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International Journal of Laboratory Hematology, 2021 July; 43 Suppl 1:103–8

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The Lancet Haematology, 2021 June; 8(6):e389–92

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Blood, 2022 February 10; 139(6):835–44

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Blood Cancer Journal, 2021 June 3; 11(6):106

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ISATUXIMAB FOR RELAPSED/REFRACTORY MULTIPLE MYELOMA:

REVIEW OF KEY SUBGROUP ANALYSES FROM THE PHASE III ICARIA-MM STUDY

Future Oncology, 2021 December; 17(34):4797–812

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BACKGROUND & AIM: Despite the availability of targeted therapies, many patients with multiple myeloma (MM) experience multiple relapses and/or become refractory to treatment. The anti-CD38 monoclonal antibody isatuximab has been approved for the treatment of MM patients who have undergone two prior therapies. ICARIA-MM was a phase III trial that investigated the efficacy of isatuximab combined with pomalidomide and dexamethasone (Isa-Pd) in patients with relapsed/refractory MM (RRMM), and the aim of this review was to discuss the findings from specified subgroup analyses of this study.

ARTICLE TYPE: Review.

FINDINGS: The specified subgroups comprised patients with poor prognostic factors, such as the elderly, those with high-risk cytogenetic markers, those with renal impairment, and those refractory to prior treatments.

In the overall ICARIA-MM population, patients with RRMM who received Isa-Pd had longer progression-free survival (PFS) than patients who received pomalidomide and dexamethasone (Pd) alone (11.5 months, 95% confidence interval 8.9–13.9 versus 6.5 months, 95% CI 4.5–8.3; hazard ratio 0.60, 95% CI 0.44–0.81, p=0.001), as well as better overall response rates (ORRs; 60.4% versus 35.3%, respectively; p<0.0001). In subgroup analyses, these benefits of Isa-Pd over Pd were extended to patients with high-risk cytogenetics or renal impairment (table). Compared with Pd, Isa-Pd also improved PFS and ORR in elderly patients (in both the 65–74 and ≥75 year age-groups), and in patients who had received or were refractory to prior therapy.

There was a consistent trend toward higher rates of serious adverse events and discontinuations due to adverse events with both Isa-Pd and Pd in elderly patients. However, the incidence of fatal adverse events was lower in patients receiving Isa-Pd who were aged ≥75 years than in those aged <65 years (6.3% versus 11.1%, respectively), while the corresponding values were 14.3% versus 5.9%, respectively, in patients receiving Pd.

CONCLUSION: Compared with Pd alone, treatment with Isa-Pd led to improvements in PFS and ORR in RRMM patients who were elderly, were refractory to prior treatments, had high-risk cytogenetic markers or had renal impairment.

PFS and ORRs in cytogenetic marker and renal subgroups of RRMM patients in the ICARIA-MM trial

	PFS (months)		ORR (%)	
	Isa-Pd	Pd	Isa-Pd	Pd
Overall ICARIA-MM population	11.5	6.5	60.4	35.3
High-risk cytogenetics				
High risk	7.5	3.7	50.0	16.7
Standard risk	11.6	7.4	65.0	42.3
Renal impairment				
<45 mL/min/1.73 m²	7.5	2.8	35.0	23.5
<60 mL/min/1.73 m²	9.5	3.7	56.4	24.5
≥60 mL/min/1.73 m²	12.7	7.9	67.8	42.7

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CAR T-CELL THERAPY FOR MULTIPLE MYELOMA:
STATE OF THE ART AND PROSPECTS

The Lancet Haematology, 2021 June; 8(6):e446–61

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BACKGROUND & AIM: People with multiple myeloma who develop resistance to therapies such as immunomodulatory drugs, proteasome inhibitors and CD38-targeting antibodies have a poor prognosis. One strategy for such individuals is to reprogram T cells to target multiple myeloma cells by introducing genes that encode chimeric antigen receptors (CARs). CAR T cells that target CD19 are approved for the treatment of B-cell malignancies such as acute lymphocytic leukaemia and diffuse large B-cell lymphoma. The aim of this article was to review the efficacy and safety of different T-cell products in multiple myeloma, as well as potential strategies to enhance their activity.

ARTICLE TYPE: Review.

FINDINGS: The B-cell maturation antigen (BCMA) is only expressed on the surface of normal and malignant plasma cells and by mature B cells, and is therefore a potential target for CAR T-cell therapy. Preclinical studies have shown that CAR T cells targeting BCMA can kill multiple myeloma cell lines and led to the first trial in people with extensively pretreated multiple myeloma, which had promising results. Since then, other CAR T-cell products have been developed, and several phase 3 trials are currently investigating BCMA-targeting CAR T-cell therapy in multiple myeloma, including in people with early disease stages and those with a high-risk cytogenetic profile or residual disease after transplantation. Other investigations are focusing on CAR T cells that target other multiple myeloma antigens, such as CD19, CD38, CD138 and SLAMF7.

The adverse effects of CAR T-cell therapy include cytokine-release syndrome, cytopenia, infections and neurotoxicity. Although treatment responses can last for a year or more, most individuals ultimately experience relapse, and this can be due to a loss of CAR T cells, loss of antigen expression on the tumour cell surface or the presence of an immunosuppressive microenvironment. A number of strategies have been explored to improve the efficacy of CAR T-cell therapy, including coadministering two different CAR T-cell products, using dual-targeted CAR T cells, optimizing CAR design and generating cell products that are enriched for specific T cells. Other strategies are under development to improve safety, including eliminating CAR T cells in cases of severe toxicity by incorporating a suicide-gene safety system.

CONCLUSION: CAR T-cell therapy has great potential for treating multiple myeloma, although strategies are needed to improve its efficacy and safety, reduce costs and improve access.

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DARATUMUMAB PLUS POMALIDOMIDE AND DEXAMETHASONE VERSUS POMALIDOMIDE AND DEXAMETHASONE ALONE IN PREVIOUSLY TREATED MULTIPLE MYELOMA (APOLLO):

AN OPEN-LABEL, RANDOMISED, PHASE 3 TRIAL

The Lancet Oncology, 2021 June; 22(6):801–12

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BACKGROUND & AIM: In a phase 1b study of people with heavily pretreated, relapsed or refractory multiple myeloma, 42% of participants achieved a very good partial response or better with intravenous daratumumab and pomalidomide plus dexamethasone. The aim of this study (the APOLLO trial) was to assess the effect of the combination on progression-free survival.

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

ENDPOINTS: Progression-free survival; treatment response; safety.

METHOD: The study involved 304 adults with relapsed or refractory multiple myeloma who had experienced a partial response or better to one or more previous lines of antimyeloma therapy, had received at least one previous line of therapy with both lenalidomide and a proteasome inhibitor and, if they had received only one previous line of therapy, were refractory to lenalidomide. Of the 304 participants, 151 were randomized to daratumumab and pomalidomide plus dexamethasone, while 153 received pomalidomide plus dexamethasone alone in 28-day cycles (control group). Daratumumab was given either subcutaneously (1800 mg) or intravenously (16 mg/kg) weekly during cycles 1 and 2, every 2 weeks during cycles 3–6 and every 4 weeks thereafter until disease progression or unacceptable toxicity. The median follow-up period was 16.9 months.

