

USE OF ANTI-CD38 ANTIBODY IN THE TREATMENT OF NEW DIAGNOSED MULTIPLE MYELOMA

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the priority benefit of U.S. Provisional Application No. 63/607,082, filed December 6, 2023, and U.S. Provisional Application No. 63/654,907, filed May 31, 2024, the content of each of which is hereby incorporated in its entirety.

REFERENCE TO AN ELECTRONIC SEQUENCE LISTING

[0002] The content of the electronic sequence listing (183952025640seqlist.xml; Size: 11,510 bytes; and Date of Creation: December 4, 2024) is herein incorporated by reference in its entirety.

FIELD OF THE INVENTION

[0003] This disclosure provides methods for treating Newly Diagnosed Multiple Myeloma (NDMM) using an anti-CD38 antibody in combination with bortezomib, lenalidomide, and dexamethasone, as well as uses, compositions, and kits related thereto.

BACKGROUND

[0004] Multiple myeloma (MM) is a malignant plasma cell disease that is characterized by clonal proliferation of plasma cells in the bone marrow (BM) and the production of excessive amounts of a monoclonal immunoglobulin (usually of the IgG or IgA type or free urinary light chain, i.e., paraprotein, M-protein or M-component). Patients with MM can experience bone pain, bone fractures, fatigue, anemia, infections, hypercalcemia, and kidney problems (Rolig et al. (2015) Lancet. 385(9983):2197-208).

[0005] Multiple myeloma treatment has improved remarkably over the last two decades with the development and introduction of numerous novel agents leading to more effective treatments, including immunomodulatory agents, proteasome inhibitors and, anti-CD38 antibodies. Even though novel agents improved the overall survival (OS) of patients with MM, the disease is fatal in the majority of cases. First-line therapeutic strategies include Autologous Stem Cell Transfer (ASCT); however, many patients are not eligible or have not received ASCT, often due to patient age or frailty. Treatment options and survival are based on the patient's age, fitness and disease status. For example, patients aged beyond 65 years are generally considered ineligible for autologous SCT. Therefore new treatment options are needed for this patient population.

BRIEF SUMMARY

[0006] Provided herein are uses of anti-CD38 antibody in the treatment of MM in a human patient, methods of treating a human patient having MM, as well as compositions and kits for the uses and methods.

[0007] In one aspect, an anti-CD38 antibody for use in treating Multiple Myeloma (MM) in a human patient is provided. In one embodiment, the MM is Newly Diagnosed MM (NDMM) and the patient is not eligible for autologous stem cell transplant. The anti-CD38 antibody is administered in a dosing schedule comprising an induction period followed by a continuous treatment period. In the induction period, the anti-CD38 antibody is administered in combination with bortezomib, lenalidomide, and dexamethasone, and in the continuous treatment period, the anti-CD38 antibody is administered in combination with lenalidomide, and dexamethasone and not bortezomib. The induction period comprises four 42 day cycles, and the continuous treatment period comprises at least one 28 day cycle.

[0008] In another aspect, an anti-CD38 antibody for use in safely increasing Progression Free Survival (PFS) in a human patient having MM is provided. In one embodiment, the MM is Newly Diagnosed MM (NDMM) and the human patient is not eligible for autologous stem cell transplant. The anti-CD38 antibody is administered in a dosing schedule comprising induction and continuous treatment periods as described herein, such that the administration of the anti-CD38 antibody in said induction and continuous treatment periods results in an increased PFS as compared to the administration of the dosing schedule of the induction and continuous treatment periods without the anti-CD38 antibody.

[0009] In another aspect, an anti-CD38 antibody for use in safely increasing Minimal Residual Disease (MRD) negativity rate in a human patient having MM is provided. The MM is Newly Diagnosed MM (NDMM) and the human patient is not eligible for autologous stem cell transplant. The anti-CD38 antibody is administered in a dosing schedule comprising an induction period followed by a continuous treatment period as described herein, such that the administration of the anti-CD38 antibody in said induction and continuous treatment periods results in an increase in MRD negativity at a threshold of at least 10^{-5} as compared to the administration of the dosing schedule of the induction and continuous treatment periods without the anti-CD38 antibody.

[0010] In another aspect, an anti-CD38 antibody for use in safely increasing Overall Survival (OS) in a human patient having MM is provided. The MM is Newly Diagnosed MM (NDMM) and the human patient is not eligible for autologous stem cell transplant. The anti-CD38 antibody is administered in a dosing schedule comprising an induction period followed by a

continuous treatment period as described herein, such that the administration of the anti-CD38 antibody results in an increase in OS as compared to the administration of the dosing schedule of the induction and continuous treatment periods without the anti-CD38 antibody.

[0011] In another aspect, methods for treating Multiple Myeloma (MM) in a human patient are provided. In some embodiments, the MM is Newly Diagnosed MM (NDMM) and the human patient is not eligible for autologous stem cell transplant. In some embodiments, the anti-CD38 antibody is administered in a dosing schedule comprising an induction period followed by a continuous treatment period as described herein, thereby treating the NDMM.

[0012] In another aspect, methods for safely increasing Progression Free Survival (PFS) in a human patient having MM are provided. In some embodiments, the MM is Newly Diagnosed MM (NDMM) and the human patient is not eligible for autologous stem cell transplant. In some embodiments, the anti-CD38 is administered in a dosing schedule comprising an induction period followed by a continuous treatment period as described herein, such that administration of the anti-CD38 antibody in said induction and continuous treatment periods results in an increased PFS as compared to the administration of the dosing schedule of said induction and continuous treatment periods without the anti-CD38 antibody.

[0013] In another aspect, methods for safely increasing Minimal Residual Disease (MRD) negativity rate in a human patient having MM are provided. In some embodiments, the MM is Newly Diagnosed MM (NDMM) and the human patient is not eligible for autologous stem cell transplant. In some embodiments, the anti-CD38 antibody is administered in a dosing schedule comprising an induction period followed by a continuous treatment period as described herein, such that administration of the anti-CD38 antibody in said induction and continuous treatment periods results in an increase in MRD negativity rate at a threshold of at least 10^{-5} as compared to the administration of the dosing regimen of the induction and continuous treatment periods without the anti-CD38 antibody.

[0014] In another aspect, methods for safely increasing Overall Survival (OS) in a human patient having MM are provided. In some embodiments, the MM is Newly Diagnosed MM (NDMM) and the human patient is not eligible for autologous stem cell transplant. In some embodiments, the anti-CD38 antibody is administered in a dosing schedule comprising an induction period followed by a continuous treatment period as described herein, such that administration of the anti-CD38 antibody results in an increase in OS as compared to the administration of the dosing schedule of the induction and continuous treatment periods without the anti-CD38 antibody.

[0015] In some embodiments of the uses and methods provided herein, the induction period comprises administering the anti-CD38 antibody together with bortezomib (Velcade®), lenalidomide (Revlimid®), and dexamethasone according to the following dosing schedule. The first part of the dosing schedule is the induction period. In the induction period, the anti-CD38 antibody is administered on days 1, 8, 15, 22, and 29 of the first 42 day cycle, and then on days 1, 15, and 29 of three subsequent 42 day cycles. The bortezomib is administered on days 1, 4, 8, 11, 22, 25, 29, and 32 of each 42 day cycle. The lenalidomide is administered on days 1-14 and days 22-35 of each 42 day cycle. The dexamethasone is administered on days 1, 2, 4, 5, 8, 9, 11, 12, 15, 22, 23, 25, 26, 29, 30, 32, and 33 or on days 1, 4, 8, 11, 15, 22, 25, 29 and 32, of each 42 day cycle.

[0016] In some embodiments of the uses and methods provided herein, a continuous treatment period follows the induction period. The continuous treatment period comprises administering the anti-CD38 antibody together with lenalidomide and dexamethasone and not bortezomib. In some embodiments, the continuous treatment period comprises at least one 28 day cycle. The anti-CD38 antibody is administered on days 1 and 15, the lenalidomide is administered on days 1-21, and the dexamethasone is administered on days 1, 8, 15, and 22 of the 28 day cycle. In some embodiments, the anti-CD38 antibody, lenalidomide and/or dexamethasone is administered until disease progression.

BRIEF DESCRIPTION OF THE DRAWINGS

[0017] FIG. 1 shows the PFS primary analysis based on disease assessment by the IRC - Kaplan-Meier Curves by treatment group-Intent to Treat population; the top line is the Isatuximab + bortezomib + lenalidomide + dexamethasone arm, the bottom line is the bortezomib + lenalidomide + dexamethasone arm, and the plus signs are censored patients.

[0018] FIG. 2 shows prespecified PFS subgroup analyses.

[0019] FIG. 3 shows the MRD rate at any time during the study among patients in the ITT population.

DETAILED DESCRIPTION

[0020] Based on phase 3 clinical trial results presented herein, anti-CD38 antibody in combination with bortezomib, lenalidomide and dexamethasone is shown to have a favorable benefit-risk profile in treatment of patients with NDMM not eligible for transplant, showing improved progression free survival in this patient population.

Definitions

[0021] As used in the specification and the appended claims, the singular forms “a”, “an” and “the” include plural referents unless the content clearly dictates otherwise. Thus, for example, reference to “a molecule” optionally includes a combination of two or more such molecules, and the like.

[0022] The term “about” as used herein refers to the usual error range for the respective value readily known to the skilled person in this technical field. Reference to “about” a value or parameter herein includes (and describes) embodiments that are directed to that value or parameter per se.

[0023] “Sustained response” refers to the sustained effect on preventing or delaying progression of a disease (e.g., multiple myeloma) and/or improving one or more response criteria after cessation of a treatment. For example, response to treatment for multiple myeloma may be measured according to the criteria in Kumar et al. (2016) “International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma.” *Lancet Oncol.* 17(8): e328-e346) and Durie et al. (2006) “International uniform response criteria for multiple myeloma. *Leukemia*. 20: 1467-1473. (See also Table 1 herein). In some embodiments, the sustained response has a duration at least the same as the treatment duration, at least 1.5X, 2.0X, 2.5X, or 3.0X length of the treatment duration.

[0024] The term “pharmaceutical formulation” refers to a preparation which is in such form as to permit the biological activity of the active ingredient to be effective, and which contains no additional components which are unacceptably toxic to a subject to which the formulation would be administered. Such formulations are sterile. “Pharmaceutically acceptable” excipients (vehicles, additives) are those which can reasonably be administered to a subject mammal to provide an effective dose of the active ingredient employed.

[0025] As used herein, the term “treatment” refers to clinical intervention designed to alter the typical course of the disease or cell (e.g., cancer cell) being treated during the course of clinical pathology. Desirable effects of treatment include decreasing the rate of disease progression, ameliorating or palliating the disease state, and remission or improved prognosis. For example, a patient is successfully “treated” if one or more symptoms associated with cancer are mitigated or eliminated, including, but are not limited to, reducing the proliferation of (or destroying) cancerous cells, decreasing symptoms resulting from the disease, increasing the quality of life of those suffering from the disease, decreasing the dose of other medications required to treat the disease, and/or prolonging survival of patients.

[0026] As used herein, “in combination with” refers to administration of one treatment modality in addition to another treatment modality. As such, “in combination with” refers to administration of one treatment modality before, during, or after administration of the other treatment modality to the patient.

[0027] The term “antibody” herein is used in the broadest sense and specifically covers monoclonal antibodies (including full length monoclonal antibodies), polyclonal antibodies, multi-specific antibodies (e.g., bispecific antibodies), and antibody fragments so long as they exhibit the desired biological activity. In some embodiments, the antibody is isatuximab.

[0028] As used herein, the term “overall response rate” or “ORR” refers to the proportion of patients with stringent complete response (sCR), complete response (CR), very good partial response (VGPR), and partial response (PR), as assessed by the IRC using the IMWG response criteria described in Kumar et al. (2016) “International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma.” *Lancet Oncol.* 17(8): e328-e346 and Durie et al. (2006) “International uniform response criteria for multiple myeloma. *Leukemia*. 20: 1467-1473.

Table 1:

Adapted from updated International Myeloma Working Group Response Criteria	
IMWG MRD criteria (requires a CR as defined below)	
Sustained MRD-negative	MRD negativity in the marrow (NGF or NGS, or both) and by imaging as defined below, confirmed minimum of 1 year apart. Subsequent evaluations can be used to further specify the duration of negativity (eg, MRD-negative at 5 years).
Flow MRD-negative	Absence of phenotypically aberrant clonal plasma cells by NGF on bone marrow aspirates using the EuroFlow standard operation procedure for MRD detection in multiple myeloma (or validated equivalent method) with a minimum sensitivity of 1 in 10^5 nucleated cells or higher.
Sequencing MRD-negative	Absence of clonal plasma cells by NGS on bone marrow aspirate in which presence of a clone is defined as less than 2 identical sequencing reads obtained after DNA sequencing of bone marrow aspirates using the LymphoSIGHT platform (or validated equivalent method) with a minimum sensitivity of 1 in 10^5 nucleated cells or higher.
Imaging-positive MRD-negative	MRD negativity as defined by NGF or NGS plus disappearance of every area of increased tracer uptake found at baseline or a preceding PET-CT or decrease to less mediastinal blood pool SUV or decrease to less than that of surrounding normal tissue.
Standard IMWG response criteria	
Response	IMWG criteria
CR	- Negative immunofixation on the serum and urine and - Disappearance of any soft tissue plasmacytomas and <5% plasma cells in bone marrow aspirates. - A normal sFLC ratio of 0.26–1.65 is required (when the only method to measure disease is by serum FLC levels). Two consecutive assessments are needed. No known evidence of progressive disease or new bone lesions if radiographic studies were performed.
sCR	CR as defined above plus: - Normal sFLC ratio (0.26 to 1.65) and - Absence of clonal cells in bone marrow by immunohistochemistry (κ/λ ratio $\leq 4:1$ or $\geq 1:2$ for κ and λ patients, respectively, after counting ≥ 100 plasma cells). Two consecutive assessments of laboratory parameters are needed. No known evidence of progressive disease or new bone lesions if radiographic studies were performed.
VGPR	- Serum and urine M-protein detectable by immunofixation but not on electrophoresis or $\geq 90\%$ reduction in serum M-protein plus urine M-protein level <100 mg/24 hours. $\geq 90\%$ decrease in the sum of maximal perpendicular diameter compared to baseline in soft tissue plasmacytoma. - In patients with only FLC disease, $>90\%$ decrease in the difference between involved and uninvolved FLC levels is required. Note: subjects who otherwise achieve a clinical CR but are either missing bone marrow data or are positive by immunofixation will be assessed as VGPR. In addition, they will be further assessed according to the following subcategories: - Biochemical CR: negative immunofixation of both serum and urine M-protein, with missing bone marrow data. - Near CR: serum and urine M-component detectable by immunofixation but not on electrophoresis. Two consecutive assessments are needed. No known evidence of progressive disease or new bone lesions if radiographic studies were performed.
	$\geq 50\%$ reduction of serum M-protein and reduction in 24 hours urinary M-protein by $\geq 90\%$ or to <200 mg/24 h.

PR	- If the serum and urine M-protein are unmeasurable, a $\geq 50\%$ decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria, - In addition to the above listed criteria, if present at baseline, a $\geq 50\%$ reduction in the size (sum of the maximal perpendicular diameter SPD) of soft tissue plasmacytomas is also required. Two consecutive assessments are needed. No known evidence of progressive disease or new bone lesions if radiographic studies were performed.
MR	$\geq 25\%$ but $\leq 49\%$ reduction in serum M-protein and reduction in 24h urine M-protein by 50-89%, which still exceed 200 mg/24 hours. In addition to the above listed criteria, if present at baseline, $\geq 50\%$ reduction in size (SPD) of soft tissue plasmacytomas is also required. Two consecutive assessments are needed. No known evidence of progressive disease or new bone lesions if radiographic studies were performed.
SD	Not meeting criteria for CR, VGPR, PR, MR or progressive disease. No known evidence of progressive disease or new bone lesions if radiographic studies were performed.
PD	Any one or more of the following criteria: Increase of $\geq 25\%$ from lowest confirmed value in any one of the following criteria: - Serum M-protein (the absolute increase must be ≥ 0.5 g/dL), if the lowest M component was < 5 g/dL. - Serum M-protein increase ≥ 1 g/dL if the lowest M component was ≥ 5 g/dL. - Urine M-component (the absolute increase must be ≥ 200 mg/24 h). - Only in patients without measurable serum and urine M-protein, the difference between involved and uninvolved FLC levels. The absolute increase must be > 10 mg/dL. Appearance of new lesion(s), $\geq 50\%$ increase from nadir in SPD of > 1 lesion, or $\geq 50\%$ increase in the longest diameter of a previous lesion ≥ 1 cm in short axis. Two consecutive assessments are needed.

Abbreviations: CR = complete response ; sFLC = serum free light chain; IMWG = International Myeloma Working Group; M = monoclonal; MR = minimal response; MRD = minimal residual disease; NGF = next-generation flow, NGS = next-generation sequencing , PD = progressive disease; PR = partial response; PET-CT = Positron emission tomography-computed tomography; sCR = stringent complete response; SD = stable disease; SPD = sum of the products of the maximal

perpendicular diameters of measured lesions; SUV = maximum standardized uptake value; VGPR = very good partial response.

[0029] The following description sets forth exemplary methods, parameters and the like. It should be recognized, however, that such description is not intended as a limitation on the scope of the present disclosure but is instead provided as a description of exemplary embodiments.

Overview

[0030] Provided herein are methods for treating Multiple Myeloma (MM) in a human patient by administering an anti-CD38 antibody in combination with bortezomib, lenalidomide, and dexamethasone. In some embodiments, the MM is Newly Diagnosed MM (NDMM) and the human patient is not eligible for autologous stem cell transplant. In some embodiments, the anti-CD38 antibody is administered in a dosing schedule comprising an induction period followed by a continuous treatment period as described herein, thereby treating the NDMM. In some embodiments of the methods and uses provided herein, PFS is improved. In some embodiments, MRD negativity rate is improved. In still other embodiments, OS is improved.

Anti-CD38 Antibodies

[0031] In some embodiments, the anti-CD38 antibody is a human antibody, a humanized antibody, or a chimeric antibody. In some embodiments, the anti-CD38 antibody comprises (a) a heavy chain variable domain (V_H) that comprises: a CDR-H1 comprising the amino acid sequence DYWMQ (SEQ ID NO: 1), a CDR-H2 comprising the amino acid sequence TIYPGDGDTGYAQKFQG (SEQ ID NO: 2), and a CDR-H3 comprising the amino acid sequence GDYYGSNSLDY (SEQ ID NO: 3), and (b) a light chain variable domain (V_L) that comprises: a CDR-L1 comprising the amino acid sequence KASQDVSTVVA (SEQ ID NO: 4), a CDR-L2 comprising the amino acid sequence SASYRYI (SEQ ID NO: 5), and a CDR-L3 comprising the amino acid sequence QQHYSPPYT (SEQ ID NO: 6). In some embodiments, the anti-CD38 antibody comprises a heavy chain variable domain (V_H) that comprises an amino acid sequence that is at least 90% identical (e.g., at least any one of 91%, 92%, 94%, 95%, 96%, 97%, 98%, or 99%, including any range between these values) to SEQ ID NO: 7. Additionally or alternatively, in some embodiments, the anti-CD38 antibody comprises a light chain variable domain (V_L) that comprises an amino acid sequence that is at least 90% identical (e.g., at least any one of 91%, 92%, 94%, 95%, 96%, 97%, 98%, or 99%, including any range between these values) to SEQ ID NO: 8 or SEQ ID NO: 9. In some embodiments, the anti-CD38 antibody comprises a V_H that comprises SEQ ID NO: 7 and a V_L that comprises SEQ ID NO: 8 or SEQ ID NO: 9.

QVQLVQSGAE VAKPGTSLVSL SCKASGYTFT DYWMQWVKQR PGQGLEWIGT IYPGDGDTGY
AQKFQKGKATL TADKSSKTVY MHLSSLASED SAVYYCARGD YYGSNSLDYW GQGTSVTVSS
(SEQ ID NO: 7)

DIVMTQSHLS MSTSLGDPVS ITCKASQDVS TVVAWYQQKP GQSPRLIYS ASYRYIGVPD
RFTGSGAGTD FTFTISSVQA EDLAVYYCQQ HYSPPYTFEGG GTKLEIKR (SEQ ID NO: 8)

DIVMAQSHLS MSTSLGDPVS ITCKASQDVS TVVAWYQQKP GQSPRRLIYS ASYRYIGVPD
RFTGSGAGTD FTFTISSVQA EDLAVYYCQQ HYSPPYTFGG GTKLEIKR (SEQ ID NO: 9)

[0032] In some embodiments, the anti-CD38 antibody is isatuximab (CAS Registry Number: 1461640-62-9). Isatuximab, also known as hu38SB19 and SAR650984, is an anti-CD38 antibody described in WO 2008/047242 and US Patent No. 8,153,765, the contents of both of which are incorporated by reference herein in their entirety.

