14 November 2024
EMA/555367/2024
Committee for Medicinal Products for Human Use (CHMP)

# Assessment report

SARCLISA

International non-proprietary name: Isatuximab

Procedure No. EMEA/H/C/004977/II/0030

## Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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# Table of contents

**1. Background information on the procedure ..... 8**
1.1. Type II variation ..... 8
1.2. Steps taken for the assessment of the product ..... 9

**2. Scientific discussion ..... 9**
2.1. Introduction ..... 9
2.1.1. About the product ..... 11
2.1.2. The development programme/scientific advice ..... 12
2.1.3. General comments on compliance with GCP ..... 12
2.2. Non-clinical aspects ..... 12
2.2.1. Ecotoxicity/environmental risk assessment ..... 12
2.3. Clinical aspects ..... 13
2.3.1. Introduction ..... 13
2.3.2. Pharmacokinetics ..... 14
2.3.3. Pharmacodynamics ..... 20
2.3.4. PK/PD modelling ..... 21
2.3.5. Discussion on clinical pharmacology ..... 22
2.3.6. Conclusions on clinical pharmacology ..... 24
2.4. Clinical efficacy ..... 24
2.4.1. Main study ..... 24
2.4.2. Discussion on clinical efficacy ..... 54
2.4.3. Conclusions on the clinical efficacy ..... 58
2.5. Clinical safety ..... 59
2.5.1. Discussion on clinical safety ..... 81
2.5.2. Conclusions on clinical safety ..... 84
2.5.3. PSUR cycle ..... 84
2.6. Risk management plan ..... 84
2.7. Update of the Product information ..... 85
2.7.1. User consultation ..... 85

**3. Benefit-Risk Balance ..... 86**
3.1. Therapeutic Context ..... 86
3.1.1. Disease or condition ..... 86
3.1.2. Available therapies and unmet medical need ..... 86
3.1.3. Main clinical studies ..... 86
3.2. Favourable effects ..... 87
3.3. Uncertainties and limitations about favourable effects ..... 87
3.4. Unfavourable effects ..... 87
3.5. Uncertainties and limitations about unfavourable effects ..... 88
3.6. Effects Table ..... 88
3.7. Benefit-risk assessment and discussion ..... 89
3.7.1. Importance of favourable and unfavourable effects ..... 89
3.7.2. Balance of benefits and risks ..... 90
3.7.3. Additional considerations on the benefit-risk balance ..... 90
3.8. Conclusions ..... 90

**4. Recommendations ..... 90**

**5. EPAR changes ..... 91**

# List of abbreviations

| | |
|---|---|
| ADA: | anti-drug antibody |
| ADCC: | antibody dependent cell mediated cytotoxicity |
| ADCP: | antibody dependent cellular phagocytosis |
| ADO: | adenosine |
| ADR: | adverse drug reaction |
| AE: | adverse event |
| AESI: | adverse event of special interest |
| AIDS: | acquired immunodeficiency syndrome |
| ALP: | serum alkaline phosphatase |
| ALT: | alanine aminotransferase |
| ASCT: | autologous stem cell transplant |
| AST: | aspartate aminotransferase |
| AUC: | area under the curve |
| B/R: | benefit/risk |
| BCMA: | B-cell maturation antigen |
| BMI: | body mass index |
| BOR: | best overall response |
| CAR-T: | chimeric antigen receptor - T |
| CD: | cluster of differentiation |
| CDC: | complement dependent cytotoxicity |
| CHMP: | Committee for Medicinal Products for Human Use |
| CI: | confidence interval |
| CL/CLinf: | clearance/clearance at steady state |
| $C_{max}$: | maximum serum concentration |
| CMQ: | company MedDRA Query |
| $C_{trough}$: | trough concentration |
| COVID-19: | coronavirus disease-19 |
| (s)CR: | (stringent) complete response |
| CrCl: | creatinine clearance |
| CSR: | clinical study report |
| CT: | computed tomography |
| CT4W: | $C_{trough}$ values at the end of 4 weeks |
| CV: | coefficient of variation |
| CYP3A4: | cytochrome P450 3A4 |
| D: | day |
| d: | low dose dexamethasone |
| Dara: | daratumumab |

| | |
|---|---|
| DHPC: | Direct Healthcare Professional Communication |
| DL: | dose level |
| DLT: | dose limiting toxicity |
| DMC: | Data Monitoring Committee |
| DOR: | Duration of response |
| DRd: | daratumumab, lenalidomide and dexamethasone |
| EC: | European Commission |
| ECG: | Electrocardiogram |
| ECOG PS: | Eastern Cooperative Oncology Group performance status |
| eCRF: | electronic case report form |
| eGFR: | estimated glomerular filtration rate |
| EMA: | European Medicines Agency |
| EORTC: | European Organisation for Research and Treatment of Cancer |
| ESMO: | European Society for Medical Oncology |
| Fc: | fragment crystallizable |
| FCGR3A: | Fc Gamma Receptor IIIa |
| FDA: | Food and Drug Administration |
| FISH: | fluorescence in situ hybridization |
| g: | gram |
| GCP: | good clinical practice |
| HIV: | human immunodeficiency virus |
| HLGT: | high-level group term |
| HLT: | high-level term |
| HR: | hazard ratio |
| I: | isatuximab |
| ICF: | informed consent form |
| IEC: | Independent Ethics Committee |
| IF: | information fraction |
| Ig: | immunoglobulin |
| IKd: | isatuximab, carfilzomib and dexamethasone |
| IMiD: | immunomodulatory drugs |
| IMP: | investigational medicinal product |
| IMWG: | International Myeloma Working Group |
| IPd: | isatuximab, pomalidomide and dexamethasone |
| IR: | infusion reaction |
| IRB: | Institutional Review Board |
| IRC: | Independent Response Committee |
| IRd: | isatuximab, lenalidomide, and dexamethasone combination |
| IRT: | interactive response technology |

| | |
|---|---|
| ISS: | international staging system |
| ITT: | intention to treat |
| IV: | intravenous |
| IVRd: | isatuximab, bortezomib, lenalidomide, and dexamethasone combination |
| $K_2$/$K_3$EDTA: | potassium ethylenediaminetetraacetic acid |
| kg: | kilogram |
| L: | liter |
| LDH: | lactate dehydrogenase |
| LDWB: | low dose whole-body |
| LLoQ: | lower limit of quantification |
| LLT: | low-level term |
| mAb: | monoclonal antibody |
| MAD: | maximum administered dose |
| MAH: | marketing authorization holder |
| mg: | milligram |
| MM: | multiple myeloma |
| mmHg: | millimeters of mercury |
| MO: | major objection |
| mPFS: | median PFS |
| MRD: | minimal residual disease |
| MRI: | magnetic resonance imaging |
| MTD: | maximum tolerated dose |
| Nab: | Neutralizing antibody |
| NCA: | non-compartmental analysis |
| NCI CTCAE: | National Cancer Institute Common Terminology Criteria for Adverse Events |
| ND: | newly diagnosed |
| NGF: | next generation flow cytometry |
| NGS: | next generation sequencing |
| NK: | natural killer |
| OR: | odds ratio |
| ORR: | overall response rate |
| OS: | overall survival |
| PBRER: | Periodic benefit-risk evaluation report |
| PD: | disease progression OR pharmacodynamics |
| PDy: | pharmacodynamic |
| PET: | positron emission tomography |
| PFS: | progression-free survival |
| PI: | proteasome inhibitors |
| PIP: | paediatric investigation plan |

| | |
|---|---|
| PK: | pharmacokinetic |
| PO: | orally |
| PR: | partial response |
| PRAC: | Pharmacovigilance Risk Assessment Committee |
| PSUR: | Periodic safety update report |
| PT: | preferred term |
| Q2W: | once every 2 weeks |
| Q4W: | once every 4 weeks |
| QW: | once a week |
| QoL: | quality of life |
| R: | lenalidomide |
| RD: | recommended dose |
| Rd: | lenalidomide and dexamethasone combination |
| R-ISS: | revised international staging system |
| RMP: | risk management plan |
| RPSFT: | Rank Preserving Structural Failure Time |
| RR: | relapsed and refractory |
| SAE: | serious adverse event |
| SAP: | Statistical Analysis Plan |
| SCS: | summary of Clinical Safety |
| SD: | standard deviation OR |
| sFLC: | serum free light chain |
| SmPC: | summary of product characteristics |
| SMQs: | standardised MedDRA queries |
| SOC: | system organ class *or* standard of care |
| SPM: | Secondary primary malignancies |
| TEAE: | treatment-emergent adverse event |
| Ti: | transplant ineligible |
| TLS: | tumour lysis syndrome |
| TTBR: | time to best response |
| TTNT: | time to next treatment |
| TTP: | time to progression |
| V: | bortezomib |
| VGPR: | very good partial response |
| VRd: | bortezomib, lenalidomide, and dexamethasone combination |
| WB-MRI: | whole body MRI |

# 1. Background information on the procedure

## *1.1. Type II variation*

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Sanofi Winthrop Industrie submitted to the European Medicines Agency on 27 March 2024 an application for a variation.

The following variation was requested:

| **Variation requested** | | **Type** | **Annexes affected** |
|---|---|---|---|
| C.I.6.a | C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one | Type II | I and IIIB |

Extension of indication to include in combination with bortezomib, lenalidomide, and dexamethasone the treatment of adult patients with newly diagnosed active multiple myeloma who are not eligible for autologous stem cell transplant (ASCT) or with no intent for ASCT as initial therapy for Sarclisa, based on results from EFC12522 (IMROZ) pivotal phase III study and the supportive TCD13983 phase 1b/2 study. EFC12522 is an ongoing prospective, multicenter, international, randomized, open-label, 2-arm parallelgroup study to assess the clinical benefit of VRd (control group) versus IVRd (active group) for the treatment of participants with NDMM who are not eligible for ASCT. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.7, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 2.0 of the RMP has also been submitted.

## *Information on paediatric requirements*

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision (P/0144/2023) on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP (P/0144/2023) was completed.

The PDCO issued an opinion on compliance for the PIP (P/0144/2023).

## *Information relating to orphan market exclusivity*

## Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the application included a critical report addressing the possible similarity with authorised orphan medicinal products.

## *Scientific advice*

The MAH received scientific advice in the form of protocol assistance from the CHMP on 20 July 2017 (EMEA/H/SA/2998/1/FU/4/2017/PA/II) and 22 June 2017 (EMEA/H/SA/2998/1/FU/2/2017/PA/III).

### 1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Peter Mol Co-Rapporteur: <N/A>

| Timetable | Actual dates |
|---|---|
| Submission date | 27 March 2024 |
| Start of procedure: | 27 April 2024 |
| CHMP Rapporteur Assessment Report | 21 June 2024 |
| PRAC Rapporteur Assessment Report | 27 June 2024 |
| PRAC members comments | 3 July 2024 |
| PRAC Outcome | 11 July 2024 |
| CHMP members comments | 15 July 2024 |
| Updated CHMP Rapporteur(s) (Joint) Assessment Report | 18 July 2024 |
| Request for supplementary information (RSI) | 25 July 2024 |
| MAH's responses submitted to the CHMP on: | 22 August 2024 |
| CHMP Rapporteur's preliminary Assessment Report on the MAH's responses circulated on | 2 October 2024 |
| CHMP members comments | 7 October 2024 |
| Updated CHMP Rapporteur Assessment Report | 10 October 2024 |
| Request for supplementary information (RSI) | 17 October 2024 |
| MAH's responses submitted to the CHMP on: | 21 October 2024 |
| CHMP Rapporteur's preliminary assessment report on the MAH's responses circulated on: | 30 October 2024 |
| Updated CHMP Rapporteur Assessment Report | 7 November 2024 |
| CHMP opinion: | 14 November 2024 |
| The CHMP adopted a report on similarity of Sarclisa with Darzalex, Farydak, Kyprolis, Ninlaro, Carvykti, Talvey and Abecma on date (Appendix 1) | 14 November 2024 |

# 2. Scientific discussion

## 2.1. Introduction

### Disease or condition

The indication sought by the MAH is:

Isatuximab in combination with bortezomib, lenalidomide and dexamethasone is indicated for the treatment of patients with newly diagnosed (ND) active multiple myeloma (MM) who are not eligible for autologous stem cell transplantation (ASCT) or with no intent for ASCT as initial therapy.

## *Epidemiology*

MM is the second most-common adult blood cancer, with an estimated incidence in Europe of 4.5-6.0/100, 000/year. More than 175,000 cases were reported in 2020, and incidence appears to be highest in countries with a higher human development index. Median age at diagnosis ranges from 65 to 70 years. MM is slightly more frequent in males than in females (approximately 1.4:1), and incidence seems to vary by ethnicity; the incidence in African Americans and Black populations is two to three times that in White populations, as shown in studies from the United States and United Kingdom. The reason for this variance is not known.

## *Aetiology and pathogenesis*

MM is a cancer of the haemopoietic system that is characterized by uncontrolled clonal expansion of plasma cells in the bone marrow. These plasma cells produce an excess amount of abnormal antibodies (so called M protein) or fragments thereof that cause a range of health issues, including impairment of the immune system and increased blood viscosity. Patients often present with bone lesions, anaemia, hypercalcaemia and renal failure.

## *Clinical presentation, diagnosis and prognosis*

Diagnosis is based on serum protein electrophoresis and immunofixation electrophoresis to detect IgG/IgA monoclonal gammopathy. Plasma cell staining in bone marrow aspirate and imaging (MRI/PET-CT) are used to confirm the MM diagnosis. The international scoring system (ISS) for MM stratifies patients into three stages based on serum β2-microglobulin level (I < 3.5 mg/L; 3.5 mg/L ≤ II < 5.5 mg/L; III ≥ 5.5 mg/L), with higher levels being unfavourable. High-risk patients are identified through cytogenetic analysis of the malignant plasma cells and Serum Lactate Dehydrogenase (LDH). The presence of del(17p) and/or translocation t(4;14) and/or translocation t(14;16) and high LDH levels are associated with a worse prognosis. The revised ISS (R-ISS) combines ISS stratification with cytogenetics and serum LDH.

## *Management*

The last two decades have seen the approval of three generations of immunomodulatory drugs (IMiDs; thalidomide, lenalidomide, and pomalidomide), two generations of proteasome inhibitors (PIs; bortezomib, then carfilzomib and ixazomib) and most recently, first generation monoclonal antibodies (mAbs), two of which target CD38 (isatuximab and daratumumab) and another targeting SLAMF7 (elotuzumab). Furthermore, daratumumab also has a formulation that allows for sc injection, which is less burdensome than iv administration.

The targeting of novel myeloma-specific antigens such as B-Cell Maturation Antigen (BCMA), and new modalities of treatment, such as chimeric antigen receptor (CAR)-T cell therapies, are gaining traction and moving towards earlier lines of treatment.

Throughout the treatment lines, fixed combinations of drugs are approved, and the choice of therapy is mostly dependent on transplant eligibility.

According to the 2017 ESMO Clinical Practice Guidelines, in transplant ineligible, older/frail patients, a typical first-line treatment strategy would consist of bortezomib-lenalidomide-dexamethasone (VRd). With the 2021 update of the ESMO guidelines, daratumumab-lenalidomide-dexamethasone (DRd) and daratumumab-bortezomib-melphalan-prednisone (DaraVMP) are now also recommended as first option for transplant ineligible patients. The VRd combination treatment was assessed in the Phase III study SWOG S0777. The median PFS was 41 months for VRd and 29 months for Rd (stratified HR [96% Wald confidence interval] was 0.742 [0.594, 0.928] and one-sided stratified log-rank P-value 0.003).

Addition of daratumumab to lenalidomide-dexamethasone (Rd) treatment was granted approval based on the results from Phase III trial MMY3008. With a median follow-up of 28 months, a PFS improvement in the DRd arm as compared to the Rd arm was seen; the median PFS had not been reached in the DRd arm and was 31.9 months in the Rd arm (HR=0.56; 95% CI: 0.43, 0.73; p < 0.0001), representing a 44% reduction in the risk of disease progression or death in patients treated with DRd. In the ALCYONE study, 706 patients with NDMM who were ineligible for ASCT were randomised to receive 9 cycles of VMP either alone or with Dara (DaraVMP); then Dara was given until disease progression. At a median follow-up of 40 months, the mPFS was 36.4 versus 19.3 months for the DaraVMP and VMP arms, respectively, while the 36-month rate of OS was 78% and 68% for the two groups (HR 0.60; P = 0.0003; EMEA/H/C/004077/II/0011).

As survival has greatly improved over the last decades, and the disease mostly manifests at a later age, the area of the highest unmet medical need may lie in refinement of current treatment strategies. Many drugs seem to be effective and have made it to the first line of treatment, where they are combined. Another unmet medical need concerns the extrapolation of clinical trial data to 'real world patients'. Many patients have significant co-morbidities (e.g. diabetes, prostate cancer), but these patients are not represented in clinical trials. Lastly, MM remains incurable, and even though survival is quite good in the standard risk patients, there is still room for improvement (e.g. prolonged disease control) particularly in the high-risk patients.

### 2.1.1. About the product

Isatuximab is an IgG1 monoclonal antibody directed against cluster of differentiation (CD) 38, which is highly expressed on plasma cells, with particularly high surface density on MM cells. However, B cell, T cells and natural killer (NK) cells can also upregulate CD38 surface expression to similar levels upon activation. *In vitro* experiments have shown that isatuximab acts by flagging CD38-expressing cells for Fc-dependent immune-mediated clearance through antibody dependent cell mediated cytotoxicity (ADCC), antibody dependent cellular phagocytosis (ADCP) and complement dependent cytotoxicity (CDC). The enzymatic activity of CD38, resulting in extracellular conversion of NAD+ to the immunosuppressive factor adenosine (ADO), has been shown to be inhibited by isatuximab *in vitro*.

On 26 March 2020, the CHMP issued a positive opinion for isatuximab in combination with pomalidomide and dexamethasone (IPd), for the treatment of adult patients with relapsed and refractory multiple myeloma (RRMM) who have received at least two prior therapies including lenalidomide and a PI and have demonstrated disease progression on the last therapy.

On 25 February 2021 an extension of indication was granted for isatuximab to add combination with carfilzomib and dexamethasone, for the treatment of patients with multiple myeloma who have received at least one prior therapy.

### 2.1.2. The development programme/scientific advice

The MAH received protocol assistance from the CHMP on 20 July 2017 (EMEA/H/SA/2998/1/FU/4/2017/PA/II) and 22 June 2017 (EMEA/H/SA/2998/1/FU/2/2017/PA/III). The following points were discussed:

- It was agreed that comparison of the quadruplet regimen (IVRd) to the theoretically best available therapy (VRd) could be acceptable.
- The proposed dose schedule of isatuximab on a weekly basis for 4 weeks followed by once every 2 weeks was agreed, although it was questioned whether subjects with low/high bodyweight are not under-/overdosed by dosing based on bodyweight. It was also agreed that lenalidomide, bortezomib and dexamethasone did not seem to impact isatuximab PK.
- Regarding the unknown safety effects of adding isatuximab to the triplet VRd regimen, it was advised to clearly pre-specify specific safety stopping rules in the protocol in order to address any potential issues on toxicity and tolerability. The safety measures already implemented into the protocol were endorsed.
- Regarding PFS censoring, the applicant was advised to add an analysis estimating the 'time to treatment failure', where events that could be regarded as a treatment failure (in particular start new anti-cancer therapy, but also treatment discontinuation, possibly lost-to-follow up, etc.) were not censored, but instead analysed as events.
- Regarding the inclusion of "symptomatic" MM patients, the Applicant was advised to define standard criteria for definition of symptomatic disease.
- Stratification criteria based on age (< 70 vs ≥ 70 years old) and Revised International Staging System (R-ISS, I vs II vs III vs not classified) were endorsed.
- It was acknowledged that cross-over from the Rd arm to the IRd arm may be ethically mandated. However, it was also stressed that this cross-over will confound the OS data.

### 2.1.3. General comments on compliance with GCP

As claimed by the sponsor, the studies used as a basis for the clinical data presented in this report were conducted in compliance with Good Clinical Practice (GCP), as required by the ICH E6 Guideline for Good Clinical Practice. The studies also meet the requirements of the Declaration of Helsinki, standard operating procedures for clinical investigations and documentation of the Sponsor, applicable national laws and regulations and the ethical principles of the Directive 2001/20/EC according to the MAH.

## *2.2. Non-clinical aspects*

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

### 2.2.1. Ecotoxicity/environmental risk assessment

Environmental risk assessment (ERA) studies were not submitted because isatuximab is a monoclonal antibody consisting of linked naturally occurring amino acids. Per the CHMP Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (ERA Guideline corr 2) (1), vitamins, electrolytes, amino acids, peptides, proteins, carbohydrates and lipids are exempt from ERA study requirements because by their nature they are unlikely to result in significant risk to the environment.

## *2.3. Clinical aspects*

### 2.3.1. Introduction

Study EFC12522 (also referred to as IMROZ in this report) was the pivotal study to support the efficacy and safety of the combination of isatuximab, bortezomib, lenalidomide, and dexamethasone (IVRd) treatment in newly diagnosed multiple myeloma patients who are not eligible for ASCT.

Supportive evidence in the new claimed indication was provided by study TCD13983.

### GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

| **Study Number** | ***Study Design and Indication*** | **Treatment regimen and sample size** |
|---|---|---|
| Pivotal Study EFC12522<br><br>(Ongoing; interim CSR cut-off date of 26 September 2023) | A prospective, multicenter, international, randomized, open-label, 2 parallel-group study to demonstrate the benefit of isatuximab in combination with bortezomib, lenalidomide and dexamethasone in the PFS as compared to bortezomib, lenalidomide and dexamethasone in participants with NDMM not eligible for transplant. | Isatuximab 10 mg/kg IV in combination with Velcade, lenalidomide and dexamethasone (IVRd) or control administered for 4 x 6-week cycles Q1W/Q2W (induction) followed by a continuous treatment period with IRd (experimental group) or Rd (control group) (cycle duration 28 days) Q2W then Q4W starting at Cycle 18.<br><br>Patients in the VRd group who progress during continuous treatment may migrate to a crossover group and receive IRd (cycle duration 28 days) QW for Cycle 1 then Q2W.<br><br>Experimental group: IVRd (N=265)<br><br>Control group: VRd (N=181) |
| Supportive TCD13983<br><br>(Ongoing; primary analyses have been completed for the 2 cohorts; CSR cut-off date of 05 April 2021 Part A, and 28 Jan 2022 Part B) | A Phase 1b multi-center, open-label study to evaluate safety, PK, and preliminary efficacy of isatuximab in combination with VRd (IVRd) in adult patients with NDMM Ti (Parts A and B) or no intent for immediate transplantation (Part B only). | IVRd cohorts Part A/Part B: Isatuximab 10 mg/kg IV in combination with VRd administered 4 x 6-week cycles QW/Q2W (Induction) followed by maintenance treatment (IRd) Q2W and then Q4W after Amendment 11.<br><br>Part A: N=27<br><br>Part B: N= 46 (33 NMDD Ti + 13 NDMM with no intent for transplant) |

| Study Number | *Study Design and Indication* | Treatment regimen and sample size |
|---|---|---|
| IIT15403<br><br>Ongoing | A prospective, multicenter, randomized, parallel arm, open-label clinical trial to compare induction therapy without isatuximab versus induction therapy with isatuximab regarding the MRD negativity | Isatuximab Induction Phase:10 mg/kg QW x 4 then Q2W (42-day cycle) - Maintenance Phase: 10 mg/kg QW x 4, then Q2W x 1, then Q4W for subsequent cycles (28-day cycles)<br><br>- VRd: 331 - IVRd: 331 |

Q1W – weekly, Q2W – once in 2 weeks, Q4W - monthly

## 2.3.2. Pharmacokinetics

PK and PD data for the IVRd combination, are form the pivotal Phase 3 study EFC12522 conducted in patients with NDMM who were not eligible for ASCT. Additional data are included from the supportive Phase 1b study TCD13983 Parts A and B, also conducted in patients with NDMM who were not eligible for transplantation or with no immediate intent for transplantation (Part B).