RESULTS: The median progression-free survival time was 12.4 months in the daratumumab group and 6.9 months in the control group (hazard ratio for progression or death 0.63, 95% confidence interval 0.47–0.85; p=0.0018). The overall response rate was 69% and 46% respectively (odds ratio 2.7, 95% CI 1.7–4.4; p<0.0001). The most common grade 3/4 adverse events were neutropenia (68% with daratumumab and 51% with control therapy), anaemia (17% and 21%) and thrombocytopenia (17% and 18%). Serious adverse events occurred in 50% of participants receiving daratumumab and 39% of those on control therapy; the most common were pneumonia (15% and 8%, respectively) and lower respiratory tract infection (12% and 9%). Serious treatment-related adverse events occurred in 27% and 10% of participants in the two groups, respectively. Adverse events resulted in death in 11 participants (7%) in both the daratumumab and control groups.

CONCLUSION: In people with previously treated, relapsed or refractory multiple myeloma, the addition of daratumumab to pomalidomide plus dexamethasone was associated with significantly longer progression-free survival.

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BIALLELIC LOSS OF BCMA AS A RESISTANCE MECHANISM TO CAR T CELL THERAPY IN A PATIENT WITH MULTIPLE MYELOMA

Nature Communications, 2021 February 8; 12(1):868

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BACKGROUND & AIM: Chimeric antigen receptor (CAR) T-cell therapy targeting the B-cell maturation antigen (BCMA) has been shown to achieve deep and durable responses in people with relapsed or refractory multiple myeloma. However, a significant proportion of people experience relapse, and progression-free survival of less than a year has been reported in some studies. Those who are re-treated with the same product rarely respond, indicating the development of mechanisms of acquired resistance. The aim of this study was to investigate resistance mechanisms to BCMA CAR T-cell therapy by analysing serial bone marrow samples from a person with multiple myeloma who had experienced disease relapse after initial CAR T-cell therapy.

ARTICLE TYPE: Case study.

FINDINGS: The individual had been treated with four lines of therapy (including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 antibody), but with a limited response. They were subsequently enrolled in a phase 1 trial of anti-BCMA CAR T-cell therapy with idecabtagene vicleucel, following which they developed grade 1 cytokine-release syndrome, and had experienced a partial response by 3 months. The individual had disease relapse at 9 months after the first infusion, and was then treated using the same CAR T-cell as previously at a higher dose, but with no response. Longitudinal bone marrow samples were collected throughout treatment and analysed using single-cell transcriptome profiling.

Analysis of changes in the bone marrow microenvironment following CAR T-cell therapy did not indicate any role for this milieu in mediating the suppression of CAR T-cell expansion or function. Soluble BCMA levels decreased significantly to a very low level following initial treatment with idecabtagene vicleucel, corresponding with the clinical response. However, levels remained low even at the time of relapse, indicating a lack of BCMA production by multiple myeloma cells. Genomic analysis showed that the initial CAR T-cell administration was followed by the selection of a clone with biallelic loss of BCMA, acquired by one copy deletion and a second copy loss-of-function mutation. This loss resulted in a lack of CAR T-cell proliferation following the second infusion, and a lack of soluble BCMA.

CONCLUSION: This report illustrates the development of an acquired resistant phenotype in a person with multiple myeloma receiving BCMA CAR T-cell therapy, suggesting one potential mechanism of resistance to this treatment.

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PREDICTING THE PROBABILITY OF GAUCHER DISEASE IN SUBJECTS WITH SPLENOMEGALY AND THROMBOCYTOPENIA

Scientific Reports, 2021 January 28; 11(1):2594

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BACKGROUND & AIM: The autosomal recessive lysosomal storage disorder Gaucher disease type 1 (GD1) is caused by genetic mutations that result in β-glucosidase enzyme deficiency. Splenomegaly, thrombocytopenia and other haematological signs and symptoms are common in patients with GD1 at presentation, but many patients experience long diagnostic delays and often inappropriate treatment due to a lack of awareness of the disease. The aim of this study was to evaluate the prevalence of GD1 in a high-risk population presenting to haematology centres with splenomegaly and/or thrombocytopenia associated with other haematological signs or symptoms suggestive of GD1.

STUDY DESIGN: Multicentre cross-sectional study.

ENDPOINT: Prevalence of GD1.

METHOD: The study comprised 455 patients (mean age 46.9 years; 31.9% women) presenting with splenomegaly and/or thrombocytopenia and at least one other haematological sign or symptom. GD1 was diagnosed using a previously published diagnostic algorithm combined with a test for β-glucosidase activity on a dried blood spot. Patients with dried blood spot activity <4.4 pmol/punch/hour were retested using the current gold standard assay (β-glucosidase activity in nucleated cell homogenates). The predictive role of ferritin levels, transferrin saturation levels and platelet count, individually and combined, was assessed using multiple logistic regression models, and calculation was made of the relevant areas under the curve (AUCs) from receiver operating characteristic curves.

RESULTS: Among 65 patients with low β-glucosidase activity on dried blood spot who were retested using the gold standard assay, 15 were diagnosed with GD1, giving a prevalence of 3.3% (95% confidence interval 1.9–5.4%). In 14 of these 15 patients, molecular analysis of the *GBA* gene identified the mutations. Among 159 patients (13 with GD1) for whom complete data on ferritin, platelets and transferrin saturation were available, platelets (AUC 0.79) provided the best discrimination between patients with and without GD1, while ferritin and transferrin saturation had lower AUCs (0.72 and 0.68, respectively). A combination of platelets, ferritin and transferrin saturation yielded an AUC of 0.89 (95% CI 0.82–0.96).

CONCLUSION: In a high-risk population, the use of a model predicting the probability of having GD1 according to ferritin levels, transferrin saturation levels and platelet count, in combination with a simple β-glucosidase activity blood test, was effective for the identification of patients with GD1.

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OUTCOME DATA FROM >10 000 MULTIPLE MYELOMA PATIENTS IN THE DANISH AND SWEDISH NATIONAL REGISTRIES

European Journal of Haematology, 2022 February; 108(2):99–108

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BACKGROUND & AIM: In patients with multiple myeloma (MM), randomized clinical trials have demonstrated improved survival with novel treatments, such as immunotherapy or immunomodulatory drugs. However, most of these patients are not eligible for clinical trials, so real-world evidence has an important role in the evaluation of treatment practices and clinical outcomes in this population. The aim of this study was to provide real-world evidence on the incidence and clinical outcomes of MM using data from the national Swedish and Danish myeloma registries.

STUDY DESIGN: Population-based study.

ENDPOINTS: Incidence and outcomes of MM.

METHOD: For the period 2005–2018, treatment data for patients with MM were collected from the Swedish Myeloma Registry and the Danish Multiple Myeloma Registry. Treatment practices and changes in treatments over time in both countries were analysed with respect to the implementation of new treatment guidelines for MM, and the incidence and survival outcomes of different patient subgroups.