[0033] The heavy chain of isatuximab comprises the amino acid sequence:

QVQLVQSGAE VAKPGTSVKL SCKASGYTFT DYWMQWVKQR PGQGLEWIGT IYPGDGDTGY
AQKFQGKATL TADKSSKTVY MHLSSLASED SAVYYCARGD YYGSNSLDYW GQGTSVTVSS
ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPTVS WNSGALTSGV HTFPAVLQSS
GLYSLSSVVT VPSSSLGTQT YICNVNHKPS NTKVDKKVEP KSCDKTHTCP PCPAPPELLGG
PSVFLFPPKP KDTLMISRTP EVTCVVVDVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYN
STYRVVSVLT VLNQDNLNGK EYKCKVSNKA LPAPIEKTIS KAKGQPREPQ VYTLPPSRDE
LTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTTPV LDSGGSFFLY SKLTVDKSRW
QQGNVFSCSV MHEALHNHYT QKSLSLSPG (SEQ ID NO: 10)

and the light chain of isatuximab comprises the amino acid sequence:

DIVMTQSHLS MSTSLGDPVS ITCKASQDVS TVVAWYQQKP GQSPRRLIYS ASYRYIGVPD
RFTGSGAGTD FTFTISSVQA EDLAVYYCQQ HYSPPYTFGG GTKLEIKRTV AAPSVEIFPP
SDEQLKSGTA SVVCLLNFEY PREAKVQWKV DNALQSGNSQ ESVTEQDSKD STYSLSSLT
LSKADYEKHK VYACEVTHQG LSSPVTKSFN RGEC (SEQ ID NO: 11)

[0034] The anti-CD38 antibodies may be produced using recombinant methods. For recombinant production of an antibody, nucleic acid encoding the antibody is isolated and inserted into a replicable vector for further cloning (amplification of the DNA) or for expression. DNA encoding the antibody may be readily isolated and sequenced using conventional procedures (e.g., by using oligonucleotide probes that are capable of binding specifically to genes encoding the heavy and light chains of the antibody). Many vectors are available. The vector components generally include, but are not limited to, one or more of the following: a signal sequence, an origin of replication, one or more marker genes, an enhancer element, a promoter, and a transcription termination sequence. The vector is typically transformed into a host cell suitable for expression of the nucleic acid. In some embodiments, the host cell is a eukaryotic cell or a prokaryotic cell. In some embodiments, the eukaryotic host cell is a mammalian cell. Examples of useful mammalian host cell lines are monkey kidney CV1 line transformed by SV40 (COS-7, ATCC CRL 1651); human embryonic kidney line (293 or 293 cells subcloned for growth in suspension culture, Graham et al., J. Gen Virol. 36:59 (1977)); baby hamster kidney cells (BHK, ATCC CCL 10); mouse sertoli cells (TM4, Mather, Biol. Reprod. 23:243-251 (1980)); monkey kidney cells (CV1 ATCC CCL 70);

African green monkey kidney cells (VERO-76, ATCC CRL-1587); human cervical carcinoma cells (HELA, ATCC CCL 2); canine kidney cells (MDCK, ATCC CCL 34); buffalo rat liver cells (BRL 3A, ATCC CRL 1442); human lung cells (W138, ATCC CCL 75); human liver cells (Hep G2, HB 8065); mouse mammary tumor (MMT 060562, ATCC CCL51); TRI cells (Mather et al., *Annals N.Y. Acad. Sci.* 383:44-68 (1982)); MRC 5 cells; FS4 cells; and a human hepatoma line (Hep G2). Other useful mammalian host cell lines include Chinese hamster ovary (CHO) cells, including DHFR-CHO cells (Urlaub et al., *Proc. Natl. Acad. Sci. USA* 77:4216 (1980)); and myeloma cell lines such as NS0 and Sp2/0. For a review of certain mammalian host cell lines suitable for antibody production, see, e.g., Yazaki and Wu, *Methods in Molecular Biology*, Vol. 248 (B. K. C. Lo, ed., Humana Press, Totowa, N.J., 2003), pp. 255-268. The anti-CD38 antibody prepared from the cells can be purified using, for example, hydroxylapatite chromatography, hydrophobic interaction chromatography, gel electrophoresis, dialysis, and affinity chromatography, with affinity chromatography being among one of the typically preferred purification steps. In general, various methodologies for preparing antibodies for use in research, testing, and clinical applications are well-established in the art, consistent with the above-described methodologies and/or as deemed appropriate by one skilled in the art.

Pharmaceutical Compositions, Formulations, Doses

[0035] Also provided herein are pharmaceutical compositions and formulations, e.g., for the treatment of NDMM, comprising an anti-CD38 antibody (such as isatuximab), bortezomib, lenalidomide, or dexamethasone. In some embodiments, each of the anti-CD38 antibody (e.g., isatuximab), the bortezomib, lenalidomide, and the dexamethasone is provided as a separate pharmaceutical composition. In some embodiments, the pharmaceutical compositions and formulations further comprise a pharmaceutically acceptable carrier.

[0036] In some embodiments, an anti-CD38 antibody described herein (such as isatuximab) is in a formulation for dilution to be administered intravenously. The formulation for dilution comprises about 20 mg/mL (500 mg/25 mL) antibody, about 20 mM histidine, about 10% (w/v) sucrose, about 0.02% (w/v) polysorbate 80 at pH 6.0. In some embodiments, an anti-CD38 antibody described herein (such as isatuximab) is in a formulation comprising about 20 mg/mL antibody, about 100 mg/mL sucrose, 2.22 mg/mL histidine hydrochloride monohydrate, about 1.46 mg/ml histidine, and about 0.2 mg/ml polysorbate 80. In some embodiments the anti-CD38 antibody is isatuximab administered intravenously at a dose of 10 mg/kg.

[0037] In some embodiments, an anti-CD38 antibody described herein (such as isatuximab) is in a formulation comprising about 140 mg/mL isatuximab, 9 mM histidine, 110 mM Arg-Cl, 2% (w/v) sucrose, and 0.4% (w/v) Poloxamer 188, and has a pH of 6.2 (high concentration isatuximab). In some embodiments, the anti-CD38 antibody is high concentration isatuximab, administered subcutaneously at a dose of 1400 mg.

[0038] Pharmaceutical formulations of bortezomib, lenalidomide, and dexamethasone are commercially available. For example, bortezomib is known under the trade name VELCADE®. Lenalidomide is known under the trade name REVLIMID®. Dexamethasone is known under a variety of trade names, including DECADRON, MAXIDEX, and HEXADROL. In some embodiments, the bortezomib, lenalidomide, and/or the dexamethasone are provided in separate containers. In some embodiments, the bortezomib, lenalidomide and/or the dexamethasone are each used and/or prepared for administration to a patient as described in the prescribing information available with the commercially available product.

[0039] In some embodiments of the methods and uses provided herein, the bortezomib is administered at a dose of 1.3 mg/m². In some embodiments, the lenalidomide is administered at a dose of 25 mg/day (or 10 mg/day in a human patient having a CrCl_{SC} ≥30 to ≤60 mL/min) during induction and continuous treatment periods. In some embodiments, the dexamethasone is administered at a dose of 20 mg/day.

Patient population and treatment

[0040] In some embodiments, the anti-CD38 antibody is administered to a human patient, wherein the patient has Newly Diagnosed MM (NDMM). In some embodiments, the patient is not eligible for autologous stem cell transplant. In some embodiments, the patient does not receive ASCT at the same time as the treatment provided herein. In some embodiments, the patient has MM as defined by the IMWG criteria (Rajkumar SV, Dimopoulos MA, Palumbo A, Blade J, Merlini G, Mateos MV, et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. *Lancet Oncol.* 2014;15:e538-48). In some embodiments, the patient has evidence of measurable disease, for example,

- 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 (sFLC) multiple myeloma without measurable M-protein in serum or urine as per previous criteria (serum immunoglobulin free light chain) ≥ 10 mg/dL and abnormal serum immunoglobulin kappa lambda free light chain ratio < 0.26 or > 1.65).

[0041] The anti-CD38 antibody is administered in a dosing schedule comprising an induction period followed by a continuous treatment period. In the induction period, the anti-CD38 antibody is administered in combination with bortezomib, lenalidomide, and dexamethasone, and in the continuous treatment period, the anti-CD38 antibody is administered in combination with lenalidomide, and dexamethasone and not bortezomib. The induction period comprises four 42 day cycles, and the continuous treatment period comprises at least one 28 day cycle.

[0042] In some embodiments of the methods and uses described herein, the patient is newly diagnosed and not considered for high-dose chemotherapy due to age ≥ 65 years; or < 65 years with important comorbidities likely to have a negative impact on tolerability of high dose chemotherapy with SCT. In some embodiments of the methods and uses of anti-CD38 antibodies described herein, the patient is ≥ 70 years of age. In some embodiments, the patient is ≥ 75 years of age. In some embodiments, the patient is < 75 years of age. In some embodiments, the patient is < 70 years of age.

[0043] In some embodiments of the methods and uses provided herein, the patient has Revised International Staging System (R-ISS) stage III MM. In some embodiments, the patient has R-ISS stage I or II MM. In some embodiments, Stage I according to the Multiple Myeloma R-ISS is defined as (a) serum beta-2 microglobulin level less than 3.5 mg/L, (b) serum albumin greater than or equal to 3.5 g/dL, (c) standard risk chromosomal/cytogenetic abnormalities detected by interphase fluorescent in situ hybridization (iFISH) and (d) a normal serum lactate dehydrogenase (LDH) level. In some embodiments, Stage II according to the Multiple Myeloma R-ISS is defined as not R-ISS Stage I or Stage III. In some embodiments, the individual is Stage III according to the Multiple Myeloma Revised International Staging System (R-ISS). In some embodiments, Stage III according to the Multiple Myeloma R-ISS is defined as (a) a serum beta-2 microglobulin level of greater than about 5.5 mg/L and either (b) high-risk cytogenetic abnormality detected by interphase fluorescent in situ hybridization (iFISH) or (c) a serum lactate dehydrogenase (LDH) level greater than the upper limit of normal. In some embodiments, the individual has a high-risk cytogenetic abnormality (CA). In some embodiments, the high-risk cytogenetic abnormality is one or more of del(17p), t(4:14), and/or t(14:16). In some embodiments, the individual is not classified according to the R-ISS. In

some embodiments, the individual is not classified according to the R-ISS due to inconclusive iFISH.

[0044] In some embodiments of the uses and methods provided herein, the administration of the anti-CD38 antibody in said induction and continuous treatment periods described herein results in an increased PFS as compared to the administration of the induction and continuous periods without an anti-CD38 antibody. In some embodiments, the increased PFS is correlated with increased rate of MRD negativity in patients administered the anti-CD38 antibody.

[0045] In some embodiments, the PFS of the patient is measured as the period of time from the start of treatment to the first occurrence of progressive disease (PD). In some embodiments, PD is assessed according to the criteria in Kumar et al. (2016) "International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma." *Lancet Oncol.* 17(8): e328-e346) and Durie et al. (2006) "International uniform response criteria for multiple myeloma. *Leukemia.* 20: 1467-1473. In some embodiments, PFS is measured as the time from the start of treatment to the time of death. In some embodiments, the methods and uses provided herein result in improved (e.g., extend) progression free survival (PFS) of the patient, as compared to a patient having MM who received treatment comprising the induction period and continuous treatment periods without the anti-CD38 antibody. In some embodiments, the treatment increases the PFS of the patient.

[0046] In some embodiments, overall survival (OS) is measured as the period of time from the start of treatment to death. In some embodiments, the treatment increases the OS of the patient as compared to a patient having MM who received treatment comprising the induction period and continuous treatment periods without the anti-CD38 antibody.

[0047] In some embodiments, the patient is negative for minimal residual disease (MRD) or "MRD-negative" or has a lower MRD rate following administration of the induction and continuous period treatments described herein with the anti-CD38 antibody compared to administration of the induction and continuous period treatments described herein in the absence of the anti-CD38 antibody. In some embodiments, MRD status is measured by next generation flow cytometry (NGF). In some embodiments, MRD-negative status as measured by NGF (or "flow MRD-negative") refers to the absence of phenotypically aberrant clonal plasma cells (such as multiple myeloma cells) in bone marrow aspirates (for example using the EUROFLOW™ high-throughput flow cytometry standard operation procedure for MRD detection in multiple myeloma (see Flores-Montero et al. (2017) *Leukemia.* 31: 2094-2103) or an equivalent method) with a minimum sensitivity of, e.g., 1 in 10^4 nucleated cells (or " 10^{-4} "), 1 in 10^5 nucleated cells (or " 10^{-5} "), 1 in 10^6 nucleated cells (or " 10^{-6} "), or 1 in 10^7 nucleated

cells (or “ 10^{-7} ”). In some embodiments, MRD status is measured by next generation sequencing (NGS). In some embodiments, MRD-negative as measured by NGS (or “sequencing MRD negative”) refers to absence of clonal plasma cells (e.g., multiple myeloma cells) in bone marrow aspirates; the presence of a clone is defined as at least two identical sequencing reads obtained after DNA sequencing of bone marrow aspirates (for example, using the LYMPHOSIGHT® high-throughput sequencing platform or equivalent method) with a minimum sensitivity of, e.g., 1 in 10^4 nucleated cells (or “ 10^{-4} ”), 1 in 10^5 nucleated cells (or “ 10^{-5} ”), 1 in 10^6 nucleated cells (or “ 10^{-6} ”), or higher. In some embodiments, the minimum sensitivity is 1 cell in 10^7 nucleated cells (“ 10^{-7} ”). In some embodiments, the patient is negative by both imaging and MRD (or “imaging + MRD negative”). In some embodiments, imaging + MRD negative refers to (a) being MRD-negative as detected by NGF or MRD-negative as detected by NGS and (b) disappearance of every area of increased tracer uptake found at baseline or a preceding positron emission tomography (PET)/computed tomography (Ct) or decrease to < mediastinal blood pool maximum standardized uptake value or decrease to less than that of surrounding normal tissue. In some embodiments, the patient is “sustained MRD-negative.”

[0048] In some embodiments, sustained MRD negativity refers to a patient who has been confirmed to be imaging + MRD-negative at two time points following the start of treatment, wherein the time points are no less than 1 year apart. In some embodiments, minimal residual disease (MRD) is assessed via NGF or NGS using a bone marrow sample collected from a patient who has received treatment with the anti-CD38 antibody (e.g., isatuximab), bortezomib, lenalidomide, and dexamethasone, as described herein. In some embodiments, the patient who is assessed for MRD has achieved complete response or better (i.e., > CR), or has achieved very good partial response or better (i.e., > VGPR) during or after treatment with the anti-CD38 antibody (e.g., isatuximab), bortezomib, lenalidomide, and dexamethasone, as described herein.

Articles of Manufacture or Kits

[0049] In another embodiment of the invention, an article of manufacture or a kit is provided comprising an anti-CD38 antibody (such as isatuximab). In some embodiments, the article of manufacture or kit further comprises bortezomib, lenalidomide, and/or dexamethasone. In some embodiments, the article of manufacture or kit further comprises package insert comprising instructions for using the anti-CD38 antibody (e.g., isatuximab) in conjunction with the bortezomib, lenalidomide, and the dexamethasone to treat or delay progression of multiple

myeloma (e.g., NDMM) in a patient. In some embodiments, the kit comprises isatuximab, bortezomib, lenalidomide, and dexamethasone.

[0050] The specification is considered to be sufficient to enable one skilled in the art to practice the invention. Various modifications of the invention in addition to those shown and described herein will become apparent to those skilled in the art from the foregoing description and fall within the scope of the appended claims. All publications, patents, and patent applications cited herein are hereby incorporated by reference in their entirety for all purposes.

EXAMPLES

[0051] The present disclosure will be more fully understood by reference to the following examples. They should not, however, be construed as limiting the scope of the invention. It is understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be included within the spirit and purview of this application and scope of the appended claims.

[0052] To assess the clinical benefit of isatuximab (I) in combination with bortezomib (Velcade®, V), lenalidomide (Revlimid®, R) and dexamethasone (d), (IVRd) versus bortezomib, lenalidomide and dexamethasone (VRd) in patients with newly diagnosed multiple myeloma NDMM not eligible for transplant, a Phase 3 randomized, open-label, multicenter study was conducted. The primary endpoint or objective was Progression Free Survival (PFS).

[0053] Key secondary endpoints/objectives included Complete Response (CR) rate, as defined by the IMWG criteria (Kumar S, Paiva B, Anderson KC, Durie B, Landgren O, Moreau P, et al. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. *Lancet Oncol.* 2016;17(8):e328-46), Minimal Residual Disease (MRD) negativity rate in patients with CR, Very Good Partial Response or better rate, as defined by the IMWG criteria, and Overall Survival (OS) evaluated in both IVRd and VRd arms. Other secondary endpoints/objectives included: Overall Response Rate (ORR) as per IMWG criteria, Time To Progression (TTP) overall and by MRD status, PFS by MRD status, Duration of Response (DOR) overall and by MRD status, Time to First Response (TT1R), Time To Best Response (TTBR), Progression-Free Survival on next line of therapy (PFS2), Sustained MRD negativity ≥ 12 months rate, safety, pharmacokinetic (PK) profile of isatuximab in combination with bortezomib, lenalidomide, and dexamethasone (IVRd arm only), the immunogenicity of isatuximab in patients receiving isatuximab (IVRd and crossover arms), and disease-specific and generic health-related quality of life (HRQL), disease and treatment-related symptoms, health state utility, and health status.

[0054] Exploratory objectives included: the relationship between immune genetic determinants and efficacy endpoints, PK and pharmacodynamic (PDy) relationships, the relationship between cytogenetic abnormalities not part of the Revised International Staging System (R-ISS), including but not limited to gain(1q) and efficacy endpoints, new serum M-protein measurement methods such as mass spectrometry, and the response of Imaging-positive MRD-negative as per IMWG criteria.

[0055] Crossover objectives (patients that switched from the VRd arm to the IVRd arm) included: ORR as per IMWG criteria, Duration of Response (DOR), safety and the immunogenicity of isatuximab in patients receiving isatuximab.

Study Design

[0056] This was a prospective, multicenter, international, randomized, open-label, parallel group, 2-arm study evaluating the efficacy of IVRd compared to VRd for the treatment of patients with NDMM not eligible for Stem Cell Transplant (SCT). It was the first phase 3 study of this drug combination in this patient population.

Inclusion Criteria

Main study

[0057] Patients were considered eligible for randomization in the IVRd or VRd arms if they met all of the following criteria:

[0058] Multiple myeloma, as defined by the IMWG criteria (Rajkumar SV, Dimopoulos MA, Palumbo A, Blade J, Merlini G, Mateos MV, et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. *Lancet Oncol.* 2014;15:e538-48).

[0059] Evidence of measurable disease:

- Serum 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 disease in serum or urine as per previous criteria (serum immunoglobulin free light chain ≥ 10 mg/dL and abnormal serum immunoglobulin kappa lambda free light chain ratio <0.26 or >1.65).

[0060] Patients who are newly diagnosed and not considered for high-dose chemotherapy due to: age ≥ 65 years; or <65 years with important comorbidities likely to have a negative impact on tolerability of high dose chemotherapy with SCT.

[0061] 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

[0062] Patients were considered eligible for crossover if they met all of the following criteria:

[0063] Patient with confirmed PD in the VRd control arm prior to crossover.

[0064] Patient has not received any other systemic anticancer therapy(ies) other than the VRd arm.

Exclusion Criteria**Main study**

[0065] Patients who met all the above inclusion criteria were screened for the following exclusion criteria:

[0066] 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.

[0067] Diagnosis of peripheral neuropathy Grade >1 or Grade 1 with pain.

[0068] Diagnosis of amyloidosis, monoclonal gammopathy of undetermined significance, or smoldering multiple myeloma (multiple myeloma with absence of related organ or tissue impairment end organ damage).

[0069] 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.

[0070] Prior or current systemic therapy or SCT for 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.

[0071] Concomitant plasma cell leukemia.

[0072] 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).

[0073] Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) >2.

[0074] Hemoglobin <8 g/dL.

[0075] Platelets <70 × 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.

[0076] Absolute neutrophil count (ANC) <1000/μL (1 × 10⁹/L). The use of granulocyte colony-stimulating factor (G-CSF) is not allowed to reach this level.

[0077] Creatinine Clearance <30 mL/min/1.73 m² (Modification of Diet in Renal Disease (MDRD) formula).

[0078] $GFR (mL/min/1.73 m^2) = 175 \times (Scr)^{-1.154} \times (Age)^{-0.203} \times (0.742 \text{ if F}) \times (1.212 \text{ if AA})$.

[0079] Abbreviations: AA = African-American; F = Female; GFR = Glomerular filtration rate; Scr = Serum creatinine.

