQoL of people with both MM and comorbidities. The aim of this study was therefore to investigate the impact of comorbidities on HRQoL in non-transplant eligible individuals with newly diagnosed multiple myeloma (NDMM).

STUDY DESIGN: Post hoc analysis of a randomized controlled trial.

ENDPOINT: Change in HRQoL.

METHOD: In the HOVON87/NMSG18 trial, adults with NDMM (age ≥65 years or age <65 years and non-transplant eligible) received induction therapy with melphalan–prednisone plus thalidomide followed by thalidomide maintenance, or with melphalan–prednisolone plus lenalidomide followed by lenalidomide maintenance. The current analysis included participants with both a Charlson Comorbidity Index score and an HRQoL assessment at baseline (n=552). HRQoL was assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30, and change in HRQoL over time was compared in participants with versus without comorbidities.

RESULTS: At baseline, 172 participants had at least one comorbidity and 380 had no comorbidities. Baseline global health status/quality of life, physical functioning and dyspnoea were significantly worse in participants with versus without comorbidities. After induction therapy, participants with comorbidities had significantly worse HRQoL in all subscales except pain. After 12 months of maintenance therapy, however, participants with versus without comorbidities had significantly worse scores only in the domains of physical functioning (p=0.015) and role functioning (p=0.037). At the same timepoint, more participants with comorbidities reported problematic functioning and symptoms in the area of physical functioning (80% versus 62%, p=0.042), but not in any other domains. There was no influence of treatment arm on the course of HRQoL between the two groups.

CONCLUSION: Although people with NDMM and comorbidities experienced greater functional limitations and more HRQoL symptoms than those without comorbidities, the difference became less pronounced with maintenance therapy.

https://doi.org/10.1097/HS9.0000000000000744

QUALITY OF LIFE, PSYCHOLOGICAL DISTRESS, AND PROGNOSTIC PERCEPTIONS IN CAREGIVERS OF PATIENTS WITH MULTIPLE MYELOMA

Blood Advances, 2022 September 13; 6(17):4967–74

AUTHORS: O'Donnell EK, Shapiro YN, Yee AJ, Nadeem O, Laubach JP, Branagan AR, Anderson KC, Mo CC, Munshi NC, Ghobrial IM, Sperling AS, Agyemang EA, Burke JN, Harrington CC, Hu BY, Richardson PG, Raje NS, El-Jawahri A
CENTRES: Massachusetts General Hospital Cancer Center; Harvard Medical School; Dana-Farber Cancer Institute; Brigham and Women's Hospital, Boston; Mass General/North Shore Cancer Center, Danvers, Massachusetts, USA

BACKGROUND & AIMS: The caregivers of people with multiple myeloma (MM) play a vital role in supporting their loved ones throughout the course of their illness. However, there is little information on the impact of this on caregivers' lives. The aims of this study were to examine the impact of MM on the quality of life (QoL) and psychological distress of caregivers, and to evaluate caregivers' prognostic perceptions.

STUDY DESIGN: Multicentre, prospective, cross-sectional study.

ENDPOINTS: Caregiver QoL; psychological distress; perceptions of prognosis.

METHOD: Caregivers were defined as a relative or friend who lived with the person with MM or had in-person contact with them at least twice per week. A total of 127 caregivers were recruited into the study and completed validated questionnaires that assessed their QoL (Caregiver Oncology QoL questionnaire), psychological distress (Hospital Anxiety and Depression Scale) and perceptions of their loved one's prognosis (Perception of Treatment and Prognosis questionnaire).

RESULTS: The median caregiver age was 61.8 years (range 24.0–81.9 years) and 91 caregivers (71.7%) were female. Neither the QoL nor the psychological distress of caregivers differed according to the number of lines of therapy their loved one had received. Clinically significant anxiety, depression and posttraumatic stress disorder symptoms were reported by 44.1%, 15.7% and 24.4% of caregivers, respectively. When assessed as patient–caregiver dyads, higher proportions of caregivers versus individuals with MM reported clinically significant anxiety (44.4% versus 22.6%). Overall, 89.6% of caregivers reported that it is 'extremely' or 'very' important to know their loved one's prognosis. Most caregivers (84.2%) said they had been informed that the disease was incurable. Despite this, only 50.9% acknowledged that the cancer was terminal and only 53.6% thought that their loved one's disease was incurable.

CONCLUSIONS: The caregivers of people being treated for MM were found to have a substantial burden of psychological distress, particularly anxiety. Most caregivers of people with MM acknowledged that they had been told the disease was incurable, yet a substantial number retained the belief that their loved one's cancer was curable.

https://doi.org/10.1182/bloodadvances.2022007127

LENALIDOMIDE, BORTEZOMIB AND DEXAMETHASONE INDUCTION THERAPY FOR THE TREATMENT OF NEWLY DIAGNOSED MULTIPLE MYELOMA:

A PRACTICAL REVIEW

British Journal of Haematology, 2022 October; 199(2):190–204

AUTHORS: McCaughan GJ, Gandolfi S, Moore JJ, Richardson PG
CENTRES: Department of Haematology, St Vincent's Hospital; Medicine and Health, University of New South Wales, Sydney, New South Wales, Australia; Translational Research Program, University of Helsinki; Haematology Research Unit, University of Helsinki and Helsinki University Hospital, Helsinki, Finland; Jerome Lipper Multiple Myeloma Center, Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, Massachusetts, USA

BACKGROUND & AIM: For people with newly diagnosed multiple myeloma (NDMM), the preferred induction regimen is a combination of lenalidomide, bortezomib and dexamethasone (RVD), which has been associated with a good response rate, clinical improvements and manageable toxicity in phase 3 trials. The use of RVD is increasing worldwide. The aim of this review was to provide practical guidance on RVD induction treatment in people with NDMM.