RESULTS: The study analysed real-world data from more than 10,000 patients representing the whole MM population in Denmark and Sweden for the period 2005–2018. Treatment strategies for MM were similar in Denmark and Sweden, and national guidelines for MM treatment had been implemented rapidly in both countries, resulting in a clear shift in treatment practices. Both the absolute incidence and prevalence of MM increased during the study period, and they are expected to continue to increase due to improved survival with novel treatments and increases in life expectancy generally. Consequently, a greater proportion of MM patients will be elderly as time goes on. The real-world population captured in MM registries differed significantly in clinical characteristics and outcomes from the populations studied in clinical trials, and the estimates of median age at diagnosis and incidence of the disease in MM registries exceeded those reported by referral centres. Some patients, such as the elderly, those with severe comorbidities or a high risk of early relapse, and patients with high-risk smouldering MM, have poor survival, and further research is required to better understand how to use novel treatments in these groups.

CONCLUSIONS: Although new and better treatments are now available, and guidelines have been rapidly implemented in Denmark and Sweden, data from the Danish and Swedish national registries reveal that many subgroups of patients still have poor outcomes and require adapted treatment strategies.

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CARDIOVASCULAR DISEASE IS A LEADING CAUSE OF MORTALITY AMONG TTP SURVIVORS IN CLINICAL REMISSION

Blood Advances, 2022 February 22; 6(4):1264–70

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BACKGROUND & AIM: Immune-mediated thrombotic thrombocytopenic purpura (iTTP) is a rare haematological disorder caused by an antibody-mediated deficiency of ADAMTS13. If promptly treated, using plasma exchange and immunosuppression, more than 90% of patients survive, but they remain at risk of a recurrence of the disease. iTTP survivors also exhibit high rates of hypertension, obesity, stroke, cognitive impairment and mood disorders, as well as a poor quality of life and higher rates of all-cause mortality than expected. The aim of this study was to evaluate causes of death in patients who survived their first iTTP episode, and to identify factors associated with earlier mortality.

STUDY DESIGN: Registry-based cohort study.

ENDPOINTS: The primary endpoint was mortality during follow-up after acute iTTP.

METHOD: Patients treated for acute iTTP (n=222; mean age 42 years; 70.3% women), enrolled in the Ohio State University and Johns Hopkins TTP registries between 2003 and 2020, were followed for a median of 4.5 years (interquartile range 0.4–11.5). Factors associated with mortality were identified using adjusted Cox proportional hazards regression models.

RESULTS: Thirty-eight patients died during follow-up, nine during a first iTTP episode and 29 after surviving a first episode (iTTP survivors). Mortality in iTTP survivors was higher than expected from an age-, sex- and race-standardized reference population (2228.3 versus 1273.8 per 100,000 person years, respectively; p=0.007). The median age at death among iTTP survivors was 49 years (IQR 39–65), which was lower than in the general US population (78.7 years). The leading causes of death among iTTP survivors were cardiovascular disease and relapse of iTTP (table). Among iTTP survivors, factors associated with mortality in an adjusted model included male sex (hazard ratio 3.74, 95% confidence interval 1.65–8.48, p=0.002), increasing age (HR 1.04, 95% CI 1.01–1.07, p=0.011) and number of iTTP episodes (HR 1.10, 95% CI 1.01–1.20, p=0.022). A trend towards shorter survival was observed in patients with lower ADAMTS13 activity during remission (p=0.078).

CONCLUSION: In iTTP survivors, the risk of death was higher than in a reference population, and cardiovascular disease was a leading cause of death.

Leading causes of death in patients surviving a first episode of iTTP and in the US general population

iTTP survivors (n=29)	General US population (Centres for Disease Control, 2017)
Relapsed iTTP (27.6%)	Cardiovascular disease (29.5%)
Cardiovascular disease (27.6%)	Cancer (21.3%)
Cancer (20.7%)	Accidents (6%)
Infectious causes (13.8%)	Chronic lung disease (5.7%)
Other/unknown (10.3%)	Alzheimer's disease (4.3%)

https://doi.org/10.1182/bloodadvances.2020004169

ADAMTS13 TESTING UPDATE: FOCUS ON LABORATORY ASPECTS OF DIFFICULT THROMBOTIC THROMBOCYTOPENIC PURPURA DIAGNOSES AND EFFECTS OF NEW THERAPIES

International Journal of Laboratory Hematology, 2021 July; 43 Suppl 1:103–8

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BACKGROUND & AIM: Patients with the rare haematological disease thrombotic thrombocytopenic purpura (TTP) produce autoantibodies that result in a deficiency in the ADAMTS13 protease which cleaves von Willebrand factor (VWF) and thus regulates platelet adhesion. In patients with severe (i.e. <10% of normal activity) ADAMTS13 deficiency, ultra-large VWF multimers promote the formation of microvascular thrombi. TTP is life-threatening in untreated patients, so there is a need for accurate and timely diagnosis and management. As testing for ADAMTS13 is becoming increasingly available, the focus of this review was on the performance of ADAMTS13 testing in patients with TTP and on the interpretation and limitations of the findings.

ARTICLE TYPE: Review.

FINDINGS: Several varieties of ADAMTS13 test are available, and a combined impression of the results can provide important diagnostic information.

ADAMTS13 activity is the most common test ordered to support a TTP diagnosis. Samples for testing for ADAMTS13 activity (and antibodies) should be collected prior to starting TTP treatment which can impact on the results. To avoid delay, treatment is often initiated on the initial suspicion of the disorder, rather than when severe ADAMTS13 deficiency is confirmed on testing. An improvement in ADAMTS13 activity is not used to assess efficacy (which is usually based on sustained platelet count recovery and resolution of organ dysfunction, if reversible), but the persistence or recurrence of severe ADAMTS13 deficiency in clinical remission is indicative of the risk of relapse.

ADAMTS13 antibody tests detect the acquired autoantibodies that cause idiopathic TTP, and can be used to differentiate acquired from inherited TTP. This is important as treatment differs: plasma exchange and immunosuppression are used in patients with acquired TTP, while plasma infusion is used in those with inherited TTP. The continued detection of antibodies when the patient is in clinical remission may indicate a higher risk of TTP relapse. Finally, ADAMTS13 Bethesda assays are used to detect and titre neutralizing antibodies (inhibitors).

Caplacizumab, an anti-VWF antibody, is a new agent for the treatment of patients with TTP. Outcomes were improved, compared with placebo, in TTP patients who received caplacizumab during plasma exchange and for 30 days afterwards. TTP recurrence has been observed in a subset of patients after caplacizumab cessation, so it may be useful to monitor ADAMTS13 activity to guide the administration of immunosuppressants and caplacizumab.

CONCLUSION: ADAMTS13 testing has improved the diagnosis and care of patients with TTP.

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RESPONSE TO FIRST VACCINATION AGAINST SARS-COV-2 IN PATIENTS WITH MULTIPLE MYELOMA

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AUTHORS: Bird S, Panopoulou A, Shea RL, Tsui M, Saso R, Sud A, West S, Smith K, Barwood J, Kaczmarek E, Panlaqui C, Kaiser M, Stern S, Pawlyn C, Boyd K
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BACKGROUND & AIM: Multiple myeloma is associated with immune suppression, and people with multiple myeloma have increased rates of severe disease following COVID-19 infection. It is therefore important to protect this group from COVID-19, but some recent evidence suggests that they might have an attenuated response to vaccination. The aim of this study was to investigate the serological response to the first SARS-CoV-2 vaccine dose in individuals with multiple myeloma.