[0080] Total bilirubin $>1.5 \times$ upper limit of normal (ULN), except for known Gilbert syndrome.

[0081] Corrected serum calcium >14 mg/dL (>3.5 mmol/L).

[0082] Aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) $>3 \times$ ULN.

[0083] 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.

[0084] 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
- Left-ventricular ejection fraction $<40\%$.

[0085] 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.

[0086] Known acquired immunodeficiency syndrome (AIDS)-related illness or known HIV disease requiring antiviral treatment, or active hepatitis A (defined as positive HA antigen or positive IgM), B (defined as either positive HBs antigen or positive hepatitis B viral DNA test above the lower limit of detection of the assay), or C infection (defined as a known positive hepatitis C antibody result or known quantitative hepatitis C (HCV) ribonucleic acid (RNA) results greater than the lower limits of detection of the assay).

[0087] Malabsorption syndrome or any condition that can significantly impact the absorption of lenalidomide (e.g., hereditary problems of galactose intolerance, Lapp lactose deficiency).

[0088] Unable or unwilling to undergo thromboprophylaxis as per local clinical practice.

[0089] 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.

[0090] 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 (e.g., systemic infection unless anti-infective therapy is employed), or inability of the patient to comply with the study procedures.

[0091] Pregnant or breastfeeding woman or woman who intends to become pregnant during the participation in the study. 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 bortezomib treatment, or 5 months after discontinuation of isatuximab, 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 bortezomib treatment, or 5 months after discontinuation of isatuximab, whichever occurs last.

[0092] Note 1: a WOCBP is a woman who: **1)** has achieved menarche at some time point, **2)** has not undergone a hysterectomy or bilateral oophorectomy or **3)** has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

[0093] Note 2: true abstinence is acceptable when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, and post-ovulation methods) and withdrawal are not acceptable methods of contraception.

[0094] 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 bortezomib treatment, or 5 months after discontinuation of isatuximab, whichever occurs last, even if he has undergone a successful vasectomy.

Crossover part

[0095] Patients were considered eligible for crossover if they did not meet any of the following criteria:

[0096] Diagnosis of amyloidosis, monoclonal gammopathy of undetermined significance, or smoldering multiple myeloma (multiple myeloma with absence of related organ or tissue impairment end organ damage).

[0097] 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.

[0098] Concomitant plasma cell leukemia.

[0099] 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).

[0100] ECOG PS >2.

[0101] Hemoglobin <8 g/dL. E 807. 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.

[0102] Absolute neutrophil count <1000/μL (1 × 10⁹/L). The use of G-CSF is not allowed to reach this level.

[0103] Creatinine clearance <30 mL/min/1.73 m² (MDRD formula; see GFR calculation above).

[0104] Total bilirubin >1.5 × ULN except for known Gilbert syndrome. E 811. Corrected serum calcium >14 mg/dL (>3.5 mmol/L).

[0105] Aspartate aminotransferase and/or ALT >3 × ULN.

[0106] 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.

[0107] Any of the following within 6 months prior to first 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.

[0108] Left-ventricular ejection fraction $<40\%$.

[0109] 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.

[0110] Known acquired immunodeficiency syndrome (AIDS)-related illness or known HIV disease requiring antiviral treatment, or active hepatitis A (defined as positive HA antigen or positive IgM), B (defined as either positive HBs antigen or antibody positive hepatitis B viral DNA test above the lower limit of detection of the assay), or C infection (defined as a known positive hepatitis C antibody result or known quantitative hepatitis C (HCV) ribonucleic acid (RNA) results greater than the lower limits of detection of the assay).

[0111] Malabsorption syndrome or any condition that can significantly impact the absorption of lenalidomide (as an example: hereditary problems of galactose intolerance, Lapp lactose deficiency).

[0112] 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.

[0113] Unable or unwilling to undergo thromboprophylaxis as per local clinical practice.

[0114] 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.

[0115] 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 (e.g., systemic infection unless anti-infective therapy is employed), or inability of the patient to comply with the study procedures.

[0116] Pregnant or breastfeeding woman or woman who intends to become pregnant during participation in the crossover part. See Exclusion Criteria.

[0117] Male participants. See Exclusion Criteria.

Investigational Medicinal Products

Isatuximab

[0118] Isatuximab was provided as a concentrate solution for infusion in vials containing 20 mg/mL (500 mg/25 mL) isatuximab in 20 mM histidine, 10% (w/v) sucrose, and 0.02% (w/v) polysorbate 80 at pH 6.0 buffer. Isatuximab was supplied for parenteral administration as a sterile, nonpyrogenic, injectable, 20 mg/mL concentrate for solution for infusion, essentially free of visible particulates, and was packaged in 30 mL glass vials fitted with elastomeric closure. Each vial contained a nominal content of 500 mg isatuximab. The fill volume was established to ensure removal of 25 mL. For patient administration, the appropriate volume of isatuximab was diluted in a 250-mL infusion bag of 0.9% sodium chloride solution or 5% dextrose solution.

Dilution method

[0119] Isatuximab concentrate for solution for infusion was diluted in an infusion bag with 0.9% sodium chloride or 5% dextrose solution to achieve the appropriate drug concentration for infusion. Infusion via a central line was preferred, if available. In case of patients with local intolerance after peripheral IV infusion, the decision to use a central line was left to the Investigator's decision. The final infusion volume corresponding to the dose of isatuximab was administered by IV infusion for the period of time that depended on total dose administered.

[0120] Prior to dosing, each patient's dose was individually prepared by the study Pharmacist and labeled with the protocol number, patient number, and treatment description. The total dose was calculated based on the most recent weight available on the day of the infusion preparation: the weight on the day of the infusion or the most recent weight, assuming it was assessed in a reasonable time frame according to investigator assessment. If the infusion was prepared with the most recent weight, assessed in a reasonable time frame, this did not prevent assessment of the weight on D1 of each cycle.

Lenalidomide

[0121] Lenalidomide was presented as capsules of 5 mg, 10 mg, 15 mg, 20 mg, and 25 mg.

Bortezomib

[0122] Bortezomib from available commercial supplies was presented as vial of 3.5 mg.

Dexamethasone

[0123] Dexamethasone IV/per os (PO) was presented as tablets (4 mg); ampules of 3.3 mg/mL, or vials of 10 mg/mL for IV injection.

Dosage and schedule

[0124] There was no limitation in the number of cycles administered in the absence of major toxicity, disease progression or any other discontinuation criteria. The patient's weight was preferably measured prior to each cycle to allow the calculation of isatuximab dose.

[0125] Dose adjustment (dose delay, dose omission, and, for lenalidomide, bortezomib, and dexamethasone specifically, dose reduction) was permitted for subsequent treatment cycles based on individual patient tolerance. No dose reductions were allowed for isatuximab infusion.

Study treatments

[0126] Study treatment was defined as isatuximab in combination with bortezomib, lenalidomide, and dexamethasone in the IVRd experimental arm or bortezomib in combination with lenalidomide and dexamethasone in the VRd control arm. Patients allocated to the IVRd arm routinely received premedications prior to isatuximab infusion to reduce the risk and severity of IRs commonly observed with monoclonal antibodies.

[0127] Lenalidomide was allowed to be taken with water and swallowed whole. Patients were not permitted to break, chew or open the capsules. Lenalidomide could be taken with or without food preferably at the same time every day. Patients were asked to maintain a paper diary to record the doses of lenalidomide. If a dose of lenalidomide was missed, it was to be taken as soon as possible on the same day. If it was missed for the entire day, no administration should have been recorded, the dose was considered omitted and was replaced. The next scheduled dose should have been taken at the next scheduled time point.

[0128] Patients with a BSA $>2.2 \text{ m}^2$ used 2.2 m^2 for the determination of bortezomib dose. Oral administration of dexamethasone and lenalidomide was recorded in patient diaries.

IVRd arm (experimental arm)

[0129] Drug administration (after premedication) for patients treated with isatuximab, lenalidomide, bortezomib, and dexamethasone combination followed the dosage regimen:

[0130] Dexamethasone 20 mg/day was given IV on the days of isatuximab administration and PO otherwise on:

- Days 1, 2, 4, 5, 8, 9, 11, 12, 15, 22, 23, 25, 26, 29, 30, 32, and 33 during the induction period (Cycles 1 to 4). If patients are ≥ 75 years old, dexamethasone was administered on days 1, 4, 8, 11, 15, 22, 25, 29 and 32,
- Days 1, 8, 15, and 22 during continuous treatment period, between 15 and 30 minutes (but no longer than 60 minutes) prior to isatuximab. Dose modifications may have been recommended based on dose toxicity. In case dexamethasone was prematurely stopped and other study treatments were continued, steroid premedication could have been considered with methylprednisolone 100 mg IV if Infusion Reaction (IR) premedication was still needed for isatuximab, according to Investigator judgment.

[0131] Isatuximab 10 mg/kg IV:

- Days 1, 8, 15, 22, and 29 of Cycle 1, and 10 mg/kg on Days 1, 15, and 29 for subsequent cycles during the induction period,
- Days 1 and 15 of each cycle during the continuous treatment period,
- Isatuximab 10 mg/kg every 2 weeks was continued for 17 cycles after first dose (Cycle 1-Day 1 [induction period]), after which the schedule was once every 4 weeks administration,
- Infusion via a central line was preferred if available. In case of patients with local intolerance after peripheral IV infusion, decision to use central line was left to Investigator decision.

[0132] For IV infusion, an IV tubing administration set with a 0.20 μ m inline filter was used for infusion. If an inline filter was unavailable, a 0.20- μ m filter unit may have been attached to the administration set before administration.

[0133] Rate and duration of isatuximab infusion:

[0134] During the course of the study, administration of isatuximab was switched to a fixed volume (250 mL), fast infusion described as follows: Premedication for the prevention of IR was given for the first isatuximab fixed volume fast infusion. Patients who did not experience an IR after 4 consecutive administrations of isatuximab may have had their need for subsequent premedication reconsidered, at the Investigator's discretion. The first isatuximab infusion was initiated at 25 mL/hour. In the absence of IRs after 1 hour of infusion, the infusion rate was increased by 25 mL/hour increments every 30 minutes, to a maximum of 150 mL/hour. In case of grade 2 IR during the first infusion, infusion could have been restarted at one-half (12.5 mL/hour) of the initial infusion rate when the IR improves to Grade ≤ 1 . If symptoms did not recur after 30 minutes, the infusion rate may have been increased by 25 mL/hour increments every 30 minutes, until the total volume was infused. The second infusion was initiated at 50 mL/hour. In the absence of Grade 2 IR after 30 minutes of infusion, the rate was increased to 100 mL/hour for 30 minutes, then, to 200 mL/hour until the total volume was infused. In case of Grade 2 IR during the second infusion, the infusion could have been restarted at one-half (25 mL/hour) of the initial infusion rate when the IR improved to Grade ≤ 1 . If symptoms did not recur after 30 minutes, the infusion rate may have been increased by 50 mL/hour increments every 30 minutes, until the total volume was infused. The third and subsequent infusions were initiated at a fixed infusion rate of 200 mL/hour, until the total volume was infused. In case of Grade 2 IR during third infusion, infusion could have been restarted at one-half (100 mL/hour) of the infusion rate when the IR improved to Grade ≤ 1 . If symptoms did not recur after 30

minutes, the infusion rate may have been increased by 50 mL/hour increments every 30 minutes, until the total volume was infused.

[0135] Bortezomib SC was given 1.3 mg/m² on Days 1, 4, 8, 11, 22, 25, 29, and 32 during the induction period only (Cycles 1 to 4).

- Lenalidomide PO was given 25 mg/day (10 mg/day for patients with CrCl $\geq$ 30 to <60 mL/min) on Days 1 to 14 and Days 22 to 35 in a 42-day cycle during induction period (Cycles 1 to 4), and from Day 1 to Day 21 in a 28-day cycle during continuous treatment period. During the treatment period, dose modifications may have been recommended based on dose toxicity
- Lenalidomide was taken at the time which was the most convenient for the patient, preferably at the same time as the previous dose.

VRd arm (control arm)

[0136] Drug administration for patients treated with the bortezomib and lenalidomide combination followed the same instructions as for the IVRd arm.

[0137] The following instructions was followed for dexamethasone:

- Days 1, 2, 4, 5, 8, 9, 11, 12, 15, 22, 23, 25, 26, 29, 30, 32, and 33 during the induction period (Cycles 1 to 4). If patients are $\geq$ 75 years old, dexamethasone was administered on Days 1, 4, 8, 11, 15, 22, 25, 29 and 32.
- Days 1, 8, 15, and 22 during continuous treatment period.

Crossover arm

[0138] Patients in the VRd arm eligible for the crossover arm received isatuximab, lenalidomide, and dexamethasone. In the crossover arm, drug administration (after premedication) followed the instructions below:

[0139] Dexamethasone 20 mg, was given IV on the days of isatuximab administration and PO otherwise on Days 1, 8, 15, and 22 of each cycle, between 15 and 30 minutes (but no longer than 60 minutes) prior to isatuximab.

- If stopped prior to start of crossover treatment for reasons other than safety (unless more than 6 months before crossover and based on Investigator's judgement), dexamethasone was added in the crossover part,
- If dexamethasone dose was decreased for safety reasons, the last dose of dexamethasone was started.

[0140] Isatuximab 10 mg/kg IV on Days 1, 8, 15, and 22 of the first crossover cycle, and then 10 mg/kg on Days 1, and 15 for subsequent cycles.

[0141] Rate and duration of isatuximab infusion:

[0142] During the course of the study, administration of isatuximab was switched to a fixed volume (250 mL), fast infusion described above for fixed volume, fast infusion of isatuximab.

[0143] Lenalidomide 25 mg PO was given on Days 1 to 21 in a 28-day cycle, or 10 mg/day for patients with CrCl ≥ 30 to < 60 mL/min (see GFR calculation see above).

- Lenalidomide was taken at the time which was the most convenient for the patient, preferably at the same time of the previous dose,
- If lenalidomide was decreased in the control arm, it was re-increased to 25 mg/day, unless the dose was decreased for safety purposes and criteria for re-increase were not met.

Dose modifications

General rules

[0144] Dose modifications were permitted according to the guidelines described in this section. Dose reductions and/or cycle delays were permitted in case of toxicity. The patient may have had one or more doses omitted (isatuximab and/or lenalidomide and/or bortezomib and/or dexamethasone) within a cycle if toxicity occurred and was not recovered by the day of planned infusion/administration. If a patient experienced several toxicities and there were conflicting recommendations, the most conservative dose adjustment recommended (dose reduction/omission/delay appropriate to the most severe toxicity) was followed. Once a dose of lenalidomide or bortezomib or dexamethasone had been decreased, intra-patient re-escalation back to the previous dose level was not permitted, unless the patient switched to the crossover arm (no re-escalations were allowed if the dose was decreased for safety reasons). If a dose reduction was required, it was to be applied compared to the last dose level received by the patient.

[0145] Administration of the study treatment (isatuximab and/or lenalidomide and/or bortezomib and/or dexamethasone) was discontinued in the event of an AE that persisted, despite appropriate dose modifications or any other AE that, in the opinion of the Investigator, warranted discontinuation.

[0146] Patients received the next cycle of study treatment after recovery of the toxicity as described below.

[0147] A new cycle of study treatment may have been begin on the scheduled Day 1 of a subsequent cycle if the following criteria were met.

- Absolute neutrophil count $\geq 1000/\text{mm}^3$.
- Platelet count $\geq 70\,000/\text{mm}^3$. For patients with plasma cells $\geq 50\%$ of BM nucleated cells at baseline, in order to initiate Cycle 2 platelet counts should be $\geq 30\,000/\text{mm}^3$ regardless response status at end of Cycle 1. During Cycles 2-4, platelet counts should have been

$\geq 30\,000/\text{mm}^3$, if last response was not better than stable disease (SD), but if last response was PR or better during Cycles 2 to 4, Day 1 next cycle could have been administered only if platelet counts $\geq 70\,000/\text{mm}^3$. For Day 1 administration beyond Cycle 4 and for the crossover part whatever the cycle, platelet counts should have been $\geq 50\,000/\text{mm}^3$.

- Any other lenalidomide, bortezomib, dexamethasone or isatuximab related AEs that may have occurred in the previous cycle has recovered to Grade ≤ 1 or baseline severity.

[0148] If these criteria were not met on the scheduled Day 1, Day 1 of the next cycle should have been delayed until patients recovered as defined above and if Day 1 delay was more than 3 days, the reason should have been documented. If these criteria were not met within 14 days of the scheduled Day 1 (planned Day 1 Cycle $n+1$ corresponds to Day 43 Cycle n for the induction period and Day 29 Cycle n for the continuous treatment period), the patient should be discontinued from study treatment, unless there is strong evidence of clinical benefit to justify continuation of dosing with study treatment. The Investigator must discuss the rationale with the Sponsor before a decision to continue the study treatment is taken. A delay for patient's convenience should have been avoided during the first cycles and a delay or IMPs temporary discontinuation more than 14 days has to be discussed with the Sponsor before a decision is taken.

[0149] If there were dose modifications within the previous cycle, these guidelines were followed for the initiation of a new cycle or during the cycle:

- No dose reduction of isatuximab was permitted.
- If lenalidomide, bortezomib or dexamethasone dosing was halted during the previous cycle and was restarted with a one-level dose reduction, then that reduced dose level was initiated on Day 1 of the new cycle. Once a dose of lenalidomide, bortezomib or dexamethasone was reduced, intra-patient re-escalation back to the previous dose level was not permitted, unless specific conditions for lenalidomide are met.
- Within cycles, no dose delay was allowed for lenalidomide and bortezomib, except a time window of ± 1 day. No dose delay was allowed to dexamethasone with the proposed initial schedule during induction period. During Cycle 1, no dose delay was allowed as well for Isatuximab (weekly administration), except a time window of ± 1 day. For subsequent cycles, time window for Day 15 administration of isatuximab was ± 2 days and any omission due to AE was documented in the eCRF.
- Patients may have had isatuximab or bortezomib or dexamethasone (weekly administration during continuous period) dose omission within a cycle because of adverse event(s), which did not recover on the day of planned administration or within

the following day (or 2 days for isatuximab every 2 weeks administration). In cases of unresolved toxicity within the allowed time windows, the IMP administration was omitted. Patients received the next administration after recovering from the toxicity.

- If one or several doses of lenalidomide were omitted during Day 1 to 14, or Day 22 to 35 (induction period) or Day 1 to 21 (continuous treatment period), no treatment was administered after Days 14 or 35 or 21 respectively, in order to compensate the omitted doses.
- If there were no other AEs that required a dose reduction and thrombocytopenia and/or neutropenia was managed with supportive measures no dose reductions were required.

[0150] If one of the study treatments was prematurely discontinued, then other drug(s) could have been continued until disease progression or unacceptable toxicity or patient's wish to discontinue further study treatment. The end of study treatment in this case would have been 30 days after the date of the last study treatment administration.

Modification of dose levels in case of dose reduction

[0151] No isatuximab dose reduction was permitted.

[0152] Dose reduction steps for lenalidomide are shown in Table A. One or several doses of lenalidomide could have been omitted. If CrCl was between 30 and 60 mL/min, the starting dose was 10 mg/day.

Table A - Dose levels for lenalidomide dose reduction

Starting dose (PO)	Dose level -1	Dose level -2	Dose level -3	Dose level -4	Dose level -5
25 mg	20 mg	15 mg	10 mg	5 mg	5 mg every 2 days

Abbreviations: PO = per os.

[0153] Dose reduction steps for dexamethasone are shown in Table B. One or several doses of dexamethasone were allowed to be omitted, and administrations were allowed to be decreased to once every week or every 2 weeks. On the days of isatuximab infusion, dexamethasone dose was allowed to be maintained at 20 mg and decreased only on the days without isatuximab, based on investigator's decision.

Table B - Dose levels for dexamethasone dose reduction

Starting dose (PO or IV)	Dose level -1	Dose level -2	Dose level -3
20 mg	12 mg	8 mg	4 mg

Abbreviations: IV = intravenous; PO = per os.

[0154] Dose reduction steps for bortezomib are shown in Table C. One or several doses of bortezomib were allowed to be omitted, and administrations were allowed to be decreased to once every week.

Table C - Dose levels for bortezomib dose reduction

Starting dose (SC)	Dose level -1	Dose level -2
1.3 mg/m ²	1.0 mg/m ²	0.7 mg/m ²

Abbreviations: SC = subcutaneous.

Dose adjustments

[0155] Dose adjustments for patients treated with isatuximab, bortezomib, lenalidomide, and dexamethasone combination in the case of hematological toxicity are shown in Table 2. Dose adjustments for patients treated with isatuximab, lenalidomide, bortezomib, and dexamethasone combination in the case of nonhematological toxicity are shown in Table 3.