TYPE OF ARTICLE: Expert review.

FINDINGS: For most transplant-eligible individuals with multiple myeloma, RVD has become the standard-of-care induction therapy. Between 45% and 67% of individuals have been reported to have a very good partial response or better and, after transplantation, the rate is 66–75%. In addition, significant improvements in progression-free and overall survival have been observed in individuals ineligible for transplantation and these benefits appear to extend to those aged ≥65 years.

Although the optimal number of RVD cycles has still to be determined, clinicians tend to use 3–6 cycles prior to transplantation and 8–12 cycles if transplantation is deferred. Cumulative toxicity needs to be considered and a balance must be found between achieving the best response and toxicity. A number of RVD schedules have been proposed, such as RVD classic, RVD lite, RVD premium lite and RVD ultra lite. These vary in cycle length and bortezomib and lenalidomide doses. For older and frailer individuals and those with significant comorbidities, less-intensive regimens with a longer cycle length and reduced doses have been suggested to lower the risks of toxicity and drug discontinuation. Consolidation therapy with RVD following transplantation remains controversial but everyone should receive maintenance lenalidomide therapy at this point.

During induction therapy, individuals should receive supportive care to minimize toxicities, including, for example: (a) antiviral prophylaxis due to the high risk of varicella zoster reactivation; (b) venous thromboembolism prophylaxis; (c) nitrogen-containing bisphosphonate therapy; and (d) saline infusion to minimize fatigue and neurotoxicity. Haematological toxicities and diarrhoeal and skin rash symptoms can be managed by dose reduction.

Adding a CD38-directed monoclonal antibody to RVD treatment has recently been shown to improve response, progression-free survival and minimal residual disease rates in transplant-eligible individuals.

CONCLUSIONS: Induction therapy with lenalidomide, bortezomib and dexamethasone is associated with excellent response rates in people with NDMM, whether or not they undergo transplantation. Toxicities can be managed by using less-intensive regimens and with supportive care.

https://doi.org/10.1111/bjh.18295

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 x 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

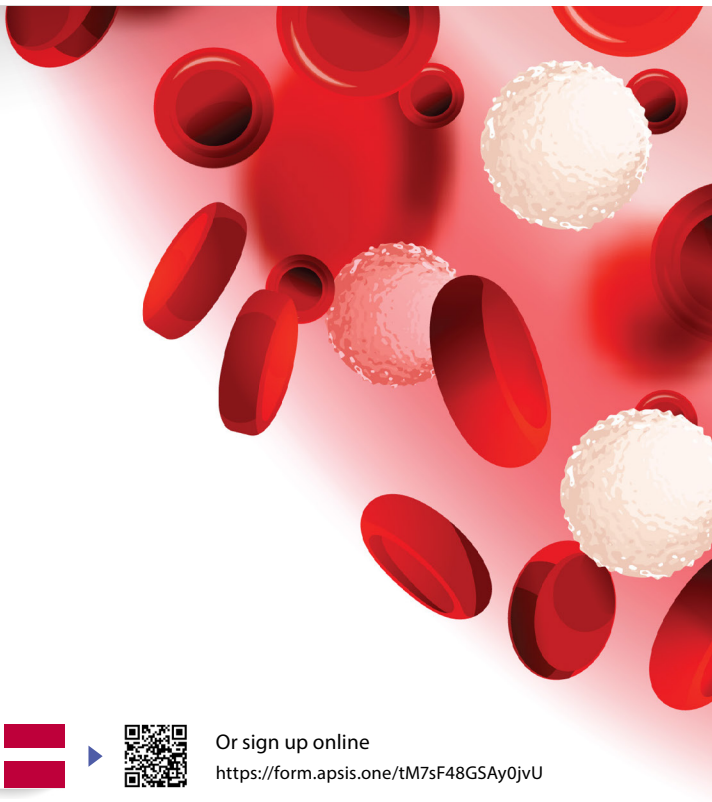
Finland
Pakkaukset ja hinnat: Sarclisa TMH 100 mg 558,04 €, 500 mg 2790,18 € Reseptilääke, sairaalalääke. Huom. Tutustu valmisteyhteenvetoon ennen lääkkeen määräämistä. **Lisätiedot:** www.sanofi.fi

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.

SIGN UP FOR AN ELECTRONIC VERSION OF FRAMINGHAM

and other digital communication from Sanofi



At Sanofi our ambition is
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.

Sign up for digital communication from Sanofi.
The information could be:

- The Framingham newsletter with publication reviews within myeloma and other hematological diseases.
- Invitations to scientific meetings, webinars and symposiums during international congresses.
- Product relevant information.

Scan the QR code to sign up.
If you at some point want to unregister, just let us know.

Or sign up online
https://form.apsis.one/tM7sF48GSAy0jvU

Or sign up online
https://form.apsis.one/LHoSGVXCai

Or sign up online
https://form.apsis.one/yvCkBTvJ0OW

Or sign up online
https://form.apsis.one/q0gRfMnDxVKQNF

sanofi

Sanofi A/S | Lyngbyvej 2 | 2100 København Ø | Denmark
Sanofi Genzyme Finland | Revontulenkuja 1 | 02101 Espoo | Finland
Sanofi AB | Box 30052 | 104 25 Stockholm | Sweden
sanofi-aventis Norge AS | Prof. Kohts vei 5-17 | 1366 Lysaker | Norway

SASE.ISX.20.04.0158 Feb 2021