STUDY DESIGN: Retrospective, single-centre cohort study.

ENDPOINT: Seropositivity for SARS-CoV-2 IgG antibodies at 21 days or more postvaccination.

METHOD: People with multiple myeloma who had received their first vaccine dose (either Pfizer or AstraZeneca) were included in the study (*n*=93). Serological response to vaccination was analysed via anti-SARS-CoV-2 spike protein S1 IgG antibody results at 21 days or more postvaccination.

RESULTS: Participants had received a median of one previous line of therapy and 71% were being treated at the time of vaccination. Overall, 52% of individuals had a complete response or very good partial response at the time of vaccination, while 17% had a partial response and 29% had stable or progressive disease. At 21 days or more postvaccination, 56% of individuals tested positive for SARS-CoV-2 IgG antibodies. Rates of seropositivity were not affected by which vaccine the person had received or by their age, sex, disease isotype, presence of leukopenia or time from vaccination to the antibody test. Test results did vary by disease status, with a higher rate of positivity in people with a complete or partial response to therapy (table) and a lower rate in those with immunoparesis at the time of vaccination and more previous lines of therapy. People on any therapy at the time of vaccination were less likely to have a positive antibody result.

CONCLUSIONS: Only 56% of individuals with multiple myeloma had a positive antibody response to their first SARS-CoV-2 vaccine dose. Lower positive antibody rates were found in those with active multiple myeloma or immunoparesis, or on any treatment.

Associations of disease status with a positive or negative antibody result

Participants, *n* (%)	Positive antibody result (*n*=52)	Negative antibody result (*n*=41)
Complete response or very good partial response (*n*=48)	30 (63)	18 (38)
Partial response (*n*=16)	12 (75)	4 (25)
Stable disease or progressive disease (*n*=27)	8 (30)	19 (70)
Unable to assess (*n*=2)	2 (100)	0

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FINAL OVERALL SURVIVAL ANALYSIS OF THE TOURMALINE-MM1 PHASE III TRIAL OF IXAZOMIB, LENALIDOMIDE, AND DEXAMETHASONE IN PATIENTS WITH RELAPSED OR REFRACTORY MULTIPLE MYELOMA

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BACKGROUND & AIM: In the TOURMALINE-MM1 trial in participants with relapsed or refractory multiple myeloma (RRMM), the oral proteasome inhibitor ixazomib plus lenalidomide and dexamethasone (ixazomib-Rd) was associated with improved progression-free survival and limited additional toxicity versus placebo plus lenalidomide and dexamethasone (placebo-Rd). The aim of this paper was to report the final overall survival analysis of TOURMALINE-MM1.

STUDY DESIGN: International, multicentre, randomized, double-blind, placebo-controlled, phase 3 study.

ENDPOINT: Overall survival (key secondary endpoint of TOURMALINE-MM1).

METHOD: In the TOURMALINE-MM1 trial, adults with RRMM after one to three prior therapies were randomized to treatment with ixazomib-Rd (n=360) or placebo-Rd (n=362). Participants were stratified by number of prior therapies, previous exposure to a proteasome inhibitor and International Staging System disease stage.

RESULTS: At a median follow-up of 85 months, median overall survival was similar in both groups, at 53.6 months in the ixazomib-Rd arm and 51.6 months in the placebo-Rd arm (hazard ratio 0.939, 95% confidence interval 0.784–1.125, p=0.495). On prespecified subgroup analyses, ixazomib-Rd showed an overall survival benefit versus placebo-Rd in participants with del(17p) (HR 0.916, 95% CI 0.516–1.626), high-risk cytogenetics (HR 0.870, 95% CI 0.580–1.305) and expanded high-risk cytogenetics (HR 0.862, 95% CI 0.660–1.124), although none of the comparisons reached significance. Similar non-significant survival benefits for ixazomib-Rd versus placebo-Rd were seen in participants refractory to any (HR 0.794, 95% CI 0.538–1.172) or last (HR 0.742, 95% CI 0.460–1.198) prior line of treatment, refractory to thalidomide (HR 0.781, 95% CI 0.461–1.322), aged more than 65–75 years (HR 0.757, 95% CI 0.559–1.027), with International Staging System stage III disease at study entry (HR 0.779, 95% CI 0.487–1.247), who had two or three prior therapies (HR 0.845, 95% CI 0.642–1.114) and who had standard-risk cytogenetics (HR 0.875, 95% CI 0.684–1.118). Overall, 71.7% and 69.9% participants received at least one anticancer therapy after treatment with ixazomib-Rd and placebo-Rd, respectively. Rates of new primary malignancies were 10.3% and 11.9%, respectively. No new safety concerns were identified.

CONCLUSION: Among people with RRMM, there was no significant difference in overall survival with ixazomib-Rd versus placebo-Rd.

https://doi.org/10.1200/JCO.21.00972

PROGNOSTIC VALUE OF MINIMAL RESIDUAL DISEASE NEGATIVITY IN MYELOMA:

COMBINED ANALYSIS OF POLLUX, CASTOR, ALCYONE, MAIA

Blood, 2022 February 10; 139(6):835–44

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BACKGROUND & AIM: Minimal residual disease (MRD) is emerging as a prognostic factor in people with multiple myeloma. Four phase 3 studies (POLLUX, CASTOR, ALCYONE and MAIA) have shown that daratumumab combination therapies improve MRD negativity rates and increase progression-free survival (PFS) versus standard care in people with newly diagnosed or relapsed or refractory multiple myeloma. The aim of this study was to use data from these four trials to further evaluate the association of MRD negativity with increased PFS.

STUDY DESIGN: Large-scale, pooled analysis of patient-level data from four randomized, open-label, phase 3 studies.

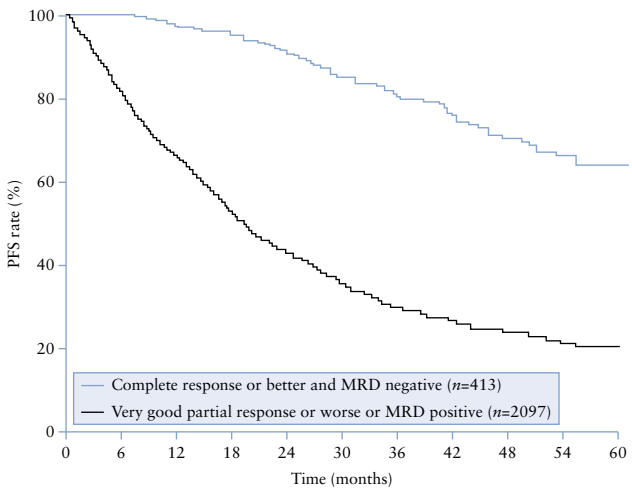
ENDPOINT: PFS.