Table 2- Guidelines for dose adjustments for hematologic toxicities - isatuximab/bortezomib/lenalidomide/dexamethasone combination

Adverse event	Recommended action			
	Isatuximab	Dexamethasone	Lenalidomide ^a	Bortezomib
Thrombocytopenia				
Thrombocytopenia Grade 3 (<50 and $\geq 25 \times 10^9/L$)	Day 1 of cycle: delay until platelet counts improve (Section 8.1.6.1) ^b and administer at same dose level ^c . Within cycle: maintain full dose of study treatment as planned.	Day 1 of cycle or within cycle: maintain full dose dexamethasone as planned.	Day 1 of cycle: delay until platelet counts improve (Section 8.1.6.1) ^b and administer at same dose level ^c . Within cycle: maintain full dose of study treatment as planned.	Day 1 of cycle: delay until platelet counts improve (Section 8.1.6.1) ^b and administer at same dose level ^c . Within cycle: maintain full dose of study treatment as planned.
Thrombocytopenia Grade 4 with or without bleeding (<25 $\times 10^9/L$)	Day 1 of cycle: delay Day 1 administration until platelet counts improve (Section 8.1.6.1) ^b and administer at the same dose level ^c . Within cycle: delay/omit isatuximab until bleeding is controlled and platelet counts improve (Section 8.1.6.1) and then administer full dose. If delay is beyond guidelines	Day 1 of cycle or within cycle: maintain full dose dexamethasone as planned.	Day 1 of cycle: delay Day 1 administration until recovery and decrease lenalidomide by 1 dose level ^c . Within cycle: hold lenalidomide until bleeding is controlled and counts improve (Section 8.1.6.1), and then restart with 1 dose level decrease up to planned Day 42 if	Day 1 of cycle: delay Day 1 administration until recovery and decrease bortezomib by 1 dose level ^c . Within cycle: hold bortezomib until bleeding is controlled and platelet counts improve (Section 8.1.6.1), and

	Section 8.1.6.1, omit isatuximab until next planned administration Further episodes: same recommendations		induction period or 28 if continuous period. Next cycle was restarted with this dose level decrease. If repeating episodes: decrease lenalidomide by 1 level at each episode, not below 5 mg daily if patient started at 25 mg, or 5 mg/2 days if patient started at 10 mg.	then restart with 1 dose level decrease up to planned Day 42 or 28 (see lenalidomide column). Next cycle was restarted with this dose level decrease. If several bortezomib doses are withheld in 1 cycle (at least 4 during twice weekly administration), dose should be reduced by 1 dose level.
Neutropenia				
Grade 3 (≥ 0.5 and $< 1.0 \times 10^9/L$)	Day 1 of cycle: delay until ANC improve to $\geq 1.0 \times 10^9/L$ and administer at same dose level^d. Within cycle: maintain full dose as planned.	Day 1 of cycle or within cycle: maintain full dose dexamethasone as planned.	Day 1 of cycle: delay until ANC improve to $\geq 1.0 \times 10^9/L$ and administer at same dose level^d. Within cycle: maintain full dose as planned.	Day 1 of cycle: delay until ANC improve to $\geq 1.0 \times 10^9/L$ and administer at same dose level^d. Within cycle: maintain full dose as planned.
Grade 4 ($< 0.5 \times 10^9/L$)	Day 1 of cycle: delay until ANC improve to $\geq 1.0 \times 10^9/L$ and administer at the same dose level^c. Within cycle: maintain same dose as planned. Further episodes: same recommendations.	Day 1 of cycle: delay Day 1 administration until recovery to $\geq 1.0 \times 10^9/L$ and restart lenalidomide. Decrease by 1 dose level or consider G-CSF use and keep same dose level^c. Within cycle: hold lenalidomide until neutrophil counts	Day 1 of cycle: delay Day 1 administration until recovery to $\geq 1.0 \times 10^9/L$ and restart bortezomib. Decrease by 1 dose level or consider G-CSF use and keep same dose level^c. Within cycle: hold bortezomib until neutrophil counts improve to $\geq 0.750 \times 10^9/L$ ($0.500 \times$	Grade 4 ($< 0.5 \times 10^9/L$)

		improve to $\geq 0.750 \times 10^9/\text{L}$ ($0.500 \times 10^9/\text{L}$ in continuous treatment period and crossover arm) and then: • Restart with 1 dose level decrease up to planned Day 42 if induction period or Day 28 if continuous treatment period or crossover. Next cycle was restarted with this dose level decrease • Or consider G-CSF use and keep same dose level. If repeating episodes: decrease lenalidomide by 1 level at each episode, not below 5 mg daily if patient started at 25 mg, or 5 mg/2 days if patient started at 10 mg.	$10^9/\text{L}$ in continuous treatment period and crossover arm) and then: • Restart with 1 dose level decrease up to planned Day 42 if induction period or Day 28 if continuous treatment period or crossover. Next cycle was restarted with this dose level decrease • Or consider G-CSF use and keep same dose level. If several bortezomib doses are withheld in 1 cycle (at least 4 during twice weekly administration), dose should be reduced by 1 dose level.	
Febrile neutropenia and/or neutropenic infection	Day 1 of cycle: delay Day 1 administration until fever and infection recover and add G-CSF until $\text{ANC} > 1 \times 10^9/\text{L}^c$. Then on Day 1 of the next cycle, administer isatuximab and dexamethasone at the same dose level, and lenalidomide and bortezomib with dose recommendations stated below. Within cycle: omit isatuximab and dexamethasone, hold lenalidomide and bortezomib doses, and add G-CSF until fever and infection have recovered and $\text{ANC} > 1 \times 10^9/\text{L}$. Then administer isatuximab and dexamethasone at the planned days at the same dose level, and restart lenalidomide and bortezomib up to planned Day 42 if induction period or Day 28 if continuous treatment period or crossover with dose	Day 1 of cycle: delay Day 1 administration until fever and infection recover and add G-CSF until $\text{ANC} > 1 \times 10^9/\text{L}^c$. Then administer Day 1 next cycle with isatuximab and dexamethasone at the same dose level, and lenalidomide and bortezomib with dose	Day 1 of cycle: delay Day 1 administration until fever and infection recover and add G-CSF until $\text{ANC} > 1 \times 10^9/\text{L}^c$. Then administer Day 1 next cycle with isatuximab and dexamethasone at the same dose level, and lenalidomide and bortezomib with dose recommendations	

	recommendations below: First episode: resume with the same dose of lenalidomide and bortezomib with G-CSF or restart with 1 dose level decrease. Further episodes: same recommendations.	recommendations stated below. Within cycle: omit isatuximab and dexamethasone, hold lenalidomide and bortezomib doses, and add G-CSF until fever and infection have recovered and ANC $>1 \times 10^9/L$. Then administer isatuximab and dexamethasone at the planned days at the same dose level, and re-start lenalidomide and bortezomib up to planned Day 42 if induction period or Day 28 if continuous treatment period or crossover with dose recommendations below: - First episode: resume with the same dose of lenalidomide and bortezomib with G-CSF or restart with 1 dose level decrease. - If repeating episodes: decrease lenalidomide by 1 level at each episode, not below 5 mg daily if patient started at 25 mg, or 5 mg/2 days if patient started at 10 mg.	stated below. Within cycle: omit isatuximab and dexamethasone, hold lenalidomide and bortezomib doses, and add G-CSF until fever and infection have recovered and ANC $>1 \times 10^9/L$. Then administer isatuximab and dexamethasone at the planned days at the same dose level, and re-start lenalidomide and bortezomib up to planned Day 42 if induction period or Day 28 if continuous treatment period or crossover with dose recommendations below: - First episode: resume with the same dose of lenalidomide and bortezomib with G-CSF or restart with 1 dose level decrease. - If several bortezomib doses are withheld in 1 cycle (at least 4 during twice weekly administration), dose should be reduced by 1 dose level.
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^a For hematological toxicities, lenalidomide dose may be introduced to the next higher dose level (up to the starting dose) upon improvement in BM function (no hematological

toxicity for at least 2 consecutive cycles: ANC $\geq 1.5 \times 10^9/L$ with platelet count $\geq 100 \times 10^9/L$ at the beginning of a new cycle).

In patients with CrCl < 60 mL/min at baseline, lenalidomide dose of 10 mg could be increased to a dose of up to 25 mg during treatment, if CrCl > 60 mL/min, with recommendation to perform this change after a duration of at least ≥ 4 weeks for the normal value. This will not be allowed if lenalidomide dose was decreased because of non-hematological adverse events.

- b* For patients with plasma cells $> 50\%$ of BM nucleated cells at baseline, to initiate Cycle 2, platelet counts should be $\geq 30\,000/mm^3$ regardless response status at end of Cycle 1. During Cycles 2 to 4, platelet counts should be $\geq 30\,000/mm^3$, if last response is not better than SD, but if last response is PR or better during Cycles 2 to 4, Day 1 next cycle can be administered only if platelet counts $\geq 70 \times 10^9/L$. For Day 1 administration beyond Cycle 4 and for crossover part, platelet counts should be $\geq 50 \times 10^9/L$.
- c* A dose delay of up to 14 days between cycles is permitted in order to recover to the patient's baseline status. Beyond 14 days, the patient must be permanently discontinued from the study treatment (see Section 8.1.6.1).
- d* Patients may have isatuximab dose omission within a cycle if certain toxicities do not recover within 1 day (2 days for every 2 weeks administration) following the day of planned infusion (see Section 8.1.6.1). Abbreviations: ANC = absolute neutrophil count; G-CSF = granulocyte colony-stimulating factor; PR = partial response; SD = stable disease.

Table 3

Adverse event	Recommended action			
	Isatuximab	Dexamethasone	Lenalidomide	Bortezomib
DVT/PE				
Grade 3	Day 1 of cycle: initiate appropriate anticoagulation therapy, and when efficient anticoagulation, administer cycle at full dose isatuximab and the same dose level of dexamethasone, bortezomib, and lenalidomide^a Within cycle: maintain full dose isatuximab and the same dose level of dexamethasone and bortezomib as planned. For lenalidomide: First episode: hold lenalidomide, initiate appropriate anticoagulation therapy and restart same dose lenalidomide when efficient anticoagulation. Second episode: despite appropriate anticoagulation lenalidomide permanently discontinued.			
Grade 4	Day 1 of cycle: delay Day 1 administration until controlled, and administer the full dose of isatuximab and the same dose level of bortezomib, and dexamethasone^a Within cycle: omit isatuximab, bortezomib and dexamethasone until stabilization, and resume without dose reduction at the next planned dates. Lenalidomide permanently discontinued.			
Edema Grade ≥3 (limiting function and unresponsive to therapy or anasarca), excluding infusion reaction	Day 1 of cycle or within cycle: maintain full dose isatuximab as planned.	Diuretics as needed, and decrease dexamethasone dose by 1 dose level; if edema persists despite above measures, decrease dose another dose level. If symptoms persist despite second reduction, dexamethasone permanently discontinued.	Day 1 of cycle or within cycle: maintain full dose lenalidomide as planned.	Day 1 of cycle or within cycle: maintain full dose bortezomib as planned.
Allergic reaction/hypersensitivity (excluding infusion reaction)				
Grade 2	Hold study treatment until Grade <2, and patient clinically stable; then, resume study treatment at the same dose level ^a . For infusion reaction related to isatuximab, refer to Section 10.6.1.	Hold study treatment until Grade <2, and patient clinically stable; then, resume study treatment at the same dose level ^a .	Hold study treatment until Grade <2, and patient clinically stable; then, resume study treatment at the same dose level ^a . For allergic reaction related to lenalidomide, refer to clinical practice.	Hold study treatment until Grade <2, and patient clinically stable; then, resume study treatment at the same dose level ^a . For allergic reaction related to bortezomib refer to site clinical practice.
Grade ≥3	Permanent discontinuation of the			

	drug responsible for the allergic reaction.			
Infection without concomitant neutropenia	Hold study treatment until infection controlled. Resume all at the same dose level.			
Herpes zoster	Hold study treatment until lesions are dry, then resume all at the same dose level.			
Neuropathy				
Grade 1 (paresthesias, weakness, and/or loss of reflexes) without pain or loss of function.	No action			
				Reduce bortezomib to 1.0 mg/m ² or change treatment schedule to 1.3 mg/m ² once per week
Grade 2 with pain or Grade 3	No action			Hold bortezomib until neuropathy improves to Grade <2 without pain. First episode: resume bortezomib with a decrease to 1.0 mg/m ² once per week. Second episode: resume bortezomib with a decrease to 0.7 mg/m ² once per week. Third episode: bortezomib permanently discontinued.
Grade 4	No action			Bortezomib permanently discontinued.
Confusion or mood alteration Grade ≥2 (interfering with function ±	Day 1 of cycle or within cycle: maintain full dose isatuximab as planned.	Hold dexamethasone until symptoms resolve. Restart with 1 dose level reduction. If symptoms persist despite above	Day 1 of cycle or within cycle: maintain full dose lenalidomide as planned.	Day 1 of cycle or within cycle: maintain full dose bortezomib as planned.

daily activities)		measures, dexamethasone should be permanently discontinued.		
Gastrointestinal dyspepsia, gastric or duodenal ulcer, gastritis				
Grade 1 to 2 (requiring medical management)	Day 1 of cycle or within cycle: maintain full dose isatuximab as planned.	Treat with H2 blockers, sucralfate, or omeprazole. If symptoms persist despite above measures, decrease dexamethasone dose by 1 dose level.	Day 1 of cycle or within cycle: maintain full dose lenalidomide as planned.	Day 1 of cycle or within cycle: maintain full dose bortezomib as planned.
Grade >3 (requiring hospitalization or surgery)	Hold study treatment until symptoms adequately controlled. Then, restart full dose isatuximab and same dose level of lenalidomide and bortezomib, and decrease dexamethasone by one dose level of current dose along with concurrent therapy with H2 blockers, sucralfate, or omeprazole. If symptoms persist despite above measures, dexamethasone permanently discontinued.			
Acute pancreatitis	Day 1 of cycle: delay Day 1 until recovery ^a , and restart full dose isatuximab and same dose level of lenalidomide and bortezomib Within cycle: hold all study treatment until recovery, and restart full dose isatuximab and same dose level of lenalidomide and bortezomib. Dexamethasone permanently discontinued.			
Hyperglycemia ≥Grade 3	Day 1 of cycle or within cycle: maintain full dose isatuximab as planned.	Treatment with insulin or oral hypoglycemic agents as needed. If uncontrolled despite above measures, decrease dose by one dose level until levels are satisfactory.	Day 1 of cycle or within cycle: maintain same dose level of lenalidomide as planned.	Day 1 of cycle or within cycle: maintain same dose level of bortezomib as planned.
Muscle weakness ≥Grade 2 (symptomatic and interfering with function ± daily activities)	Day 1 of cycle or within cycle: maintain full dose isatuximab as planned.	Decrease dexamethasone by one dose level. If weakness persists despite above measures decrease dose by one level. If symptoms persist dexamethasone permanently discontinued.	Day 1 of cycle or within cycle: maintain same dose level of lenalidomide as planned.	Day 1 of cycle or within cycle: maintain same dose level of bortezomib as planned.
Renal dysfunction				
CrCl <30 mL/min (MDRD formula)	Day 1 of cycle: delay Day 1 administration until CrCl returns to ≥30 mL/min ^a . Within cycle: hold study treatment until improvement to ≥30 mL/min. Then re-start full dose isatuximab, same dose level of dexamethasone, bortezomib, and lenalidomide up to planned Day 42 or 28. If could not be administered within the provided time window, see Section 8.1.6.1, /omit isatuximab, bortezomib, and dexamethasone.			

Any other drug related nonhematologic Grade 3 to 4 AE	Day 1 of cycle: delay Day 1 administration until recovery and apply same rules of dose modification given the rules below ^a . Within cycle: for isatuximab attribution, omit dose if the event has not recovered within recommended interval (Section 8.1.6.1). Resume at full dose when toxicity has improved to Grade 2 or less or to baseline grade. Second episode, isatuximab discontinuation.	Day 1 of cycle: delay Day 1 administration until recovery and apply same rules of dose modification given the rules below ^a . Within cycle: for dexamethasone attribution omit dose if the event has not recovered within recommended interval (Section 8.1.6.1). Resume with 1 dose level decrease when toxicity has resolved to Grade 2 or less or to baseline grade. Second episode, apply new dose reduction. Third episode, dexamethasone discontinuation.	Day 1 of cycle: delay Day 1 administration until recovery and apply same rules of dose modification given the rules below ^a . Within cycle: for lenalidomide attribution, hold dose. Resume with 1 dose level decrease when toxicity has improved to Grade 2 or less or recovered to baseline grade. Second episode, apply new dose reduction. Third episode, lenalidomide discontinuation.	Day 1 of cycle: delay Day 1 administration until recovery and apply same rules of dose modification given the rules below ^a . Within cycle: for bortezomib attribution omit dose if the event has not recovered within recommended interval (Section 8.1.6.1). Resume with 1 dose level decrease when toxicity has resolved to Grade 2 or less or to baseline grade. Second episode, apply new dose reduction. Third episode, bortezomib discontinuation.
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^a A dose delay of up to 14 days between cycles is permitted in order to recover to the patient's baseline status. Beyond 14 days, the patient must be permanently discontinued from the study (see Section 8.1.6). Abbreviations: AE = adverse event; CrCl = creatinine clearance; DVT/PE = deep vein thrombosis/pulmonary embolism.

Noninvestigational Medicinal Products

Premedication for the prevention of infusion reactions

[0156] Patients allocated to the IVRd and crossover arms routinely received premedication prior to isatuximab infusion to reduce the risk and severity of IRs commonly observed with monoclonal antibodies. The recommended premedication agents were: diphenhydramine 25 to 50 mg IV (or equivalent), dexamethasone IV/PO (dose defined below), ranitidine 50 mg IV (or equivalent), and acetaminophen (paracetamol) 650 to 1000 mg PO prior to isatuximab infusion. Once the premedication regimen is completed, isatuximab infusion started immediately. Patients who do not experience an IR upon 4 consecutive administrations of isatuximab may have had their need for subsequent premedication reconsidered, at the Investigator's discretion.

Dexamethasone

[0157] On the day of isatuximab infusion, a total of 20 mg of dexamethasone was administered as premedication and as part of the backbone treatment before isatuximab.

[0158] The day of isatuximab administration, the following order was recommended:

- Acetaminophen 650 mg to 1000 mg PO.
- Ranitidine 50 mg IV (or equivalent).
- Diphenhydramine 25 mg to 50 mg IV (or equivalent).
- Dexamethasone 20 mg IV.

[0159] Whatever the route of administration (IV or PO), dexamethasone was administered only once (the single administration is used for both premedication and study treatment).

[0160] In case of dexamethasone was prematurely stopped and other study treatment was continued, steroid premedication could have been considered with methylprednisolone 100 mg IV if IR premedication was still needed for isatuximab according to Investigator judgment.

Ranitidine or equivalent

[0161] The use of ranitidine or equivalent to be part or not of IR premedication was left to the medical judgement. Ranitidine was presented as a solution for IV infusion. If given, the medication was given at a dose of 50 mg, 15 to 30 minutes (but no longer than 60 minutes) before isatuximab infusion.

[0162] Equivalent medications may have been given (e.g., other approved H2 antagonists such as cimetidine, oral proton pump inhibitors such as omeprazole, esomeprazole).

Diphenhydramine or equivalent.

[0163] Diphenhydramine was presented as a solution for IV infusion. This medication was given at a dose of 25 to 50 mg, 15 to 30 minutes (but no longer than 60 minutes) before isatuximab infusion.

[0164] Equivalent medications may be given (e.g., cetirizine, promethazine, dexchlorpheniramine. Intravenous route was preferred for at least the first 4 infusions). However, in countries where there was no IV formulation of diphenhydramine or equivalent, per os formulation was allowed from the first isatuximab infusion. In this case, it was taken 1 to 2 hours prior to isatuximab infusion start.

Acetaminophen (paracetamol)

[0165] This medication was given at a dose of 650 to 1000 mg, 15 to 30 minutes (but no longer than 60 minutes) before isatuximab infusion.

Method of Assigning Patients to Treatment Group

[0166] All eligible patients were randomly assigned to a treatment arm (either IVRd arm or VRd arm) in a 3:2 ratio using an IRT centralized randomization system. Patient assignment to a treatment arm was performed according to a stratified randomization list considering, age (<70 versus ≥ 70 years) and R-ISS stage (I or II versus III versus not classified).

[0167] After each patient completed the necessary screening visit procedures, the corresponding baseline eCRFs were completed and the patient was deemed eligible for study entry by the Investigator or designee based on the laboratory evaluations.

[0168] Screen failure patients could be re-screened and all procedures re-started for these patients.

[0169] The site entered the following information regarding the clinical site and study patient:

- Personal identifier number.
- Patient's date of birth (in line with country specific regulations).
- Revised International Staging System stage.

[0170] The randomization strata above was used by the IRT to assign the patient to the IVRd or VRd arm according to the predefined randomization schedule.