Supplemental information was provided by the investigator-sponsored IVRd study IIT15403, conducted in patients with NDMM who were eligible for ASCT.

Intensive blood sampling schedules were implemented in the Phase 1 study TCD13983 Parts A and B to allow for non-compartmental analysis (NCA), while sparse sampling was implemented for the Phase 3 studies EFC12522 (IVRd arm only) and IIT15403 (subgroup of patients from IVRd arms only). Blood samples for PK analysis were collected up to Cycle 10 in EFC12522 and TCD13983 Parts A and B, and up to Cycle 9 in IIT15403. NCA was used to assess the PK of isatuximab within the Phase 1 Study TCD13983. PK parameters estimated were limited to exposure parameters because the elimination of isatuximab was not fully captured during the dosing interval (7 or 14 days). Similarly, NCA was used to assess the PK of bortezomib and lenalidomide in TCD13983 Parts A and B.

Population PK analysis

Individual PK parameters were generated for patients from the Phase 3 study EFC12522 with a Bayesian method using the previously developed population PK model POH0503 (included in the initial submission for isatuximab) as prior information and the concentration-time data for each patient. Briefly, this was a 2-compartment PK model with parallel nonlinear Michaelis-Menten (concentration-dependent) elimination and linear time-dependent elimination (sigmoidal $E_{max}$ function, where $E_{max}$ is maximum effect) from the central compartment. In the model, linear ("non-specific") clearance (CL) at steady state ($CL_{inf}$) was significantly related to β2 microglobulin, body weight, and Ig MM type (IgG versus non-IgG), whereas the central volume of distribution was found to be related to body weight, gender, and race (Asian versus non-Asian).

Graphical and statistical analyses were then performed in order to identify potentially influential covariates on posterior individual $C_{trough}$ values at the end of 4 weeks (CT4W), the best PK predictor for efficacy.

Consistent with previous submissions, isatuximab exhibited a low linear clearance (CL) and low volume of distribution in the NDMM population not eligible for transplant who received IVRd in the pivotal Phase 3 study EFC12522 in the current submission (**Table 1**).

**Table 1.** Descriptive statistics of individual population PK parameters (mean [CV%]) in NDMM patients study EFC12522 (IVRd treatment) and in the approved indications in patients with MM studies EFC15246 (IKd treatment) and EFC14335 (IPd treatment)

| Parameter | EFC12522 (N=281) (POH0643) | EFC15246 (N=172) (POH0630) | EFC14335 (N=148) (POH0503) |
|---|---|---|---|
| $CL_{inf}$ (L/h) | 0.00445 (45.3) | 0.00486 (50.6) | 0.00822 (52.3) |
| $CL_m$ | 0.969 (71.1) | 0.491 (175) | 0.735 (103) |
| KCL (h) | 1400 (69.1) | 1210 (101) | 938 (67.8) |
| $\gamma$ | 5.42 (47.2) | 5.06 (31.5) | 4.86 (49.1) |
| $V_{max}$ (µg/mL.h) | 0.112 (25.2) | 0.118 (34.2) | 0.166 (40.1) |
| $K_m$ (µg/mL) | 0.300 (7.24) | 0.300 (1.01) | 0.292 (15.3) |
| Q (L/h) | 0.0420 (33.9) | 0.0407 (25.3) | 0.0414 (35.6) |
| $V_1$ (L) | 3.42 (24.2) | 3.07 (29.5) | 3.95 (25.1) |
| $V_2$ (L) | 3.30 (32.4) | 3.15 (26.3) | 3.31 (31.5) |
| $t_{1/2}$ (days) | 51.4 (36.2) | 45.4 (38.7) | 33.1 (46.1) |

$CL_{inf}$ = the linear CL at steady-state; $CL_m$ = maximal change of linear CL from baseline value; $\gamma$ = the sigmoidal coefficient; KCL = the time needed to reach 50% change in linear clearance; Km = Michaelis-Menten parameter; Q = inter-compartmental clearance; $t_{1/2}$ = half-life; $V_1$ = volume of distribution of the central compartment; $V_2$ = volume of distribution of the peripheral compartment; $V_{max}$ = maximum binding capacity

Furthermore, while the distribution of CL estimates over the course of IVRd treatment presented the same pattern for time dependency in CL as was seen for IPd, the decrease in CL with IVRd appeared to be slightly delayed and slightly more pronounced than for IPd as was also observed for IKd population in the supplemental submission. The difference in PK parameters between the IVRd and IPd populations translated into smaller differences in isatuximab exposure during the weekly period (Cycle 1) compared to those observed between IKd and IPd populations during Cycle 1, with these differences more noticeable at steady state (**Table 2**).

**Table 2.** Simulated mean (%CV) post-hoc isatuximab exposure by study at Cycle 1 and at steady state by study at 10 mg/kg QW/Q2W in MM patients (POH0503, POH0630, and POH0643 = study EFC12522)

| Study (N) Assay | Cycle 1[a] | | | | | Steady state[b] | | |
|---|---|---|---|---|---|---|---|---|
| | $C_{max}$ (µg/mL) | $AUC_{1week}$ (µg•h/mL) | CT1W (µg/mL) | AUC4W (µg•h/mL) | CT4W (µg/mL) | $C_{max}$ (µg/mL) | $AUC_{2weeks}$ (µg•h/mL) | $C_{trough}$ (µg/mL) |
| **Combination with bortezomib/lenalidomide/dexamethasone (IVRd) - NDMM** | | | | | | | | |
| EFC12522 (N=281)[h] Gyrolab® Assay DOH1586 | 210 (22.5) | 17 500 (28.1) | 65.3 (38.2) | 122 000 (31.2) | 196 (42.4) | 494 (25.5) | 119 000 (31.8) | 282 (38.1) |
| EFC12522 (N= 256)[j] Gyrolab® Assay DOH1586 | 211 (23.0) | 17 700 (28.2) | 66.4 (38.0) | 123 000 (31.1) | 199 (42.0) | 499 (25.3) | 120 000 (31.4) | 287 (37.6) |
| TCD13983 Part A and Part B (N=72)[g,h] ELISA assay DOH0716 | 184 (45.8) | 15 800 (42.8) | 55.3 (36.5) | 105 000 (33.9) | 163 (39.3) | 425 (28.7) | 102 000 (31.2) | 239 (37.3) |
| IIT15403 (N=33)[h] Gyrolab® Assay DOH1586 | 196 (19.2) | 16 400 (28.4) | 58.7 (46.1) | 116 000 (34.5) | 191 (46.7) | [j] | [j] | [j] |
| **Combination with pomalidomide/dexamethasone (IPd) - RRMM** | | | | | | | | |
| TCD14079 Part A (N=44)[c] ELISA assay DOH0716 | 163 (30.7) | 12 900 (30.2) | 45.7 (46.4) | 94 100 (35.3) | 161 (46.8) | 366 (33.6) | 85 300 (44.9) | 201 (54.6) |
| EFC14335 (N=148) [c] ELISA assay DOH1417 | 192 (35.0) | 15 100 (30.4) | 50.1 (46.3) | 102 000 (31.5) | 158 (42.5) | 351 (36.0) | 72 600 (51.7) | 157 (68.1) |
| **Combination with carfilzomib/dexamethasone (IKd) - RRMM** | | | | | | | | |
| EFC15246 (N=168)[f] Gyrolab® Assay DOH1586 | 258 (37.6) | 21 000 (28.0) | 83.1 (35.8) | 160 000 (29.6) | 290 (36.6) | 637 (30.9) | 152000 (37.8) | 377 (43.3) |

Abbreviations: AUC = area under the plasma concentration curve; $AUC_{1week}$ and $AUC_{2weeks}$ = area under the plasma concentration time curve over the dosing interval of 1 or 2 weeks, respectively; AUC4W = cumulative AUC over the first 4 weeks; $C_{max}$ = maximum plasma concentration; CT1W = $C_{trough}$ at 1 week; CT4W = $C_{trough}$ at 4 weeks; ELISA = enzyme-linked immunosorbent assay; IKd = isatuximab in combination with carfilzomib and dexamethasone; IPd = isatuximab in combination with pomalidomide and dexamethasone

*a* Represents the 1st and 4th administration (QW loading regimen) in Cycle 1.

*b* Represents Cycle 6 (Q2W maintenance regimen, predose [Week 20], $C_{max}$ and $AUC_{2weeks}$ [ie, $AUC_{Week20-Week22}$] after the first dose of the cycle) in RRMM and Cycle 4 in NDMM (Q2W maintenance regimen, predose [Week 20], $C_{max}$ and $AUC_{2weeks}$ [ie, $AUC_{Week20-Week22}$] after the second dose of the cycle).

*c* The report was submitted in the initial IPd submission.

*d* A non-compartmental analysis was used in TCD14906. N=8 for CT1W.

*e* Updated data for TCD14906 are contained in study report PHD0104, available upon request.

*f* The updated EFC15246 study report is contained in supplemental IKd submission.

*g* The PK parameters between TCD13983 Parts A and B are comparable, suggesting that there was no impact on isatuximab PK due to the infusion method (ie, weight-based or fixed-volume infusion; see Section 2.7.3.2). Thus the PK data for TCD13983 Parts A and B are pooled with N=72.

*h* The report is contained in the current IVRd submission.

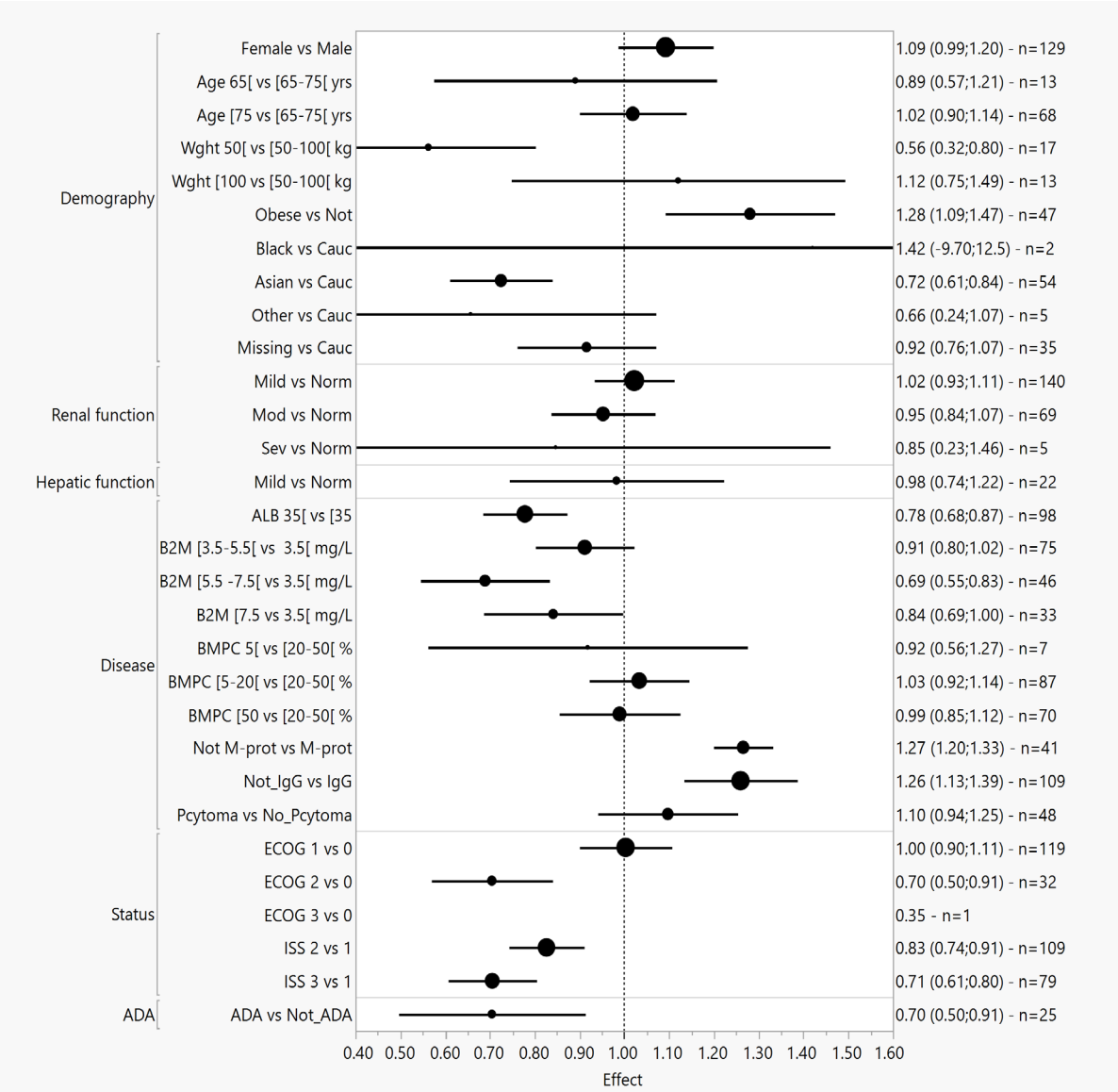
*i* There was no Cycle 4 during the induction period of IIT15403, and data from the maintenance period were not available as of the data cut-off date.

*j* Represents data without patients from the Chinese expansion.

## *Special populations*

The effect of intrinsic factors on the PK of isatuximab in the IVRd Phase 3 study in NDMM population is presented in **Figure *1***.

**Figure 1**. Post-hoc isatuximab exposure parameter (CT4W) at the end of the weekly dosing by covariates (ratio ±95% CI) - EFC12522 in NDMM (POH0643)




## *Interaction between isatuximab, bortezomib and lenalidomide*

The effect of isatuximab on bortezomib and lenalidomide has been evaluated based on the comparison of PK data from TCD13983 and data published in literature. After the administration of bortezomib at 1.3 mg/m2 in combination with isatuximab at 10 mg/kg and lenalidomide 25 mg and dexamethasone, bortezomib PK parameters were consistent with published data for bortezomib administered as a single agent (**Table 3**).

**Table 3.** Comparison of bortezomib PK parameters after SC administration of 1.3 mg/m$^2$ of bortezomib alone (published data) or in combination with isatuximab and lenalidomide (study TCD13983) - Arithmetic mean (± SD)

| Studies | Population | Treatment regimen | N | Cycle/Days | $C_{max}$ (ng/mL) | $AUC_{0-72}$ (ng•h/mL) |
|---|---|---|---|---|---|---|
| TCD13983 Part A | NDMM not eligible for transplantation | IVRd | 6/5[d] | Cycle 1 Day 1 | 18.4 (5.45) | 62.5 (29.6) |
| | | IVRd | 7 | Cycle 3 Day 1 | 24.6 (4.82) | 137 (82.4) |
| TCD13983 Part B | NDMM not eligible for transplantation or no intent for immediate transplantation | IVRd | 21/15[a] | Cycle 1 Day 1 | 20.6 (11.7) | 72.1 (40.4) |
| | | IVRd | 20/18[b] | Cycle 3 Day 1 | 20.0 (7.44) | 121 (30.6) |
| Phase I study, CAN-1004 (14) | RRMM | Bortezomib monotherapy | 10 | Day 1 | 16.5 (8.35) | 92.1 (17.8)[c] |
| | | Bortezomib monotherapy | 10 | Day 11 | 22.5 (5.36) | 195 (51.2)[c] |
| Phase III Study of SC versus IV administration of bortezomib in relapsed MM (15) | Relapsed MM | Bortezomib monotherapy | 16 | Day 11 | 20.4 (8.87) | 155 (56.8)[c] |

Abbreviations: IV = intravenous; IVRd = isatuximab in combination with bortezomib, lenalidomide, and dexamethasone; MM = multiple myeloma; NDMM = newly diagnosed multiple myeloma; RRMM = relapsed or refractory multiple myeloma; P =, pharmacokinetics; SC = subcutaneous; SD, = standard deviation

*a* 21 and 15 patients were included in the calculation of $C_{max}$ and $AUC_{0-72h}$, respectively.

*b* 20 and 18 patients were included in the calculation of $C_{max}$ and $AUC_{0-72h}$, respectively.

*c* AUC0-72 was not available in these studies; however, the authors calculated the AUClast (tlast assumed to be at 72h).

*d* 6 and 5 patients were included in the valculation of $C_{max}$ and $AUC_{0-72}$, respectively.

In the initial MAA submission, the exposure of lenalidomide at 25 mg dose when given with isatuximab was within the range reported for lenalidomide single agent. The addition of bortezomib to this combination did not impact the PK of lenalidomide. After the administration of lenalidomide at 25 mg in combination with isatuximab at 10 mg/kg and bortezomib 1.3 mg/m$^2$, lenalidomide PK parameters were consistent with published data for lenalidomide administered with dexamethasone (**Table 4**).

**Table 4.** Comparison of lenalidomide PK parameters after oral administration of 25 mg of lenalidomide alone (published data) or in combination with isatuximab and bortezomib (study TCD13983) - Arithmetic mean (CV%)

| Studies | Treatment regimen | Population | N | Cycle/Days | $AUC_{0-24}$ (ng•h/mL) | CL/F (L/h) |
|---|---|---|---|---|---|---|
| TCD13983 Part A | IVRd | NDMM not eligible for transplantation | 4 | Cycle 1 Day 1 | 2530 (21.1) | 10.2 (22.8) |
| | | | 5 | Cycle 3 Day 1 | 2300 (40.2) | 12.5 (41.5)[c] |
| TCD13983 Part B | IVRd | NDMM not eligible for transplantation or no intent for immediate transplantation | 24/18[a] | Cycle 1 Day 1 | 3200 (42.7) | 9.05 (37.2) |
| | | | 9/6[b] | Cycle 3 Day 1 | 2730 (24.4) | 10.0 (18.5)[c] |
| TCD11863[d] (included in the initial submission) | Isatuximab with lenalidomide and dexamethasone | RRMM | 29 | 1 | 2720 (54) | 13.8 (128) |
| | | | 14 | 15 | 2950 (44) | - |
| FDA approval package. Clinical Pharmacology and Biopharmaceutics NDA review. NDA 21-880, 1P (16) | Lenalidomide monotherapy | Relapsed MM | 3 | Day 1 | 2231 (22)[e] | 11.04 (24)[e] |
| EMEA review 2007 Study CC-5013-PK-001 | Lenalidomide monotherapy | Normal renal function | 7 | Day 1 | 2065 (33) | 12.4 (29) |
| Phase I Study of Oral Lenalidomide in Refractory Metastatic cancer (17) | Lenalidomide monotherapy | Refractory Metastatic Cancer | 6 | Day 1 | 3820[f] | 11.5 |
| Dose escalation of lenalidomide in relapsed or refractory acute leukemias (18) | Lenalidomide monotherapy | Relapsed or refractory acute leukemias | 4 | Day 1 | 2415 (57) | 12.1 (53) |
| Clinical PK and PD of lenalidomide (19) | Lenalidomide monotherapy | MM | 34 | - | 2124[f] | 11.8 |
| | | Mantle Cell lymphoma | 24 | - | 2538[f] | 9.36 |

Abbreviations: $AUC_{0-24}$ = area under the curve from time 0 to 24 hours; CL/F = apparent total body clearance after a single extravascular dose; CV = coefficient of variation; IVRd = isatuximab in combination with bortezomib, lenalidomide, and dexamethasone; MM = multiple myeloma; NDMM = newly diagnosed multiple myeloma; PD = pharmacodynamics; PK = pharmacokinetics

*a* 24 and 18 patients were included in the calculation of $AUC_{0-24}$ and CL/F, respectively.

*b* 9 and 6 patients were included in the calculation of $AUC_{0-24}$ and CL/F, respectively.

*c* On Cycle 3 Day 1; value of $CL_{ss}/F$ is reported.

*d* $AUC_{0-24h}$ or AUC, arithmetic or geometric mean

*e* Geometric mean (CV%). In TCD13983 Part A, the geometric mean of $AUC_{0-24}$ was 2940 ng.h/mL and CL/F was 9.99 L/hr. In TCD13983 Part B, the geometric mean of $AUC_{0-24}$ was 2940 ng.h/mL and CL/F was 8.44 L/hr.

*f* $AUC_{0-24h}$ or AUC, arithmetic or geometric mean

## *Immunogenicity*

Among the 3 studies in NDMM with IVRd combination, a total of 48 patients exhibited a positive response in the ADA assay in at least one patient sample. Among them, 3 patients were positive at baseline (pre-

existing ADA before the first administration); none of these 3 patients had a boosted response after treatment.

The incidence of treatment-induced ADAs in the pivotal study EFC12522 was 9.1% (25/275, including the Chinese expansion), 16.9% (12/71) in the supportive study TCD13983 (Parts A and B) and 21.6% (8/37) in supplemental study IIT15403; ADA titres were low, with the exception of 4 patients for whom the peak titres were high.

Among the two phase 3 studies where the neutralising status was determined (EFC12522 and IIT15403), the majority of the ADA that were formed were neutralizing (15 out of 25 (60%) and 4 out of 8 (50%) in studies EFC12522 and in IIT15403, respectively). It should be noted that there were 5 patients with NAbs-inconclusive status in EFC12522.

The effect of ADA on isatuximab was assessed by two different approaches: 1) by visual inspection of individual plasma concentration profiles of isatuximab for ADA-positive patients, i.e., with treatment-emergent ADA, versus those having an ADA-negative status, for example by plotting the simulated median (with the 5th and 95th percentiles) PK profiles of ADA-negative patients, following the same actual dosing history of the concerned ADA-positive patient, and adding observed plasma concentrations of patients with at least one ADA-positive sample; and 2) by comparison of the PK parameters (such as CLinf) and exposure parameters (early and later cycles) of ADA-positive versus ADA-negative patients.

A clinically meaningful impact of ADA on isatuximab PK was observed in 9 patients (i.e., 7, 1, and 1 patients from studies EFC12522, TCD13983, and IIT15403, respectively), whose isatuximab plasma concentrations were close to, or below, the LLOQ at the time of the ADA response (which was persistent for 1 of them and indeterminate for 3). Among those impacted, all ADA responses were neutralizing when assessed in studies EFC12522 and IIT15403.

A trend for lower AUC4W was seen in patients that were ADA positive across studies with geometric mean ratio (ADA+/ADA-) of 0.62 in IIT15403, 0.80 in TCD13983, and 0.82 in EFC12522.

Similarly, lower CT4W was noted in patients that were ADA positive across studies, with the geometric mean ratio (ADA+/ADA-) of CT4W ranging from 0.38 (IIT15403) to 0.66 (TCD13983) and 0.70 (EFC12522). The higher impact of ADA status observed in IIT15403 was mainly due to one patient who presented LLOQ concentrations, considering the small data set.