METHOD: MRD was assessed using next-generation sequencing throughout all four trials, and the minimum sensitivity for a negative MRD test result was defined as one in 100,000 nucleated cells. The MRD negativity rate was defined as the proportion of participants who had a complete response or better and at least one negative MRD test result during treatment.

RESULTS: The study analysis included data from 2510 participants, of who 16.7% were MRD negative and 34.0% had a complete response or better (of who 48.4% were also MRD negative). The MRD negativity rate was higher among participants who received daratumumab combination therapy, at 26.8% compared with 6.5% among those who received control therapy ($p<0.0001$). Overall, the estimated 48-month PFS rate was significantly higher in those who had a complete response or better and MRD negativity compared with those who had a very good partial response or worse or who were MRD positive (figure). This finding was not affected by the treatment or disease setting.

CONCLUSION: In people with newly diagnosed or relapsed or refractory multiple myeloma, a complete response or better combined with MRD-negative status was strongly associated with improved PFS, irrespective of the treatment received.

PFS by response and MRD status



https://doi.org/10.1182/blood.2021011101

MINIMAL RESIDUAL DISEASE ASSESSMENT BY MULTIPARAMETER FLOW CYTOMETRY IN TRANSPLANT-ELIGIBLE MYELOMA IN THE EMN02/HOVON 95 MM TRIAL

Blood Cancer Journal, 2021 June 3; 11(6):106

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CENTRE FOR CORRESPONDENCE: Myeloma Unit, Division of Hematology, University of Torino, Azienda Ospedaliero-Universitaria Città della Salute e della Scienza di Torino, Torino, Italy

BACKGROUND & AIM: Assessing minimal residual disease (MRD) is currently the most sensitive way to measure the depth of treatment response in people with multiple myeloma. MRD is much quicker to evaluate than progression-free survival (PFS), and people who are positive for MRD have worse survival than those who are MRD negative. Therefore, it has been suggested that MRD negativity might be used as a surrogate endpoint for survival. The aim of this study was to investigate this possibility in people with multiple myeloma enrolled in the EMN02/HO95 phase 3 trial.

STUDY DESIGN: Post hoc analysis of a phase 3 trial.

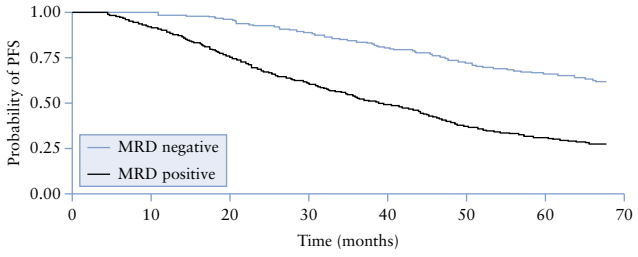
ENDPOINTS: Progression-free and overall survival.

METHOD: The EMN02/HO95 trial enrolled 1493 transplant-eligible individuals with multiple myeloma who were treated with bortezomib, cyclophosphamide and dexamethasone induction therapy, followed by mobilization and stem-cell collection. They were then randomized to treatment intensification with bortezomib, melphalan and prednisone or high-dose melphalan, followed by autologous stem-cell transplantation. This was followed by consolidation with bortezomib, lenalidomide and dexamethasone or no consolidation, and lenalidomide maintenance therapy. MRD status was assessed in bone marrow samples using multiparameter flow cytometry in 321 participants with a suspected complete response before starting maintenance, and then every 6 months during maintenance therapy until progression.

RESULTS: Overall, 76% of evaluable participants were MRD negative before starting lenalidomide maintenance therapy. After a median follow-up of 75 months (interquartile range 66–83 months), compared with MRD-positive participants, those who were MRD negative had significantly higher rates of 5-year progression-free survival (66% versus 31%; hazard ratio 0.39, 95% confidence interval 0.31–0.48, $p<0.001$; figure) and 5-year overall survival (86% versus 69%; HR 0.41, 95% 0.30–0.56, $p<0.001$). An MRD analysis after 1 year of lenalidomide maintenance therapy ($n=118$) found that 42% of MRD-positive participants had become MRD negative after treatment with lenalidomide.

CONCLUSION: MRD evaluated by multiparameter flow cytometry was a strong prognostic factor for survival in transplant-eligible people with multiple myeloma.

Estimated PFS in MRD-negative and -positive participants



https://doi.org/10.1038/s41408-021-00498-0

▼ Cablivi 1«Ablynx»1

Antitrombotisk middel. ATC-nr.: B01A X07

PULVER OG VÆSKE TIL INJEKSJONSVÆSKE, oppløsning *10 mg:* *Hvert sett inneh.:* I) Hetteglass: Kaplasizumab 10 mg, sukrose, vannfri sitronsyre, trinatriumsitratdihydrat, polysorbat 80. II) Ferdigfylt sprøyte: Vann til injeksjonsvæsker 1 ml.1

Indikasjoner: *Voksne og ungdom ≥12 år (≥40 kg):* Pasienter med en episode av ervervet trombotisk trombocytopenisk purpura (aTTP), i tillegg til plasmautskiftning og immunsuppresjon.

Dosering: Mht. sporbarhet skal preparatnavn og batchnr. noteres i pasientjournalen. Behandling skal startes og overvåkes av lege med erfaring i behandling av trombotiske mikroangiopatier. ***Voksne, inkl. eldre og ungdom ≥12 år (≥40 kg):*** *1. dose:* 10 mg i.v. før plasmautskiftning. *Påfølgende doser:* 10 mg s.c. daglig etter hver fullførte plasmautskiftning i hele perioden med daglige plasmautskiftninger, deretter 10 mg s.c. daglig i 30 dager etter avsluttet plasmautskiftning. Ved tegn på vedvarende immunologisk sykdom ved slutten av perioden, anbefales optimalisering av immunsuppressivt regime og fortsatt bruk av 10 mg kaplasizumab s.c. daglig inntil tegn på bedring av underliggende immunologisk sykdom (f.eks. vedvarende normalisering av ADAMTS13-aktivitetsnivå). ***Glemt dose:*** Uteblitt dose kan gis innen 12 timer. Hvis det er >12 timer siden planlagt dosering skal den ikke gis, men neste dose gis iht. vanlig doseringsplan. ***Spesielle pasientgrupper:*** *Nedsatt leverfunksjon:* Ingen dosejustering nødvendig. Ingen data ved alvorlig nedsatt leverfunksjon, og behandling krever nytte-/risikovurdering og nøye klinisk overvåkning. *Nedsatt nyrefunksjon:* Ingen dosejustering nødvendig. *Barn og ungdom:* Data mangler. ***Tilberedning/Håndtering:*** Se pakningsvedlegg. Pulveret i hetteglasset rekonstitueres vha. hetteglassadapteren og all oppløsningsvæsken i den ferdigfylte sprøyten. Tilsett oppløsningsvæsken sakte og bland forsiktig for å unngå skumdannelse. La hetteglasset med tilkoblet sprøyte stå i 5 minutter ved romtemperatur, før hele volumet overføres til sprøyten. Hele volumet gis umiddelbart etter rekonstituering. Kontrolleres visuelt for partikler før bruk, og bruk unngås ved partikler. Kun til engangsbruk. *Blandbarhet:* Skal ikke blandes med andre legemidler. ***Administrering:*** 1. dose gis i.v. Påfølgende doser gis s.c. i abdomen. Injeksjon i området rundt navlen unngås, og påfølgende injeksjoner skal ikke gis i samme abdominale kvadrant. Pasient/omsorgspersoner kan injisere legemidlet etter tilfredsstillende opplæring i s.c. teknikk. Se for øvrig pakningsvedlegg.