Concomitant Medication

[0171] A concomitant medication is any treatment received by the patient concomitantly to any study treatment(s). All treatments being taken by the patient 21 days prior to randomization, at any time during the treatment period and up to 30 days after the last dose are respectively regarded as prior and concomitant treatments, and were reported on the appropriate pages of the eCRF.

[0172] Concomitant medications were allowed if not listed as prohibited medications, if considered necessary for the patient's welfare and were unlikely to interfere with the investigational product. They were allowed to be given at the discretion of the Investigator and recorded in the eCRF. It was highly recommended to give prophylactic uric acid lowering agents (e.g., allopurinol or rasburicase) and IV fluids in patients at risk for TLS. In agreement with current guidelines and literature (NCCN v1.2018, [Drayson MT, Bowcock S, Planché T, Iqbal G, Wood J, Raynes K, et al. Tackling early morbidity and mortality in myeloma (TEAMM): assessing the benefit of antibiotic prophylaxis and its effect on healthcare associated infections in 977 patients. *Blood*. 2017;130:903]), anti-bacterial prophylactic treatment was recommended to all patients during induction therapy.

[0173] Recommended anti-bacterial prophylaxis included either cotrimoxazol PO or quinolone PO (quinolone was preferred option, as per NCCN guidelines version 1.2018 regarding intermediate category of risk like MM disease).

As an example:

Cotrimoxazol 2 x 960 mg/day PO. or

Ciprofloxacin 2 x 500 mg/day PO.

[0174] Other prophylaxis was allowed as deemed appropriate at Investigator's discretion. It was recommended that this prophylaxis should start no later than Day 1 of the study treatment and continue until 6 weeks after the end of the induction treatment period.

[0175] Anti-fungal prophylaxis: Anti-fungal prophylaxis was performed according to local policy. For B-hepatitis seronegative patients, B-hepatitis vaccination was considered.

Viral prophylaxis

[0176] For patients receiving bortezomib, prophylaxis was required against herpes zoster using oral acyclovir, or valacyclovir, or equivalent antiviral therapy per institutional guidelines and at the discretion of the site Investigator, unless the participant developed hypersensitivity to the agents. The dose was adjusted based upon serum creatinine levels according to package insert.

Antithrombotic therapy

[0177] Lenalidomide increases the risk of venous thromboembolism. Anticoagulation prophylaxis was required after an assessment of each patient's underlying risk factors. Unless there was an excessive risk of bleeding, all patients received prophylactic antithrombotic treatment. If aspirin was contraindicated, patients received another form of antithrombotic therapy according to hospital guidelines or physician preference.

[0178] Aspirin prophylaxis was recommended for patients with standard risk and low-molecular weight heparin for patients with at least 1 risk factor (i.e., history of prior venous thromboembolism, immobilization, and concomitant use of an erythropoiesis-stimulating agent).

Granulocyte colony-stimulating factor prophylaxis

[0179] Prophylactic administration of G-CSF in a patient who was experiencing recurrent difficulties with neutropenia, or therapeutic use in patients with serious neutropenic complications (such as tissue infection, sepsis syndrome, or fungal infection) was allowed to be considered at the Investigator's discretion, consistent with American Society of Clinical Oncology guidelines (2006) in order to decrease the risk of neutropenia specially in patients with baseline extensive BM involvement and/or low neutrophil count (Smith TJ, Khatcheressian J, Lyman GH, Ozer H, Armitage JO, Balducci L, et al. 2006 update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline. J Clin Oncol. 2006;24:3187-205.).

Prohibited concomitant therapy

[0180] Concurrent treatment with any other anti-myeloma therapy not specified in the protocol, including immunotherapy, hormonal therapy, targeted therapy or biological therapies, other investigational drugs, or curative radiotherapy was prohibited. However, palliative

radiotherapy was allowed to be given to control pain. The irradiated area was as small as possible and did not involve more than 20% of the BM in any given 3 week period. In all such cases, the possibility of tumor progression was ruled out by physical, biochemical, and radiological assessments of the tumor. The irradiated area was not used as a parameter for response assessment.

[0181] Concomitant systemic corticosteroids, other than as part of the protocol-specified therapeutic regimen or for treatment of hypersensitivity reaction, were prohibited. Additional glucocorticoids, antihistamines, and analgesics, for the management of IRs were permitted. Inhaled glucocorticosteroids were also allowed to be given whenever indicated.

[0182] Live vaccines were avoided. However, giving the increased risk of infection, routine vaccinations was recommended for the patients and their contacts. Prophylactic vaccination was recommended for influenza A and B virus, *Pneumococci*, and *Haemophilus influenza*.

[0183] Co-administration of strong inhibitors of CYP 3A4 was avoided. Patients receiving bortezomib were monitored for safety and bortezomib dose reduced if it was given in combination with strong CYP3A4 inhibitors. Co-treatment of dexamethasone with CYP3A inhibitors was avoided unless the benefit outweighed the increased risk of systemic corticosteroid side-effects, in which case patients were monitored for systemic corticosteroid side-effects.

[0184] Concomitant use of strong CYP3A4 inducers was not recommended (e.g., rifampicin). St. John's Wort (*Hypericum perforatum*) may decrease bortezomib exposure unpredictably and was avoided.

[0185] There is an increased risk of rhabdomyolysis when statins are administered with lenalidomide. Enhanced clinical and lab monitoring was warranted notably during the first weeks of treatment. Creatine phosphokinase (CPK) was monitored when clinically indicated.

[0186] Concomitant administration with lenalidomide increased the plasma exposure of digoxine. Therefore, monitoring of the digoxin concentration was advised during lenalidomide treatment.

Hepatitis B reactivation

[0187] In case of viral reactivation during study treatment (greater than 1 log₁₀ IU/mL increase in HBV DNA or reappearance of HBsAg or detection of HBV DNA in patients with resolved infection), study treatment was held and specialist consulted for initiation of anti-viral treatment and monitoring of the patient. Re-start of study treatment was allowed upon agreement between sponsor, investigator and specialist (hepatologist) if infection was

controlled. Close monitoring of ALT, AST every month was required up to study treatment discontinuation. HBV DNA was done as per specialist advice.

[0188] *previous known history of acute or chronic hepatitis B or the presence of total anti-HBc with/without anti-HBs; HBsAg negative; undetectable serum HBV DNA; normal ALT levels.

ASSESSMENT OF INVESTIGATIONAL MEDICINAL PRODUCT

PRIMARY ENDPOINT

[0189] The primary endpoint was Progression free survival (PFS) defined as the time from the date of randomization to the date of first documentation of Progressive Disease (PD) (as determined by the IRC), or the date of death from any cause, whichever occurs first.

[0190] The following disease assessment procedures were performed at screening (for eligibility), at Cycle 1 Day 1 prior to study treatment administration (baseline for response assessment), on Day 1 of every remaining cycle during treatment until progression or discontinuation due to other reason, at the EOT visit and during the follow-up period:

- M-protein quantification (serum and 24-hour urine, protein immunoelectrophoresis and immunofixation; central laboratory). After Cycle 1 Day 1, immunofixation was done in case of undetectable M-protein (serum and urine).
- Serum free light chains quantification (central laboratory).
- Quantitative immunoglobulins (central laboratory).

[0191] Other examinations for disease assessment were done as below:

- Bone marrow sample to assess potential CR (local laboratory) at time of VGPR or better.
- Bone marrow aspiration for MRD assessment at baseline, and in case of CR or VGPR at the end of induction period and during continuous treatment period (central laboratory).
- Radiological bone lytic disease assessment:
 - Skeletal survey (plain X-rays) or low-dose whole-body (LDWB) CT scan or PET-CT scan or WB-MRI at baseline, then once a year (± 7 days) (except if patient presents with soft tissue plasmacytoma) and anytime during the study if clinically indicated.
- Bone disease and soft tissue plasmacytoma assessment:
 - PET-CT scan was the preferred option to be done at baseline, and if positive, to be repeated at the time of CR and/or at the end of induction period. These examinations were not be performed within 1 month of each other. During the continuous

treatment period, radiological examinations were repeated during following time points:

- At the time of CR and /or at the end of induction period. These examinations were not to be performed within 1 month of each other.
- After 1 year of study treatment initiation, i.e., after 6 months (± 7 days) of continuous treatment.
- Every 6 months (± 7 days) during the second year of study treatment.
- From 3rd year of study treatment, once a year until PD (even for patients who would initiate further anti-myeloma therapy without PD), or if PD is suspected, or until PFS final analysis cut-off date (whichever occurs first).
- Only plasmacytoma measurements were collected in e-CRF, all the other bone parameters were evaluated on PET by a Centralized Imaging Review. In case of unavailability of PET-CT scan at baseline, WB-MRI was allowed as an alternative option.
- In the crossover arm, CT or MRI scans were required; if known soft tissue plasmacytoma, assessments were performed prior to crossover Cycle 1 Day 1 and, repeated every 12 weeks, and if clinically indicated during the treatment period until PD, or until final PFS analysis cut-off date (whichever occurred first). If suspected soft tissue plasmacytoma, CT or MRI scans were done before Cycle 1 Day 1. If soft tissue plasmacytoma was confirmed, the same scheduled mentioned above was carried out.
- PET-CT scan or MRI was done in case PD was suspected, or if clinically indicated in a patient with no previous positive image for soft tissue plasmacytoma.
- Note: for bone lesion or soft tissue plasmacytoma assessments, the same modality (skeletal survey or LDWB CT; PET-CT or MRI) was used throughout the study for each individual patient. Except baseline, during treatment MRI exam allowed to be limited only on the disease involved area. However, for patients who performed only WB-MRI at baseline, if lytic lesions were present, the same exam was repeated once per year.

[0192] All imaging scans were sent for central review (except during crossover).

[0193] Efficacy assessments that may impact the decision to resume treatment and for the primary and secondary endpoints were performed on the basis of central laboratory findings on Day 1 of every cycle. Response/progression was determined according to the IMWG criteria.

[0194] Response/progression based on paraprotein assessments were confirmed based on 2 consecutive assessments. A blinded IRC evaluated disease assessments at each cycle and determined the progression and response status of each patient per the IMWG criteria (Appendix D), and as described in the IRC Charter.

[0195] No IRC was required during crossover period.

[0196] Progressive disease was assessed as per IMWG response criteria.

KEY SECONDARY EFFICACY ENDPOINTS

[0197] Four key secondary efficacy endpoints were considered:

- Complete response rate: defined as the proportion of patients with CR/sCR as assessed by the IRC using the IMWG criteria.
- Minimal residual disease negativity rate for CR patients, defined as the proportion of patients for whom MRD is negative. Bone marrow aspirates were collected at screening, and for patients with CR or VGPR, at the end of induction period, then every 6 months during the first 2 years (at 12, 18, and 24 months after randomization), and then once a year until PD or until final PFS analysis cut-off date, whichever occurs first. Threshold for negativity was at least 10^{-5} .
- Very good partial response or better rate: defined as the proportion of patients with sCR, CR and VGPR as assessed by the IRC using the IMWG criteria.
- Overall survival (OS): defined as the time from the date of randomization to death from any cause.

[0198] M-protein follow-up by serum immunofixation electrophoresis (IFE) is part of the IMWG criteria to assess treatment response. Therefore, it was important that the isatuximab band was not confused with the endogenous M-protein of the patient during IFE interpretation. For participants with suspected isatuximab interference on serum IFE, the SEBIA HYDRASHIFT 2/4 isatuximab IFE test was used by the central lab to specifically measure the endogenous M-protein. Participants that met all other IMWG criteria for CR, and for whom negative immunofixation was confirmed after using the HYDRASHIFT isatuximab test, were considered complete responders. This defined the final CR rate as per IMWG criteria.

[0199] Minimal residual disease negativity was defined in accordance with IMWG criteria.

OTHER SECONDARY ENDPOINTS

[0200] Other secondary efficacy endpoints were as follows:

- **Overall response rate:** defined as the proportion of patients with BOR recorded as sCR, CR, VGPR, and PR, as assessed by the IRC using the IMWG response criteria. The following assessments were taken into account for the derivation of the BOR:
 - Randomized arms: from the randomization date until the first documentation of PD, death, initiation of anti-myeloma treatment or crossover, whichever occurs first,
 - For crossover arm: the best sequential response, from the first isatuximab drug intake until the first documentation of PD, death or initiation of anti-myeloma treatment, whichever occurred first.
- **Time to Progression:** defined as the time from the date of randomization to the date of first documentation of PD (as determined by IRC). The same definition of progression as for the PFS endpoint was used.
- **Duration of response:** defined as the time from the date of the first IRC determined response to the date of first IRC PD or death, whichever occurred first. Duration of response was determined only for patients who achieved sCR, CR, VGPR or PR.
- **TT1R:** defined as the time from randomization to the first IRC determined response (PR or better) that was subsequently confirmed
- **TTBR:** defined as the time from randomization to the date of occurrence of IRC determined best response (PR or better) that is subsequently confirmed
- **PFS2:** defined as the time from randomization to the date of first documentation of PD (as assessed by investigator) after initiation of further anti-myeloma treatment, or death from any cause, whichever occurred first. The crossover arm was considered as a next-line treatment.
- **PFS by MRD status.**
- **Sustained MRD negativity ≥ 12 months rate:** defined as the proportion of patients with the maintenance of MRD negativity confirmed ≥ 12 months apart with no MRD positive test in between.

Safety endpoints

[0201] Safety in terms of AEs/SAEs, laboratory parameters, vital signs (blood pressure, heart rate and temperature), weight, ECOG PS, and physical examination were assessed through the study and were reported in the eCRF.

[0202] Adverse event data was collected by reporting at specified intervals throughout the study. Treatment-emergent adverse events were defined as AEs that developed, worsened (according to the Investigator opinion), or became serious during the treatment period.

Crossover TEAEs were defined as AEs that developed, worsened (according to the Investigator opinion), or became serious during the crossover treatment period.

[0203] Adverse events and laboratory parameters were graded using NCI CTCAE v4.03 online at the following NCI website: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

Immunogenicity

[0204] Human ADAs to isatuximab were assessed throughout the study for the IVRd and crossover arms only. Blood samples were collected for ADA detection Bioanalytical method used for immunogenicity assessment is summarized in Table 4.

Table 4 - Bioanalytical method for anti-drug antibodies immune response assessment

Analyte	Anti-drug antibodies	Neutralizing antibodies
Matrix	Plasma	Plasma
Analytical technique	Polyethylene glycol precipitation and acid dissociation method	Non-cell based NAb assay using Competitive Ligand Binding (CLB) assay
Lower limit of detection	Not applicable	Not applicable
Site of bioanalysis	Sanofi Biomarkers and Clinical Bioanalyses department (Chilly-Mazarin, France)	Sanofi Biomarkers and Clinical Bioanalyses department (Chilly-Mazarin, France)

[0205] A sample was considered as ADA positive if ADA is detected, i.e., the sample generated an assay signal equal to or greater than the cut-point in the screening assay and tested positive in the confirmatory assay. A sample was considered as ADA inconclusive if ADAs were not detected but drug was present in the same sample at a level that could interfere in the ADA detection method, thus the negative ADA result could not be incontrovertibly confirmed.

[0206] In case of ADA positive or inconclusive sample at Cycle 10, additional ADA was sampled 3 months later. No further ADA was sampled, even if this 3-month sample was positive. If isatuximab was stopped prior to lenalidomide, bortezomib and dexamethasone before Cycle 10 and the last ADA was positive or inconclusive, additional ADA was sampled 3 months later. No further ADA was sampled, even if this 3-month sample was positive. For patients with less than 10 cycles at the final PFS analysis cut-off date, the ADA sample collection was stopped from the cut-off date. If last ADA before final PFS analysis cut-off date was positive or inconclusive, 1 additional sampling time for ADA evaluation was collected 3 months later. No further ADA was sampled, even if this 3-month sample was positive.

Definitions:

[0207] Pre-existing ADA: defined as ADAs that were present in samples drawn during the pre-treatment period (i.e., before the first isatuximab administration).

[0208] Treatment-induced ADA: defined as ADAs that developed at any time during the treatment on study observation period in patients without pre-existing ADAs (including patients without pre-treatment samples).

[0209] Treatment boosted ADA: defined as pre-existing ADAs with an increase in titer during the ADA on study observation period.

[0210] Transient ADA response:

- Treatment-induced ADAs detected only at 1 sampling time point during the treatment or follow-up observation period (excluding the last sampling time point, which ought to be considered persistent unless shown to be undetectable at a later time) or,
- Treatment-induced ADAs detected at 2 or more sampling time-points during the treatment (including follow-up period if any), where the first and last ADA-positive samples (irrespective of any negative samples in between) were separated by a period less than 16 weeks, and the patient's last sampling time point was ADA-negative.
- Persistent ADA response:
 - Treatment-induced ADAs detected at 2 or more sampling time-points during the treatment (including follow-up period, if any), where the first and last ADA-positive samples (irrespective of any negative samples in between) were separated by at least 16 weeks.

[0211] Indeterminate ADA response:

- Treatment-induced ADA detected only the last sampling time point with all prior samples being negative, OR,
- The last two samples are ADA-positive and separated by a period of less than 16 weeks.

[0212] ADA response endpoints:

- ADA negative patients were patients without any treatment induced or treatment boosted ADA during the on study observation period.
- ADA incidence was defined as proportion of ADA positive patients, i.e., patients with at least one treatment induced or treatment boosted ADA at any time during the on study observation period.
- ADA prevalence was defined as proportion of all patients tested positive for ADAs (including preexisting ADAs, treatment boosted ADAs and treatment induced ADAs) at any time point.

EXPLORATORY ENDPOINTS

[0213] Blood samples were collected and analyzed for immune genetic determinants such as Fcγ receptor polymorphism and correlated with efficacy endpoints, including ORR, DOR, PFS, and OS.

[0214] Pharmacokinetic estimates were investigated as prognostic factors for clinical outcome including safety and efficacy endpoints if possible.

[0215] In addition to the 3 cytogenetic abnormalities (del[17p], t[4;14], and t[14;16]) assessed by FISH at baseline to determine R-ISS stage which was a stratification factor, BM was analyzed for other cytogenetic abnormalities such as but not limited to gain(1q), and correlated with parameters of clinical response.

[0216] In the IVRd arm only, an additional serum sample was collected at all time-points at which M-protein was assessed, to evaluate new serum M-protein measurement methods such as mass spectrometry (central laboratory) up to Cycle 30. This sample was collected after Cycle 30 and until disease progression only for patients who reached at least VGPR by this cycle. In case isatuximab was stopped before progression, this sample was collected up to 3 months after discontinuation or when PD was observed, whichever occurred first.

[0217] Exploratory analysis on PET imaging for Imaging-positive MRD-negative response was performed by Independent Centralized Imaging Review, which will include assessment of (but not limited to): BM involvement, focal lesions, extra / para medullary lesions.

Treatment period

[0218] A cycle duration was 42 days (± 3 days) for the induction period and 28 days (± 3 days) for the continuous treatment period. Cycle 1 Day 1 refers to the day the patient received the first study treatment administration. Day 1 of each subsequent cycle corresponded to Day 43 or 29 of the previous cycle in the induction and continuous treatment period, respectively. The time window for Cycle 1 Days 8, 15, and 22 was ± 1 day. For subsequent cycles, Day 15 time window was ± 2 days, and any delay above these time windows or any omission due to AE was documented in the eCRF. For Bortezomib administration ± 1 day window was acceptable.

DURATION OF STUDY PARTICIPATION

[0219] The duration of the study for each patient included a screening period of up to 4 weeks, an induction period of 24 weeks (4 cycles with a duration of 42 ± 3 days), a continuous treatment period, and a crossover treatment period (when applicable). The cycle duration was 28 ± 3 days during the continuous treatment and crossover arm. Patients continued study treatment until disease progression, unacceptable AE or patient's decision to discontinue the study, whichever occurred first.

[0220] After study treatment discontinuation, patients (including patients in the crossover arm) returned to the study site 30 days after the last dose of study treatment for end of treatment (EOT) assessments, and 90 days after the last dose of study treatment for HRQL questionnaires. In addition, related AEs and all (related or not) serious adverse events (SAEs) ongoing at the time of study treatment discontinuation were followed during the follow-up period until resolution or stabilization, regardless of their relationship to study treatment. During the follow-up period, all (serious or nonserious) new AEs related to study treatment were collected and followed until resolution or stabilization.

RESULTS

PATIENT DISPOSITION

[0221] A total of 446 patients were randomized (ITT population) in the global part of study: 181 in VRd arm, 265 in IVRd arm. Of the 446 randomized patients, 263 patients received IVRd and 181 patients received VRd, and 2 patients were not treated. Median follow-up was 59.73 months. At data cutoff (September 26, 2023), 47.2% (Isa-VRd) and 24.3% (VRd) of patients remained on treatment; 138 (52.1%, Isa-VRd) and 137 (75.7%, VRd) discontinued treatment, mostly from AEs or progressive disease; 2 randomized Isa-VRd patients were not treated; 25 VRd patients switched to Isa-Rd. Of AEs contributing to definitive treatment discontinuation, 8 (3.0%, Isa-VRd) and 4 (2.2%, VRd) were COVID-19 related.