In addition, ADA-positive patients tended to have slightly lower concentrations over time, even from the start of treatment, as reflected by slightly lower AUC over the first week of treatment (i.e., geometric mean ratio of 0.89 [TCD13983], 0.90 [EFC12522], and 0.76 [IIT15403]). The more marked effect in study IIT15403 may be attributed to the unbalanced influential PK covariates between ADA positive and ADA negative patients, as ADA positive patients showed more advanced disease. Therefore, assuming a negligible formation of ADA during the week following the first intravenous administration of isatuximab, the effect of ADA on exposure parameters over cycle 1 may be confounded by the unbalanced distribution PK influential covariates, at least for IIT15403.

## 2.3.3. Pharmacodynamics

### *Primary and secondary pharmacology*

In EFC12522, the polymorphism of FCGR3A was analysed in blood samples from 407 patients, among whom 246 patients received IVRd therapy.

There was improvement in PFS in favour of the IVRd group over the VRd group for genotypes 158F/F (HR 0.631) and 158F/V (HR 0.532) and similar PFS between the IVRd and VRd groups for genotype 158V/V (HR 1.062). Of note, the analysis by genotype group showed no significant interaction at the 10% level between the genotype subgroups and the treatment groups (p=0.4835) indicating an overall consistent treatment effect across subgroups.

The ORR was high and similar for IVRd group versus VRd group in all genotypes, respectively 94.8% versus 90.0% in genotype 158F/F, 92.8% versus 93.8% in 158F/V, and 84.2% versus 100% in 158V/V.

There was a higher CR rate for IVRd group versus VRd group in genotypes 158F/F (79.4% versus 58.3%) and 158F/V (75.7% versus 60.5%). For 158V/V genotype, the CR rate was not higher for IVRd group versus VRd group (60.5% versus 95.0%).

### 2.3.4. PK/PD modelling

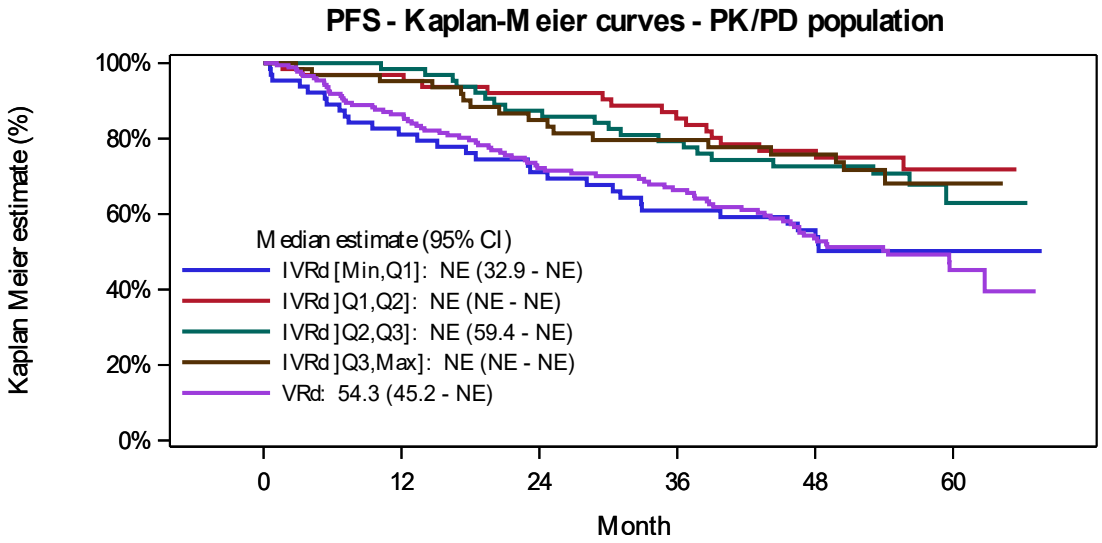
A PK/PD analysis (CTS0101) was conducted to correlate key efficacy and safety endpoints to isatuximab exposure in the IVRd setting, using data from study EFC12522 to support the selection of the IVRd dose/regimen.

Exposure-response-efficacy

Demographic, disease, and baseline characteristics potentially influential for the efficacy endpoints in the absence of isatuximab administration were screened based on the control arm population only. Using a Cox regression model (for PFS) or logistic regression model (for CR/sCR and MRD-CR), a univariate analysis was conducted. In case more than 2 covariates were associated with p values <0.10, a stepwise procedure including those covariates followed the univariate analysis. The final set of covariates was used to identify the best PK predictor and link function (linear, log-linear, $E_{max}$ and sigmoid $E_{max}$) with PFS, CR/sCR or MRD-CR, in comparing these covariate adjusted models using the Akaike information criterion (AIC), Bayesian information criterion and area under the ROC curve (AUC-ROC), based on the whole population. Once the PK predictor and link function were identified, a univariate analysis was conducted to assess the effect of each covariate adjusted on the PK effect and the covariates selected in the first step. Those covariates significant at the 0.10 level were used in a multivariate analysis. The multivariate analyses were performed with the best PK predictor and stepwise inclusion and deletion of covariates using a significance level of 10% for variable entry and of 5% for removal at each step. In the final analysis for PFS, a parametric hazard model was used, assuming Weibull distribution including the final set of covariates resulting from the two steps of selection described above.

Overall, the analyses showed a positive association of isatuximab exposure and the probability of improving PFS (**Figure 2**) and achieving higher Complete Response (CR) and Minimal Residua; Disease (MRD) rates (data not shown) with subjects in the lowest exposure quartile having a lower benefit compared to subjects with the higher exposures.

**Figure 2.** Kaplan Meier estimates of PFS by Ctrough at the end of 4 weeks (CT4W) quartiles (CTS0101)




| stratum | # of patients at risk(KM estimates) | | | | | |
|---|---|---|---|---|---|---|
| IVRd [Min,Q1] | 65 (100.0%) | 51 (81.1%) | 42 (71.1%) | 36 (60.9%) | 31 (55.7%) | 10 (50.2%) |
| IVRd ]Q1,Q2] | 64 (100.0%) | 61 (96.9%) | 56 (92.1%) | 50 (85.3%) | 43 (76.8%) | 9 (71.8%) |
| IVRd ]Q2,Q3] | 64 (100.0%) | 63 (98.4%) | 55 (87.4%) | 48 (79.3%) | 42 (72.6%) | 12 (62.9%) |
| IVRd ]Q3,Max] | 63 (100.0%) | 59 (95.2%) | 48 (84.9%) | 43 (79.6%) | 37 (75.8%) | 12 (68.1%) |
| VRd | 181 (100.0%) | 141 (86.4%) | 104 (72.2%) | 89 (66.4%) | 70 (53.5%) | 20 (45.2%) |

Among the 65 patients in the lowest quartile of the E-R curve (Q1), 38 patients (58.5%) received < 4 weekly isatuximab administration. 35 of these patients encountered isatuximab dose delay and/or dose omissions due to the occurrence of certain AEs. Consistently, among these patients, 30/35 also had lenalidomide and/or bortezomib dose reductions/omissions at Cycle 1.

This subgroup had a higher proportion of patients with parameters which are associated with higher disease burden or poor prognosis characteristics in multiple myeloma such as baseline β2 microglobulin ≥5.5 mg/L, baseline albumin <35 g/L, haemoglobin <10 g/dL, R-ISS/ISS Stage III at study entry, chromosomal abnormality 1q21+. and with ECOG score >1.

Exposure-response-safety

Exploratory analyses were conducted using PK exposure parameters and safety endpoints of interest (IRs, thrombocytopenia, neutropenia, infections, respiratory infections, respiratory events [ie, lower respiratory events] and peripheral neuropathy) with the incidence rates of AEs summarized according to quartiles of the exposure metrics and the corresponding 95% CIs. Analyses were performed for the overall EFC12522 population (PK/PD safety population) and subgroup analysis (Ig MM type). Univariate and multivariate analyses using logistic regressions were to be performed based on the findings from these exploratory analyses.

There was no apparent relationship between an increase of isatuximab exposure and an increase in the incidence of any of the examined AEs of interest.

## 2.3.5. Discussion on clinical pharmacology

The clinical pharmacology of isatuximab for treatment of patients with newly diagnosed active multiple myeloma (NDMM) who are not eligible for ASCT as initial therapy is primarily based on a comparator-controlled Phase 3 study, EFC12522 and supported by the phase Ib study TCD13983.

The PK of isatuximab is characterized by a linear, time-dependent and a nonlinear Michaelis-Menten (concentration-dependent) elimination pathways. Isatuximab CL decreases over time in patients who respond to isatuximab treatment. This is consistent with the pharmacokinetics of isatuximab in patients with RRMM in the previous submissions, and it is thought that the decrease in CL is due to the status improvement on the PK of isatuximab trough by mechanisms such as reduction in inflammation and IgG MM protein, leading to a greater proportion of isatuximab going through salvage pathways and subsequently resulting in lower clearance.

The isatuximab exposure at steady state in patients with NDMM was in between steady-state exposures of patients with RRMM treated with IPd and IKd. The main influential covariates are body weight, β2 microglobulin, and myeloma type (IgG versus non-IgG MM patients), supporting the weight-based dosing. No dose adjustments are needed for β2 microglobulin, and myeloma type or any other intrinsic factor. In the pivotal EFC12522 study for the new indication, the mean (CV%) predicted maximum plasma concentration $C_{max}$ and $AUC_{2weeks}$ at steady state were 494 µg/mL (25.5%) and 119,000 µg.h/mL (31.8%), respectively. Exposure parameters were consistent in EFC12522 and TCD13983 studies.

Overall, isatuximab exposure in NDMM patients from the pivotal IVRd study EFC12522 is consistent with exposure observed in RRMM patients from previous submissions.

As isatuximab is an antibody, PK interactions with bortezomib and lenalidomide by means of enzyme or transporter mediated interactions are not expected. As demonstrated by across study comparisons for isatuximab or with literature for bortezomib and lenalidomide, concomitant administration of isatuximab with VRd did not alter isatuximab exposure, or vice versa.

Only one dose 10 mg/kg isatuximab was evaluated in the pivotal clinical study. Placebo was included in the exposure-response model assuming that the exposure-response relationship is similar over the concentration range 0-lowest CT4W concentration for 10 mg/kg (concentration range not studied) compared to the exposure-response relationship over the lowest to highest CT4W isatuximab concentration range observed for isatuximab 10 mg/kg. By introducing placebo in the model, the weight of placebo to the exposure-response relationship is high for two reasons: 1) half of the data used consists of subjects with placebo have isatuximab = 0 imputed and 2) 0 is an outlier compared the range of isatuximab exposures on 10 mg/kg, and outliers can substantially affect regression coefficients. Because of these issues, an exposure-response without placebo included is preferred.

Since only one dose 10 mg/kg isatuximab was evaluated, the robustness of the exposure-response relationship can be questioned considering the confounding effect of patient disease/health status has on the clearance of monoclonal antibodies in oncology (Bajaj 2017, Turner 2018). Indeed, the lowest exposure quartile consisted of a higher proportion of patients with low baseline albumin and haemoglobin, as well as presence of high-risk cytogenetic characteristics including chromosomal abnormality 1q21+, which would make them less responsive to the treatment and which would be associated with a higher risk of developing AEs (particularly infections, neutropenia or thrombocytopenia) leading to isatuximab and bortezomib/lenalidomide dose modifications. In addition, this lowest exposure quartile was comprised of patients who did not receive all 4 weekly administrations of isatuximab within the first 4 weeks of treatment because of dose modifications due to AEs. Overall, the exposure-response for efficacy is considered not robust because of confounding effect of patients' disease/health condition on the clearance of isatuximab.

The exploratory exposure-response analyses for safety did not show an apparent relationship between an increase of isatuximab exposure and an increase in the incidence of the safety endpoints of interest.

There was a higher incidence of ADA+ (9.1% to 21.6% across the 3 studies) associated with an early onset in NDMM patients compared to RRMM patients (<2%). This might be attributed to a more immunocompetent status in NDMM patients compared to RRMM patients. A meaningful impact on PK

was observed in 9 of 45 ADA+ patients. A trend toward lower exposure was observed in ADA-positive patients in NDMM patients from EFC12522, with a geometric mean ratio (ADA-positives versus ADA-negatives) of 0.82 and 0.70 for cumulative AUC over the first 4 weeks of treatment (AUC4W) and $C_{trough}$ at 4 weeks (CT4W), respectively. However, as ADA kinetics was transient with an onset time primarily at the beginning of isatuximab treatment (i.e. during the first month of isatuximab treatment), the mean linear CL at steady state between ADA-positive and ADA-negative patients remained comparable. Further, this was considered not clinically relevant since, in patients with ADA-positive status including those with neutralizing antibodies, no meaningful impact of ADAs on safety or efficacy of isatuximab was observed. Subgroups of patients with positive ADA/NAb result were too small to evaluate an effect on efficacy or safety.

The observations derived from EFC12522 are consistent with prior observations regarding the lack of association between FCGR3A polymorphism at amino acid 158 and PFS and a positive treatment effect of IVRd group versus VRd group for the 158F/F and 158F/V subgroups. The effects in the 158V/V subgroup need to be interpreted with caution because of the small sample size and imbalanced baseline characteristics.

### 2.3.6. Conclusions on clinical pharmacology

The clinical pharmacology of isatuximab in the new claimed indication had been sufficiently characterised and relevant information has been included in the SmPC section 5.2. The pharmacokinetics of isatuximab in patients with NDMM from the pivotal IVRd study EFC12522 is consistent with pharmacokinetics observed in RRMM patients from other studies which have previously been submitted to support the currently approved indications of isatuximab.

## *2.4. Clinical efficacy*

Efficacy data to support the current application come from one pivotal Phase 3 trial EFC12522 (IMROZ) and a supportive Phase 1b/2 open-label study (TCD13983) of isatuximab-based regimens in patients with NDMM who are transplant-ineligible (Ti) or with no intent for immediate transplant.

### 2.4.1. Main study

EFC12522 (IMROZ): A pivotal randomized, open-label Phase 3 study in NDMM patients not eligible for ASCT. The standard triplet regimen that was approved for first line treatment of MM at the time of initiation of the study, bortezomib, lenalidomide and dexamethasone (VRd) was tested with or without addition of isatuximab (IVRd).

#### *Methods*

#### Study participants

*Inclusion criteria:*

- Multiple myeloma, as defined by the International Myeloma Working Group (IMWG) criteria.
- Evidence of measurable disease:

  - Serum monoclonal (M)-protein ≥1.0 g/dL measured using serum protein immunoelectrophoresis, and/or
  - Urine M-protein ≥200 mg/24 hours measured using urine protein immunoelectrophoresis, and/or
  - Serum free light chain (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).
- 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 ASCT.
- Patient has given voluntary written informed consent.

*Inclusion criteria for cross-over to IRd arm:*

- Patient with confirmed PD in the VRd control arm prior to crossover.
- Patient has not received any other systemic anticancer therapy(ies) other than the VRd arm.

*Exclusion criteria:*

- 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.
- Diagnosis of peripheral neuropathy Grade > 1 or Grade 1 with pain.
- 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).
- 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.
- 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 randomisation.
- Concomitant plasma cell leukemia.
- 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).
- ECOG PS >2.
- Abnormal lab values that could predict vulnerability for anaemia, thrombocytopenia, neutropenia, renal (clearance <30 mL/min/1.73 m²) or hepatic impairment or hypercalcemia.
- 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.
- Any of the following within 6 months prior to randomisation:
  - 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%.

- 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.
- Known acquired immunodeficiency syndrome (AIDS)-related illness or known HIV disease requiring antiviral treatment or active hepatitis A, B or C infection.
- Malabsorption syndrome or any condition that can significantly impact the absorption of lenalidomide.
- Unable or unwilling to undergo thromboprophylaxis as per local clinical practice.
- Any of the following within 3 months prior to randomisation: treatment resistant peptic ulcer disease, erosive esophagitis or gastritis, infectious or inflammatory bowel disease, diverticulitis, pulmonary embolism, or other uncontrolled thromboembolic event.
- 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.
- Pregnant or breastfeeding woman.
- Men or woman of childbearing potential who are unwilling to prevent pregnancy for ≥4 weeks before the start of study treatment and for at least 28 days following discontinuation of study lenalidomide, or for 3 months after discontinuation of bortezomib, or 5 months after discontinuation of isatuximab treatment, whichever occurs last.

*Exclusion criteria for cross-over to IRd arm:*

- The exclusion criteria for cross-over largely overlap with the exclusion criteria for study entry, except for the following differences:

*Exclusion criteria for study entry that are <u>not</u> valid for cross-over*

- ≥ 80 years of age.
- Peripheral neuropathy Grade > 1 or Grade 1 with pain.
- 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 randomisation.
- Lab values related to serum calcium.

*Exclusion criteria not valid for study entry that are <u>mandatory</u> for cross-over*

- More lenient platelet count cut-off ($<50 \times 10^9$/L, instead of $<70 \times 10^9$/L).
- 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.

## Treatments

Participants received isatuximab, bortezomib, lenalidomide and dexamethasone (IVRd) or bortezomib, lenalidomide and dexamethasone (VRd) for an induction period of 24 weeks (four 42-day cycles) followed by continuous treatment in 28-day cycles with the isatuximab, lenalidomide and dexamethasone (IRd) or lenalidomide and dexamethasone (Rd) intervention. Treatment continued until disease progression,

unacceptable AE, or participant's decision to discontinue. During the continuous treatment period, participants in the Rd group who had confirmed disease progression as assessed by the Investigator were allowed to cross over to the IRd combination.

*Treatment periods*

Treatment administration consisted of an induction period and a continuous treatment period. Dose reduction, omission, delay, or treatment discontinuation were planned in case of associated drug reactions. Infusion reactions (IRs) were monitored for patients receiving isatuximab.

Induction period

The total duration of the induction period was 24 weeks (4 cycles). The duration of each cycle in the induction period was 42 days (6 weeks) and a total of 4 cycles were planned. Induction therapy was stopped in case of disease progression, unacceptable AE, patient's decision to discontinue, or completion of the induction period, whichever occurred first. The following medications were used during the induction period:

- Isatuximab (IVRd arm only) was given intravenously (IV) at the dose of 10 mg/kg on Days 1, 8, 15, 22, 29 in Cycle 1; from Cycle 2 onwards, it was given on Days 1, 15, 29 of each cycle.
- Bortezomib was given subcutaneously (SC) at a dose of 1.3 mg/m² on Days 1, 4, 8, 11, 22, 25, 29, and 32 of each cycle.
- Lenalidomide was given per o.s. (PO) at a dose of 25 mg/day (10 mg/day for patients with creatinine clearance [CrCl] ≥30 to <60 mL/min) from Day 1 to Day 14 and from Day 22 to Day 35 of each cycle.
- Dexamethasone IV was given at a dose of 20 mg/day on the days of isatuximab administration (for patients in the IVRd arm) and PO otherwise:
    - Days 1, 2, 4, 5, 8, 9, 11, 12, 15, 22, 23, 25, 26, 29, 30, 32, and 33 (IVRd and VRd arms),
    - If patients were ≥ 75 years old, dexamethasone was administered on Days 1, 4, 8, 11, 15, 22, 25, 29 and 32 (IVRd and VRd arms).

Continuous treatment period

After completion of Cycle 4, patients entered the continuous treatment period. The duration of each cycle was 28 days (4 weeks). Continuous treatment continued until disease progression, unacceptable AE, or patient's decision to discontinue. The following medications were used during this period:

- Isatuximab IV (IVRd arm only) was given at a dose of 10 mg/kg on Days 1 and 15 of each cycle. Starting with Cycle 18 of treatment (counting from the beginning of the induction period), if the patient was still on the trial, the schedule was switched to administration once every 4 weeks.
- Lenalidomide PO was given at a dose of 25 mg/day from Days 1 to 21 (10 mg/day for patients with CrCl ≥ 30 to <60 mL/min), with recommendation for dose modification based on dose toxicity throughout the treatment period. Last lenalidomide dose during induction period, if lower due to safety reasons, was followed in continuous treatment period, unless criteria for re-increase were met.
- Dexamethasone IV was given at a dose of 20 mg/day on the days of isatuximab administration (for patients in IVRd arm only), or PO otherwise on Days 1, 8, 15, and 22, with recommendation for dose modification based on dose toxicity throughout the treatment period.

Cross-over:

The duration of each cycle was 28 days (4 weeks). Treatment with isatuximab + lenalidomide + dexamethasone continued until disease progression, unacceptable AE, or patient's decision to discontinue. The following medications were used during this period:

- Isatuximab 10 mg/kg IV on Days 1, 8, 15, and 22 Cycle 1, and then 10 mg/kg on Days 1 and 15 for subsequent cycles.
- Lenalidomide at 25 mg/day, or 10 mg/day for patients with CrCl ≥30 to <60 mL/min (unless decrease was done for safety purposes) and was given from Days 1 to 21.
- 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. Dexamethasone was added if previously stopped for reasons other than safety in the last 6 months before crossover and based on the Investigator's judgment.

## Objectives

The primary objective of the study was to demonstrate the benefit of isatuximab in combination with bortezomib, lenalidomide, and dexamethasone in the prolongation of progression free survival (PFS) as compared to bortezomib, lenalidomide, and dexamethasone in participants with newly diagnosed multiple myeloma (NDMM) not eligible for transplant

## Outcomes/endpoints

### Primary

Progression Free Survival (PFS) defined as the time from the date of randomisation to the date of first documentation of Progressive Disease (PD) as determined by the central Independent Response Committee (IRC), or the date of death from any cause, whichever occurred first.

PFS was based on M-protein and SFLC measurements and radiological assessment as per International Myeloma Working Group (IMWG) criteria. If clinical and biological data all together provided clear evidence of clinical progression based on IRC judgement in the absence of radiological or M-protein progression, IRC could consider clinical progression as PFS event.
M-protein and SFLC quantification was performed on the first day of every treatment cycle. Skeletal survey (plain X-rays) or low dose whole-body CT scan or PET-CT scan or WB-MRI were performed yearly for all participants and anytime during the study if clinically indicated.

**Table 5** presents the primary event and censoring definitions for the PFS analysis. Patients who initiated new anti-myeloma therapy before a IRC-determined progression were censored at the last available assessment. This reflects the question of what the treatment effect would be assuming no patients were able to receive new anti-cancer therapy before a confirmed progression. One of the pre-specified sensitivity analyses for PFS will not censor for use of new anti-cancer therapy, which reflects a treatment policy estimand strategy and estimates the treatment effect regardless of whether new anti-cancer therapy was initiated before progression.