Kontraindikasjoner: Overfølsomhet for innholdsstoffene.

Forsiktighetsregler: *Aktiv klinisk signifikant blødning:* Behandling bør avbrytes. Ved behov kan von Willlebrands faktor (VWF)-konsentrat vurderes gitt for å korrigere hemostase. Behandling bør kun gjenopptas etter råd fra lege med erfaring i behandling av trombotiske mikroangiopatier. *Økt blødningsrisiko:* Samtidig behandling med orale antikoagulantia, høydose heparin, blodplatehemmere og/eller lavmolekylært heparin (LMWH) krever nytte-/risikovurdering og nøye overvåkning. Pasienter med underliggende koagulopatier (f.eks. hemofili, andre koagulasjonsfaktormangler) skal overvåkes nøye. Ved elektiv operasjon eller tannbehandling, bør kaplasizumabbehandlingen avbrytes minst 7 dager før planlagt inngrep. Lege/tannlege bør informeres om bruk av kaplasizumab, og legen som overvåker kaplasizumabbehandlingen bør informeres om den planlagte prosedyren. Ved behov for akuttkirurgi, kan bruk av VWF-konsentrat vurderes for å korrigere hemostase. *Alvorlig nedsatt leverfunksjon:* Se Dosering.

Interaksjoner: For utfyllende informasjon om relevante interaksjoner, bruk interaksjonsanalyse. Ikke studert. Ved samtidig bruk av orale antikoagulantia, høydose heparin, blodplatehemmere og/eller lavmolekylært heparin (LMWH), se Forsiktighetsregler.

Graviditet, amming og fertilitet: *Graviditet:* Data mangler. Bruk bør unngås. *Amming:* Data mangler. Overgang i morsmelk er ukjent. Risiko for barn som ammes kan ikke utelukkes. Beslutning må tas om amming skal opphøre eller behandling avstås fra, basert på nytte-/risikovurdering. *Fertilitet:* Data mangler. Ingen effekt er sett i dyrestudier.

Bivirkninger: Blødninger kan oppstå i ulike kroppssystemer, uavhengig av behandlingsvarighet. Alvorlige blødninger som krever medisinsk tilsyn er sett, men er som oftest selvbegrensende. *Svært vanlige (≥1/10):* Gastrointestinale: Gingival blødning. Generelle: Fatigue, feber. Hud: Urticaria. Luftveier: Epistakse. Nevrologiske: Hodepine. *Vanlige (≥1/100 til <1/10):* Gastrointestinale: Abdominalveggshematom, hematemese, hematochezi, hemoroideblødning, melena, rektalblødning, øvre gastrointestinalblødning. Generelle: Blødning, kløe, erytem og reaksjon på injeksjonsstedet. Kar: Hematom. Kjønnsorganer/bryst: Menoragi, vaginalblødning. Luftveier: Dyspné, hemoptyse. Muskel-skjelettsystemet: Myalgi. Nevrologiske: Cerebralt infarkt. Nyre/urinveier: Hematuri. Skader/komplikasjoner: Subaraknoidalblødning. Øye: Øyeblødning.

Overdosering/Forgiftning: *Symptomer:* Mulig økt blødningsrisiko. Nøye overvåkning for blødningssymptomer anbefales. Se Giftinformasjonens anbefalinger B01A X07 på www.felleskatalogen.no.

Egenskaper: *Klassifisering:* Humanisert bivalent nanoantistoff fremstilt ved rekominant DNA-teknikk i E. coli. *Virkningsmekanisme:* Bindes til A1-domenet til von Willebrands faktor (VWF), og hemmer interaksjon mellom VWF og blodplater. Forhindrer dermed VWF-mediert blodplateadhesjon karakteristisk for aTTP. Påvirker også disponeringen av VWF og fører til forbigående reduksjon av totalt VWF-antigennivå og samtidig reduksjon av faktor VIII:C-nivåer. *Absorpsjon:* Raskt og nesten fullstendig i systemisk sirkulasjon etter s.c. bruk. Tmax 6-7 timer ved s.c. bruk. *Fordeling:* Sentralt Vd 6,33 liter. Distribueres til godt perfunderte organer. *Halveringstid:* Ikke doseproporsjonal, målmediert disposisjon. Konsentrasjons- og målnivåavhengig. Høyere nivåer av VWF-antigen øker fraksjon av kaplasizumab-VWF-komplekser i sirkulasjonen. Steady state nås etter 1. administrering, med minimal akkumulering. *Utskillelse:* Målbundet kaplasizumab nedbrytes i leveren, mens ubundet fraksjon utskilles renalt.

Oppbevaring og holdbarhet: Oppbevares i kjøleskap (2-8°C). Skal ikke fryses. Oppbevares i originalemballasjen for å beskyttes mot lys. Kan oppbevares ved høyst 25°C i en enkeltperiode på ≤2 måneder. Skal ikke returneres til kjøleskap for oppbevaring etter oppbevaring i romtemperatur. *Rekonstituert oppløsning:* Fysisk og kjemisk stabil i 4 timer. Bør fra et mikrobiologisk synspunkt brukes umiddelbart med mindre rekonstitueringsmetoden utelukker risiko for mikrobiell kontaminasjon. Brukeren er ansvarlig for oppbevaringstid og -forhold før bruk.

Andre opplysninger: Hetteglassadapter, hypodermisk kanyle og spritserviett medfølger i pakningen.

Pakninger og priser: 1 sett (hettegl. + ferdigfylt sprøyte) kr 56558,50.

Sist endret: October 2020
Basert på SPC godkjent av SLV/EMA: 09.06.2020

▼ Sarclisa 1«sanofi-aventis»1

Antineoplastisk middel, monoklonalt antistoff. ATC-nr.: L01X C38

KONSENTRAT TIL INFUSJONSVÆSKE, oppløsning *20 mg/ml:* *1 ml inneh.:* Isatuksimab 20 mg, sukrose, histidinhydrokloridmonohydrat, histidin, polysorbat 80, vann til injeksjonsvæsker.

Indikasjoner: I kombinasjon med pomalidomid og deksametason for behandling av voksne med tilbakevendende og refraktær myelomatose etter minst 2 tidligere behandlinger, inkl. lenalidomid og proteasomhemmer, og med påvist sykdomsprogresjon ved siste behandling. I kombinasjon med karfilzomib og deksametason for behandling av voksne med myelomatose, som har fått minst én tidligere behandling.

