KURZPROTOKOLL
EFC12522 IMROZ

Öffentlicher Titel	Phase III Studie zu Isatuximab bei neudiagnostiziertem Multiplem Myelom
Wissenschaftl. Titel	A Phase 3 Randomized, Open-label, Multicenter Study Assessing the Clinical Benefit of Isatuximab (SAR650984) in Combination With Bortezomib (Velcade®), Lenalidomide (Revlimid®) and Dexamethasone Versus Bortezomib, Lenalidomide and Dexamethasone in Patients With Newly Diagnosed Multiple Myeloma (NDMM) Not Eligible for Transplant
Kurztitel	EFC12522 IMROZ
Studienart	multizentrisch, prospektiv, Therapiestudie, randomisiert, offen/unverblindet, Pharma-Studie, dreiarmig
Studienphase	Phase III
Erkrankung	Blut: Multiples Myelom: neu diagnostiziert / de novo
Einschlusskriterien	- 1. Symptomatic multiple myeloma, as defined by the IMWG criteria - 2. Evidence of measurable disease: - - Serum monoclonal (M)-protein >=1.0 g/dL measured using serum protein immunoelectrophoresis and/or - - Urine M-protein >=200 mg/24 hours measured using urine protein - - immunoelectrophoresis and/or - - Serum free light chain multiple myeloma without measurable M-protein in serum or urine as per previous criteria (serum immunoglobulin free light chain (sFLC) >=10 mg/dL and abnormal serum immunoglobulin kappa lambda free light chain ratio <0.26 or >1.65). - 3. Patients who are newly diagnosed and not considered for high-dose chemotherapy due to: being age 65 years; or <65 years with important comorbidities likely to have a negative impact on tolerability of high dose chemotherapy with SCT - 4. Patient has given voluntary written informed consent before performance of any study related procedures not part of normal medical care, with the understanding that consent may be withdrawn by the patient at any time without prejudice to his/her medical care - Crossover part: patients will be considered eligible for crossover if they meet all of the following criteria: - 1. Patient with confirmed PD in the VRd control arm prior to crossover - 2. Patient has not received any other systemic anticancer therapy(ies) other than the VRd arm.I
Ausschlusskriterien	- Main study: patients who meet all the inclusion criteria will be screened for the following exclusion criteria: - 1. Less than 18 years (or country’s legal age of majority if the legal age is >18 years) and more than 80 years of age. - 2. Diagnosis of peripheral neuropathy Grade >1 or Grade 1 with pain. - 3. Diagnosis of primary amyloidosis, monoclonal gammopathy of undetermined significance, or smoldering multiple myeloma (asymptomatic multiple myeloma with absence of related organ or tissue impairment end organ damage). - 4. Diagnosis of Waldenström's disease, or other conditions in which IgM M-protein is present in the absence of a clonal plasma cell infiltration with lytic bone lesions. - 5. Prior or current systemic therapy, or SCT for symptomatic multiple myeloma, with the exception of an emergency use of a short course (equivalent of dexamethasone 40 mg/day for 4 days) of corticosteroids, if completed within 14 days prior to randomization. - 6. Concomitant plasma cell leukemia.