**Table 5**. PFS Primary analysis events and censoring definitions, blinded IRC disease assessment

| Situation | Date of progression or censoring | Outcome |
|---|---|---|
| No valid baseline disease assessments | Date of Randomization | Censored |
| No valid post-baseline disease assessments | Date of Randomization | Censored |
| Documented Progression according to IRC prior to initiation of new anti-myeloma treatment and prior to the cut-off date and within 13 weeks from last valid disease assessment | Earliest date among all disease assessments with evidence of progression | Event |
| Death without both documented progression and initiation of new anti-myeloma treatment prior to the cut-off date and within 13 weeks from last valid disease assessment | Date of death | Event |
| Both documented progression prior to initiation of new anti-myeloma treatment and death prior to the cut-off date, and within 13 weeks from last valid disease assessment | Date of progression | Event |
| No documented progression according to IRC prior to initiation of new anti-myeloma treatment and no death prior to the cut-off date | Earliest of the date of last valid disease assessment with no evidence of progression before initiation of new anti-myeloma treatment and cut-off date | Censored |
| Symptomatic deterioration reported and no documented progression according to IRC and no death | Ignored | Ignored |
| Initiation of new anti-myeloma treatment before documented progression according to IRC or before death | Earliest of the date of last valid disease assessment with no evidence of progression before initiation of new anti-myeloma treatment and cut-off date | Censored |
| Earliest of Death or progression occurring more than 13 weeks[a] after the last valid disease assessment | Earliest of the date of last valid disease assessment with no evidence of progression before initiation of new anti-myeloma treatment and cut-off date | Censored |

*a* 13 weeks corresponds to >2 consecutive missed scheduled disease assessments

**Key secondary**

- Proportion of participants with stringent complete response (sCR) and complete response (CR) as best overall response (BOR), as assessed by the IRC
- Proportion of participants with CR and for whom MRD is negative by next-generation sequencing (NGS) at any time point after first dose of study intervention
- Proportion of participants with sCR, CR, and VGPR as Best Objective Response (BOR), as assessed by the IRC
- Time from date of randomisation to death from any cause (overall survival)

**Other secondary (selection)**

- Proportion of participants with sCR, CR, VGPR, and partial response (PR) as BOR, as assessed by the IRC
- Time from date of randomisation to first documentation of PD (determined by IRC)
- PFS based on MRD status as assessed by NGS

- Time from date of first IRC determined response for patients achieving PR or better to first documentation of PD determined by IRC or death, whichever occurred first; also determined based on MRD as assessed by NGS
- Time from randomisation to first IRC determined response (PR or better)
- Time from randomisation to first IRC determined best response (PR or better)
- Time from randomisation to first documentation of PD (assessed by investigator) after initiation of further myeloma therapy, or death, whichever occurred
- Proportion of participants with the maintenance of MRD negativity ≥12 months apart with no MRD positive test in between.
- Anti-drug antibodies (ADA), including neutralising and non-neutralising antibodies.
- European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Cancer specific module with 30 items (EORTC QLQ-C30), EORTC QLQ myeloma-specific module with 20 items (MY20), EuroQol measure with 5-dimensions and 5-levels per dimension (EQ-5D-5L)

## Sample size

Sample size calculation for the pivotal study EFC12522 was based on the primary efficacy endpoint (PFS), using the following assumptions:

- PFS would have an exponential distribution in both treatment arms.
- The VRd arm would have a median PFS of 40 months.
- The IVRd arm would have 36% risk reduction in hazard rate in comparison to VRd arm.
- The targeted HR was 0.64, which corresponds to an improvement in the true median PFS time from 40 months to 62.5 months.
- A stratified log-rank test at an overall 1-sided 2.5% significance level with 90% power.
- An interim analysis for efficacy assessment on PFS was planned to be done when 60% of the PFS events had been observed. An O'Brien and Fleming α-spending function was to be used to obtain the nominal significance levels for the interim and final analyses of PFS.
- A randomization ratio of 3:2 (IVRd:VRd).

Based on the above assumptions, 222 PFS events were needed to achieve a 90% power for the study. A total of 440 participants (264 in the IVRd arm and 176 in the VRd arm) would be adequate to achieve the targeted number of PFS events.
Assuming a uniform accrual rate of 30 participants per month, the final analysis cut-off date of PFS was expected to be approximately 60 months after the first participant was enrolled. With the addition of one interim analysis when 75% of the PFS events would be observed, the power was decreased from 90.1% to 89.7%.

The OS final analysis is planned to be performed when approximately 202 deaths have been observed. A total of 202 deaths will provide approximately 80% power for the OS endpoint.

## Randomisation

A total of 446 participants were randomized into the global part of EFC12522. Participants were randomised using an interactive response technology (IRT) in a 2:3 ratio of VRd to IVRd. Randomisation

was stratified by country (Non-China versus China), age (<70 years versus ≥70 years) and revised international staging system (R-ISS) I or II versus III versus not classified (i.e., inconclusive fluorescence in situ hybridization [FISH] unless randomisation stratum could be determined on lactate dehydrogenase, albumin and β2 microglobulin only).

## Blinding (masking)

This was an open-label study.

Radiological and laboratory assessments for disease response were assessed by an IRC blinded to study treatment groups.

## Statistical methods

The primary analysis consisted of a PFS comparison between IVRd and VRd arms through a log-rank test procedure stratified by the stratification factors (age and R-ISS) as entered in the IRT. The significance levels at the interim and final analyses were to be determined using alpha-spending in order to control the overall one-sided type 1 error at 2.5%. Based on the planned number of events, the 1-sided nominal significance level to declare overwhelming efficacy at respectively 60% information fraction (133 PFS events), 75% IF (167 events) and 85% IF (189 events) are 0.003782, 0.008620 and 0.012036 (corresponding to HRs of 0.623, 0.686 and 0.715). The 1-sided nominal significance level to declare superiority of IVRd at the final analysis (222 events) is 0.019937 (corresponding to a HR of 0.755). The actual alpha spending was to be based on the actual number of events included in the analyses and determined by the O'Brien-Fleming spending function at the time of interim and final analyses.

The hazard ratio and corresponding 2-sided confidence interval were to be estimated using the Cox proportional hazards model stratified by age and R-ISS. Kaplan-Meier estimates of the 25th, 50th and 75th percentiles and their associated 2-sided 95% CIs were also to be provided.
Several sensitivity analyses for PFS were pre-planned:

- PFS analysis without censoring for further anti-myeloma treatment.
- PFS analysis using investigator assessment of response and considering symptomatic deterioration.
- PFS analysis using investigator assessment of response and ignoring symptomatic deterioration
- Initiation of further anti-myeloma treatment considered as PFS event.
- PFS analysis without censoring of progression or death occurring more than 13 weeks after the last valid disease assessment.
- Unstratified PFS analysis.
- PFS analysis censoring death event due to Covid-19 infections
- Primary PFS analysis will be performed on all patients from both ITT population and Chinese expansion cohort.

The secondary endpoints of CR rate, MRD[-] CR rate, VGPR or better rate, and minimal residual disease negativity rate by NGS in CR patients, were to be analyzed in the ITT population
at the time of the primary and/or the final analysis of PFS. For these, two-sided confidence intervals at (1-2α) % level (α being the adjusted one-sided nominal significance level using alpha-spending function specific to each endpoint at interim and final analyses) were to be computed using the Clopper-Pearson method and these endpoints compared between treatment arms using a Cochran Mantel Haenszel test

stratified by stratification factors as entered in the IRT (age and R-ISS). The stratified odd ratios and corresponding 2-sided CI at (1-2α) % level was also to be also provided.

Hypothesis testing of the key secondary efficacy endpoints was to be carried out. A closed test procedure was planned be used to control the Type I error rate meaning that testing on key secondary efficacy endpoints was to be performed only if the significance level had been reached on PFS and testing on subsequent endpoints was to continue only if the null hypothesis for the previously tested endpoint is rejected. The hierarchical procedure will be performed according to the following order:

- Complete response rate at the time of the primary PFS analysis and/or the final PFS analysis.
- Minimal residual disease negativity rate at the time of the primary PFS analysis and/or the final PFS analysis.
- Very good partial response or better rate at the time of the primary PFS analysis and/or the final PFS analysis.
- Overall survival.

For the key secondary endpoints, it was planned to determine the significance levels at the interim and final analyses using α-spending function specific to each endpoint, except if the information fraction is 100% at the interim analysis of PFS (i.e., information on secondary endpoint available for every patient). For the rate of VGPR or better, a Pocock-type boundary was to be used. For rate of CR and MRD negative CR rate, the O'Brien-Fleming alpha-spending function was to be used.

The overall survival analysis was to be performed at the time of interim and the final analyses of PFS, and when approximately 202 deaths have occurred in the ITT population. A log-rank test procedure stratified by the stratification factors (age and R-ISS) as entered in the IRT was planned, along with estimates of the effect as specified for the PFS analysis. For the main OS analysis, patients in the VRd arm who crossed over to the experimental arm post-progression remained in the VRd arm. The SAP stated that sensitivity analysis of OS to account for crossover post-PD to the experimental arm may be performed (e.g., Rank Preserving Structural Failure Time (RPSFT) model).

OS analysis was planned to be conducted up to five times, which are at PFS interim analysis 1 with 133 PFS events, PFS interim analysis 2 with 167 PFS events, PFS interim analysis 3 with 189 PFS events, PFS final analysis with 222 PFS events and OS final analysis with approximately 202 deaths. A user defined α-spending function will be used. The cumulative α spent from the first look to the final look will be 0.0001, 0.0002, 0.0003, 0.01 and 0.025 respectively.

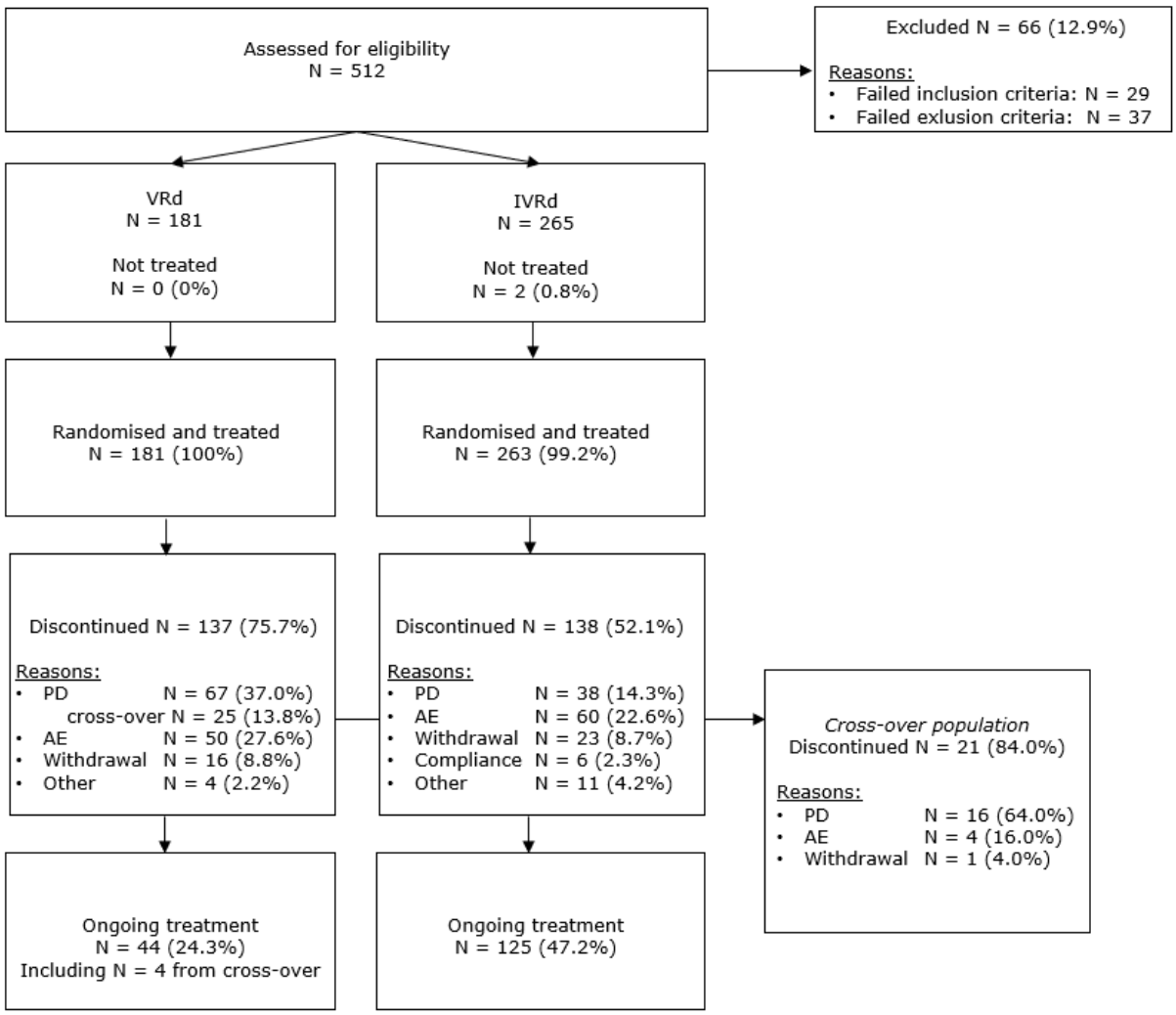
In addition, up to 3 non-binding futility analyses of OS were to be performed. At the PFS interim analysis 1 with 133 PFS events (60% information fraction), DMC may consider stopping the study if the observed hazard ratio (HR) of OS is above 1.15. If the overwhelming efficacy of the study was not declared by the DMC and OS futility boundary was not met at the PFS interim analysis 1, then the second futility analysis for OS was to be performed at the PFS interim analysis 2 with 167 PFS events (75% information fraction). At the PFS interim analysis 2 with 167 PFS events and PFS interim analysis 3 with 189 PFS events, DMC may consider stopping the study if the HR of OS is above 1.1.

## *Results*

## Participant flow

Patient disposition in study EFC12522 is summarised in **Figure 3.**

**Figure 3.** Participant flow in study EFC12522




## Recruitment

Study Initiation Date: 27 December 2017

Data Cutoff Date: 26 September 2023 (planned PFS interim analysis 2 cut-off date (i.e., date when 167 PFS events [75% information fraction] from the global population were expected to be observed))

## Conduct of the study

Protocol amendments

A total of 7 protocol amendments were made during the study. All patients had been enrolled at the second protocol amendment. 5 amendments were considered substantial:

1. Amended protocol 03 (14-May-2019): some clarifications were needed due to longer follow-up in the trial conduction and questions raised as regard to final efficacy analysis (radiology, bone marrow aspirate, M-protein assessment). In addition to these mandatory clarifications, minor inconsistencies were corrected. 'Imaging-positive MRD-negative' was added as an exploratory endpoint.

2. Amended protocol 04 (04-Jun-2020): censoring rules for the PFS analysis were changed following interaction with Health Authorities at the time of submission of another isatuximab Phase 3 study. PFS2 definition was updated according to this change. Change in definition of VGPR or better rate, CR rate, ORR, and DOR (sCR was included in the key secondary endpoints). Previously missing dexamethasone administration on Days 8 and 22 for all cycles (from Cycle 2 onwards) in crossover arm were added. Isatuximab administration was switched to a faster infusion schedule with a fixed distribution volume. Addition of evaluation of time to best response (TTBR) as secondary objective.

3. Amended protocol 05 (17-Nov-2021): key secondary endpoints were modified and the order of analysis was changed in order to better reflect the priorities in treatment evaluation for NDMM patients. Evaluation of sustained MRD negativity≥12 months rate was added to other secondary endpoints. Response assessment was clarified, more particularly CR evaluation, as HYDRASHIFT isatuximab immunofixation test was considered as a complementary method to define the final CR rate. Consequently, impact of M-protein interference was removed from exploratory endpoints. New exploratory objective and endpoint was added (mass spectrometry). Instead of having an analysis on OS only 4 years after the primary PFS analysis cut-off date, additional interim analyses on OS were added at time of PFS analyses.

4. Amended protocol 06 (10-Jun-2022): upon request from health authorities, futility criteria were added for the 2 first interim analyses for overall survival. In addition, the timing of the final analysis of overall survival was revised to be based on a number of targeted events instead of calendar time. Clarified that the PFS2 analysis will be conducted at the time of the final OS analysis.

5. Amended protocol 07 (28-Sep-2023): A third interim analysis for PFS was added to be conducted at 85% information fraction for taking into consideration the long duration of the study. Another interim analysis for OS was also added at the same time and futility criterion for OS was specified.

Protocol deviations

A detailed overview of major protocol deviations is provided in **Table 6**.

**Table 6.** Overview of critical or major protocol deviations in study EFC15255.

| | **VRd (N=181)** | **IVRd (N=265)** |
|---|---|---|
| Inclusion/exclusion criteria | 4 (2.2) | 8 (3.0) |
| No Multiple Myeloma diagnosis as per IMWG criteria | 1 (0.6) | 4 (1.5) |
| Main part: Known AIDS related illness or HIV disease requiring antiretroviral treatment or known active Hepatitis A, B or C infection | 1 (0.6) | 1 (0.4) |

| | VRd (N=181) | IVRd (N=265) |
|---|---|---|
| Main part: ANC < 900 /uL | 0 | 1 (0.4) |
| Main part: Creatinine Clearance < 25 ml/min/1.73 m2 MDRD formula) | 0 | 1 (0.4) |
| Main part: Prior malignancy, except basal cell, squamous cell skin, superficial bladder, low risk prostate, or in situ cancer after therapy, or any cancer from which patient is disease free for > | 0 | 1 (0.4) |
| No evidence of measurable disease | 1 (0.6) | 0 |
| Patient eligible for transplant: age < 65 year-old and/or no associated comorbidities | 1 (0.6) | 0 |
| Randomization procedure | 11 (6.1) | 15 (5.7) |
| IMP given without IRT procedure at resupply visit | 1 (0.6) | 6 (2.3) |
| IMP kit number actually dispensed to the subject is different from the IMP kit number allocated | 0 | 1 (0.4) |
| Wrong stratum of randomization | 10 (5.5) | 8 (3.0) |
| Assessments/Procedures | 19 (10.5) | 25 (9.4) |
| ADA no baseline assessment or no post baseline | 0 | 1 (0.4) |
| BMA was done but not on time. | 0 | 1 (0.4) |
| BMA was not done | 3 (1.7) | 8 (3.0) |
| Central lab M protein done but not performed monthly during FU while patient discontinued for other reason than PD | 3 (1.7) | 2 (0.8) |
| Central lab M protein not done | 0 | 2 (0.8) |
| Central lab M protein not performed during FU while patient discontinued for other reason than PD | 6 (3.3) | 1 (0.4) |
| Cycle duration during continuous period or during cross-over period< duration specified in the protocol | 1 (0.6) | 0 |
| Follow-up study physical visit, phone call or safety contact not performed within the protocol-specified time window for patients without PD1 diagnosed. | 6 (3.3) | 5 (1.9) |
| Method of radiological assessment different than the one requested in protocol at baseline or method different between baseline and during study | 1 (0.6) | 3 (1.1) |
| Miscellaneous issues with procedures | 0 | 1 (0.4) |
| No PK sample at all at baseline or post baseline | 0 | 1 (0.4) |
| No baseline radiological assessment for extramedullary disease | 3 (1.7) | 1 (0.4) |
| No valid post baseline disease assessment sample, central lab | 1 (0.6) | 0 |
| Other deviation related to Assessments and Procedures | 2 (1.1) | 0 |
| Predefined bone lytic lesion assessments not performed as per protocol | 2 (1.1) | 6 (2.3) |
| Predefined plasmacytoma assessment not performed as per protocol | 0 | 2 (0.8) |
| Sample handled incorrectly during collection, processing, storage or shipment | 0 | 1 (0.4) |
| Study procedure performed by unqualified / unauthorized personnel | 0 | 1 (0.4) |
| Clinical Safety | 13 (7.2) | 25 (9.4) |
| Central lab M protein not performed during FU while patient discontinued for other reason than PD | 0 | 1 (0.4) |
| Failure to report AESI/SAE/Pregnancy/Overdose to sponsor within the protocol-specified time window | 13 (7.2) | 23 (8.7) |
| Major procedure or major surgery within 14 days before randomization: plasmapheresis, radiotherapy, major surgery (excluding kyphoplasty) | 0 | 1 (0.4) |
| Other deviation related to Clinical Safety | 1 (0.6) | 0 |
| Deviation other than protocol deviation | 0 | 1 (0.4) |
| Delegation of duties/responsibilities not granted/documented to site staff | 0 | 1 (0.4) |
| IMP Management | 3 (1.7) | 9 (3.4) |
| Administration of IMP, deemed as invalid for use | 2 (1.1) | 2 (0.8) |
| Commercial IMP used | 0 | 2 (0.8) |
| IMP infusion rate errors | 0 | 2 (0.8) |
| Other deviation related to IMP | 0 | 3 (1.1) |
| Overdose of IMP | 1 (0.6) | 0 |
| Informed consent procedures | 2 (1.1) | 8 (3.0) |
| Informed consent/Assent form not obtained for an amendment requiring a re-consent | 1 (0.6) | 2 (0.8) |
| Informed consent/Assent form obtained with a MAJOR misconduct in consent process or documentation | 1 (0.6) | 6 (2.3) |
| Study Informed Consent/ Assent form not obtained before intervention(s) performed as specified in protocol/ amendment | 0 | 1 (0.4) |

| | VRd (N=181) | IVRd (N=265) |
|---|---|---|
| Regulatory | 1 (0.6) | 0 |
| Other Non Compliance to regulatory requirements | 1 (0.6) | 0 |

n (%) = number and percentage of patients with at least one critical or major deviation
Note: Percentages are calculated using the number of patients randomized as denominator
A patient can be counted in several deviation categories

Even though dose reductions were not permitted for isatuximab, a total of 2 (0.8%) participants had at least 1 dose reduction.

## Baseline data

**Table 7**. Summary of demographics at baseline of the ITT population – Study EFC12522

| | EFC12522 VRd (N=181) | IVRd (N=265) |
|---|---|---|
| Age (years) | | |
| Number | 181 | 265 |
| Mean (SD) | 71.5 (4.8) | 71.7 (4.0) |
| Median | 72.0 | 72.0 |
| Min ; Max | 55 ; 80 | 60 ; 80 |
| Age group (years) [n(%)] | | |
| Number | 181 | 265 |
| <65 | 9 (5.0) | 8 (3.0) |
| ≥65 to <75 | 115 (63.5) | 188 (70.9) |
| ≥75 | 57 (31.5) | 69 (26.0) |
| Age group (years) [n(%)] | | |
| Number | 181 | 265 |
| <65 | 9 (5.0) | 8 (3.0) |
| ≥65 to <70 | 47 (26.0) | 73 (27.5) |
| ≥70 to <80 | 121 (66.9) | 180 (67.9) |
| ≥80 | 4 (2.2) | 4 (1.5) |
| Gender [n(%)] | | |
| Number | 181 | 265 |
| Male | 94 (51.9) | 143 (54.0) |
| Female | 87 (48.1) | 122 (46.0) |
| Race [n(%)] | | |
| Number | 181 | 265 |
| White | 131 (72.4) | 192 (72.5) |
| Black or African American | 2 (1.1) | 2 (0.8) |
| Asian | 17 (9.4) | 31 (11.7) |
| Other | 2 (1.1) | 5 (1.9) |
| Not reported or Unknown | 29 (16.0) | 35 (13.2) |
| Ethnicity [n(%)] | | |
| Number | 181 | 265 |
| Hispanic or Latino | 3 (1.7) | 4 (1.5) |
| Not Hispanic or Latino | 150 (82.9) | 225 (84.9) |
| Not reported or Unknown | 28 (15.5) | 36 (13.6) |
| Geographical Region [n(%)] | | |
| Number | 181 | 265 |
| Europe | 106 (58.6) | 169 (63.8) |
| America | 6 (3.3) | 6 (2.3) |
| Asia | 15 (8.3) | 31 (11.7) |
| Other countries/regions | 54 (29.8) | 59 (22.3) |
| Weight (kg) | | |
| Number | 181 | 265 |

| | EFC12522 VRd (N=181) | IVRd (N=265) |
|---|---|---|
| Mean (SD) | 75.2 (15.5) | 72.4 (15.5) |
| Median | 75.0 | 70.8 |
| Min ; Max | 41 ; 125 | 36 ; 140 |
| ECOG performance status [n(%)] | | |
| Number | 181 | 265 |
| 0 | 79 (43.6) | 123 (46.4) |
| 1 | 83 (45.9) | 112 (42.3) |
| 2 | 19 (10.5) | 29 (10.9) |
| 3 | 0 | 1 (0.4) |
| 4 | 0 | 0 |

*Reasons for transplant ineligibility*

The reason for transplant ineligibility was age ≥ 65 years for 95.7% of participants and comorbidities for 4.3% of participants. The most common comorbidities were cardiac disorders, metabolism and nutrition disorders and vascular disorders.