[0222] Median treatment duration was 53.2 months (range, 0.5–68.8; Isa-VRd) and 31.3 months (0.6–67.2; VRd); median number of cycles started was 52 (range, 1–69) and 29 (1–69), respectively. Median relative dose intensity for isatuximab was 93.6%; 90.3% (Isa-VRd) and 86.7% (VRd) for bortezomib; 77.7% and 83.5% for lenalidomide; and 81.6% and 79.3% for dexamethasone, respectively.

Patient Disposition		VRd (n=181)	IVRd (n=263)
Discontinued		137 (75.7%)	138 (52.1%)
	PD	67 (37.0%)	38 (14.3%)
		*CO IRd: 25 (13.8%)	
	AE	50 (27.6%)	60 (22.6%)
	Withdrawal by subject	16 (8.8%)	23 (8.7%)
	Poor compliance to protocol		6 (2.3%)
	Other	4 (2.2%)	11 (4.2%)
Ongoing treatment		44 (24.3%)	125 (47.2%)
Median duration of follow-up : 59.73 months			

*Cross-over to isatuximab + lenalidomide + dexamethasone during continuous treatment period.

DEMOGRAPHICS AND BASELINE CHARACTERISTICS

[0223] Median age was 72 years (range, 55–80), 16.6% had high-risk cytogenetics, 37.0% had chromosomal 1q21+ abnormality, and 28.7% had eGFR <60 ml/min/1.73 m². Patient demographics and baseline disease characteristics were well balanced between the IVRd and VRd arms. A total of 237 (53.1%) patients were male and 323 (72.4%) were White, and 48 (10.8%) were Asian. The median age was 72 years and 67.9% of the population was 65 to <75 years of age and 28.3% was ≥75 years of age. The median time from initial diagnosis of MM to randomization was 1.18 months (range 0.3 to 48.9). The ISS stage at study entry was stage I for 30.7% of patients, stage II for 41.9%, stage III for 26.9%, and unknown for 0.4%.

ITT population	Isa-VRd (n=265)	VRd (n=181)
Age, median (range), years	72.0 (60–80)	72.0 (55–80)
Age by category, years, n (%)		
<65	8 (3.0)	9 (5.0)
65–<70	73 (27.5)	47 (26.0)
70–<75	115 (43.4)	68 (37.6)
75–80	69 (26.0)	57 (31.5)
ECOG PS, n (%)		
0	123 (46.4)	79 (43.6)
1	112 (42.3)	83 (45.9)
2*	29 (10.9)	19 (10.5)
eGFR <60 mL/min/1.73 m ² (MDRD), n (%)	66 (24.9)	62 (34.3)

*One patient in the Isa-VRd arm had an ECOG PS of 3.

ITT population	Isa-VRd (n=265)	VRd (n=181)
R-ISS stage at baseline (IRT strata), n (%)		
Stages I and II	234 (88.3)	157 (86.7)
Stage III	29 (10.9)	21 (11.6)
Not classified	2 (0.8)	3 (1.7)
Cytogenetic risk at baseline, n (%)		
Standard	207 (78.1)	140 (77.3)
High [†]	40 (15.1)	34 (18.8)
High and 1q21+ [‡]	19 (7.2)	15 (8.3)

1q21+/amplification 1q21,[§] n (%)	95 (35.8)/ 32 (12.1)	70 (38.7)/ 23 (12.7)
Del(17p) (50% cutoff), n (%)	15 (5.7)	9 (5.0)
Extramedullary disease at study entry[¶] (per IRC), n (%)	18 (6.8)	6 (3.3)

High risk defined as the presence of del(17p) and/or t(4;14) and/or t(14;16), with cutoffs defined in footnote [‡]. [‡]Abnormality defined as present in at least 30% of abnormal bone marrow plasma cells for t(4;14) and t(14;16) and 1q21+ (at least 3 copies), and at least 50% of abnormal plasma cells for del(17p). Only one patient had 2 high-risk cytogenetic abnormalities: del(17p) and t(4;14). [§] 1q21+ defined as at least 3 copies of 1q21. Amplification 1q21 defined as at least 4 copies of 1q21. [¶] In addition, there were 67 (25.3%; Isa-VRd) and 49 (27.1%; VRd) patients with paramedullary disease and 1 patient in each group with both extramedullary and paramedullary disease. IRC, independent review committee; IRT, interactive response technology.

Treatment Exposure

[0224] The median duration of exposure was longer in the IVRd arm than the VRd arm: 53.2 months (range 0.5 to 68.8) in the IVRd arm and 31.3 months (range 1 to 114) in the VRd arm.

Summary of Treatment Exposure – Safety population

Safety population	VRd	IVRd
	(n=181)	(n=263)
Median treatment duration, months (range)	31.3 (0.6 – 67.2)	53.2 (0.5 – 68.8)
Relative dose intensity (%), median (range)		
Isatuximab	-	93.58 (24.2 - 120.0)
Lenalidomide	83.45 (18.5 - 220.6)	77.74 (16.9 - 246.6)
Bortezomib	86.65 (39.4 - 160.2)	90.28 (40.5 - 157.5)
Dexamethasone	79.34 (22.4 - 157.2)	81.58 (15.7 - 144.1)

Efficacy

Primary endpoint:

[0225] Adding isatuximab to VRd treatment significantly increased PFS based on a blinded IRC assessment compared to VRd. At the cutoff date, 84 (31.7%) and 78 (43.1%) patients had PFS events in the IVRd and VRd arms, respectively, and the median follow-up was 59.73 months. The hazard ratio was 0.596 (98.5% CI: 0.406 to 0.876), corresponding to a reduction of 40.4% in risk for disease progression or death with IVRd compared to VRd. Median PFS was not reached in the IVRd arm and was 54.34 months (95% CI: 45.207 and upper limit not reached) in the VRd arm. The 1-sided stratified log rank test resulting from the comparison of

PFS between the 2 arms was statistically significant with a one-sided p-value of 0.0005, which met the prespecified efficacy boundary of 0.0074. An early separation between the IVRd and VRd arms was observed in the PFS curve (FIG. 1).

[0226] The results of the PFS sensitivity analyses were consistent with the primary PFS analysis results supporting the robustness of the primary PFS analysis. For all of the analyses, the HRs ranged from 0.509 to 0.632, median PFS was not reached in the IVRd arm and ranged from 45.86 to 59.66 months in the VRd arm. They all showed statistically significant differences favoring of IVRd over VRd (range p-values <0.0001 to 0.0012).

PFS – Summary of main sensitivity analyses – ITT population

ITT population	VRd (n=181)		IVRd (n=265)		HR, 98.5% CI, 1-sided p-value
	N (%) events	Median (Mos) (95% CI)	N (%) events	Median (Mos) (95% CI)	
Primary analysis: PFS as per IRC censoring for further anti myeloma therapy	78 (43.1)	54.34 (45.207 to NC)	84 (31.7)	NC (NC to NC)	0.596 (0.406 to 0.876) 0.0005
PFS as per IRC without censoring for further anti-MM	78 (43.1)	59.66 (45.864 to NC)	87(32.8)	NC (NC to NC)	0.625 (0.427 to 0.916) 0.0012
PFS as per investigator (including symptomatic deterioration)	96 (53.0)	47.08 (38.768 to 56.246)	87 (32.8)	NC (NC to NC)	0.509 (0.355 to 0.731) <.0001
PFS as per investigator (ignoring symptomatic deterioration)	94 (51.9)	47.9 (39.129 to 56.246)	87 (32.8)	NC (NC to NC)	0.520 (0.362 to 0.748) <0.0001
PFS as per IRC including initiation of further anti-MM as an event	99 (54.7)	45.86 (34.891 to 53.749)	97 (36.6)	NC (NC to NC)	0.546 (0.385 to 0.774) <0.0001
PFS censoring for death events due to covid 19	76 (42.0)	59.66 (46.160 to NC)	77 (29.1)	NC (NC to NC)	0.566 (0.382 to 0.841) 0.0002
PFS not censoring event occurring > 13 weeks after last valid assessment	82 (45.3)	51.19 (44.123 to NC)	95 (35.8)	NC (NC to NC)	0.632 (0.437 to 0.914) 0.0011
PFS pooled global and China extension cohort	83 (43.0)	53.91 (44.123 to NC)	89 (30.6)	NC (NC to NC)	0.573 (0.395 to 0.832) 0.0001

[0227] Prespecified PFS subgroup analyses confirmed consistent benefit across most subgroups, including some difficult-to-treat populations with negative prognostic factors (FIG.

2). Time to progression was longer for Isa-VRd versus VRd (HR 0.414; 95% CI 0.286–0.598) (FIG. 2).

Key secondary endpoints:

[0228] A consistent and clinical meaningful improvement across all response-based key secondary endpoints was observed. The key secondary endpoints complete response rate and MRD negativity CR rate by NGS were statistically significant, meeting the prespecified efficacy boundary of 0.025. The VGPR or better rate (p-value=0.0259) marginally missed the efficacy boundary of 0.025). The interim overall survival result shows a favorable OS trend for IVRd vs VRd (OS HR: 0.776, 99.97%CI 0.407 to 1.48).

Results of Key Secondary Endpoints – ITT population

	VRd (N=181)	IVRd (N=265)	Stratified Odds ratio/ hazard ratio (95% CI)	1-sided p-value
Complete response (sCR or CR)	116 (64.1)	198 (74.7)	1.656 (1.097 to 2.500)	0.008
NGS MRD[-] CR rate	74 (40.9)	147 (55.5)	1.803 (1.229 to 2.646)	0.0013
VGPR or better rate	150 (82.9)	236 (89.1)	1.729 (0.994 to 3.008)	0.0259
Overall survival	59 (32.6)	69 (26.0)	0.776 (0.407 to 1.48)*	0.076

* OS was tested at one-sided significance level is 0.0001375 using the user-defined alpha spending function. The 99.97% confidence interval was provided.

[0229] In the ITT population, while overall response rate was similarly high with Isa-VRd and VRd (91.3% and 92.3%, respectively), significantly more patients achieved $\geq$ CR with Isa-VRd than VRd (74.7% vs. 64.1%; P=0.008). In addition, significant improvement was seen for MRD- CR rate at any time (55.5% vs. 40.9%; P=0.0013) (FIG. 3).

[0230] FIG. 3 shows the MRD rate at any time during the study among patients in the ITT population. Median (95% CI) time to MRD- was 14.72 (11.53–24.08) months in the Isa-VRd group and 32.79 (17.51–45.11) months in the VRd group. *Response was assessed on the basis of IMWG recommendations (details on the criteria for disease response are provided in the protocol). The following secondary endpoints were tested sequentially, each with an overall two-sided alpha level of 0.05, with the use of a hierarchical testing approach: $\geq$ CR, MRD- CR, and $\geq$ VGPR. Criteria for a sCR include the criteria for a CR plus a normal free light-chain ratio and absence of clonal plasma cells, as assessed by immunofluorescence or immunohistochemical analysis or by two-color to four-color flow cytometry. †The sensitivity

threshold for MRD was defined as 1 in 10^5 nucleated cells at any time during the study. Bone marrow aspiration was conducted for central laboratory assessment at baseline, and in case of CR or VGPR, at the end of the induction period and during the period of continuous treatment. Status regarding MRD was based on a post-randomization assessment performed on bone marrow samples using a Food and Drug Administration-approved next-generation sequencing assay (clonoSEQ® Assay, version 2.0; Adaptive Biotechnologies) in accordance with IMWG guidelines on assessment of MRD. (Kumar, et al.) ‡P value not reported; not a key secondary endpoint. §The one-sided P value was calculated with the use of the stratified Cochran–Mantel–Haenszel chi-square test. CI, confidence interval; CR, complete response; IRC, Independent Review Committee; Isa-VRd, isatuximab–bortezomib–lenalidomide–dexamethasone; ITT, intention-to-treat; MRD, minimal residual disease; MRD-, MRD negativity; NC, not calculated; ORR, overall response rate; sCR, stringent complete response; VRd, bortezomib–lenalidomide–dexamethasone; VGPR, very good partial response. Proportions with MRD- (58.1% vs. 43.6%) and sustained MRD- ≥ 12 months (46.8% vs. 24.3%) were higher for Isa-VRd than VRd.

[0231] Patients with MRD- showed PFS benefit versus MRD-positive patients with Isa-VRd (HR 0.220; 95% CI 0.139–0.349) and to a lesser extent with VRd (HR 0.314; 95% CI 0.190–0.517). Patients with sustained MRD- ≥ 12 months had PFS benefit versus MRD- < 12 months

Hierarchical testing results*.

Key secondary endpoint	Isa-VRd (N=265)	VRd (N=181)	OR/HR (CI)	P-value (one-sided)
Rate of $\geq$ CR – no. (%)	198 (74.7)	116 (64.1)	OR 1.656 (95% CI 1.097–2.500)	0.008
MRD- rate in $\geq$ CR patients (NGS at 10^{-5}) – no. (%)	147 (55.5)	74 (40.9)	OR 1.803 (95% CI 1.229–2.646)	0.0013
Rate of $\geq$ VGPR – no. (%)	236 (89.1)	150 (82.9)	OR 1.729 (95% CI 0.994–3.008)	$>0.025^\dagger$
Interim OS – 25% quantile (95% CI)	55.46 (37.717–NC)	49.12 (37.618–56.706)	HR 0.776 (99.97% CI 0.407–1.48)	

*A hierarchical procedure was used to test the key secondary endpoints while controlling for multiplicity. † The efficacy p-value boundary was 0.025, so this result was not significant and no additional comparisons were tested.

CI, confidence interval; $\geq$ CR, complete response or better; HR, hazard ratio; Isa-VRd, isatuximab–bortezomib–lenalidomide–dexamethasone; MRD-, minimal residual disease negativity; NGS, next-generation sequencing; OR, odds ratio; OS, overall survival; $\geq$ VGPR, very good partial response or better; VRd, bortezomib–lenalidomide–dexamethasone.

PFS by MRD status.

	Isa-VRd (n=265)		VRd (n=181)	
	MRD+ (n=111)	MRD- (n=154)	MRD+ (n=102)	MRD- (n=79)
Number (%) of events	54 (48.6)	30 (19.5)	56 (54.9)	22 (27.8)
Number (%) of patients censored	57 (51.4)	124 (80.5)	46 (45.1)	57 (72.2)
Kaplan-Meier estimates of PFS in months				
Median (95% CI)	43.14 (25.232–NC)	NC (NC–NC)	37.45 (22.735–47.014)	NC (59.696–NC)
Stratified* hazard ratio (95% CI) vs MRD+		0.220 (0.139–0.349)		0.314 (0.190–0.517)
PFS probability (95% CI) [†]				
6 months	0.884 (0.805–0.933)	1.000 (1.000–1.000)	0.850 (0.760–0.909)	1.000 (1.000–1.000)
12 months	0.815 (0.725–0.878)	1.000 (1.000–1.000)	0.749 (0.646–0.826)	1.000 (1.000–1.000)
18 months	0.719 (0.620–0.797)	0.987 (0.949–0.997)	0.655 (0.546–0.744)	0.960 (0.880–0.987)
24 months	0.630 (0.525–0.718)	0.967 (0.923–0.986)	0.576 (0.464–0.673)	0.890 (0.792–0.943)
36 months	0.529 (0.423–0.624)	0.906 (0.846–0.943)	0.519 (0.406–0.621)	0.829 (0.718–0.899)
48 months	0.457 (0.353–0.556)	0.850 (0.781–0.899)	0.371 (0.263–0.479)	0.719 (0.595–0.811)
54 months	0.444 (0.340–0.543)	0.806 (0.731–0.862)	0.341 (0.236–0.449)	0.682 (0.553–0.781)
60 months	0.397 (0.286–0.505)	0.776 (0.690–0.841)	0.296 (0.191–0.410)	0.625 (0.458–0.754)
66 months	0.397 (0.286–0.505)	0.776 (0.690–0.841)	0.237 (0.117–0.381)	0.625 (0.458–0.754)

*Stratified by age (<70 years vs ≥70 years) and Revised International Staging System (R-ISS) stage (I or II vs III or not classified) according to Interactive Response Technology.

[†]Estimated using Kaplan–Meier method.

CI, confidence interval; Isa-VRd, isatuximab–bortezomib–lenalidomide–dexamethasone; MRD, minimal residual disease; NC, not calculated; PFS, progression-free survival; VRd, bortezomib–lenalidomide–dexamethasone.

Additional response data.

Variable	Isa-VRd (N=265)	VRd (N=181)
Time to first response – months, median (95% CI)*	1.51 (NC–NC)	1.48 (1.48–1.51)
Time to best response – months, median (95% CI)*	6.51 (5.65–6.87)	5.59 (4.30–5.88)
Time to complete response or better (CR or sCR) – months, median (95% CI)*	6.97 (6.54–7.62)	7.98 (6.70–9.92)
Duration of response – months, median (95% CI)*	NC (NC–NC)	58.25 (44.58–NC)

*Response was assessed on the basis of International Myeloma Working Group recommendations (details on the criteria for disease responses are provided in the protocol).

CI, confidence interval; Isa-VRd, isatuximab–bortezomib–lenalidomide–dexamethasone; MRD-, minimal residual disease negativity; NC, not calculated; VRd, bortezomib–lenalidomide–dexamethasone.

[0232] At data cutoff, 128 patients had died (69 [26.0%] Isa-VRd; 59 [32.6%] VRd). Median OS was NR in either group (HR 0.776; 99.97% CI 0.407–1.48), but HR passed the prespecified futility threshold (>1.1); follow-up is ongoing. Overall incidence of death (including treatment-emergent AEs [TEAEs] and post-treatment periods) trended in favor of Isa-VRd (26.2% and 32.6% [VRd]) largely from lower incidence of death from disease progression (4.9% [Isa-VRd]; 12.2% [VRd]), supported by time to death by cause-specific analysis of competing risks.

[0233] At data cutoff, 19.6% (Isa-VRd) and 44.2% (VRd) of patients initiated further antimyeloma therapy; of these, fewer received anti-CD38 in the Isa-VRd (34.6%) versus VRd (68.8%) group. Although median PFS2 was NR in either arm, fewer patients had second progression events with Isa-VRd (31.7%) versus VRd (41.4%). Isa-VRd benefit continued through subsequent line of therapy (PFS2 HR 0.697; 95% CI 0.510–0.952). Time to next treatment was longer for Isa-VRd versus VRd (HR 0.376; 95% CI 0.265–0.534).

[0234] EORTC-QLQ-C30 global health status domain score remained stable over time in both groups, with no negative impact from adding isatuximab.

SAFETY:**Overview of Treatment Emergent Adverse Events (TEAEs)**

[0235] The safety of IVRd was consistent with the established safety profiles of isatuximab and the VRd regimen. No new safety concerns were identified. The rate of Grade 5 TEAEs was 11.0% in the IVRd arm and 5.5% in the VRd arm.

[0236] The following tables summarize hematologic laboratory abnormalities and common AEs; Serious TEAEs were reported in 70.7% (Isa-VRd) and 67.4% (VRd) of patients. Incidence of grade ≥ 3 infections was 44.9% and 38.1% for Isa-VRd and VRd, and was lower

in patients who received antibiotic prophylaxis versus those who did not (43.5% vs. 51.0%, Isa-VRd; 35.2% vs. 48.7%, VRd). There were 29 (11.0%, Isa-VRd) and 10 (5.5%, VRd) grade 5 TEAEs, including 4 (1.5%) and 1 (0.6%), respectively, within 60 days of first dose; such difference was driven partly by different treatment exposure (0.031 [Isa-VRd] and 0.019 [VRd] events/patient-year). Grade 5 TEAEs were mainly caused by infections, including COVID-19-related deaths (12, Isa-VRd; 6, VRd).