- 7. Any major procedure within 14 days before the initiation of the study treatment: plasmapheresis, major surgery (kyphoplasty is not considered a major procedure), radiotherapy (except if palliative intent).
- 8. ECOG PS >2.
- 9. Hemoglobin <8 g/dL.
- 10. Platelets <70 × 109/L if <50% of bone marrow (BM) nucleated cells are plasma cells, and <=30 × 109/L if >=50% of BM nucleated cells are plasma cells. Platelet transfusion is not allowed within 3 days before the screening hematological test.
- 11. Absolute neutrophil count (ANC) <1000/L (1 × 109/L). The use of granulocyte colony-stimulating factor (G-CSF) is not allowed to reach this level.
- 12. Creatinine clearance <30 mL/min/1.73 m² (modification of diet in renal disease MDRD formula).
- Total bilirubin >1.5 × upper limit of normal (ULN), except for known Gilbert syndrome.
- Corrected serum calcium >14 mg/dL (>3.5 mmol/L).
- 15. Aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) >3 × ULN.
- 16. Hypersensitivity (or contraindication) to dexamethasone, sucrose histidine (as base and hydrochloride salt), boron, mannitol, and polysorbate 80 or any of the components of study therapy that are not amenable to premedication with steroids, or H2 blockers that would prohibit further treatment with these agents.
- 17. Any of the following within 6 months prior to randomization:
- - Second/third degree heart block
- - Poorly controlled hypertension
- - Myocardial infarction
- - Severe/unstable angina pectoris
- - Coronary/peripheral artery bypass graft
- - New York Heart Association class III or IV congestive heart failure
- - Grade >=3 arrhythmias
- - Stroke or transient ischemic attack
- 18. Left-ventricular ejection fraction <40%.
- Prior malignancy. Adequately treated basal cell or squamous cell skin, or superficial (pTis, pTa, and pT1) bladder cancer, or low risk prostate cancer, or any in situ malignancy after curative therapy are allowed, as well as any other cancer for which cytotoxic chemotherapy has been completed >=3 years prior to enrollment and from which the patient has been disease-free for >=3 years.
- 20. Known acquired immunodeficiency syndrome (AIDS)-related illness or known HIV disease requiring antiviral treatment or active hepatitis A (defined as positive HA antigen), B (defined as either positive HBs antigen or negative HBs antigen with positive HBc antibody), or C infection (defined as a known positive hepatitis C
- 21. Malabsorption syndrome or any condition that can significantly impact the absorption of lenalidomide (as an example: hereditary problems of galactose intolerance, Lapp lactose deficiency).
- 22. Unable or unwilling to undergo thromboprophylaxis as per local clinical practice.
- 23. Any of the following within 3 months prior to randomization: treatment resistant peptic ulcer disease, erosive esophagitis or gastritis, infectious or inflammatory bowel disease, diverticulitis, pulmonary embolism, or other uncontrolled thromboembolic event.

- 24. Any severe acute or chronic medical condition which could impair the ability of the patient to participate in the study or interfere with interpretation of study results (eg, systemic infection unless anti-infective therapy is employed), or inability of the patient to comply with the study procedures.
- 25. Pregnant or breastfeeding woman or woman who intends to become pregnant during the participation in the study. Woman of childbearing potential (WOCBP) unwilling to prevent pregnancy by the use of 2 reliable methods of contraception for 4 weeks before the start of study treatment, during treatment (including dose interruptions), and for at least 28 days following discontinuation of study lenalidomide, or for 3 months after discontinuation of isatuximab or bortezomib treatment, whichever occurs last, and/or who are unwilling or unable to be tested for pregnancy before study treatment initiation (2 negative tests), weekly during the first 6 weeks of treatment, every 21 days for induction Cycles 2 to 4, and then every 28 days while on therapy (or every 14 days in case of irregular menstrual cycles) and, for at least 28 days following discontinuation of study lenalidomide (14 and 28 days for in case of irregular menstrual cycles), or monthly for 3 months after discontinuation of isatuximab or bortezomib treatment, whichever occurs last
- 26. Male participants who disagree to practice true abstinence or disagree to use a condom during sexual contact with a pregnant woman or a WOCBP while participating in the study, during dose interruptions, and for at least 28 days following discontinuation of study lenalidomide, or for 3 months after discontinuation of isatuximab or bortezomib treatment, whichever occurs last, even if he has undergone a successful vasectomy.
- Crossover part: patients will be considered eligible for crossover if they do not meet any of the following criteria:
- 1. Diagnosis of primary amyloidosis, monoclonal gammopathy of undetermined significance, or smoldering multiple myeloma (asymptomatic multiple myeloma with absence of related organ or tissue impairment end organ damage).
- 2. Diagnosis of Waldenström's disease, or other conditions in which IgM M-protein is present in the absence of a clonal plasma cell infiltration with lytic bone lesions.
- 3. Concomitant plasma cell leukemia.
- 4. Any major procedure within 14 days before the initiation of the study treatment: plasmapheresis, major surgery (kyphoplasty is not considered a major procedure), radiotherapy (except if palliative intent).
- 5. ECOG PS >2.
- 6. Hemoglobin <8 g/dL.
- 7. Platelets <50 × 109/L if <50% of BM nucleated cells are plasma cells, and <=30 × 109/L if >=50% of BM nucleated cells are plasma cells. Platelet transfusion is not allowed within 3 days before the screening hematological test.
- 8. Absolute neutrophil count <1000/L (1 × 109/L). The use of G-CSF is not allowed to reach this level.
- 9. Creatinine clearance <30 mL/min/1.73 m^2 (MDRD formula).
- 10. Total bilirubin >1.5 × ULN except for known Gilbert syndrome.
- 11. Corrected serum calcium >14 mg/dL (>3.5 mmol/L).
- 12. Aspartate aminotransferase and/or ALT >3 × ULN.
- 13. Hypersensitivity (or contraindication) to dexamethasone, sucrose histidine (as base and hydrochloride salt), boron, mannitol, and polysorbate 80 or any of the components of study therapy that are not amenable to premedication with steroids, or H2 blockers that would prohibit further treatment with these agents
- 14. Any of the following within 6 months prior to first investigational medicinal product (IMP) dosing in the crossover arm:

- - Second/third degree heart block.
- - Poorly controlled hypertension.
- - Myocardial infarction.
- - Severe/unstable angina pectoris.
- - Coronary/peripheral artery bypass graft.
- - New York Heart Association class III or IV congestive heart failure.
- - Grade >=3 arrhythmias.
- - Stroke or transient ischemic attack.
- 15. Left-ventricular ejection fraction <40%.
- 16. Prior malignancy. Adequately treated basal cell or squamous cell skin, or superficial (pTis, pTa, and pT1) bladder cancer, or low risk prostate cancer, or any in situ malignancy after curative therapy are allowed, as well as any other cancer for which cytotoxic chemotherapy has been completed >=3 years prior to first dosing and from which the patient has been disease-free for >=3 years.
- 17. Known acquired immunodeficiency syndrome (AIDS)-related illness or known HIV disease requiring antiviral treatment, or active hepatitis A (defined as positive HA antigen), B (defined as either positive HBs antigen or negative HBs antigen with positive HBc antibody), or C infection (defined as a known positive hepatitis C antibody result and known quantitative hepatitis C 􀀀HCV􀀀 ribonucleic acid 􀀀RNA􀀀 results greated than the lower limits of detection of the assay). HIV serology at screening will be tested only for German patients.
- 18. Malabsorption syndrome or any condition that can significantly impact the absorption of lenalidomide.
- 19. During the main study, premature discontinuation of lenalidomide and dexamethasone due to a related AE occurring less than 6 months before the start of crossover part, consent withdrawal, or for any reason other than PD.
- 20. Unable or unwilling to undergo thromboprophylaxis as per local clinical practice.
- 21. Any of the following, within 3 months prior to first IMP dosing in the crossover arm: treatment resistant peptic ulcer disease, erosive esophagitis or gastritis, infectious or inflammatory bowel disease, diverticulitis, pulmonary embolism, or other uncontrolled thromboembolic event.
- 22. Any severe acute or chronic medical condition which could impair the ability of the patient to participate in the study or interfere with interpretation of study results (eg, systemic infection unless anti-infective therapy is employed), or inability of the patient to comply with the study procedures.
- 23. Pregnant or breastfeeding woman or woman who intends to become pregnant during participation in the crossover part. Woman of childbearing potential unwilling to prevent pregnancy by the use of 2 reliable methods of contraception for 4 weeks before the start of study treatment, during treatment (including dose interruptions), and for at least 28 days following discontinuation of study lenalidomide, or for 3 months after discontinuation of isatuximab treatment, whichever occurs last, and/or who are unwilling or unable to be tested for pregnancy before study treatment initiation (2 negative tests), weekly during the first 4 weeks of treatment, and every 28 days while on therapy (or every 14 days in case of irregular menstrual cycles), and for at least 28 days following discontinuation of study lenalidomide (14 and 28 days for in case of irregular menstrual cycles), or monthly for 3 months after discontinuation of isatuximab treatment, whichever occurs last.

	- 24. Male participants who disagree to practice true abstinence or disagree to use a condom during sexual contact with a pregnant woman or a WOCBP while participating in the crossover part, during dose interruptions, and for at least 28 days following discontinuation of study lenalidomide, or for 3 months after discontinuation of isatuximab treatment,whichever occurs last, even if he has undergone a successful vasectomy.
Alter	65 Jahre und älter
Prüfzentren	**Universitätsklinikum Frankfurt** (Rekrutierung beendet) Medizinische Klinik II, Hämatologie/Onkologie Theodor-Stern-Kai 7 60590 Frankfurt am Main Beate Kienzler-Sach beate-ursula.kienzler-sach@kgu.de
Sponsor	Sanofi Aventis GmbH
Registrierung in anderen Studienregistern	ClinicalTrials.gov NCT03319667 EudraCT 2017-002238-21
Links	Studiendokumente zum Download (roXtra)