**Table 8**. Disease characteristics at study entry- ITT population, Study EFC12522

| | VRd (N=181) | IVRd (N=265) | All (N=446) |
|---|---|---|---|
| Initial diagnosis [n(%)] | | | |
| Number | 181 | 265 | 446 |
| Multiple Myeloma | 181 (100) | 265 (100) | 446 (100) |
| Time from initial diagnosis of MM to randomization (months) | | | |
| Number | 181 | 265 | 446 |
| Mean (SD) | 1.82 (3.27) | 2.03 (3.74) | 1.94 (3.56) |
| Median | 1.18 | 1.22 | 1.18 |
| Q1 ; Q3 | 0.79 ; 1.81 | 0.79 ; 2.10 | 0.79 ; 1.97 |
| Min ; Max | 0.3 ; 37.7 | 0.3 ; 48.9 | 0.3 ; 48.9 |
| MM subtype at study entry[a] [n(%)] | | | |
| Number | 181 | 265 | 446 |
| Ig G | 115 (63.5) | 171 (64.5) | 286 (64.1) |
| Ig A | 41 (22.7) | 57 (21.5) | 98 (22.0) |
| Ig M | 1 (0.6) | 1 (0.4) | 2 (0.4) |
| Ig D | 2 (1.1) | 3 (1.1) | 5 (1.1) |
| Ig E | 0 | 0 | 0 |
| Kappa light chain only | 11 (6.1) | 21 (7.9) | 32 (7.2) |
| Lambda light chain only | 10 (5.5) | 11 (4.2) | 21 (4.7) |
| Unknown/undetected | 1 (0.6) | 1 (0.4) | 2 (0.4) |
| Biclonal status at study entry[a] [n(%)] | | | |
| Number | 181 | 265 | 446 |
| Yes | 3 (1.7) | 3 (1.1) | 6 (1.3) |
| No | 178 (98.3) | 262 (98.9) | 440 (98.7) |
| Beta 2-microglobulin (mg/L) | | | |
| Number | 181 | 264 | 445 |
| Mean (SD) | 4.72 (2.72) | 4.50 (2.60) | 4.59 (2.65) |
| Median | 3.90 | 3.65 | 3.70 |
| Min ; Max | 1.2 ; 18.1 | 1.2 ; 18.7 | 1.2 ; 18.7 |
| Beta 2-microglobulin (mg/L) [n(%)] | | | |
| Number | 181 | 264 | 445 |
| < 3.5 | 77 (42.5) | 124 (47.0) | 201 (45.2) |
| ≥ 3.5 and <5.5 | 51 (28.2) | 73 (27.7) | 124 (27.9) |
| ≥ 5.5 | 53 (29.3) | 67 (25.4) | 120 (27.0) |
| Albumin (g/L) | | | |
| Number | 180 | 265 | 445 |
| Mean (SD) | 35.7 (6.74) | 36.4 (6.19) | 36.1 (6.42) |
| Median | 36.05 | 37.40 | 36.90 |
| Min ; Max | 19.9 ; 52.0 | 16.0 ; 52.5 | 16.0 ; 52.5 |
| Albumin (g/L) [n(%)] | | | |
| Number | 180 | 265 | 445 |
| < 35 | 83 (46.1) | 99 (37.4) | 182 (40.9) |
| ≥ 35 | 97 (53.9) | 166 (62.6) | 263 (59.1) |

| | VRd (N=181) | IVRd (N=265) | All (N=446) |
|---|---|---|---|
| Serum LDH [n(%)] | | | |
| Number | 178 | 263 | 441 |
| ≤ ULN | 156 (87.6) | 229 (87.1) | 385 (87.3) |
| > ULN | 22 (12.4) | 34 (12.9) | 56 (12.7) |
| ISS stage at study entry [n(%)] | | | |
| Number | 181 | 265 | 446 |
| Stage I | 47 (26.0) | 90 (34.0) | 137 (30.7) |
| Stage II | 80 (44.2) | 107 (40.4) | 187 (41.9) |
| Stage III | 53 (29.3) | 67 (25.3) | 120 (26.9) |
| Unknown | 1 (0.6) | 1 (0.4) | 2 (0.4) |
| R-ISS stage at study entry [n(%)] | | | |
| Number | 181 | 265 | 446 |
| Stage I | 35 (19.3) | 66 (24.9) | 101 (22.6) |
| Stage II | 123 (68.0) | 163 (61.5) | 286 (64.1) |
| Stage III | 17 (9.4) | 27 (10.2) | 44 (9.9) |
| Not classified | 6 (3.3) | 9 (3.4) | 15 (3.4) |
| Fish done but risk not classified | 4 (66.7) | 8 (88.9) | 12 (80.0) |
| Fish assessment missing | 1 (16.7) | 0 | 1 (6.7) |
| At least one biological assessment missing | 1 (16.7) | 2 (22.2) | 3 (20.0) |

*a* as per eCRF
MM: Multiple Myeloma, Ig: Immunoglobulin, LDH: Lactate Dehydrogenase, ULN: Upper Limit of Normal, ISS: International staging system, R-ISS: Revised International staging system

## Numbers analysed

Intent-to-treat (ITT) population: this population included all patients from the global study part who had given their informed consent and for whom there was a confirmation of successful allocation of a randomization number by the IRT. This population was the primary population for all efficacy parameters. All analyses using this population were based on the treatment assigned at randomization.

Safety population: this population included ITT patients who had received at least 1 dose or a part of a dose of the study treatments. This population was the primary population for the analysis of all safety parameters. All analyses using this population were based on the treatment actually received.

The crossover population included all patients from the VRd arm who crossed over and received at least 1 dose of isatuximab. This population was used for exploratory analysis of BOR, exposure and safety data after the crossover date.

Anti-drug antibodies population: the ADA population included safety patients from the IVRd arm with at least 1 sample taken post-baseline after drug administration during the treatment or follow-up observation period that was appropriate for ADA testing with a reportable result. Patients from the VRd arm who crossed over to receive isatuximab were considered separately.

The number of participants included in each analysis population, as defined in the Statistical Analysis Plan (SAP), is provided in **Table 9**.

**Table 9.** Analysis populations- Study EFC12522

| | VRd (N=181) | IVRd (N=265) |
|---|---|---|
| Randomized population | 181 (100) | 265 (100) |
| Efficacy population: Intent-To-Treat (ITT) | 181 (100) | 265 (100) |
| Crossover population (IRd) | 25 (13.8) | 0 |
| Safety population | 181 | 263 |
| ADA population | 1 | 253 |
| PK population | 0 | 256 |

| | VRd (N=181) | IVRd (N=265) |
|---|---|---|

Note: For the randomized, ITT, Crossover, without trial impact due to Covid-19 populations, patients are tabulated according to their randomized treatment
For other populations, patients are tabulated according to the treatment actually received (as treated)
No patients are randomized in a group and taking another study treatment.

## Outcomes and estimation

***Primary endpoint***

Data from the pre-planned PFS interim analysis #2 with 75% information fraction are shown in **Table 10** and **Figure 4**. The median duration of exposure was 31.3 months (range 0.6 to 67.2) in the VRd group and 53.2 months (range 0.5 to 68.8) in the IVRd group. Median follow-up time was 59.73 months.

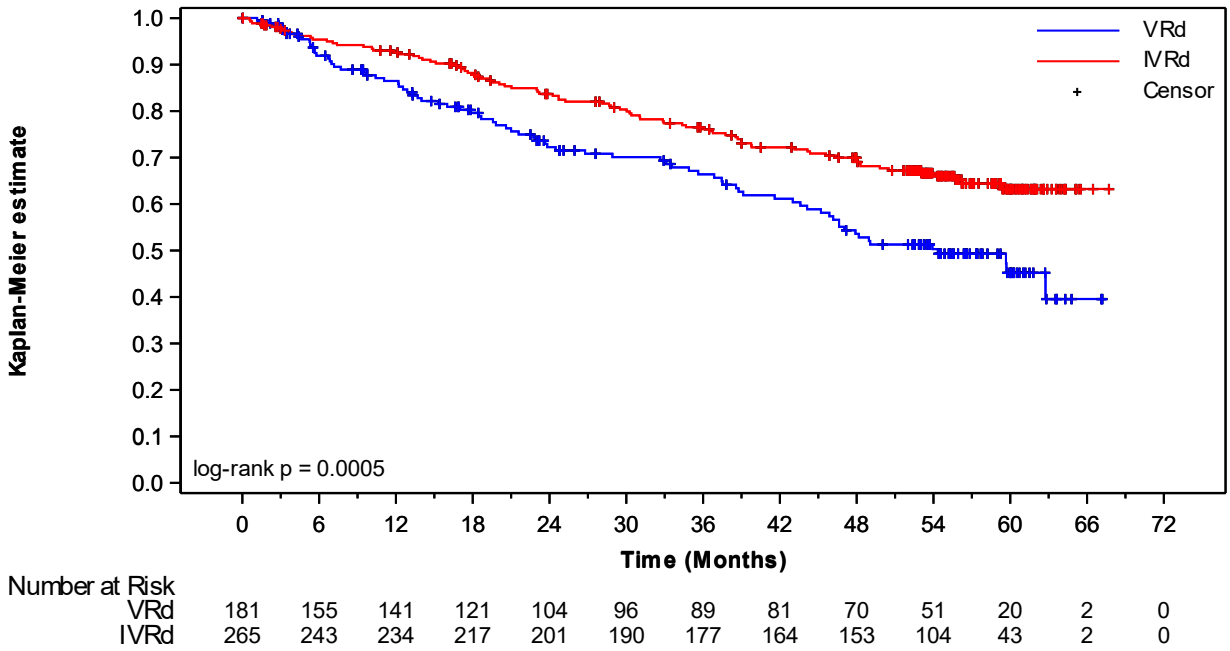
The main reason for censoring was follow-up ended (35.4% and 34.7% in the VRd and IVRd groups, respectively). Reasons for censoring are provided in **Table *11***.

**Table 10.** PFS - Primary analysis based on disease assessment by the IRC by treatment group - ITT population- Study EFC12522

| | VRd (N=181) | IVRd (N=265) |
|---|---|---|
| Number (%) of events | 78 (43.1) | 84 (31.7) |
| Number (%) of patients censored | 103 (56.9) | 181 (68.3) |
| Kaplan-Meier estimates of PFS in months | | |
| 25% quantile (95% CI) | 21.59 (15.310 to 33.544) | 37.75 (29.503 to 48.033) |
| Median (95% CI) | 54.34 (45.207 to NC) | NC (NC to NC) |
| 75% quantile (95% CI) | NC (NC to NC) | NC (NC to NC) |
| Stratified[a] Log-Rank test p-value[b] | | |
| vs VRd | - | 0.0005 |
| Stratified[a] Hazard ratio (98.5154% CI) | | |
| vs VRd | - | 0.596 (0.406 to 0.876) |
| PFS probability (95% CI)[c] | | |
| 6 Months | 0.919 (0.867 to 0.951) | 0.953 (0.920 to 0.973) |
| 12 Months | 0.864 (0.803 to 0.908) | 0.926 (0.886 to 0.952) |
| 24 Months | 0.722 (0.646 to 0.785) | 0.837 (0.785 to 0.877) |
| 48 Months | 0.535 (0.451 to 0.613) | 0.699 (0.637 to 0.753) |
| 54 Months | 0.503 (0.417 to 0.582) | 0.666 (0.602 to 0.723) |
| 60 Months | 0.452 (0.356 to 0.542) | 0.632 (0.562 to 0.694) |
| 66 Months | 0.395 (0.264 to 0.523) | 0.632 (0.562 to 0.694) |

PFS: Progression-free survival, CI: Confidence interval, NC: Not calculated, HR: Hazard ratio, IRC: Independent Response Committee, IRT: Interactive Response Technology
Cut-off date: 26SEP2023. Median follow-up time = 59.73 months. HR<1 favors IVRd arm
CI for Kaplan-Meier estimates are calculated with log-log transformation of survival function and methods of Brookmeyer and Crowley
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 IRT
*a* One-sided significance level is 0.007423.
*b* Estimated using the Kaplan-Meier method
*c* Events occurring more than 13 weeks after the last valid disease assessment are censored

**Figure 4.** Kaplan-Meier estimate of PFS for the IVRd vs the VRd arm based on disease assessment by the IRC – ITT population, Study EFC12522




Cut-off date = 26SEP2023

Median follow-up time = 59.73 months.

PFS: Progression-free survival, IRC: Independent Response Committee, IRT: Interactive Response Technology

Log-Rank p value: Stratified on age (<70 years vs ≥70 years) and Revised International Staging System (R-ISS) stage (I or II vs. III or not classified) according to IRT.

One-sided significance level is 0.007423.

Events occurring more than 13 weeks after the last valid disease assessment are censored

**Table 11.** PFS - Primary analysis based on disease assessment by the IRC – description of censoring, ITT population, Study EFC12522

| | VRd (N=181) | IVRd (N=265) |
|---|---|---|
| Number of patients without event [n(%)] | 103 (56.9) | 181 (68.3) |
| Reason of censoring | | |
| Censored, follow-up ongoing | 39 (21.5) | 89 (33.6) |
| Censored, follow-up ended | 64 (35.4) | 92 (34.7) |
| No post-baseline assessment | 0 | 2 (0.8) |
| Lost to follow-up[a] | 34 (18.8) | 63 (23.8) |
| Patients still on treatment | 12 (6.6) | 40 (15.1) |
| Patients with definitive treatment discontinuation | 22 (12.2) | 23 (8.7) |
| Patients who remain in the study | 12 (6.6) | 11 (4.2) |
| Patients who ended the study | 10 (5.5) | 12 (4.5) |
| Events more than 13 weeks from last valid disease assessment | 4 (2.2) | 11 (4.2) |
| Progression confirmed by IRC | 1 (0.6) | 3 (1.1) |
| Death | 3 (1.7) | 8 (3.0) |
| Further anti-myeloma treatment | 26 (14.4) | 16 (6.0) |
| With confirmed investigator PD | 16 (8.8) | 9 (3.4) |

| | VRd (N=181) | IVRd (N=265) |
|---|---|---|
| With unconfirmed investigator PD or symptomatic deterioration | 1 (0.6) | 0 |
| Without investigator PD | 9 (5.0) | 7 (2.6) |

IRC: Independent Response Committee
Cut-off date = 26SEP2023
Events occurring more than 13 weeks after the last valid disease assessment are censored
[a]: A patient is considered as lost to follow-up if the reason for censoring is 'last valid disease assessment before cutoff' and if the time from last disease assessment to cutoff is > 13 weeks.

***PFS sensitivity analysis***

The main PFS sensitivity analyses are summarized in

**Table 12**.

**Table 12.** Summary of main sensitivity analyses, Study EFC12522

| | | VRd | | IVRd | | | |
|---|---|---|---|---|---|---|---|
| | **Total number of events** | **N (%) of events** | **Median (months) (95% CI)** | **N (%) of events** | **Median (months) (95% CI)** | **Hazard ratio (98.5% CI) vs VRd** | **P-value** |
| Main analysis - PFS: | 162 | 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 analysis without censoring for further anti-myeloma treatment | 165 | 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 |

| | | VRd | | IVRd | | | |
|---|---|---|---|---|---|---|---|
| | **Total number of events** | **N (%) of events** | **Median (months) (95% CI)** | **N (%) of events** | **Median (months) (95% CI)** | **Hazard ratio (98.5% CI) vs VRd** | **P-value** |
| PFS analysis using investigator assessment of response and considering symptomatic deterioration | 183 | 96 (53.0) | 47.08 (38.768 to 56.246) | 87 (32.8) | NC (NC to NC) | 0.509 (0.355 to 0.731) | <0.0001 |
| PFS analysis using investigator assessment of response and ignoring symptomatic deterioration | 181 | 94 (51.9) | 47.90 (39.129 to 56.246) | 87 (32.8) | NC (NC to NC) | 0.52 (0.362 to 0.748) | <0.0001 |
| PFS including initiation of further anti-myeloma treatment considered as PFS event | 196 | 99 (54.7) | 45.86 (34.891 to 53.749) | 97 (36.6) | NC (NC to NC) | 0.546 (0.385 to 0.774) | <.00001 |
| PFS analysis without censoring of progression or death occurring more than 13 weeks after the last valid disease assessment | 177 | 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 analysis censoring deaths due to Covid-19 infection by treatment group | 153 | 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 analysis based on disease assessment on participants from both global ITT population and Chinese expansion cohort | 172/482 | 83/193 (43.0) | 53.91 (44.123 to NC) | 89/291 (30.6) | NC (NC to NC) | 0.573 (0.395 to 0.832) | 0.0001 |

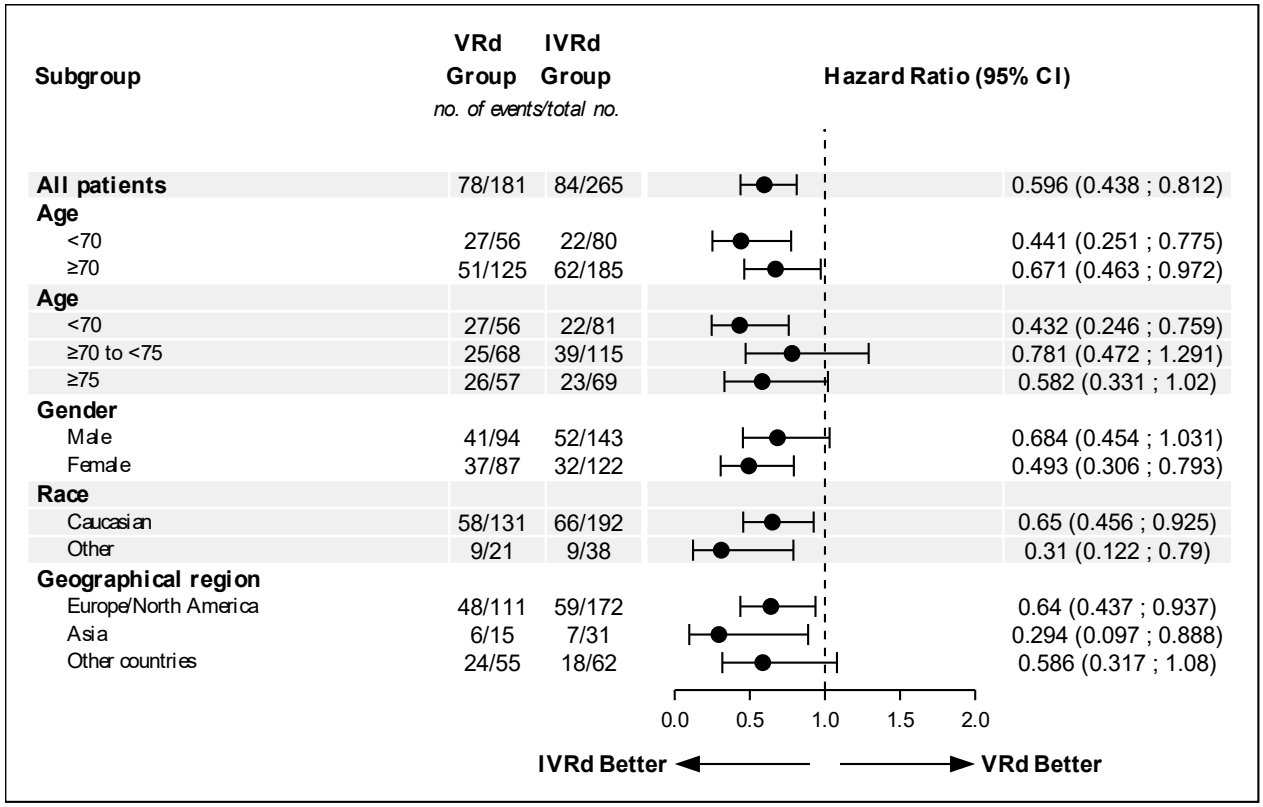
PFS, progression-free survival; NC, not calculated. Cut-off date = 26 September 2023

***PFS subgroup analysis***

Forrest plots of multiple subgroup analyses of the primary endpoint are shown in **Figure 5.** - **Figure 8.**

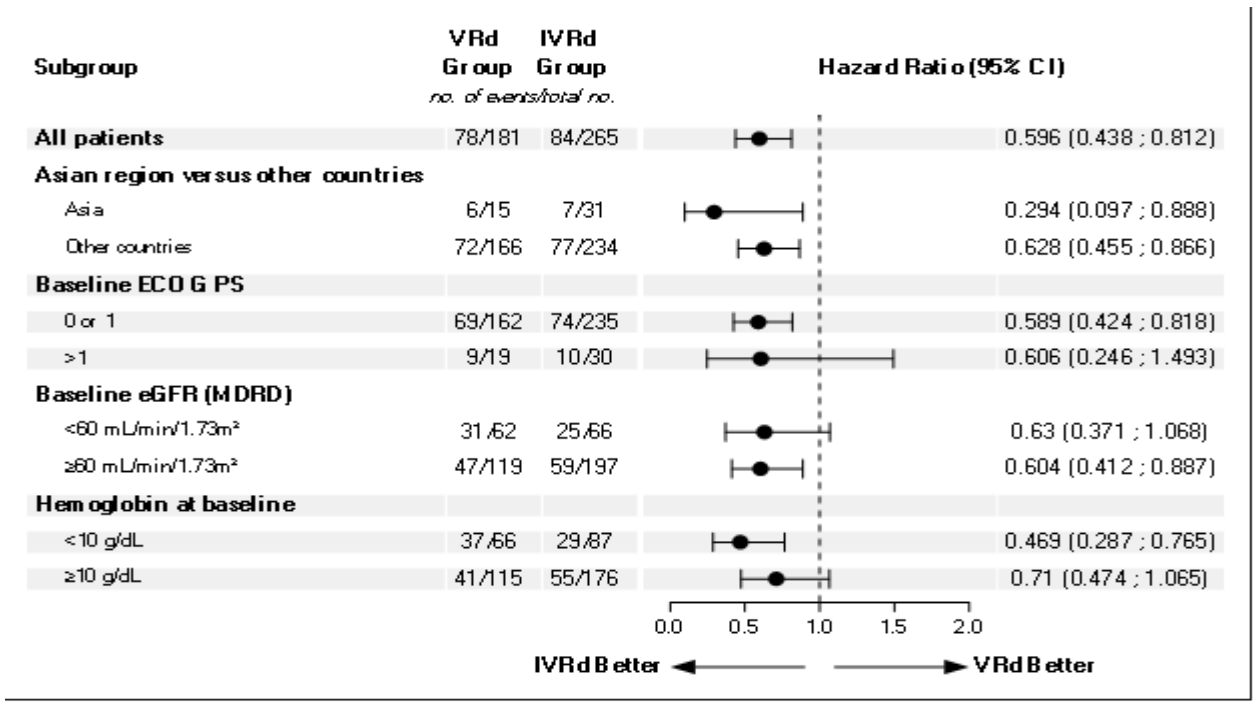
Cut-off date for these analyses was 26 September 2023. In all cases, events occurring more than 13 weeks after the last valid disease assessment are censored.