Dosering: Mht. sporbarhet skal preparatnavn og batchnr. noteres i pasientjournalen. ***Voksne:*** Skal administreres av helsepersonell med tilgang til gjenopplivningsutstyr. Anbefalt dosering er 10 mg/kg kroppsvekt gitt som i.v. infusjon i kombinasjon med pomalidomid og deksametason (Isa-Pd) eller i kombinasjon med karfilzomid og deksametason (Isa-Kd) iht. følgende tidsplan: Syklus 1: Dag 1, 8, 15 og 22 (ukentlig). Syklus 2 og utover: Dag 1, 15 (annenhver uke). Hver behandlingssyklus er 28 dager. Behandling gjentas frem til sykdomsprogresjon eller uakseptabel toksisitet. For andre legemidler som administreres samtidig, henvises det til respektive preparatomtaler. Tidsplan for dosering skal følges nøye. Dersom planlagt dose ikke blir gitt, skal dosen administreres så snart som mulig. Tidsplanen skal justeres slik at behandlingsintervallene opprettholdes. Ingen doreduksjon anbefales. ***Spesielle pasientgrupper:*** *Nedsatt leverfunksjon:* Dosejustering ikke nødvendig ved lett nedsatt leverfunksjon. Begrensede data ved moderat og alvorlig nedsatt leverfunksjon, men ingen tegn på at dosejustering er nødvendig. *Nedsatt nyrefunksjon:* Dosejustering ikke nødvendig ved lett til alvorlig nedsatt nyrefunksjon. *Barn og ungdom <18 år:* Ingen data. *Eldre:* Dosejustering ikke nødvendig. Begrensede data hos eldre ≥85 år. ***Tilberedning/Håndtering:*** Nødvendig volum konsentrat fra 1 eller flere hetteglass fortynnes med natriumklorid 9 mg/ml (0,9%) infusjonsvæske eller 5% glukoseoppløsning til totalt 250 ml. Se pakningsvedlegg. Skal ikke ristes. ***Administrering:*** Fortynnet oppløsning gis som i.v. infusjon med følgende infusjonshastighet:

	Fortynnings-volum	Starthastighet	Fravær av infusjonsreaksjoner	Gradvis økning av hastighet	Maks. hastighet
1. infusjon	250 ml	25 ml/time	I 60 minutter	25 ml/time hvert 30. minutt	150 ml/time
2. infusjon	250 ml	50 ml/time	I 60 minutter	50 ml/time i 30 minutter, deretter økning med 100 ml/time hvert 30. minutt	200 ml/time
Påfølgende infusjoner	250 ml	200 ml/time			200 ml/time

Gradvis økning av infusjonshastigheten kan overveies ved fravær av infusjonsreaksjoner. Administreringen bør justeres ved infusjonsreaksjoner. Ved grad 2 (moderat) infusjonsreaksjon bør infusjonsstans og symptomdempende legemidler vurderes. Etter forbedring til grad ≤1 (mild), kan infusjonen gjenopptas med halvparten av starthastigheten under nøye overvåkning og støttebehandling ved behov. Dersom symptomene ikke tilbakevender etter 30 minutter kan infusjonshastigheten økes til starthastigheten, og deretter gradvis som vist i tabellen. Dersom symptomene ikke forsvinner eller forbedres til grad ≤1 etter stoppet infusjon, vedvarer eller forverres til tross for egnede legemidler, eller krever sykehusinnleggelse eller er livstruende, skal behandlingen seponeres permanent og ytterligere støttebehandling gis ved behov.

Kontraindikasjoner: Overfølsomhet for innholdsstoffene.

Forsiktighetsregler: *Infusjonsreaksjoner:* Primært milde eller moderate. De fleste oppstår i løpet av 1. infusjon og bedres samme dag. Vanligste symptomer på infusjonsreaksjon er dyspné, hoste, kuldeskjelving og kvalme. De vanligste alvorlige tegn/symptomer er hypertensjon, dyspné og bronkospasme. Alvorlige infusjonsreaksjoner, inkl. anafylaktisk reaksjon er sett. For å redusere risiko for og alvorlighetsgrad av infusjonsreaksjoner, bør premedisinering med paracetamol samt difenhydramin eller tilsvarende gis før infusjon. Deksametason brukes både som premedisinering og antimyelombehandling. Vitale tegn bør kontrolleres hyppig under hele infusjonen. *Nøytropeni:* Fullstendig blodcelletelling bør utføres regelmessig under behandling. Pasienter med nøytropeni bør overvåkes for tegn på infeksjon. Doseutsettelse og bruk av kolonistimulerende faktorer (f.eks. G-CSF) bør vurderes for å redusere risikoen. *Infeksjon:* Økt forekomst av infeksjoner, inkl. grad ≥3, primært pneumoni, øvre luftveisinfeksjoner og bronkitt, er sett. Pasienten skal overvåkes nøye for tegn på infeksjon, og hensiktsmessig standard behandling skal iverksettes. Antibiotisk og antiviral profylakse kan vurderes under behandling. *Andre primære maligniteter:* Pasienten skal vurderes for og under behandling iht. IMWG-retningslinjer mht. utvikling av andre primære maligniteter, og nødvendig behandling iverksettes. *Interferens med serologisk testing:* Isatuksimab bindes til CD38 på røde blodceller, og kan potensielt gi falske positive reaksjoner i indirekte antiglobulintester (indirekte Coombs-test), antistoff-deteksjonstester (screeningtester), antistoff-identifikasjonspaneler og antihumanglobulin (AHG)-krysstester. Metoder for å redusere interferens inkluderer ditiotreitol (DTT)-behandling av reagensen med røde blodceller for å splitte bindingen av isatuksimab, eller andre lokalt validerte metoder. Ettersom blodtypesystemet Kell også er sensitivt mot DTT-behandling, bør Kell-negative enheter bli gitt etter utelukkelse eller identifisering av alloantistoffer vha. DTT-behandlede røde blodceller. For å unngå potensielle problemer med transfusjon av røde blodceller, skal blodtype- og screeningtester utføres før 1. infusjon. Fenotyping iht. lokal praksis kan vurderes før behandlingsoppstart. Dersom behandling har startet, bør blodbanken informeres. Pasienten bør overvåkes for risiko for hemolyse. Ved behov for akutt transfusjon kan det gis ikke-kryssmatchede ABO/Rh-kompatible røde blodceller iht. lokal blodbankpraksis. Varighet av interferens med indirekte Coombs test er ukjent, men basert på t1/2 til isatuksimab forventes ca. 6 måneder etter siste infusjon. *Interferens med bestemmelse av komplett respons:* Isatuksimab er et IgG-kappa monoklonalt antistoff som kan påvises ved både serumprotein-elektroforese (SPE) og immunfikseringsanalyse (IFE) som brukes ved klinisk overvåkning av endogent M-protein. Denne interferensen kan påvirke nøyaktigheten til bestemmelsen av komplett respons hos enkelte pasienter med IgG-kappa myelomprotein. *Bilkjøring og bruk av maskiner:* Ingen/ubetydelig påvirkning på evnen til å kjøre bil og bruke maskiner.

Interaksjoner: For utfyllende informasjon om relevante interaksjoner, bruk interaksjonsanalyse.