Hematologic Laboratory Abnormalities, Adverse Events (≥20% of Patients in Either Group) of Any Grade (Worst Grade by Patient), and Second Primary Malignancies Reported in the Safety Population.*

Event, no. of patients (%)	Isa-VRd (n=263)		VRd (n=181)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Hematologic laboratory abnormalities [†]				
Anemia	260 (98.9)	46 (17.5)	177 (97.8)	29 (16.0)
Lymphopenia	251 (95.4)	158 (60.1)	167 (92.3)	96 (53.0)
Neutropenia	230 (87.5)	143 (54.4)	145 (80.1)	67 (37.0)
Leukopenia	256 (97.3)	83 (31.6)	160 (88.4)	30 (16.6)
Thrombocytopenia	251 (95.4)	79 (30.0)	153 (84.5)	50 (27.6)
Nonhematologic adverse events				
Infections [‡]				
Pneumonia	79 (30.0)	53 (20.2)	35 (19.3)	23 (12.7)
Bronchitis	58 (22.1)	7 (2.7)	32 (17.7)	3 (1.7)
Upper respiratory tract infection	90 (34.2)	2 (0.8)	61 (33.7)	2 (1.1)
Diarrhea	144 (54.8)	20 (7.6)	88 (48.6)	15 (8.3)
Peripheral sensory neuropathy	143 (54.4)	19 (7.2)	110 (60.8)	11 (6.1)
Cataract	100 (38.0)	41 (15.6)	46 (25.4)	20 (11.0)
Constipation	94 (35.7)	6 (2.3)	74 (40.9)	3 (1.7)
Fatigue	91 (34.6)	21 (8.0)	48 (26.5)	12 (6.6)
Peripheral edema	86 (32.7)	0	59 (32.6)	2 (1.1)
Infusion-related reaction	62 (23.6)	1 (0.4)	2 (1.1)	0
COVID-19 [§]	78 (29.7)	23 (8.7)	37 (20.4)	12 (6.6)
Insomnia	59 (22.4)	10 (3.8)	44 (24.3)	4 (2.2)
Back pain	58 (22.1)	9 (3.4)	31 (17.1)	3 (1.7)
Asthenia	57 (21.7)	7 (2.7)	44 (24.3)	4 (2.2)
Second primary malignancies [¶]				
Solid tumors	22 (8.4)	14 (5.3)	8 (4.4)	6 (3.3)
Hematologic	3 (1.1)	1 (0.4)	2 (1.1)	2 (1.1)

*The safety population included all patients who received at least one dose of the trial treatment. Adverse events of any grade that were reported in at least 20% of patients in either treatment group are listed. Listed by preferred term (worst grade by patient).

[†]Laboratory abnormalities during the on-treatment period (worst grade per patient). Toxicity grades are derived based on NCI CTCAE v4.03.

[‡]The 3 categories presented are not exclusive.

[§]Includes both COVID-19 and COVID-19 pneumonia. Two patients in the Isa-VRd arm and 1 patient in the VRd arm experienced both COVID-19 pneumonia and COVID-19. They are only counted once when grouping all events of COVID-19-related TEAEs.

[¶]The presence of a second primary malignancy was prespecified in the statistical analysis plan as an adverse event of special interest. Identified using MedDRA Custom MedDRA Query (CMQ) 'Second Primary Malignancies.' Includes treatment-emergent and post-treatment emergent.

^{||}Includes melanoma and 1 case of metastasis to the peritoneum. In addition, 19 (Isa-VRd) and 7 (VRd) patients had non-melanoma skin cancer. In the Isa-VRd arm, 2/19 patients also had melanoma. In the VRd arm, 1/7 patients also presented with adenocarcinoma of the colon. Isa-VRd, isatuximab–bortezomib–lenalidomide–dexamethasone; no., number; VRd, bortezomib–lenalidomide–dexamethasone.

Overview of Treatment-Emergent Adverse Events (TEAE) – Safety population

	Isa-VRd (n=263)	VRd (n=181)
Any TEAE	262 (99.6)	178 (98.3)
Any Grade ≥ 3 TEAE	241 (91.6)	152 (84.0)
Any treatment-related* Grade ≥ 3 TEAE	202 (76.8)	123 (68.0)
Serious TEAE	186 (70.7)	122 (67.4)
Serious treatment-related TEAE	87 (33.1)	58 (32.0)
Any TEAE leading to definitive treatment discontinuation	60 (22.8)	47 (26.0)
Any TEAE leading to premature discontinuation of isatuximab	6 (2.3)	NA
Any TEAE leading to premature discontinuation of bortezomib	32 (12.2)	17 (9.4)
Any TEAE leading to premature discontinuation of lenalidomide	34 (12.9)	4 (2.2)
Any TEAE leading to premature discontinuation of dexamethasone	18 (6.8)	31 (17.1)
Any Grade 5 TEAE [†]	29 (11.0)	10 (5.5)

Isa-VRd, isatuximab–bortezomib–lenalidomide–dexamethasone; TEAE, treatment-emergent adverse event; VRd, bortezomib–lenalidomide–dexamethasone.

Data are n (%).

*Treatment-related TEAEs are TEAEs related to at least 1 drug of the combination.

[†]Causes of death occurring during the treatment period for the Isa-VRd group included COVID-19 pneumonia (n=7), COVID-19 pneumonia/multiorgan failure (n=1), renal tubular acidosis/TLS (n=1), septic shock (n=1), pneumonia (n=4), sudden death (n=4), undetermined (n=1), pneumonia pseudomonal (n=1), candida sepsis (n=1), hepatic cirrhosis (n=1), neuroendocrine carcinoma of the skin (n=1), pulmonary embolism (n=1), febrile neutropenia (n=1), pneumonia klebsiella and sepsis (n=1), respiratory failure (n=1), dyspnea (n=1), and sepsis (n=1). Causes of death for the VRd group included pneumonia (n=2), COVID-19 (n=2), pneumonia aspiration (n=1), undetermined (n=1), pulmonary embolism (n=1), sepsis (n=1), and bronchitis (n=1).

[0237] Since the median duration of exposure was substantially longer in the IVRd arm compared to the VRd arm (53.2 months in the IVRd arm and 31.3 months in the VRd arm), TEAE incidence was also assessed based on duration of exposure. Overall, the exposure-adjusted incidence was similar between the IVRd and VRd arms. The exposure adjusted incidence of any grade 5 TEAE was 0.03 vs. 0.02 events per patient year in the IVRd and VRd arms, respectively.

Patient years analysis: overview of TEAEs - Safety population

	VRd (N=181)		IVRd (N=263)	
	n (%)	Event rate per patient year ^a	n (%)	Event rate per patient year ^a
Patients with any TEAE	178 (98.3)	12.69	262 (99.6)	13.39
Patients with any grade ≥ 3 TEAE	152 (84.0)	0.99	241 (91.6)	1.17
Patients with any grade 5 TEAE ^b	10 (5.5)	0.02	29 (11.0)	0.03
Patients with any treatment emergent SAE	122 (67.4)	0.43	186 (70.7)	0.37
Patients with any TEAE leading to definitive treatment discontinuation	47 (26.0)	0.09	60 (22.8)	0.07

TEAE: Treatment emergent adverse event, SAE: Serious adverse event

n (%) = number and percentage of patients with at least one TEAE

^a Calculated as number of patients with an event divided by total patient years.

^b: TEAE with fatal outcome during the treatment period

Treatment-related TEAEs are TEAEs related to at least one drug of the combination

TEAEs with a start date before the operational Cut-off date and becoming serious after the operational Cut-off date were not counted as serious TEAE in this analysis.

Incidence of TEAEs by Preferred Term

[0238] The most frequent TEAEs of 5% or greater frequency in any treatment arm are presented below.

Number (%) of patients with TEAE(s) with an incidence $\geq 5\%$ in any treatment group by PT (worst grade by patient) – Safety population

Preferred Term [n(%)]	VRd (N=181)		IVRd (N=263)	
	All grades	Grade ≥ 3	All grades	Grade ≥ 3
Any event	178 (98.3)	152 (84.0)	262 (99.6)	241 (91.6)
Diarrhea	88 (48.6)	15 (8.3)	144 (54.8)	20 (7.6)
Peripheral sensory neuropathy	110 (60.8)	11 (6.1)	143 (54.4)	19 (7.2)
Cataract	46 (25.4)	20 (11.0)	100 (38.0)	41 (15.6)
Constipation	74 (40.9)	3 (1.7)	94 (35.7)	6 (2.3)
Fatigue	48 (26.5)	12 (6.6)	91 (34.6)	21 (8.0)

Preferred Term [n(%)]	VRd (N=181)		IVRd (N=263)	
	All grades	Grade ≥ 3	All grades	Grade ≥ 3
Upper respiratory tract infection	61 (33.7)	2 (1.1)	90 (34.2)	2 (0.8)
Oedema peripheral	59 (32.6)	2 (1.1)	86 (32.7)	0
Neutropenia	39 (21.5)	37 (20.4)	79 (30.0)	79 (30.0)
Pneumonia	35 (19.3)	23 (12.7)	79 (30.0)	53 (20.2)
Infusion related reaction	2 (1.1)	0	62 (23.6)	1 (0.4)
Covid-19	30 (16.6)	5 (2.8)	59 (22.4)	2 (0.8)
Insomnia	44 (24.3)	4 (2.2)	59 (22.4)	10 (3.8)
Back pain	31 (17.1)	3 (1.7)	58 (22.1)	9 (3.4)
Bronchitis	32 (17.7)	3 (1.7)	58 (22.1)	7 (2.7)
Asthenia	44 (24.3)	4 (2.2)	57 (21.7)	7 (2.7)
Rash	36 (19.9)	4 (2.2)	52 (19.8)	8 (3.0)
Arthralgia	36 (19.9)	2 (1.1)	50 (19.0)	0
Fall	29 (16.0)	7 (3.9)	50 (19.0)	13 (4.9)
Nasopharyngitis	25 (13.8)	0	46 (17.5)	0
Cough	24 (13.3)	0	43 (16.3)	0
Nausea	29 (16.0)	1 (0.6)	42 (16.0)	1 (0.4)
Pyrexia	21 (11.6)	1 (0.6)	42 (16.0)	2 (0.8)
Muscle spasms	22 (12.2)	0	38 (14.4)	3 (1.1)
Thrombocytopenia	23 (12.7)	19 (10.5)	38 (14.4)	31 (11.8)
Urinary tract infection	27 (14.9)	5 (2.8)	37 (14.1)	8 (3.0)
Decreased appetite	30 (16.6)	2 (1.1)	34 (12.9)	2 (0.8)
Dizziness	22 (12.2)	3 (1.7)	33 (12.5)	2 (0.8)
Dyspnea	25 (13.8)	6 (3.3)	29 (11.0)	2 (0.8)
Vomiting	14 (7.7)	0	28 (10.6)	0
Pain in extremity	21 (11.6)	1 (0.6)	27 (10.3)	0
Paraesthesia	13 (7.2)	1 (0.6)	26 (9.9)	1 (0.4)
Muscular weakness	17 (9.4)	4 (2.2)	25 (9.5)	4 (1.5)
Deep vein thrombosis	20 (11.0)	4 (2.2)	23 (8.7)	3 (1.1)
Headache	14 (7.7)	0	22 (8.4)	2 (0.8)
Peripheral swelling	10 (5.5)	0	22 (8.4)	0
Atrial fibrillation	16 (8.8)	7 (3.9)	21 (8.0)	9 (3.4)
Covid-19 pneumonia	8 (4.4)	7 (3.9)	21 (8.0)	21 (8.0)
Influenza	9 (5.0)	1 (0.6)	21 (8.0)	0
Lower respiratory tract infection	10 (5.5)	1 (0.6)	21 (8.0)	2 (0.8)
Rhinitis	13 (7.2)	0	21 (8.0)	0
Tremor	16 (8.8)	2 (1.1)	21 (8.0)	0
Abdominal pain	16 (8.8)	1 (0.6)	20 (7.6)	2 (0.8)
Hypertension	15 (8.3)	5 (2.8)	20 (7.6)	12 (4.6)
Dysgeusia	8 (4.4)	0	19 (7.2)	1 (0.4)
Hypotension	19 (10.5)	5 (2.8)	18 (6.8)	2 (0.8)
Gastroenteritis	6 (3.3)	3 (1.7)	17 (6.5)	0

Preferred Term [n(%)]	VRd (N=181)		IVRd (N=263)	
	All grades	Grade ≥ 3	All grades	Grade ≥ 3
Weight decreased	15 (8.3)	4 (2.2)	17 (6.5)	4 (1.5)
Abdominal pain upper	10 (5.5)	0	16 (6.1)	0
Depression	8 (4.4)	2 (1.1)	16 (6.1)	0
Musculoskeletal chest pain	10 (5.5)	0	16 (6.1)	0
Myalgia	11 (6.1)	0	16 (6.1)	0
Anaemia	16 (8.8)	7 (3.9)	15 (5.7)	8 (3.0)
Dyspepsia	10 (5.5)	0	15 (5.7)	0
Herpes zoster	10 (5.5)	0	15 (5.7)	0
Productive cough	4 (2.2)	0	15 (5.7)	0
Pruritus	12 (6.6)	0	15 (5.7)	1 (0.4)
Rash maculo-papular	6 (3.3)	2 (1.1)	15 (5.7)	4 (1.5)
Syncope	12 (6.6)	10 (5.5)	15 (5.7)	15 (5.7)
Accidental overdose	5 (2.8)	0	14 (5.3)	0
Conjunctivitis	13 (7.2)	0	14 (5.3)	0
Influenza like illness	11 (6.1)	0	14 (5.3)	0
Peripheral sensorimotor neuropathy	14 (7.7)	2 (1.1)	14 (5.3)	4 (1.5)
Vertigo	10 (5.5)	0	14 (5.3)	0

TEAE: Treatment emergent adverse event, PT: Preferred term

MedDRA 26.0

n(%) = number and percentage of patients with at least one TEAE

Note: Table sorted by decreasing frequency of PT for all grades in IVRd group

Only PTs with an incidence $\geq 5\%$ in at least one treatment group are displayed

[0239] AEs leading to definitive discontinuation were 22.8%, Isa-VRd; and 26.0%, VRd).

Treatment-emergent adverse events leading to definitive treatment discontinuation by primary system organ class and preferred term (safety population).

	Isa-VRd (n=263)		VRd (n=181)	
	All grades	Grade ≥ 3	All grades	Grade ≥ 3
Any class	60 (22.8)	57 (21.7)	47 (26.0)	37 (20.4)
Infections and infestations				
COVID-19 pneumonia	8 (3.0)	8 (3.0)	1 (0.6)	1 (0.6)
Pneumonia	6 (2.3)	6 (2.3)	4 (2.2)	4 (2.2)
Sepsis	2 (0.8)	2 (0.8)	1 (0.6)	1 (0.6)
Bronchitis fungal	1 (0.4)	1 (0.4)	0	0
Candida sepsis	1 (0.4)	1 (0.4)	0	0
Diarrhea infectious	1 (0.4)	1 (0.4)	0	0
Lower respiratory tract infection viral	1 (0.4)	1 (0.4)	0	0

	Isa-VRd (n=263)		VRd (n=181)	
	All grades	Grade ≥3	All grades	Grade ≥3
Pneumonia klebsiella	1 (0.4)	1 (0.4)	0	0
Pneumonia pseudomonal	1 (0.4)	1 (0.4)	1 (0.6)	1 (0.6)
Septic shock	1 (0.4)	1 (0.4)	1 (0.6)	1 (0.6)
Bronchitis	0	0	1 (0.6)	1 (0.6)
Clostridium difficile colitis	0	0	1 (0.6)	1 (0.6)
Covid-19	0	0	3 (1.7)	3 (1.7)
Escherichia sepsis	0	0	1 (0.6)	1 (0.6)
Meningitis cryptococcal	0	0	1 (0.6)	1 (0.6)
Osteomyelitis	0	0	1 (0.6)	0
Pneumonia aspiration	0	0	1 (0.6)	1 (0.6)
Respiratory syncytial virus infection	0	0	1 (0.6)	1 (0.6)
Urinary tract infection	0	0	2 (1.1)	2 (1.1)
Urosepsis	0	0	1 (0.6)	1 (0.6)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)				
Rectal adenocarcinoma	2 (0.8)	2 (0.8)	0	0
Colorectal cancer	1 (0.4)	1 (0.4)	0	0
Lung neoplasm malignant	1 (0.4)	1 (0.4)	0	0
Malignant melanoma stage iv	1 (0.4)	1 (0.4)	0	0
Myelodysplastic syndrome	1 (0.4)	1 (0.4)	1 (0.6)	1 (0.6)
Neuroendocrine carcinoma of the skin	1 (0.4)	1 (0.4)	0	0
Prostate cancer	1 (0.4)	1 (0.4)	0	0
Small cell lung cancer	1 (0.4)	1 (0.4)	0	0
Squamous cell carcinoma of lung	1 (0.4)	1 (0.4)	0	0
Squamous cell carcinoma of skin	1 (0.4)	1 (0.4)	0	0
Adenocarcinoma of colon	0	0	2 (1.1)	2 (1.1)
Bladder transitional cell carcinoma	0	0	1 (0.6)	0
Invasive ductal breast carcinoma	0	0	1 (0.6)	1 (0.6)
Skin cancer	0	0	1 (0.6)	0
Blood and lymphatic system disorders				
Febrile neutropenia	1 (0.4)	1 (0.4)	0	0
Anemia	0	0	1 (0.6)	1 (0.6)
Aplasia pure red cell	0	0	1 (0.6)	1 (0.6)
Thrombocytopenia	0	0	1 (0.6)	1 (0.6)
Metabolism and nutrition disorders				
Tumor lysis syndrome	1 (0.4)	1 (0.4)	0	0
Nervous system disorders				

	Isa-VRd (n=263)		VRd (n=181)	
	All grades	Grade ≥ 3	All grades	Grade ≥ 3
Chronic inflammatory demyelinating polyradiculoneuropathy	2 (0.8)	2 (0.8)	0	0
Dementia	1 (0.4)	1 (0.4)	1 (0.6)	0
Hypersomnia	1 (0.4)	1 (0.4)	0	0
Ischemic stroke	1 (0.4)	1 (0.4)	0	0
Memory impairment	1 (0.4)	0	0	0
Neuralgia	1 (0.4)	0	0	0
Parkinson's disease	1 (0.4)	1 (0.4)	0	0
Peripheral sensory neuropathy	1 (0.4)	0	0	0
Guillain-Barre syndrome	0	0	1 (0.6)	1 (0.6)
Loss of consciousness	0	0	1 (0.6)	1 (0.6)
Peripheral sensorimotor neuropathy	0	0	1 (0.6)	1 (0.6)
Cardiac disorders				
Atrial fibrillation	1 (0.4)	1 (0.4)	1 (0.6)	1 (0.6)
Atrial flutter	0	0	1 (0.6)	0
Cardiac failure	0	0	1 (0.6)	1 (0.6)
Cardiac failure acute	0	0	1 (0.6)	1 (0.6)
Vascular disorders				
Hypotension	0	0	1 (0.6)	1 (0.6)
Orthostatic hypotension	0	0	1 (0.6)	1 (0.6)
Respiratory, thoracic, and mediastinal disorders				
Dyspnea	1 (0.4)	1 (0.4)	2 (1.1)	0
Pulmonary embolism	1 (0.4)	1 (0.4)	1 (0.6)	1 (0.6)
Chronic obstructive pulmonary disease	0	0	1 (0.6)	1 (0.6)
Gastrointestinal disorders				
Diarrhea	0	0	5 (2.8)	1 (0.6)
Hepatobiliary disorders				
Congestive hepatopathy	1 (0.4)	1 (0.4)	0	0
Hepatic cirrhosis	1 (0.4)	1 (0.4)	0	0
Hepatitis cholestatic	1 (0.4)	1 (0.4)	0	0
Skin and subcutaneous tissue disorders				
Drug eruption	1 (0.4)	0	0	0
Rash	1 (0.4)	1 (0.4)	0	0
Erythema multiforme	0	0	1 (0.6)	1 (0.6)
Musculoskeletal and connective tissue disorders				
Spinal osteoarthritis	0	0	1 (0.4)	1 (0.4)

	Isa-VRd (n=263)		VRd (n=181)	
	All grades	Grade ≥ 3	All grades	Grade ≥ 3
Muscular weakness	1 (0.6)	1 (0.6)	0	0
Renal and urinary disorders				
Renal impairment	1 (0.4)	1 (0.4)	0	0
Renal tubular acidosis	1 (0.4)	1 (0.4)	0	0
Acute kidney injury	0	0	1 (0.6)	1 (0.6)
Chronic kidney disease	0	0	1 (0.6)	1 (0.6)
General disorders and administration site conditions				
Sudden death	4 (1.5)	4 (1.5)	0	0
Asthenia	1 (0.4)	1 (0.4)	1 (0.6)	0
Death	1 (0.4)	1 (0.4)	1 (0.6)	1 (0.6)
Multiple organ dysfunction syndrome	1 (0.4)	1 (0.4)	0	0
Fatigue	0	0	1 (0.6)	1 (0.6)
General physical health deterioration	0	0	1 (0.6)	1 (0.6)
Generalized edema	0	0	1 (0.6)	1 (0.6)
Investigations				
Amylase increased	1 (0.4)	1 (0.4)	0	0
Injury, poisoning, and procedural complications				
Fall	2 (0.8)	2 (0.8)	0	0
Femur fracture	2 (0.8)	2 (0.8)	0	0

Isa-VRd, isatuximab–bortezomib–lenalidomide–dexamethasone; TEAE, treatment-emergent adverse event; VRd, bortezomib–lenalidomide–dexamethasone.

Data are *n* (%) of patients.