**Figure 5.** PFS based on disease assessment by the IRC - Subgroup analyses 1 (forest plot) - By demographics/baseline characteristics - ITT population, Study EFC12522



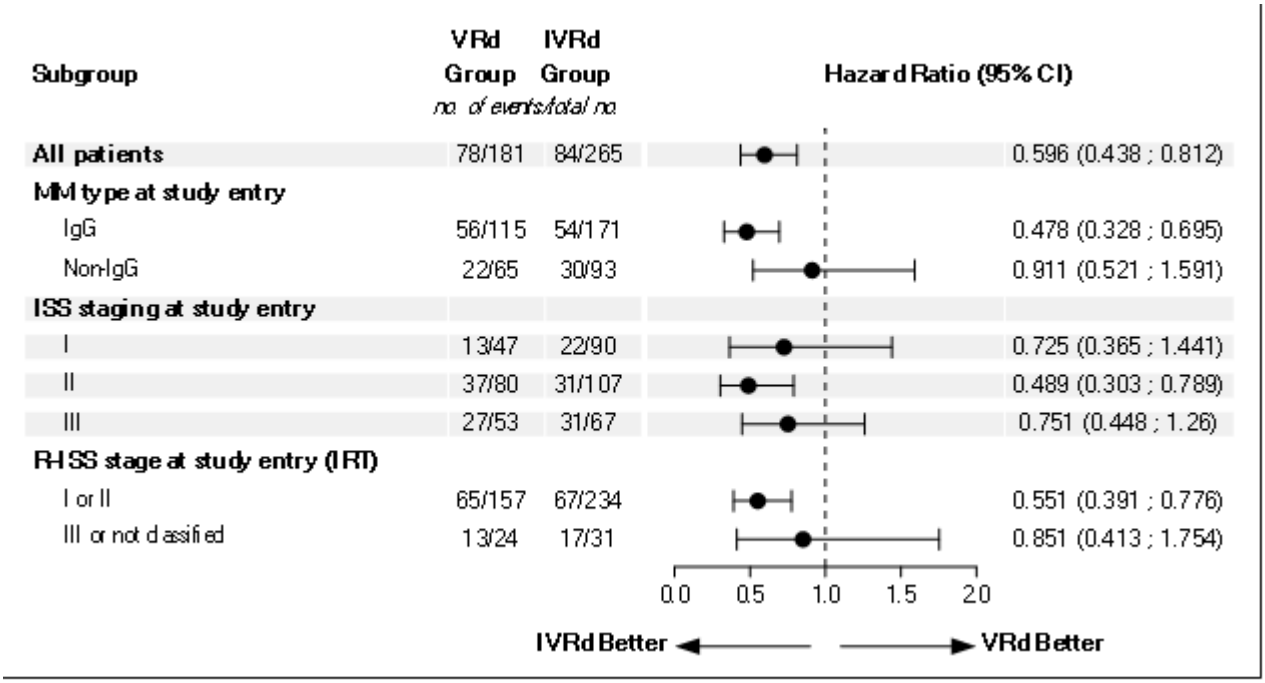

HR: Hazard ratio, CI: Confidence interval, PFS: Progression-free survival, IRC: Independent Response Committee

**Figure 6.** PFS based on disease assessment by the IRC - Subgroup analyses 2 (forest plot) - By demographics/baseline characteristics - ITT population, Study EFC12522




HR: Hazard ratio, CI: Confidence interval, PFS: Progression-free survival, IRC: Independent Response Committee

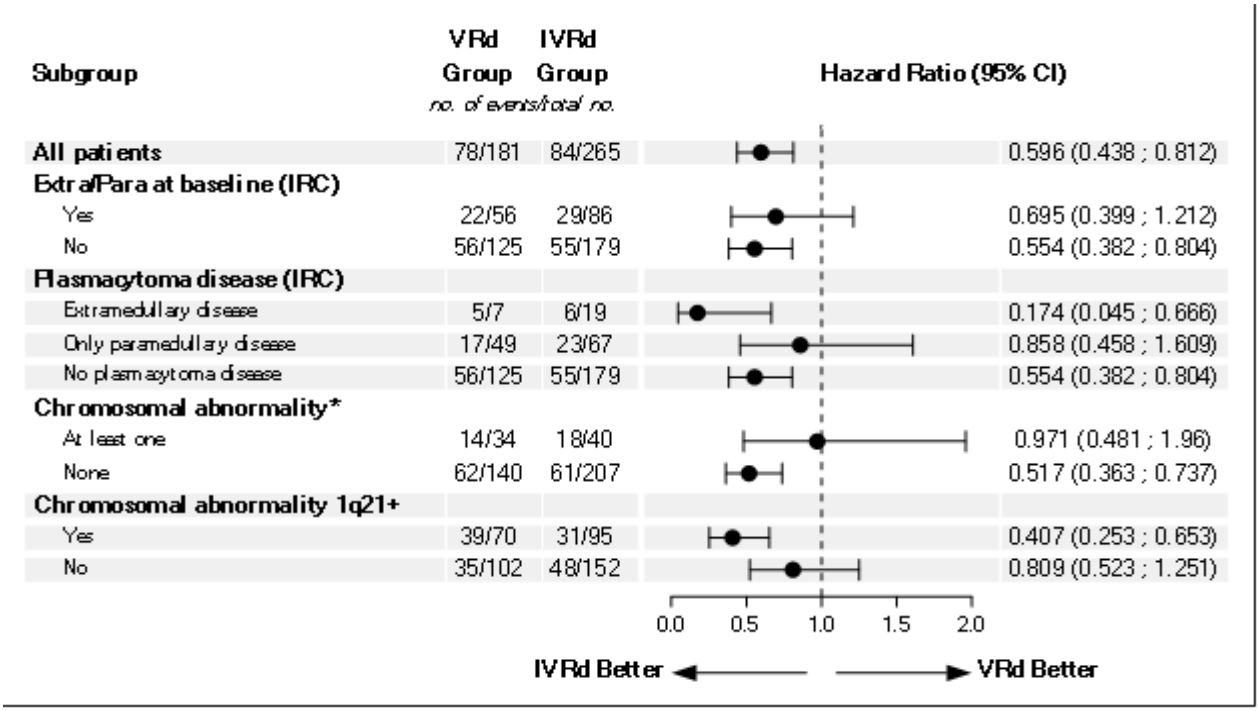
**Figure 7.** PFS based on disease assessment by IRC - Subgroup analyses 3 (forest plot) - By disease characteristics at study entry - ITT population, Study EFC12522




HR: Hazard ratio, CI: Confidence interval, PFS: Progression-free survival, IRC: Independent Response Committee MM: Multiple Myeloma, Ig: Immunoglobulin, ISS: International staging system, R-ISS: Revised International staging system

* Chromosomal abnormality: del(17p), t(4;14), t(14;16) At least one = high risk ; none = standard risk

**Figure 8.** PFS based on disease assessment by IRC - Subgroup analyses 4 (forest plot) - By disease characteristics at study entry - ITT population, Study EFC12522




HR: Hazard ratio, CI: Confidence interval, PFS: Progression-free survival, IRC: Independent Response Committee MM: Multiple Myeloma, Ig: Immunoglobulin, ISS: International staging system, R-ISS: Revised International staging system
* Chromosomal abnormality: del(17p), t(4;14), t(14;16) At least one = high risk; none = standard risk

***Key secondary endpoints***

An overview of CR rate, MRD negativity rate in CR patients and VGPR or better rate is summarised in **Table 13**.

**Table 13.** Summary of overall response rate as per IRC and main secondary endpoints - ITT population, Study EFC12522

| | **VRd (N=181)** | **IVRd (N=265)** |
|---|---|---|
| Best Overall Response [n(%)] | | |
| Stringent complete response | 10 (5.5) | 29 (10.9) |
| Complete response | 106 (58.6) | 169 (63.8) |
| Very good partial response | 34 (18.8) | 38 (14.3) |
| Biochemical CR but with missing bone marrow[a] | 8 (4.4) | 2 (0.8) |
| Near-CR[b] | 7 (3.9) | 23 (8.7) |
| Partial response | 17 (9.4) | 6 (2.3) |
| Minimal response | 0 | 0 |
| Stable disease | 11 (6.1) | 18 (6.8) |
| Non Progressive disease | 0 | 0 |
| Progressive disease | 1 (0.6) | 0 |
| Unconfirmed progressive disease | 0 | 0 |
| Not evaluable/Not assessed | 2 (1.1) | 5 (1.9) |
| Overall Response | | |
| Responders (sCR, CR, VGPR or PR) | 167 (92.3) | 242 (91.3) |

| | VRd (N=181) | IVRd (N=265) |
|---|---|---|
| 95% CI[c] | 0.8736 to 0.9571 | 0.8726 to 0.9442 |
| Stratified[d] Odds ratio (95% CI) vs VRd | | 0.888 (0.439 to 1.794) |
| Stratified Cochran-Mantel-Haenszel test p-value[g] vs VRd | | 0.6295 |
| Complete response (sCR or CR) | 116 (64.1) | 198 (74.7) |
| 95% CI[c] | 0.5664 to 0.7107 | 0.6904 to 0.7984 |
| Stratified[d] Odds ratio (95% CI) vs VRd | | 1.656 (1.097 to 2.500) |
| Stratified Cochran-Mantel-Haenszel test p-value[d] vs VRd | | 0.0080* |
| NGS MRD[-] CR rate[e] | 74 (40.9) | 147 (55.5) |
| 95% CI[c] | 0.3365 to 0.4842 | 0.4927 to 0.6155 |
| Stratified[d] Odds ratio (95% CI) vs VRd | | 1.803 (1.229 to 2.646) |
| Stratified Cochran-Mantel-Haenszel test p-value[d] vs VRd | | 0.0013* |
| VGPR or better | 150 (82.9) | 236 (89.1) |
| 95% CI[c] | 0.7658 to 0.8806 | 0.8466 to 0.9255 |
| Stratified[d] Odds ratio (95% CI) vs VRd | | 1.729 (0.994 to 3.008) |
| Stratified Cochran-Mantel-Haenszel test p-value[d] vs VRd | | 0.0259 |
| NGS MRD negativity rate[e] | 79 (43.6) | 154 (58.1) |
| 95% CI[c] | 0.3630 to 0.5120 | 0.5192 to 0.6412 |
| Stratified[d] Odds ratio (95% CI) vs VRd | | 1.791 (1.221 to 2.627) |
| Stratified Cochran-Mantel-Haenszel test p-value[g] vs VRd | | 0.0014 |
| NGS Sustained MRD negativity ≥ 12 months rate[f] | 44 (24.3) | 124 (46.8) |
| 95% CI[c] | 0.1825 to 0.3123 | 0.4066 to 0.5300 |
| Stratified[d] Odds ratio (95% CI) vs VRd | | 2.729 (1.799 to 4.141) |
| Stratified Cochran-Mantel-Haenszel test p-value[g] vs VRd | | <.0001 |

IRC: Independent Response Committee, IRT: Interactive Response Technology, sCR: stringent Complete Response, CR: Complete Response, VGPR: Very Good Partial Response, PR: Partial Response, MRD: Minimal Residual Disease, NGS: Next Generation Sequencing

*a* Two consecutive negative M-protein and negative immunofixation with missing bone marrow

*b* All criteria for a complete response were met except that immunofixation remained positive

*c* Estimated using Clopper-Pearson method.

*d* Stratified on randomization factors as per IRT. P-value is followed by a '*' if statistically significant according to the fixed hierarchical approach used to control the overall type-I error rate. One-sided significance level is 0.025. Biochemical CR and Near-CR were assessed only for patients with confirmed VGPR as BOR. Criteria for confirmation was not applied to Near-CR subcategory.

*e* For analysis purpose, subjects in the ITT population but without MRD assessment by NGS will be considered as having positive MRD. Sensitivity of 1 in $10^5$ nucleated cells.

*f* Sustained MRD negativity ≥ 12 months rate is the proportion of patients with the maintenance of MRD negativity by NGS confirmed ≥ 12 months apart with no MRD positive test in between. [g] Non inferential.

***Overall survival***

At a median duration of follow-up of 59.73 months, median OS was not reached, and 26.0% of participants in the IVRd group and 32.6% in the VRd group died, which represents an OS information fraction of 63% compared to the planned final analysis with 202 events. An overview is provided in

**Table 14** and **Figure 9**.

**Table 14.** Overall survival by treatment group - ITT population, Study EFC12522

| | VRd (N=181) | IVRd (N=265) |
|---|---|---|
| Number (%) of deaths | 59 (32.6) | 69 (26.0) |
| Number (%) of patients censored | 122 (67.4) | 196 (74.0) |
| Kaplan-Meier estimates of OS in months | | |
| 25% quantile (95% CI) | 49.12 (37.618 to 56.706) | 55.46 (37.717 to NC) |
| Median (95% CI) | NC (NC to NC) | NC (NC to NC) |

| | VRd (N=181) | IVRd (N=265) |
|---|---|---|
| 75% quantile (95% CI) | NC (NC to NC) | NC (NC to NC) |
| Stratified[a] Lonk test p-value[b] | | |
| vs VRd | - | 0.0760 |
| Stratified[a] Hazard ratio (99.9725% CI) | | |
| vs VRd | - | 0.776 (0.407 to 1.48) |
| Survival probability (95% CI)[c] | | |
| 6 Months | 0.956 (0.913 to 0.978) | 0.962 (0.930 to 0.979) |
| 12 Months | 0.933 (0.885 to 0.961) | 0.946 (0.911 to 0.968) |
| 24 Months | 0.881 (0.824 to 0.921) | 0.911 (0.870 to 0.940) |
| 36 Months | 0.835 (0.772 to 0.882) | 0.810 (0.756 to 0.853) |
| 48 Months | 0.753 (0.681 to 0.810) | 0.766 (0.710 to 0.813) |
| 54 Months | 0.722 (0.649 to 0.783) | 0.750 (0.692 to 0.799) |
| 66 Months | 0.613 (0.518 to 0.695) | 0.723 (0.661 to 0.775) |

OS: Overall survival, CI: Confidence interval, NC: Not calculated, HR: Hazard ratio, IRT: Interactive Response Technology

Cut-off date: 26SEP2023 . Median follow-up time = 59.73 months. HR<1 favors IVRd arm

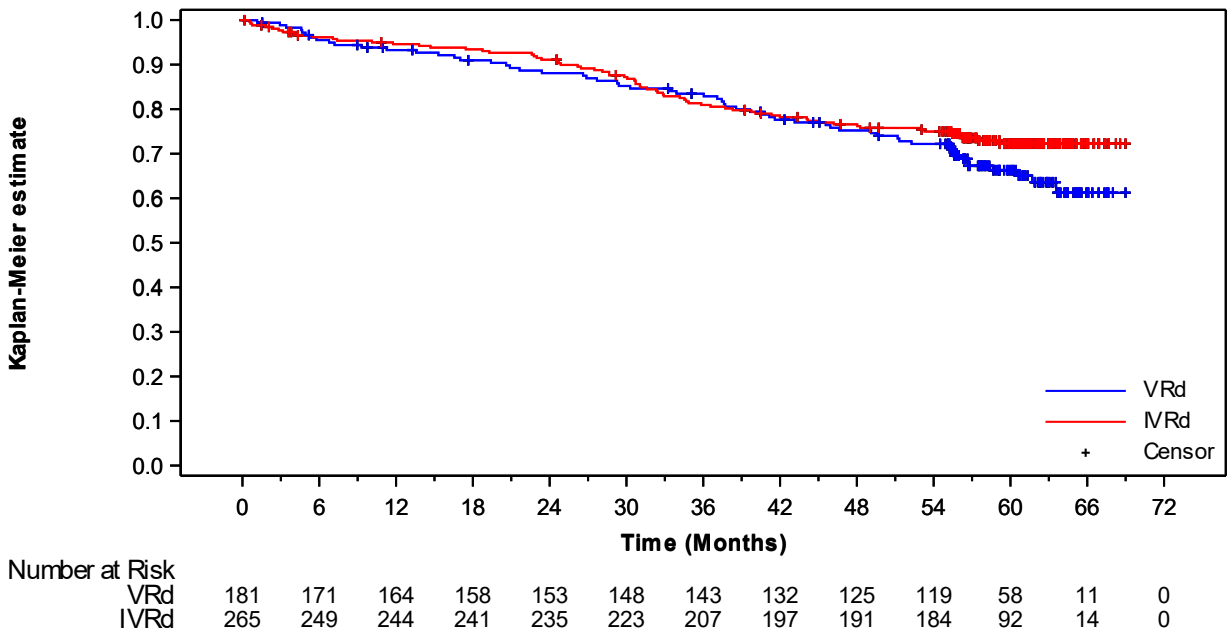
CI for Kaplan-Meier estimates are calculated with log-log transformation of survival function and methods of Brookmeyer and Crowley

*a* 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 IRT

*b* One-sided significance level is 0.0001375 using the user-defined alpha spending function.

*c* Estimated using the Kaplan-Meier method

**Figure 9**. Overall survival - Kaplan-Meier curves by treatment group - ITT population, Study EFC12522




Cut-off date = 26SEP2023

The analysis for OS was performed based on outcomes of patients regardless of the subsequent therapies that they received, which included the option to crossover from the Rd arm to the active treatment arm

following progression. The MAH also performed analyses that sought to account for this cross-over (i.e. targeting the treatment effect under the situation where the option to cross-over would not have been available).

At the cut-off date, 25 (13.8%) participants from the VRd group switched to IRd treatment after confirmation of a first disease progression. Twelve (48%) of the 25 patients that crossed over had died at the time of the cut-off date. Analyses using the rank-preserving structural failure time (RPSFT) model and inverse probability of censoring weighting (IPCW) method were performed. Based on the RPSFT model the estimated HR was 0.839 (95% CI: 0.588 to 1.199) and based on the IPCW method this was estimated to be 0.834 (95% CI: 0.583 to 1.193). These results suggest that the treatment effect would have been weaker if these patients had not crossed over to IRd treatment.

***Other secondary endpoints***

- Time To Progression: the TTP was consistent with the primary PFS analysis, with a HR of 0.414 [95% CI: 0.286 to 0.598], the median TTP was not reached in the IVRd group and was 59.70 months in the VRd group.
- Duration of Response: among the responder (PR or better) participants, 242 and 167, in the IVRd and VRd groups, respectively, the median duration of response was not reached (95% CI: NC to NC) for the IVRd group and was 58.25 (95% CI: 44.583 to NC) months for the VRd group. A lower percentage of these participants in the IVRd group compared to the VRd group, had disease progression, or died (30.2% versus 41.9%).
- Time to first response: the median time to first response was similar in the IVRd and VRd groups (1.51 months and 1.48 months, respectively).
- Time to best response: the time to best response was approximately one month longer in the IVRd group compared to the VRd group (6.51 months and 5.59 months, respectively).
- Sustained MRD negativity (≥12 months) rate: the sustained MRD negativity rate (at $10^{-5}$ sensitivity level by central laboratory NGS) for at least 12 months was numerically higher in the IVRd group compared to the VRd group with 46.8% and 24.3%, respectively. The odds ratio (OR) of IVRd over VRd was 2.729 [95% CI: 1.799 to 4.141]. In the IVRd group, the sustained MRD negativity rates (10-5) for at least 12 months, at least 24 months and at least 36 months were 46.8%, 35.8%, and 25.7%, respectively.
- PFS2: the incidence of PFS2 events was lower in the IVRd group than in the VRd group (31.7% versus 41.4%). The median PFS2 was not reached in either treatment group; the PFS2 HR was 0.697 (95%CI 0.51 to 0.952).

## Ancillary analyses

Time to next therapy: The addition of isatuximab to VRd delayed the initiation of a subsequent anti-myeloma therapy with HR 0.376 [95% CI: 0.265 to 0.534] consistent with the primary PFS analysis. The median time to next anti-myeloma treatment was not reached for the IVRd group and was 63.57

months in the VRd group, with fewer patients in the IVRd group receiving subsequent therapy (19.6% versus 44.2%).

If patients in the VRd arm progressed during the continuous phase, they could be eligible for cross-over to the IRd arm. For the VRd arm, the timing from PD to subsequent therapy (be it cross-over to the IRd arm or other anti-myeloma therapy) is summarised in **Table 15**.

**Table 15.** Summary of time from PD to first further anti-myeloma treatment in VRd arm by receiving alternative anti-myeloma therapy or crossover to IRd treatment - ITT population

| | **Alternative anti-myeloma therapy (N=32)** | **Crossover IRd (N=25)** |
|---|---|---|
| Time from PD per investigator to first further anti-myeloma treatment (weeks)[a] | | |
| Number | 32 | 25 |
| Mean (SD) | 16.0 (18.7) | 12.0 (9.6) |
| Median | 11.5 | 9.9 |
| Min ; Max | 1 ; 104 | 2 ; 49 |
| Time from PD per investigator to first further anti-myeloma treatment (class)[a] | | |
| Number | 32 | 25 |
| ≤ 2 weeks | 3 (9.4) | 1 (4.0) |
| > 2 weeks and ≤ 1 month | 1 (3.1) | 0 |
| > 1 months and ≤ 2 months | 4 (12.5) | 8 (32.0) |
| > 2 months and ≤ 3 months | 10 (31.3) | 11 (44.0) |
| > 3 months | 14 (43.8) | 5 (20.0) |

[a] In case patient discontinued due to progressive disease but the confirmation of biological progression with two consecutive overall response is missing, the single overall response of PD is used for calculation

Renal function: In the global population, 15.5% of the participants had eGFR <50 mL/min/1.73 m2 at baseline with 37 and 32 participants in the IVRd and VRd groups, respectively. Complete renal response and durable (≥60 days) renal response were similar in both treatment groups with 73% versus 75% and 37.8% versus 46.9% of the participants with baseline eGFR < 50 mL/min/1.73 m² in the IVRd and VRd groups, respectively.

Cytogenetic abnormalities: Improvement in PFS in participants with chromosomal 1q21 abnormalities (95% CI: HR 0.407 [0.253 to 0.653]) was consistent with the analysis done for all participants (95% CI: HR 0.596 [0.438 to 0.812]).