Graviditet, amming og fertilitet: *Graviditet:* Ingen data. Anbefales ikke hos gravide. Fertile kvinner skal bruke sikker prevensjon under og i 5 måneder etter avsluttet behandling. *Amming:* Overgang i morsmelk er ukjent. Humant IgG utskilles i morsmelk de første dagene etter fødsel, og avtar til lave konsentrasjoner etter kort tid. Risiko for barn som ammes i perioden like etter fødsel kan ikke utelukkes. Det må tas en beslutning om amming skal opphøre eller behandling avstås fra, basert på nytte-/risikovurdering. Deretter kan isatuksimab brukes under amming dersom klinisk nødvendig. *Fertilitet:* Ingen data.

Bivirkninger: ***Bivirkninger sett hos pasienter med myelomatose behandlet med isatuksimab i kombinasjon med pomalidomid og deksametason:*** *Svært vanlige (≥1/10):* Blod/lymfe: Febril nøytropeni, nøytropeni. Gastrointestinale: Diaré, kvalme, oppkast. Infeksiøse: Bronkitt, pneumoni[1], øvre luftveisinfeksjon. Luftveier: Dyspné. Skader/komplikasjoner: Infusjonsrelatert reaksjon. *Vanlige (≥1/100 til <1/10):* Hjerte: Atrieflimmer. Stoffskifte/ernæring: Redusert appetitt. Svulster/cyster: Kutant plateepitelkarsinom. Undersøkelser: Redusert vekt. *Mindre vanlige (≥1/1000 til <1/100):* Immunsystemet: Anafylaktisk reaksjon.

[1]Inkl. atypisk pneumoni, bronkopulmonal aspergillose, pneumoni, haemophilus-pneumoni, influensa-pneumoni, pneumokokkpneumoni, streptokokkpneumoni, viral pneumoni, candida-pneumoni, bakteriell pneumoni, haemophilus-infeksjon, lungeinfeksjon, fungal pneumoni og pneumocystis jirovecii-pneumoni.

Bivirkninger sett hos pasienter med myelomatose behandlet med isatuksimab i kombinasjon med karfilzomib og deksametason: *Svært vanlige (≥1/10):* Gastrointestinale: Diaré, oppkast. Generelle: Fatigue. Infeksiøse: Bronkitt, pneumoni[1], øvre luftveisinfeksjon. Kar: Hypertensjon. Luftveier: Dyspné, hoste. Skader/komplikasjoner: Infusjonsrelatert reaksjon. *Vanlige (≥1/100 til <1/10):* Blod/lymfe: Nøytropeni. Svulster/cyster: Hudkreft, solide svulster annet enn hudkreft. *Mindre vanlige (≥1/1000 til <1/100):* Immunsystemet: Anafylaktisk reaksjon.

[1]Inkl. atypisk pneumoni, bronkopulmonal aspergillose, pneumoni, haemophilus-pneumoni, influensa-pneumoni, pneumokokkpneumoni, streptokokkpneumoni, viral pneumoni, candida-pneumoni, bakteriell pneumoni, haemophilus-infeksjon, lungeinfeksjon, fungal pneumoni og pneumocystis jirovecii-pneumoni.

Overdosering/Forgiftning: Ingen erfaring med overdosering. Opptil 20 mg/kg i.v. er gitt. Ved mistenkt overdose bør det overvåkes for tegn/symptomer på bivirkninger, og nødvendige tiltak igangsettes umiddelbart. Se Giftinformasjonens anbefalinger L01X C38 på www.felleskatalogen.no.

Egenskaper: *Virkningsmekanisme:* Bindes til CD38-reseptoren, som i stor grad utrykkes på myelomatoseceller. Virker gjennom IgG Fc-avhengige mekanismer, inkl. antistoffavhengig cellemediert cytotoksisitet (ADCC), antistoffavhengig cellulær fagocytose (ADCP) og komplementavhengig cytotoksisitet (CDC). Isatuksimab kan også trigge tumorcelledød ved induksjon av apoptose via en Fc-uavhengig mekanisme. Blokkerer enzymaktiviteten til CD38, som katalyserer syntese og hydrolyse av syklisk ADP-ribose (cADPR), og hemmer dermed produksjon av cADPR fra ekstracellulær nikotinamidadenindinukleotid (NAD) i myelomatoseceller. Isatuksimab kan aktivere NK-celler i fravær av CD38-positive måltumorceller. Kan redusere absolutt antall av totale CD16+ og CD56+ NK-celler, CD19+ B-celler, CD4+ T-celler og TREG (CD3+, CD4+, CD25+, CD127-) i perifert blod. Sammenlignet med isatuksimab alene øker kombinasjonen av isatuksimab og pomalidomid in vitro cellelyseringen av CD38-uttrykkende myelomatoseceller via effektorceller (ADCC) og direkte tumorcelledrap. *Fordeling:* Vd ca. 8,75 liter. *Halveringstid:* Terminal t1/2 ca. 28 dager og gjennomsnittlig tilsynelatende clearance ca. 9,55 ml/time. Steady state nås etter 8 uker med en akkumulering på 3,1 ganger.

Oppbevaring og holdbarhet: Oppbevares i kjøleskap (2-8°C) og i originalemballasjen for å beskytte mot lys. Skal ikke fryses. *Etter fortynning:* Bør fra et mikrobiologisk synspunkt brukes umiddelbart. Brukeren er ansvarlig for oppbevaringstid og -forhold, som normalt bør være <24 timer ved 2-8°C, med mindre fortynning er utført under aseptiske forhold.

Pakninger og priser: 5 ml (hettegl.) kr 7908,50. 25 ml (hettegl.) kr 39397,30.

Sist endret: 2021.11.23
Basert på SPC godkjent av SLV/EMA: 17.06.2021

SIGN UP FOR AN ELECTRONIC VERSION OF FRAMINGHAM

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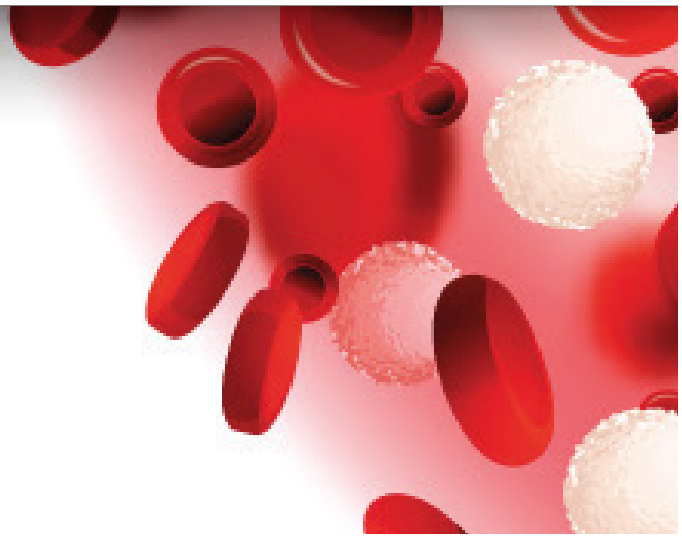

At Sanofi our ambition is to make a difference for patients with hematological diseases.

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.
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