CONCLUSION:

[0240] This interim analysis shows an overwhelming efficacy in favor of patients receiving IVRd treatment compared to patients receiving VRd treatment. The addition of isatuximab to VRd demonstrated a statistically significant improvement in PFS as assessed by blinded IRC. This clinically meaningful improvement was robust as confirmed by multiple sensitivity analyses. The addition of isatuximab to VRd also resulted in an improvement in the depth of response as assessed by response rate of CR, MRD negativity CR (at 10^{-5} sensitivity by NGS) rate and VGPR or better rate. An OS trend favoring IVRd arm is also observed.

[0241] Adding isatuximab to VRd significantly reduced risk of progression or death by 40.4%, at a unprecedented median 5-year follow-up, with median PFS NR versus 54.34 months for Isa-VRd versus VRd, highlighting profound PFS benefit for transplant-ineligible NDMM patients aged ≤ 80 years. Median PFS with VRd was longer in this phase 3 trial versus other

phase 3 trials of comparable populations. Importantly, PFS benefit with Isa-VRd was maintained through subsequent line of therapy and time to next treatment, and was achieved across most subgroups.

[0242] Isa-VRd yielded deep and sustained responses, with significant improvements in MRD-CR rate, higher MRD- rates, and sustained MRD- for ≥ 12 months (at any point; ITT population). Exploratory analysis of MRD-CR rate at 10^{-6} sensitivity showed consistent results with those at 10^{-5} (40% vs. 22.7%; OR 2.270 [95% CI 1.483–3.477]). Additionally, MRD- was associated with improved PFS.

[0243] Isa-VRd demonstrated favorable safety, with no new safety signals. Higher rates of grade ≥ 3 infections (44.9% vs. 38.1%) and grade ≥ 3 neutropenia (laboratory abnormalities; 54.4% vs. 37.0%) were observed with Isa-VRd versus VRd; however, lower infection rates were observed with antibiotic prophylaxis (starting at induction) versus no prophylaxis in both groups. Peripheral sensory neuropathy did not increase with Isa-VRd versus VRd in IMROZ. Overall, 78 (29.7%; Isa-VRd) and 37 (20.4%; VRd) patients experienced COVID-19-related TEAEs. Despite the study occurring during the COVID-19 pandemic, grade ≥ 3 COVID infection incidences, including COVID-19 pneumonia, were low (8.7%, Isa-VRd; 6.6%, VRd). Twelve (4.5%) and 6 (3.3%) COVID-19-related deaths occurred.

[0244] Although the rate of deaths attributed to AEs was higher for Isa-VRd (11%) versus VRd (5.5%), including more deaths due to COVID-19, the VRd group had a higher rate of all-cause deaths and deaths from disease progression (12.2% vs. 4.9%). Overall, the imbalance in grade 5 TEAEs between treatment arms may be attributed to differences in treatment exposure and imbalance in COVID-19-related deaths. Similarly, differences in SPM and grade ≥ 3 infection rates between treatment arms appeared largely due to longer treatment duration for Isa-VRd versus VRd (53.2 vs. 31.3 months).

CLAIMS

What is claimed is:

1. An anti-CD38 antibody for use in treating Multiple Myeloma (MM) in a human patient, wherein the MM is Newly Diagnosed MM (NDMM) and the human patient is not eligible for autologous stem cell transplant, wherein the anti-CD38 antibody is administered in a dosing schedule comprising an induction period followed by a continuous treatment period, wherein in the induction period, the anti-CD38 antibody is administered in combination with bortezomib, lenalidomide, and dexamethasone, and in the continuous treatment period, the anti-CD38 antibody is administered in combination with lenalidomide, dexamethasone and not bortezomib, and wherein the induction period comprises four 42 day cycles, and the continuous treatment period comprises at least one 28 day cycle; wherein during the induction period,

- the anti-CD38 antibody is administered on days 1, 8, 15, 22, and 29, of the first 42 day cycle, then on days 1, 15, and 29 of the three subsequent 42 day cycles;
- the bortezomib is administered on days 1, 4, 8, 11, 22, 25, 29, and 32 of each induction cycle
- the lenalidomide is administered on days 1-14 and days 22-35 of each induction cycle;
- the dexamethasone is administered on days 1, 2, 4, 5, 8, 9, 11, 12, 15, 22, 23, 25, 26, 29, 30, 32, and 33 or on days 1, 4, 8, 11, 15, 22, 25, 29 and 32, of each induction cycles; and wherein

during the continuous treatment period,

- the anti-CD38 antibody is administered on days 1 and 15 of the 28 day cycle;
- the lenalidomide is administered on days 1-21 of the 28 day cycle until disease progression; and
- the dexamethasone is administered on days 1, 8, 15, and 22 of the 28 day cycle until disease progression,

thereby treating MM in the patient.

2. An anti-CD38 antibody for use in safely increasing Progression Free Survival (PFS) in a human patient having Multiple Myeloma (MM), wherein the MM is Newly Diagnosed MM (NDMM) and the human patient is not eligible for autologous stem cell transplant, wherein the anti-CD38 antibody is administered in a dosing schedule comprising an induction period followed by a continuous treatment period,

wherein in the induction period, the anti-CD38 antibody is administered in combination with bortezomib, lenalidomide, and dexamethasone, and in the continuous treatment period, the anti-CD38 antibody is administered in combination with lenalidomide, dexamethasone, and not bortezomib, and wherein

- the anti-CD38 antibody is administered on days 1, 8, 15, 22, and 29, of the first 42 day cycle, then on days 1, 15, and 29 of the three subsequent 42 day cycles;
- the bortezomib is administered on days 1, 4, 8, 11, 22, 25, 29, and 32 of each induction cycle
- the lenalidomide is administered on days 1-14 and days 22-35 of each induction cycle;
- the dexamethasone is administered on days 1, 2, 4, 5, 8, 9, 11, 12, 15, 22, 23, 25, 26, 29, 30, 32, and 33 or on days 1, 4, 8, 11, 15, 22, 25, 29 and 32, of each induction cycles; and wherein

during the continuous treatment period,

- the anti-CD38 antibody is administered on days 1 and 15 of the 28 day cycle;
- the lenalidomide is administered on days 1-21 of the 28 day cycle until disease progression; and
- the dexamethasone is administered on days 1, 8, 15, and 22 of the 28 day cycle until disease progression,

wherein the administration of the anti-CD38 antibody in said induction and continuous treatment periods results in an increased PFS as compared to the administration of induction and continuous treatment periods without the anti-CD38 antibody.

3. An anti-CD38 antibody for use in safely increasing Minimal Residual Disease (MRD) negativity in a human patient having Multiple Myeloma (MM), wherein the MM is Newly Diagnosed MM (NDMM) and the human patient is not eligible for autologous stem cell transplant, wherein the anti-CD38 antibody is administered in a dosing schedule comprising an induction period followed by a continuous treatment period, wherein in the induction period, the anti-CD38 antibody is administered in combination with bortezomib, lenalidomide, and dexamethasone, and in the continuous treatment period, the anti-CD38 antibody is administered in combination with lenalidomide, dexamethasone, and not bortezomib, and wherein

- the anti-CD38 antibody is administered on days 1, 8, 15, 22, and 29, of the first 42 day cycle, then on days 1, 15, and 29 of the three subsequent 42 day cycles;

- the bortezomib is administered on days 1, 4, 8, 11, 22, 25, 29, and 32 of each induction cycle
- the lenalidomide is administered on days 1-14 and days 22-35 of each induction cycle;
- the dexamethasone is administered on days 1, 2, 4, 5, 8, 9, 11, 12, 15, 22, 23, 25, 26, 29, 30, 32, and 33 or on days 1, 4, 8, 11, 15, 22, 25, 29 and 32, of each induction cycles; and wherein

during the continuous treatment period,

- the anti-CD38 antibody is administered on days 1 and 15 of the 28 day cycle;
- the lenalidomide is administered on days 1-21 of the 28 day cycle until disease progression; and
- the dexamethasone is administered on days 1, 8, 15, and 22 of the 28 day cycle until disease progression,

wherein the administration of the anti-CD38 antibody in said induction and continuous treatment periods results in an increase in MRD negativity at a threshold of at least 10^{-5} as compared to the administration of induction and continuous treatment periods without the anti-CD38 antibody.

4. An anti-CD38 antibody for use in safely increasing Overall Survival (OS) in a human patient having Multiple Myeloma (MM), wherein the MM is Newly Diagnosed MM (NDMM) and the human patient is not eligible for autologous stem cell transplant, wherein the anti-CD38 antibody is administered in a dosing schedule comprising an induction period followed by a continuous treatment period, wherein in the induction period, the anti-CD38 antibody is administered in combination with bortezomib, lenalidomide, and dexamethasone, and in the continuous treatment period, the anti-CD38 antibody is administered in combination with lenalidomide, dexamethasone, and not bortezomib, and wherein

- the anti-CD38 antibody is administered on days 1, 8, 15, 22, and 29, of the first 42 day cycle, then on days 1, 15, and 29 of the three subsequent 42 day cycles;
- the bortezomib is administered on days 1, 4, 8, 11, 22, 25, 29, and 32 of each induction cycle
- the lenalidomide is administered on days 1-14 and days 22-35 of each induction cycle;
- the dexamethasone is administered on days 1, 2, 4, 5, 8, 9, 11, 12, 15, 22, 23, 25, 26, 29, 30, 32, and 33 or on days 1, 4, 8, 11, 15, 22, 25, 29 and 32, of each induction cycles; and wherein

during the continuous treatment period,

- the anti-CD38 antibody is administered on days 1 and 15 of the 28 day cycle;
- the lenalidomide is administered on days 1-21 of the 28 day cycle until disease progression; and
- the dexamethasone is administered on days 1, 8, 15, and 22 of the 28 day cycle until disease progression,

wherein the administration of the anti-CD38 antibody results in an increase in OS as compared to the administration of induction and continuous treatment periods without the anti-CD38 antibody.

5. The anti-CD38 antibody of any one of claims 1-4, wherein the anti-CD38 antibody is isatuximab.

6. The anti-CD38 antibody of claim 5, wherein the isatuximab is administered at a dose of 10 mg/kg.

7. The anti-CD38 antibody of claim 5, wherein the isatuximab is administered at a dose of 1400 mg.

8. The anti-CD38 antibody of any one of claims 1-4, wherein the human patient is not a candidate for autologous transplant and/or the human patient does not receive an autologous transplant as part of this line of treatment.

9. The anti-CD38 antibody of any one of claims 1-4, wherein after cycle 17, the anti-CD38 antibody is administered once every four weeks.

10. The anti-CD38 antibody of claim 9, wherein the anti-CD38 antibody is administered on day 1 of each cycle until disease progression.

11. The anti-CD38 antibody of claims 1, 3, or 4, wherein the administration of the anti-CD38 antibody in said induction and continuous treatment periods results in an increased PFS as compared to the administration of the induction and continuation periods without an anti-CD38 antibody.

12. The anti-CD38 antibody of any one of claims 1-4, wherein the bortezomib is administered at a dose of 1.3 mg/m².
13. The anti-CD38 antibody of any one of claims 1-4, wherein the lenalidomide is administered at a dose of 25 mg/day (or 10 mg/day in a human patient having a CrCl $\geq$ 30 to $\leq$ 60 mL/min) during induction period and continuous treatment periods.
14. The anti-CD38 antibody of any one of claims 1-4, wherein the dexamethasone is administered at a dose of 20 mg/day.
15. The anti-CD38 antibody of claim 2, wherein increased PFS is correlated with increased rate of MRD negativity in patients administered the anti-CD38 antibody.
16. The anti-CD38 antibody of any one of claims 1-4, wherein the patient has Revised International Staging System (R-ISS) stage III MM.
17. The anti-CD38 antibody of any one of claims 1-4, wherein the patient has R-ISS stage I or II MM.
18. The anti-CD38 antibody of any one of claims 1-4, wherein the patient is $\geq$ 70 years of age.
19. The anti-CD38 antibody of any one of claims 1-4, wherein the patient is $\geq$ 75 years of age.
20. The anti-CD38 antibody of any one of claims 1-4, wherein the patient is < 75 years of age.
21. The anti-CD38 antibody of any one of claims 1-4, wherein the patient is < 70 years of age.
22. The anti-CD38 antibody of claim 3, wherein the MRD is measured by Next Generation Sequencing (NGS) or Next Generation Flow Cytometry (NGF).

23. A method for safely treating Multiple Myeloma (MM) in a human patient, wherein the MM is Newly Diagnosed MM (NDMM) and the human patient is not eligible for autologous stem cell transplant, comprising administering the anti-CD38 antibody in a dosing schedule comprising an induction period followed by a continuous treatment period, wherein in the induction period, the anti-CD38 antibody is administered in combination with bortezomib, lenalidomide, and dexamethasone, and in the continuous treatment period, the anti-CD38 antibody is administered in combination with lenalidomide, dexamethasone, and not bortezomib, and wherein the induction period comprises four 42 day cycles, and the continuous treatment period comprises at least one 28 day cycle; wherein during the induction period,

- the anti-CD38 antibody is administered on days 1, 8, 15, 22, and 29, of the first 42 day cycle, then on days 1, 15, and 29 of the three subsequent 42 day cycles;
- the bortezomib is administered on days 1, 4, 8, 11, 22, 25, 29, and 32 of each induction cycle
- the lenalidomide is administered on days 1-14 and days 22-35 of each induction cycle;
- the dexamethasone is administered on days 1, 2, 4, 5, 8, 9, 11, 12, 15, 22, 23, 25, 26, 29, 30, 32, and 33 or on days 1, 4, 8, 11, 15, 22, 25, 29 and 32, of each induction cycles; and wherein

during the continuous treatment period,

- the anti-CD38 antibody is administered on days 1 and 15 of the 28 day cycle;
- the lenalidomide is administered on days 1-21 of the 28 day cycle until disease progression; and
- the dexamethasone is administered on days 1, 8, 15, and 22 of the 28 day cycle until disease progression,

thereby treating MM in the patient.

24. A method for safely increasing Progression Free Survival (PFS) in a human patient having Multiple Myeloma (MM), wherein the MM is Newly Diagnosed MM (NDMM) and the human patient is not eligible for autologous stem cell transplant, comprising administering an anti-CD38 antibody in a dosing schedule comprising an induction period followed by a continuous treatment period,

wherein in the induction period, the anti-CD38 antibody is administered in combination with bortezomib, lenalidomide, and dexamethasone, and in the continuous treatment period, the

anti-CD38 antibody is administered in combination with lenalidomide, dexamethasone, and not bortezomib, and wherein

- the anti-CD38 antibody is administered on days 1, 8, 15, 22, and 29, of the first 42 day cycle, then on days 1, 15, and 29 of the three subsequent 42 day cycles;
- the bortezomib is administered on days 1, 4, 8, 11, 22, 25, 29, and 32 of each induction cycle
- the lenalidomide is administered on days 1-14 and days 22-35 of each induction cycle;
- the dexamethasone is administered on days 1, 2, 4, 5, 8, 9, 11, 12, 15, 22, 23, 25, 26, 29, 30, 32, and 33 or on days 1, 4, 8, 11, 15, 22, 25, 29 and 32, of each induction cycles; and wherein

during the continuous treatment period,

- the anti-CD38 antibody is administered on days 1 and 15 of the 28 day cycle;
- the lenalidomide is administered on days 1-21 of the 28 day cycle until disease progression; and
- the dexamethasone is administered on days 1, 8, 15, and 22 of the 28 day cycle until disease progression,

wherein the administration of the anti-CD38 antibody in said induction and continuous treatment periods results in an increased PFS as compared to the administration of said induction and continuous treatment periods without the anti-CD38 antibody.

25. A method for safely increasing Minimal Residual Disease (MRD) negativity rate in a human patient having Multiple Myeloma (MM), wherein the MM is Newly Diagnosed MM (NDMM) and the human patient is not eligible for autologous stem cell transplant, wherein the anti-CD38 antibody is administered in a dosing schedule comprising an induction period followed by a continuous treatment period, wherein in the induction period, the anti-CD38 antibody is administered in combination with bortezomib, lenalidomide, and dexamethasone, and in the continuous treatment period, the anti-CD38 antibody is administered in combination with lenalidomide, dexamethasone, and not bortezomib, and wherein

- the anti-CD38 antibody is administered on days 1, 8, 15, 22, and 29, of the first 42 day cycle, then on days 1, 15, and 29 of the three subsequent 42 day cycles;
- the bortezomib is administered on days 1, 4, 8, 11, 22, 25, 29, and 32 of each induction cycle
- the lenalidomide is administered on days 1-14 and days 22-35 of each induction cycle;

- the dexamethasone is administered on days 1, 2, 4, 5, 8, 9, 11, 12, 15, 22, 23, 25, 26, 29, 30, 32, and 33 or on days 1, 4, 8, 11, 15, 22, 25, 29 and 32, of each induction cycles; and wherein

during the continuous treatment period,

- the anti-CD38 antibody is administered on days 1 and 15 of the 28 day cycle;
- the lenalidomide is administered on days 1-21 of the 28 day cycle until disease progression; and
- the dexamethasone is administered on days 1, 8, 15, and 22 of the 28 day cycle until disease progression,

wherein the administration of the anti-CD38 antibody in said induction and continuous treatment periods results in an increase in MRD negativity at a threshold of at least 10^{-5} as compared to the administration of induction and continuous treatment periods without the anti-CD38 antibody.

26. An anti-CD38 antibody for use in safely increasing Overall Survival (OS) in a human patient having Multiple Myeloma (MM), wherein the MM is Newly Diagnosed MM (NDMM) and the human patient is not eligible for autologous stem cell transplant, wherein the anti-CD38 antibody is administered in a dosing schedule comprising an induction period followed by a continuous treatment period, wherein in the induction period, the anti-CD38 antibody is administered in combination with bortezomib, lenalidomide, and dexamethasone, and in the continuous treatment period, the anti-CD38 antibody is administered in combination with lenalidomide, dexamethasone, and not bortezomib, and wherein

- the anti-CD38 antibody is administered on days 1, 8, 15, 22, and 29, of the first 42 day cycle, then on days 1, 15, and 29 of the three subsequent 42 day cycles;
- the bortezomib is administered on days 1, 4, 8, 11, 22, 25, 29, and 32 of each induction cycle
- the lenalidomide is administered on days 1-14 and days 22-35 of each induction cycle;
- the dexamethasone is administered on days 1, 2, 4, 5, 8, 9, 11, 12, 15, 22, 23, 25, 26, 29, 30, 32, and 33 or on days 1, 4, 8, 11, 15, 22, 25, 29 and 32, of each induction cycles; and wherein

during the continuous treatment period,

- the anti-CD38 antibody is administered on days 1 and 15 of the 28 day cycle;

- the lenalidomide is administered on days 1-21 of the 28 day cycle until disease progression; and
- the dexamethasone is administered on days 1, 8, 15, and 22 of the 28 day cycle until disease progression,

wherein the administration of the anti-CD38 antibody results in an increase in OS as compared to the administration of induction and continuous treatment periods without the anti-CD38 antibody.

27. The method of any one of claims 23-26, wherein the anti-CD38 antibody is isatuximab.

28. The method of claim 27, wherein the isatuximab is administered at a dose of 10 mg/kg.

29. The method of claim 27, wherein the isatuximab is administered at a dose of 1400 mg.

30. The method of any one of claims 23-26, wherein the human patient is not a candidate for autologous transplant and/or the human patient does not receive an autologous transplant as part of this line of treatment.

31. The method of any one of claims 23-26, wherein after cycle 17, the anti-CD38 antibody is administered once every four weeks.

32. The method of claim 31, wherein the anti-CD38 antibody is administered on day 1 of each cycle until disease progression.

33. The anti-CD38 antibody of claims 23, 25, or 26, wherein the administration of the anti-CD38 antibody in said induction and continuous treatment periods results in an increased PFS as compared to the administration of the induction and continuation periods without an anti-CD38 antibody.

34. The method of any one of claims 23-26, wherein the bortezomib is administered at a dose of 1.3 mg/m².

35. The method of any one of claims 23-26, wherein the lenalidomide is administered at a dose of 25 mg/day (or 10 mg/day in a human patient having a $\text{CrCl} \geq 30$ to ≤ 60 mL/min) during induction period and continuous treatment periods.
36. The method of any one of claims 23-26, wherein the dexamethasone is administered at a dose of 20 mg/day.
37. The method of claim 24, wherein increased PFS is correlated with increased rate of MRD negativity in patients administered the anti-CD38 antibody.
38. The method of any one of claims 23-26, wherein the patient has Revised International Staging System (R-ISS) stage III MM.
39. The method of any one of claims 23-26, wherein the patient has R-ISS stage I or II MM.
40. The method of any one of claims 23-26, wherein the patient is ≥ 70 years of age.
41. The method of any one of claims 23-26, wherein the patient is ≥ 75 years of age.
42. The method of any one of claims 23-26, wherein the patient is < 75 years of age.
43. The method of any one of claims 23-26, wherein the patient is < 70 years of age.