FCGR3A polymorphism: There was consistent improvement in PFS in favour of the IVRd group over the VRd group for FCGR3A genotypes 158F/F (HR 0.631) and 158F/V (HR 0.532) and similar PFS between the IVRd and VRd groups for genotype 158V/V (HR 1.062). The observations derived from EFC12522 were consistent with prior observations in EFC15246 and EFC14335 regarding 1) the lack of association between FCGR3A polymorphism at amino acid 158 and PFS and 2) a positive treatment effect of IVRd group versus VRd group for the 158F/F and 158F/V subgroups, while the effects in the 158V/V

subgroup needs to be interpreted with caution because of the small sample size and imbalanced baseline characteristics.

Patient-reported outcomes: Overall quality of life as measured by EORTC QLQ-C30 Global Health Score was maintained over time and similar in both treatment groups. Similarly, functioning, disease and treatment-related-symptoms, health status and health utility as measured by QLQ-C30, QLQ-MY20, and QLQ-EQ-5D-5L were maintained/did not significantly differ over time.

## *Summary of main study*

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

**Table 16.** Summary of Efficacy for trial EFC12522

| **Title: IMROZ** | | | |
|---|---|---|---|
| Study identifier | EFC12522 | | |
| Design | Prospective Phase 3 randomized, open-label, multicenter study evaluating the efficacy of Isatuximab combined with the approved triplet regimen bortezomib, lenalidomide + dexamethasone compared to the triplet regimen alone in patients with NDMM who are not eligible for transplant | | |
| | Duration of main phase: | | 27 December 2017 (first patient enrolled) to 26 September 2023 (interim analysis, study ongoing) |
| | Duration of Run-in phase: | | not applicable |
| | Duration of Extension phase: | | not applicable |
| Hypothesis | Superiority | | |
| Treatments groups | IVRd | | Isatuximab (10 mg/kg), bortezomib (1.3 mg/m$^2$), lenalidomide (25 mg), dexamethasone (20 mg) until disease progression, unacceptable toxicity, or participant's choice to discontinue (n = 265) |
| | VRd | | Bortezomib (1.3 mg/m$^2$), lenalidomide (25 mg), dexamethasone (20 mg) until disease progression, unacceptable toxicity, or participant's choice to discontinue (n = 181) |
| Endpoints and definitions | Primary endpoint | PFS | Time from the date of randomization to the date of first documentation of PD (as determined by IRC or the date of death from any cause, whichever occurred first |
| | Secondary endpoint | CR/sCR | Proportion of participants with stringent CR and CR as BOR, as assessed by the IRC |
| | Secondary endpoint | MRD$^-$ CR rate | Proportion of participants with CR and for whom MRD is negative (< $10^{-5}$) by NGS at any time point after first dose of study intervention |
| | Secondary endpoint | VGPR or better | Proportion of participants with sCR, CR, and VGPR as BOR, as assessed by the IRC |
| | Secondary endpoint | OS | Time from date of randomization to death from any cause |
| Database lock | 03 November 2023 | | |
| **Results and Analysis** | | | |
| **Analysis description** | **Primary Analysis** | | |
| Analysis population and time point description | Intent to treat | | |

| | | | |
|---|---|---|---|
| Descriptive statistics and estimate variability | Treatment group | VRd | IVRd |
| | Number of subject | 181 | 265 |
| | Median PFS (months) | 54.34 | NC |
| | 95% CI | 45.20 - NC | NC - NC |
| | CR/sCR rate (%) | 116 (64.1) | 198 (74.7) |
| | 95% CI | 0.57 - 0.71 | 0.69 - 0.80 |
| | MRD$^-$ CR rate (%) | 74 (40.9) | 147 (55.5) |
| | 95% CI | 0.34 - 0.48 | 0.49 - 0.62 |
| | VGPR or better (%) | 150 (82.9) | 236 (89.1) |
| | 95% CI | 0.77 - 0.88 | 0.85 - 0.93 |
| | median OS (months) | NC | NC |
| | 95% CI | NC - NC | NC - NC |
| Effect estimate per comparison | Primary endpoint Median PFS | Comparison groups | IVRd vs VRd |
| | | HR | 0.596 |
| | | 98.5154% CI | 0.41 - 0.88 |
| | | P-value | 0.0005 |
| | Secondary endpoint CR/sCR | Comparison groups | IVRd vs VRd |
| | | OR | 1.656 |
| | | 95% CI | 1.10 - 2.50 |
| | | P-value | 0.0080 |
| | Secondary endpoint MRD$^-$ CR rate | Comparison groups | IVRd vs VRd |
| | | OR | 1.803 |
| | | 95% CI | 1.23 - 2.65 |
| | | P-value | 0.0013 |
| | Secondary endpoint VGPR or better | Comparison groups | IVRd vs VRd |
| | | OR | 1.729 |
| | | 95% CI | 0.99 - 3.01 |
| | | P-value | 0.0259 |
| | Secondary endpoint 25% quantile OS | Comparison groups | IVRd vs VRd |
| | | HR | 0.776 |
| | | 99.9725% CI | 0.41 - 1.48 |
| | | P-value | 0.0760 |

## *Clinical studies in special populations*

**Table 17.** Subgroups per age-ITT population, Study EFC12522

| | **Age 65-74 (Older subjects number /total number)** | **Age 75-84 (Older subjects number /total number)** | **Age 85+ (Older subjects number /total number)** |
|---|---|---|---|
| Controlled Trials EFC12522 | 303/446 | 126/446* | 0/446 |

* patients older than 80 years of age were excluded from study entry.

## *Supportive study*

TCD13983 is an ongoing Phase 1b/2 open-label study of isatuximab-based regimens in patients with NDMM, in 3 study parts (reported as separate studies):

- TCD13983 VCDI: Isatuximab in combination with cyclophosphamide, bortezomib, and dexamethasone in NDMM patients not eligible for ASCT

- TCD13983 VRDI Part A: IVRd (called VRDI in the protocol) in NDMM patients not eligible for ASCT;
- TCD13983 VRDI Part B: IVRd in NDMM patients not eligible for ASCT, or with no intent for ASCT as initial therapy;

*Dose escalation in the TCD13983 VCDI study*

This study part consisted of two separate parts; part 1 was a dose escalation part and part 2 was an expansion part (not reported here). In part 1 dose escalation of isatuximab (5-10-20mg/kg) was performed according to a 3+3 design and the recommended isatuximab dose for combination studies was determined.

Dose limiting toxicity (DLTs) had to occur during Cycle 1 (DLT observation period). Hematologic DLTs were defined as: Grade 4 neutropenia interfering (dose omission, dose delay, and dose reduction) with the administration of:- >2 doses of bortezomib or >1 dose of cyclophosphamide; Grade 3 or 4 febrile neutropenia or Grade 3 or 4 neutropenic infection; Grade 3 thrombocytopenia associated with bleeding requiring transfusion (Grade 3 or 4) and/or interfering with the administration of:- >2 doses of bortezomib or >1 dose of cyclophosphamide; Grade 4 thrombocytopenia lasting more than 7 days despite omission of bortezomib or interfering with the administration of: - >2 doses of bortezomib or >1 dose of cyclophosphamide; Non-hematologic DLT were defined as: Any Grade ≥3 non-hematologic IMP related AE excluding: Grade 3 fatigue, Grade ≥3 laboratory abnormalities improving at least to Grade 2 in less than 1 week, Grade 3 nausea/vomiting/diarrhoea responsive to optimal medical management within 48 hours, infusion associated reactions attributed to isatuximab, delay in initiation of Cycle 2 >14 days due to IMP related laboratory abnormalities or TEAEs and any other AE that the Investigator and the Sponsor deemed to be dose limiting, regardless of its severity, may have also been considered as a DLT.

A total of 13 patients were enrolled at 10 mg/kg DL and 4 patients at 20 mg/kg DL; of these, there were 3 patients in each DL in the dose escalation phase who were evaluable for DLTs. No patient in the DLT-evaluable population experienced a DLT. With no DLT reported at isatuximab 10 mg/kg and 20 mg/kg DLs, the MAD and the MTD were not reached. The MAH states that the RD of 10 mg/kg was chosen based on PK/PD modelling and simulations made for TCD11863 study. The PK/PD analyses performed with TCD11863 study data including trial simulations and simulations of serum monoclonal protein showed higher predicted ORR and reduction of monoclonal protein at 8 and 12 weeks at doses ≥10 mg/kg. However, the benefit in terms of increase in ORR or reduction in serum monoclonal protein appeared limited, when increasing the isatuximab dose from 10 to 20 mg/kg QWx4, Q2W. Therefore, based on PK simulations and PK/PD analyses, the dose selected for further isatuximab combination studies was determined as 10 mg/kg QWx4, followed by 10 mg/kg Q2W.

*Part A and B*

The primary objective for supportive Study TCD13983 was to evaluate the preliminary efficacy (CR rate) of IVRd according IMWG criteria in adult patients with NDMM not eligible for transplant (Parts A and B) or with no intent for immediate transplant (Part B). Enrolment in the IVRd Part B cohort initiated once the accrual in the IVRd Part A cohort was completed. The primary endpoint was CR rate (CR or sCR) using the IMWG response criteria based on local laboratory values. Amongst others, MRD negativity (at least $10^{-5}$), ORR, DOR and PFS were secondary endpoints.

In Parts A and B of the study, the VRDI regimen was similar to that of study EFC12522.

Efficacy data for study participants up to a cut-off date of 05 April 2021 for Part A and 28 January 2022 for Part B is reported. In total, 73 participants were enrolled and treated in both IVRd study parts (Part A, N=27 and Part B, N=46). All patients in Part A and B received the 10 mg/kg QW/Q2W dose.

In Part A, from May 2017 to April 2018, 26 (96.3%) participants were included in the efficacy analyses. At the time of primary analysis cut-off date, of the 27 participants treated, 13 (48.1%) discontinued treatment most commonly due to an AE (7 participants) including 1 AE leading to death that was considered related to lenalidomide and dexamethasone during the on-treatment period.

In Part B, from March 2019 to January 2020, a total of 46 participants with NDMM received at least 1 dose of study treatment: isatuximab 10 mg/kg IV in combination with VRd and 45 (97.8%) were included in the efficacy analyses. At the time of primary analysis cut-off date, of the 18 (39.1%) participants who discontinued treatment, the most common reasons for stopping were AEs (8 participants), progressive disease (4 participants), and 2 withdrawal consents.

In Part A participants had a median age of 71.0 years (range 63 to 77 years) with 7 (25.9%) participants ≥75 years of age and two-thirds were female (66.7%). The majority had an ECOG score of 0 or 1 (92.6%) at baseline. At baseline ISS Stage I was seen in 8 (29.6%) patients, Stage II in 17 (63.0%) and Stage III in 2 patients (7.4%). Three patients (11.1%) presented with high risk cytogenetic at baseline as per IMWG criteria (1 with del 17p and 2 with t(4,14)). In addition, 9 patients (33.3%) presented with gain 1q21, including one pt with associated presence of t(4,14).

In Part B, participants had a median age of 70.0 years (range: 49 to 87 years), with 8 (17.4%) participants ≥75 years of age (4 participants were ≥80 years of age. All participants had an ECOG PS score of 0 or 1 with the exception of 1 (2.2%) participant. In total 52.2% were females. In total 22 (47.8%) presented with ISS Stage I at baseline, 20 (43.3%) with Stage II and 4 (8.7%) with ISS stage III. Two patients (4.3%) had soft tissue plasmacytoma at baseline and 8 patients (17.4%) high risk cytogenetic as per IMWG: 4 with del 17p and 4 with t(4,14). More patients were positive for gain 1q21: 16 (34.8%), including 3 patients with associated t(4,14) and 2 patients with associated del 17p.

Thirteen patients eligible for transplant with no immediate intent for transplant have been enrolled in Part B of study. Their median of age was 57 (range 49-71), including 9 patients at 65 or less years old and 1 patient at >65years old. Patients presented with clinical or biological risk factors: age below 65 years old (9 patients), ISS stage I (9 patients; 69.2%), II (3 patients (23.1%) and III (1 patient, 7.7%), plasmacytoma positive at baseline (4 patients), high risk cytogenetic criteria including 1q21 abnormality (5 participants). The median exposure 114.93 weeks (range 3.9:144.3).

*Outcomes and estimations part A and B*

In Part A sCR/CR rate was 38.5% (CR: N=7 (26.9%), sCR: N=3 (11.5%)). The ORR was 100% with VGPR achieved in 14 (31.1%) participants and PR in 1 (3.8%) participant. Of the 22 (84.6%) participants with at least one MRD sample, 12 (46.2%) participants were MRD negative at a sensitivity level of $10^{-5}$. A total of 7 (26.9%) patients had sCR/CR and MRD negativity at a sensitivity level of $10^{-5}$ by combining NGF and NGS method. This represents 70.0% of patients with sCR/CR. The median follow up duration was 35.83 months and the median DOR was 34.43 months (range: 2.1-44.7 months). PFS events had occurred in 6 patients (23.1%) with a median follow up of 37.90 months (range: 4.6-47.0 months) The number of patients censored was 20 (76.9%) and the median estimated PFS was not calculable.

In Part B the CR/sCR rate is 53.3% (24 of 45 participants). In total, 17 (37.8%) patients achieved a CR, 7 (15.6%) a sCR. The ORR was 97.8% (N=44) with 17 (37.8%) patients a VGPR and 3 (6.7%) a PR. A total of 24 participants with at least one MRD sample (N = 35) achieved MRD negativity status (combining NGF and NGS), at a sensitivity level $10^{-5}$. In patients with a BOR of CR or sCR using the adjusted response, 20 of 45 (44.4% of evaluable population) had MRD negativity at $10^{-5}$ by combining both

methods representing 74.1% of patients with adjusted sCR/CR (20 of 27). The median follow-up duration was 25.26 months and the median duration of response was NC (NC to NC). PFS events occurred in 10 patients (22.2%) and the median number of months of PFS was not calculable (not reached).

Efficacy of 13 participants for transplant eligible with no intent for transplant as initial therapy was presented separately. The ORR for these participants during study treatment (prior to any ASCT) was 100%, with an adjusted sCR/CR rate of 46.2% and VGPR rate of 38.5%. Three participants (23.1%) had MRD negativity at $10^{-5}$ by NGS and a BOR of CR or better. Two (15.4%) participants had a PFS event: one disease progression after 10 cycles and one death (unrelated to the disease or the treatment) that occurred approximately 14 months after transplant procedure, while patient being still relapse free. Since last cut-off date, no new PFS event was reported for this cohort.
In total, 7 (53.8%) participants proceeded to stem cell mobilization. Four (30.8%) participants proceeded with ASCT after study treatment discontinuation in Part B of study. Before being transplanted, 2 participants had a BOR of PR and 2 participants had an adjusted BOR of VGPR or CR, respectively.

Additional complete response data adjusted with Hydrashift assay to correct for immunofixation interference, and data for the 13 patients with no intent for ASCT as initial therapy are summarised in **Table 18**.

**Table 18**. Comparison of efficacy parameters in EFC12522 and TCD13983

| | EFC12522<br>IVRd<br><br>(n = 265) | TCD13983<br>Part A+B<br><br>(n = 71) | TCD13983<br>no intent for transplant<br>new<br>(n = 13) |
|---|---|---|---|
| CR and better rate | 198 (74.7%) | 45 (63.4%) Adjusted | 7 (53.8%) Adjusted |
| MRD neg ($10^{-5}$) rate* | 154 (58.1%) | 40 (56.3%) | 4 (30.8%) |

MRD negative (1 in $10^{-5}$) by NGS method

## 2.4.2. Discussion on clinical efficacy

## Design and conduct of clinical studies

The pivotal study is EFC12522, a Phase 3 randomised, open-label, study comparing isatuximab in combination with bortezomib, lenalidomide and dexamethasone (IVRd) to VRd in patients with newly diagnosed MM who are transplant ineligible due to age or significant comorbidities. In general, the study design of pivotal study EFC12522 is considered acceptable; the add-on design allows the evaluation of the addition of isatuximab on top of the established VRd regimen. One pivotal study could be acceptable when data from this study are statistically compelling and clinically relevant and results are replicated (CPMP/EWP/2330/99).

The dosing regimen selected for study EFC12522 was based on previous experience from combination and monotherapy regimens across the isatuximab developmental program. The dose of 10 mg/kg Q1W for 5 weeks in the 6 week induction cycle, followed by once every 2 weeks in cycles 2-4 has been previously used in combination with pomalidomide and dexamethasone or carfilzomib and dexamethasone. During the continuous dosing phase, from cycle 18 and beyond the dose of isatuximab is adjusted to 10 mg/kg Q4W.

In the pivotal study, patients from the VRd group were allowed to cross over during the continuous treatment phase, in which bortezomib (V) was no longer administered, from the Rd arm to the IRd arm after confirmation of disease progression (by an Independent Sponsor team) and recovery from any potential toxicity that occurred under treatment with VRd. The inclusion of this option was mandated on the basis of ethical considerations however it does complicate the interpretation of the OS and PFS2 data. A total of 25 patients (13.8%) crossed over to the IRd arm.

The population that was selected for study EFC15255 were not considered eligible for high-dose chemotherapy due to: age ≥ 65 years or co-morbidities. Frail patients were not allowed to be included in the study, given the requirement for ECOG PS $\leq 2$ and the upper age limit for study entry at 80 years old. While acceptable, it is unclear whether frail patients can withstand the physical demands of this quadruplet treatment regimen and therefore, the patient characteristics of the study participants are clearly described in the SmPC, including a summary of comorbidities that were excluded in this trial to inform the treating physician.

The choice for PFS as the main outcome variable is agreed because of the long OS time that is expected in first-line MM patients. For PFS, the treatment effect of interest for this assessment is the one that includes the PFS events regardless of whether patients received new anti-myeloma therapy before progression (i.e. where patients are not censored for this reason). The sample size for PFS was calculated based on a clinically relevant effect. The targeted HR was 0.64, which corresponds to an improvement in the true median PFS time from 40 months to 62.5 months

Randomisation, stratification factors are considered acceptable.

Overall, the statistical methods as described in the SAP are acceptable. In order to account for cross-over from the comparator to treatment arm in patients who progressed on VRd, the RPSFT and IPCW methods were used. Details of these were not pre-specified in the SAP and alternative methods are available (e.g. the two-stage approach). The MAH also performed the two-stage approach as requested.

Amendments were made to study EFC12522. Censoring rules for the PFS analysis were changed in June 2020. In November 2021, the definition of PFS2, VGPR or better rate, CR rate, ORR, and DoR was changed, and additional interim analyses for OS were added to coincide with PFS interim analyses. In September 2023, a third interim analysis for PFS with concomitant OS analysis was added to be conducted at 85% information fraction. Due to the open label design, the amendments in an ongoing study are considered unfortunate, however it appears that the study outcomes remained largely the same, the definition of the primary endpoint was not changed and changes to the secondary endpoints are minor and do not hinder interpretation of the data. The MAH has provided the number of participants per treatment arm that were already included in the study before each amendment was made: 168 patients were randomized to the IVRd arm and 119 patients to the VRd arm in the initial protocol; All patients had been included (265 IVRd and 181 VRd) at the timing of protocol amendment 2. It appears that changes were based on external information rather than information from the trial. It was noted that protocol amendment 3 allowed clinical progression to be judged as a PD event, however this option was not pursued in practice.

Given the addition of further interim analyses for PFS was done while the study was well underway, it is difficult to rule-out that this amendment was not based on data in this open-label trial. It is important to understand whether the final analysis, based on 222 events would have resulted in the same conclusion. While this cannot be answered based on actual observed events, results based on a simulation exercise for various (conservative) assumptions suggest that a conclusion on a treatment effect in favour of IVRd would have been consistent with the current conclusions had the study proceeded to the final analysis for PFS.

Supportive data comes from study TCD13983. In total, 73 participants were enrolled and treated in both IVRd study parts (Part A, N=27 and Part B, N=46). Of note, thirteen of the 46 participants in Part B were patients with no immediate intent for ASCT and were therefore not comparable to the study population in EFC12522. Thus, supportive study data come from a total of 60 subjects, divided over 2 parts. The study design of both studies was similar apart from the infusion method which was weight-based in study EFC12522 but fixed volume in study TCD13983 and the dosing after the induction phase which was every 2 weeks in cycles 5 to 17 followed by once every 4 weeks in study EFC12522 but once every 4 weeks in study TCD13983.

Both studies included patients with active MM according to the IMWG criteria but study TCD1398 also included a small percentage (8/71; 11.0% total) of ultra-high risk smoldering MM. Overall, the differences are small and study TCD13983 can be considered as supportive of the claimed indication.

## Efficacy data and additional analyses

### EFC12522

A total of 512 participants were tested for eligibility. Of these participants, 181 were randomized and treated with VRd, and 263 patients were randomized and treated with IVRd. As of the cut-off date of September 26th 2023 the discontinuation rate was much higher (75.7%) in the VRd arm than in the IVRd arm (52.1%), leaving 44 patients (24.3%) on treatment in the VRd arm and 125 patients (47.2%) in the IVRd arm. This may be indicative of a positive treatment effect of isatuximab. Of note, 4 of the 44 patients in the VRd arm crossed over to receive isatuximab + Rd in the continuous treatment phase. 42 of the 67 patients with PD in the Rd arm eventually did not cross over to the IRd arm. Crossover was not mandated by the study, but was undertaken at the investigator's discretion. Five of these 42 participants progressed during the induction period, in which case the protocol does not allow the switch to the crossover arm. For 32 of the remaining 37 patients, the subsequent anti-myeloma treatment was recorded. More than half of these 32 patients received an anti-CD38 antibody (daratumumab n = 13; isatuximab n = 4).

At the 2nd interim analysis with a 75% information fraction, the primary endpoint of PFS was met. The study demonstrated a significant improvement in PFS for patients treated with isatuximab in combination with VRd vs. VRd alone: HR = 0.596 (98.5% CI: 0.406 to 0.876) with a median follow-up time of 59.73 months. The one-sided p-value of 0.0005 met the prespecified p-value boundary of 0.008620. Median PFS was 54.34 months in the VRd arm and was not reached in the IVRd arm. In the Kaplan-Meier curve, the IVRd arm separates from the VRd arm at about 5 months after initiation of treatment. The IVRd arm then remains above the VRd arm (indicating a lower risk of disease progression) throughout the rest of the study, with the lines separating more towards the end of the study, i.e. a steeper drop for the VRd arm than for the IVRd arm. Thus, indicating that patients in the IVRd arm remain progression free for longer than in the VRd arm. The prolonged progression free survival is considered to be clinically relevant to the patient. The MAH provided an overview of reasons for censoring, which revealed that just under 20% of patients in both arms were lost to follow up, defined as not having had an assessment in at least 13 weeks.

Several sensitivity analyses were conducted for PFS with slightly different definitions. Some of these analyses target different treatment effects, including one for which patients are not censored for using new anti-cancer medication. Only three additional events were recorded in this analysis which is lower than expected. The MAH was requested to provide details on how many patients who received new anti-cancer therapy continued assessments for progression. It was stated by the MAH that the number of patients who continued to be assessed by the IRC is small because most of these patients were assessed by the investigator as having progressed prior to the initiation of further anti-myeloma treatment and

therefore did not continue the central laboratory sampling used for IRC assessment. Given there is no ability to follow up these patients for an IRC-progression, the estimate of the treatment effect regardless of the use of new anti-myeloma treatment will remain an uncertainty.

All PFS subgroup analyses point towards a positive treatment effect for IVRd compared to VRd. For high-risk cytogenetics status, the positive impact of isatuximab treatment was less noticeable. HR = 0.971 (95% CI: 0.481 to 1.96) in IVRd vs VRd treated patients was found. This may be due to the relatively low number of patients in the high-risk stratum.

PFS is supported by secondary endpoints CR rate (CR+sCR) and MRD negativity rate at $10^{-5}$ in patients with CR. The CR rate was 74.7% (95% CI: 0.69 to 0.80) in the IVRd arm and 64.1% (95% CI: 0.57 to 0.71) in the VRd arm, indicating that the addition of isatuximab to VRd leads to a higher chance of achieving a CR (1-sided p = 0.008; 2-sided p = 0.0160). The MRD[-] CR rate also differed between the groups, with a 55.5% (95%CI: 0.49 to 0.62) MRD[-] CR rate seen in IVRd treated patients vs. a 40.9% (95% CI: 0.34 to 0.48) MRD[-] CR rate in the VRd (1-sided p = 0.0013; 2-sided p = 0.0026). Overall, these outcomes are considered to be compelling.

The VGPR or better rate was similarly high in both treatment groups 89.1% (95% CI: 0.85 to 0.93) in the IVRD arm vs 82.9% (95% CI: 0.77 to 0.88) with no statistically significant difference was shown. The ORR was 91.3% in the IVRd arm and 92.3% in the VRd arm.

As no statistically significant difference in VGPR or better rate was observed between the treatment arms, OS analysis, which was next in the hierarchical testing procedure, is not considered inferential. OS data were not mature at the interim analysis, since 26.0% and 32.6% of the events were met in the IVRd and VRd arm (OS information fraction of 63%). The difference between the two arms was HR = 0.776 [99.97% CI: 0.407 to 1.48], nominal p = 0.0760. The median OS was not reached in both study arms. The OS Kaplan Meyer curves are largely overlapping for the two treatment arms. In the first 6 months, the VRd curve lies slightly above the IVRd arm after which the curves overlap. This is likely due to the higher number of on-treatment deaths in the IVRd arm versus the VRd arm (See Clinical Safety discussion). Towards the end of the curve, the IVRd curve is slightly higher than the VRd curve.

Cross-over from the Rd arm to the IRd arm may have influenced the OS data. The MAH performed OS analyses in which cross-over was corrected for. Conversely, these analyses showed a slightly less favourable OS effect for IVRd (RPSFT: HR = 0.839 [95% CI: 0.588 to 1.199]; IPCW: HR = 0.834 [95% CI: 0.583 to 1.193]). The MAH has provided an explanation for why the treatment effect accounting for crossover was estimated to be weaker than for the primary OS analysis and performed the additional 2-stage analysis with and without re-censoring. Based on this additional information and analyses, as well as the low number of deaths in the crossover TEAE period due to AEs (2 deaths), it can be concluded that there is no strong signal that crossing over to the VRd arm was detrimental

Overall, more mature data is needed for a conclusion on OS. The CHMP recommended that the MAH provides the updated OS data at the next interim and final analysis, estimated in Q3 2025 and Q4 2027 respectively.

PFS2 can facilitate interpretation of the relevance of meaningful PFS improvements in the absence of (mature) OS data. The incidence of PFS2 events was lower in the IVRd group than in the VRd group (31.7% versus 41.4%), which is confirmative of the primary endpoint. Median PFS2 was not reached in either treatment group; HR = 0.697 (95%CI 0.51 to 0.952).

Addition of isatuximab to VRd delayed the initiation of a subsequent anti-myeloma therapy (TTNT) with HR 0.376 (95% CI: 0.265 to 0.534), consistent with the primary PFS analysis. The median time to next anti-myeloma treatment was not reached for the IVRd group and was 63.57 months in the VRd group, with fewer patients in the IVRd group receiving subsequent therapy (19.6% versus 44.2%). Even though

cross-over from the Rd arm to the IRd arm may have caused TTNT to be shorter in the VRd group, the observed effect is sufficiently large to assume it cannot be fully explained by the crossover patients.

**TCD13983**

In an initial analysis of study TCD13983, efficacy of IVRd seemed to be lower than in the pivotal trial (EFC12522). The MAH provided an updated CSR addendum for which the duration of follow-up for study TCD13983 was more in line with the follow-up time of study EFC1252. The pooled data of study TCD13983 (Part A + Part B) at the latest follow-up show a sCR/CR rate of 63.4% (74.7% in EFC12522). 47.9% of participants with a CR were MRD negative (55.5% in EFC12522). With this longer follow-up, the results of study TCD13583 have aligned more with the results seen in EFC12522. Therefore, data from TCD13583 can be considered supportive for the pivotal trial.

**Indication**

Based on the results from EFC12522 and TCD13983, the initially applied indication was for the treatment of adult patients with newly diagnosed active multiple myeloma who are not eligible for autologous stem cell transplant (ASCT) (EFC12522) or with no intent for ASCT as initial therapy (TCD13983). However, the CHMP considered that submitted results did not support the use of the product in patients with no intent for ASCT as initial therapy. This subgroup of patients was not included in the pivotal study but only in supportive Study TCD13983 part B. The sample size of patients with no intent for transplant was considered too limited to support an indication (n = 13) and supportive Study TCD13983 was an uncontrolled (and therefore non-randomized) study, while a randomized study would be expected. Therefore, extrapolation from the transplant ineligible population to the population with no intent for transplant as initial therapy would be needed to support an indication. However, even with a longer follow-up and a more accurate technique to measure the response rate, sCR/CR rate and $MRD^-$ CR rate in the 'no intent for ASCT' population remained lower than the responses seen in the transplant ineligible patients in EFC12522. Thus, this population responds differently to the IVRd regime, and therefore, extrapolation is not justified. Lastly, a population "with no intent for ASCT" i.e., who are eligible for ASCT but with no intent for ASCT, cannot be clearly defined.

Finally, the MAH was requested to delete the word active from the indication as this was considered redundant since smoldering MM does not require treatment and to replace not eligible with ineligible. The proposed modifications to the indication were accepted by the MAH.

## 2.4.3. Conclusions on the clinical efficacy

Data from the pivotal study EFC12522 indicate a statistically significant and clinically relevant PFS benefit of IVRd over VRd in patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant. Supportive evidence of efficacy in support of IVRd in the claimed indication comes from study TCD13983.

The efficacy is considered to be robust and consistent over almost all subgroups and supported by secondary endpoints CR rate (CR+sCR) and MRD negativity rate, thus results from the pivotal study are considered compelling. PFS2 and TTNT are supportive of the primary PFS analysis. Therefore, the clinical benefit of isatuximab as add-on to the SOC VRd triplet has been shown. The MAH has committed to providing updated OS data at the next interim and final analysis.

## 2.5. Clinical safety

### Introduction

Isatuximab is indicated in RRMM patients either in combination with pomalidomide and dexamethasone or in combination with carfilzomib and dexamethasone.

The most frequent (>20%) adverse reactions reported in patients with multiple myeloma treated with isatuximab in combination with pomalidomide and dexamethasone (IPd) are neutropenia (46.7%), infusion reactions (38.2%), pneumonia (30.9%), upper respiratory tract infection (28.3%), diarrhoea (25.7%) and bronchitis (23.7%). The most frequent serious adverse reactions are pneumonia (25.7%) and febrile neutropenia (6.6%). Adverse reactions with a fatal outcome during treatment were reported in 7.9% of patients treated with IPd, mostly due to pneumonia (1.3%) and other infections (2.0%).

The most frequent (≥20%) adverse reactions reported in patients with multiple myeloma treated with isatuximab in combination with carfilzomib and dexamethasone (IKd) are infusion reactions (45.8%), hypertension (36.7%), diarrhoea (36.2%), upper respiratory tract infection (36.2%), pneumonia (28.8%), fatigue (28.2%), dyspnoea (27.7%), insomnia (23.7%), bronchitis (22.6%), and back pain (22.0%). The most frequent serious adverse reaction is pneumonia (21.5%). Adverse reactions with a fatal outcome during treatment were reported in 3.4% of patients treated with IKd, mostly due to pneumonia and cardiac failure (both 1.1%).

The following safety concerns have been identified for isatuximab at the initial MAA; important identified risks are interference for blood typing, Infusion Related Reactions of Grade ≥ 3 and Anaphylactic Reactions. Important potential risks are viral reactivation, Second Primary Malignancies and Tumour Lysis Syndrome. Missing information is reproductive and developmental toxicity and off label use in paediatric population.

The safety is primarily based on the safety results from the EFC12522 (IMROZ; N = 263) with supportive safety data from supportive study TCD13983 (Part A: N=27; Part B: N=46). Additionally, safety data from other clinical studies in patients with RRMM and NDMM receiving different isatuximab- based combinations treatments were pooled (i.e., All-Isa group; N=1787).

### Patient exposure

In study EFC12522 a total of 446 participants were randomised into the global part of the study between 27 December 2017 and 15 March 2019. At time of the cut-off date (i.e., 26 September 2023), 275 participants have discontinued study intervention (137 [75.7%] in the VRd group and 138 [52.1%] in the IVRd group. An overview of the exposure to isatuximab in study EFC12522 is summarised in **Table 19**.

**Table 19**. Overall extent of exposure - Safety population, study EFC12522

| | **VRd (N=181)** | **IVRd (N=263)** |
|---|---|---|
| Total number of cycles started | 5718 | 10795 |
| Cumulative exposure to treatment (patient years) | 490.75 | 909.60 |
| Number of cycles started by patient | | |
| Mean (SD) | 31.59 (21.76) | 41.05 (21.98) |
| Median | 29.00 | 52.00 |
| Min ; Max | 1.0 ; 69.0 | 1.0 ; 69.0 |
| Duration of exposure (months) | | |
| Mean (SD) | 32.54 (21.71) | 41.50 (21.39) |
| Median | 31.28 | 53.16 |

| | VRd (N=181) | IVRd (N=263) |
|---|---|---|
| Min ; Max | 0.6 ; 67.2 | 0.5 ; 68.8 |

The median duration of exposure for bortezomib was 5.52 months (range 0.3 to 6.7) in the VRd group and 5.52 months (range 0.2 to 6.5) in the IVRd group. The median duration of exposure for lenalidomide was 31.28 months (range 0.6 to 67.2) in the VRd group and 46.13 months (range 0.5 to 68.8) in the IVRd group. The median duration of exposure to dexamethasone was 20.34 months (range 0.4 to 66.3) in the VRd group and 46.69 months (range 0.2 to 68.8) in the IVRd group.

There were 12.1% cycles delayed in the VRd group and 11.5% cycles delayed in the IVRd group. A total of total of 2 (0.8%) participants had at least 1 isatuximab dose reduction and 168 (63.9%) participants had at least 1 dose isatuximab omission (dose reductions for isatuximab were not allowed in the study protocol). The following dose modifications and omissions for bortezomib, lenalidomide, and dexamethasone were observed;

Bortezomib: a total of 76 (42.0%) and 92 (35.0%) participants in the VRd and IVRd groups, respectively, had at least 1 dose reduction and 127 (70.2%) and 183 (69.6%) participants, respectively, had at least 1 dose omission.
Lenalidomide: a total of 102 (56.4%) and 159 (60.5%) participants in the VRd and IVRd groups, respectively, had at least 1 dose reduction and 133 (73.5%) and 214 (81.4%) participants, respectively, had at least 1 dose omission.
Dexamethasone: a total of 96 (53.0%) and 139 (52.9%) participants in the VRd and IVRd groups, respectively, had at least 1 dose reduction and 146 (80.7%) and 227 (86.3%) participants, respectively, had at least 1 dose omission.

*Supportive study*

In study TCD13983, a total 27 participants (part A) and 46 participants (part B) received at least 1 dose of study treatment. The rates of definitive treatment discontinuation for IVRd were: Part A: 48.1% and Part B: 39.1%. The isatuximab median duration of exposure in study TCD13983 Part A and Part B was 36.6 months and 26.5 months, respectively.

An All-Isa population was also presented from all MM studies, including crossover patients receiving IRd and patients from China expansion part in EFC12522. This population includes 1787 patients with a cumulative exposure to isatuximab of 2412.47 patient years. In the All-Isa group, the median duration of exposure was 4.24 months (range 0.5 to 67.2) in the VRd group, 5.03 months (range 0.2 to 68.8) in the IVRd group, and 5.77 months (range 0.2 to 68.8) in the All-Isa group. The median number of cycles started  6 cycles (range 1 to 69) in the All-Isa group.

## *Adverse events*

An overview of TEAEs in Study EFC12522 is presented in **Table 20**.

**Table 20***.* Overview of treatment-emergent adverse events– Safety population, Study EFC12522

| | VRd (N=181) | IVRd (N=263) |
|---|---|---|
| Patients with any TEAE | 178 (98.3) | 262 (99.6) |
| Patients with any grade ≥ 3 TEAE | 152 (84.0) | 241 (91.6) |
| Patients with any grade 3-4 TEAE | 151 (83.4) | 236 (89.7) |

| | VRd (N=181) | IVRd (N=263) |
|---|---|---|
| Patients with any grade 5 TEAE | 10 (5.5) | 29 (11.0) |
| Patients with any treatment emergent SAE [b] | 122 (67.4) | 186 (70.7) |
| Patients with any TEAE leading to definitive treatment discontinuation | 47 (26.0) | 60 (22.8) |
| Patients with any TEAE leading to premature discontinuation of Isatuximab | NA | 6 (2.3) |
| Patients with any TEAE leading to premature discontinuation of Bortezomib | 17 (9.4) | 32 (12.2) |
| Patients with any TEAE leading to premature discontinuation of Lenalidomide | 4 (2.2) | 34 (12.9) |
| Patients with any TEAE leading to premature discontinuation of Dexamethasone | 31 (17.1) | 18 (6.8) |
| Patients with any AESI [c] | 13 (7.2) | 36 (13.7) |
| Patients with any IR of grade ≥ 3 | 0 | 2 (0.8) |
| Patients with any treatment-related TEAE [d] (any grade) | 175 (96.7) | 257 (97.7) |
| Patients with any treatment-related grade ≥ 3 TEAE | 123 (68.0) | 202 (76.8) |
| Patients with any serious treatment-related TEAE | 58 (32.0) | 87 (33.1) |

TEAE: Treatment emergent adverse event, AESI: Adverse event of special interest, SAE: Serious adverse event, IR: Infusion reaction, NIMP: non investigational medicinal product

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

[b]: 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

[c]: AESIs include IR of grade ≥ 3, pregnancy (female patient or female partner), symptomatic overdose with study treatment or NIMP and second primary malignancy

[d]: Treatment-related TEAEs are TEAEs related to at least one drug of the combination

NA: Not Applicable

The most frequently reported TEAEs (≥10% of participants in either group) by primary SOC in the VRd and IVRd groups, respectively, were as follows:

- Infections and Infestations (157 [86.7%] participants in the VRd group and 240 [91.3%] participants in the IVRd group),
- Nervous system disorders (148 [81.8%], 212 [80.6%]),
- Gastrointestinal disorders (143 [79.0%], 207 [78.7%]),
- General disorders and administration site conditions (131 [72.4%], 193 [73.4%]).

The most frequently reported TEAEs, with a ≥5% difference in number of participants between treatment groups, by primary SOC were as follows: Eye disorders (36.5% in the VRd group and 51.3% in the IVRd group), Injury, poisoning and procedural complications (29.3%, 50.6%]), Blood and lymphatic system disorders (36.5, 42.6%), Neoplasms benign, malignant and unspecified (incl cysts and polyps) (9.9%, 19.0%), and Reproductive system and breast disorders (5.5%, 11.0%) were also reported with a lower incidence for VRd than for IVRd, respectively. Respiratory, thoracic and mediastinal disorders (48.6%, 39.2%), Metabolism and Nutrition disorders (36.5%, 30.0%), and Vascular disorders (35.4%, 30.4%) were reported with a higher incidence for VRd than for IVRd.

The most frequently reported Grade ≥3 TEAEs (≥5% difference in number of participants between treatment groups) by primary SOC were as follows:

- Infections and Infestations (69 [38.1%] participants in the VRd group and 118 [44.9%] participants in the IVRd group),
- Blood and Lymphatic System Disorders (60 [33.1%], 101 [38.4%]),
- Metabolism and Nutrition Disorders (25 [13.8%], 22 [8.4%]),
- Respiratory, Thoracic and Mediastinal Disorders (23 [12.7%], 19 [7.2%]),
- Eye Disorders (21 [11.6%], 45 [17.1%]).

The most frequently reported Grade ≥3 TEAEs ≥10% of participants in either intervention group) by PT were: neutropenia (37 [20.4%] participants in the VRd group and 79 [30.0%] participants in the IVRd group), pneumonia (23 [12.7%], 53 [20.2%]), cataract (20 [11.0%], 41 [15.6%]), and thrombocytopenia (19 [10.5%], 31 [11.8%]).

***Treatment-related TEAEs***

The most frequently reported treatment-related TEAEs, with an incidence, reported for at least ≥ 5% of patients in any treatment group by PT are summarised in

**Table 21**.

**Table 21.** TEAEs related to IMP with an incidence ≥ 5% in any treatment group by PT (worst grade by patient) - Safety population, Study EFC12522

| | VRd (N=181) | | IVRd (N=263) | |
|---|---|---|---|---|
| **Preferred Term [n(%)]** | **All grades** | **Grade ≥ 3** | **All grades** | **Grade ≥ 3** |
| Any event | 175 (96.7) | 123 (68.0) | 257 (97.7) | 202 (76.8) |
| Peripheral sensory neuropathy | 105 (58.0) | 11 (6.1) | 142 (54.0) | 19 (7.2) |
| Diarrhoea | 66 (36.5) | 14 (7.7) | 96 (36.5) | 14 (5.3) |
| Neutropenia | 38 (21.0) | 36 (19.9) | 77 (29.3) | 77 (29.3) |
| Fatigue | 40 (22.1) | 10 (5.5) | 65 (24.7) | 16 (6.1) |
| Constipation | 47 (26.0) | 2 (1.1) | 62 (23.6) | 4 (1.5) |
| Infusion related reaction | 0 | 0 | 61 (23.2) | 1 (0.4) |
| Cataract | 25 (13.8) | 11 (6.1) | 55 (20.9) | 21 (8.0) |
| Insomnia | 29 (16.0) | 4 (2.2) | 44 (16.7) | 10 (3.8) |
| Asthenia | 27 (14.9) | 4 (2.2) | 38 (14.4) | 4 (1.5) |
| Rash | 22 (12.2) | 4 (2.2) | 37 (14.1) | 8 (3.0) |
| Oedema peripheral | 34 (18.8) | 2 (1.1) | 36 (13.7) | 0 |
| Thrombocytopenia | 21 (11.6) | 17 (9.4) | 35 (13.3) | 29 (11.0) |
| Upper respiratory tract infection | 20 (11.0) | 1 (0.6) | 33 (12.5) | 1 (0.4) |
| Pneumonia | 17 (9.4) | 12 (6.6) | 31 (11.8) | 24 (9.1) |
| Muscle spasms | 12 (6.6) | 0 | 27 (10.3) | 3 (1.1) |
| Bronchitis | 12 (6.6) | 0 | 21 (8.0) | 3 (1.1) |
| Muscular weakness | 16 (8.8) | 3 (1.7) | 20 (7.6) | 3 (1.1) |
| Deep vein thrombosis | 17 (9.4) | 3 (1.7) | 19 (7.2) | 3 (1.1) |
| Decreased appetite | 16 (8.8) | 1 (0.6) | 18 (6.8) | 1 (0.4) |
| Nausea | 13 (7.2) | 0 | 18 (6.8) | 0 |
| Paraesthesia | 8 (4.4) | 1 (0.6) | 17 (6.5) | 1 (0.4) |
| Dizziness | 7 (3.9) | 1 (0.6) | 16 (6.1) | 1 (0.4) |
| Tremor | 13 (7.2) | 2 (1.1) | 16 (6.1) | 0 |
| Dysgeusia | 5 (2.8) | 0 | 15 (5.7) | 1 (0.4) |
| Peripheral sensorimotor neuropathy | 14 (7.7) | 2 (1.1) | 13 (4.9) | 4 (1.5) |
| Pulmonary embolism | 10 (5.5) | 9 (5.0) | 10 (3.8) | 10 (3.8) |
| Hypotension | 10 (5.5) | 5 (2.8) | 9 (3.4) | 1 (0.4) |

***Exposure- adjusted TEAEs***

Exposure-adjusted rates are shown in **Table 22** and **Table 23**.

**Table 22**. Patient years analysis : overview of TEAEs - Safety population, Study EFC12522

| | 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) | 12.691 | 262 (99.6) | 13.386 |
| Patients with any grade ≥3 TEAE | 152 (84.0) | 0.986 | 241 (91.6) | 1.171 |
| Patients with any grade 5 TEAE | 10 (5.5) | 0.019 | 29 (11.0) | 0.031 |
| Patients with any treatment emergent SAE | 122 (67.4) | 0.435 | 186 (70.7) | 0.375 |
| Patients with any TEAE leading to definitive treatment discontinuation | 47 (26.0) | 0.090 | 60 (22.8) | 0.066 |

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.
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.

**Table 23** Patient years analysis: TEAEs with an incidence ≥5% in any treatment group in patient years by Primary SOC and PT - Safety population, Study EFC12522

| Primary System Organ Class Preferred Term | VRd (N=181) | | IVRd (N=263) | |
|---|---|---|---|---|
| | n (%) | Event rate per patient year*a* | n (%) | Event rate per patient year*a* |
| Any class | 178 (98.3) | 12.691 | 262 (99.6) | 13.386 |
| Infections and infestations | 157 (86.7) | 1.166 | 240 (91.3) | 1.181 |
| Upper respiratory tract infection | 61 (33.7) | 0.170 | 90 (34.2) | 0.140 |
| Pneumonia | 35 (19.3) | 0.078 | 79 (30.0) | 0.105 |
| COVID-19 | 30 (16.6) | 0.059 | 59 (22.4) | 0.070 |
| Bronchitis | 32 (17.7) | 0.071 | 58 (22.1) | 0.075 |
| Nasopharyngitis | 25 (13.8) | 0.053 | 46 (17.5) | 0.058 |
| Urinary tract infection | 27 (14.9) | 0.056 | 37 (14.1) | 0.044 |
| COVID-19 pneumonia | 8 (4.4) | 0.015 | 21 (8.0) | 0.023 |
| Influenza | 9 (5.0) | 0.018 | 21 (8.0) | 0.024 |
| Lower respiratory tract infection | 10 (5.5) | 0.020 | 21 (8.0) | 0.024 |
| Rhinitis | 13 (7.2) | 0.026 | 21 (8.0) | 0.024 |
| Gastroenteritis | 6 (3.3) | 0.011 | 17 (6.5) | 0.019 |
| Herpes zoster | 10 (5.5) | 0.020 | 15 (5.7) | 0.017 |
| Conjunctivitis | 13 (7.2) | 0.026 | 14 (5.3) | 0.016 |
| Viral upper respiratory tract infection | 12 (6.6) | 0.024 | 9 (3.4) | 0.010 |
| Blood and lymphatic system disorders | 66 (36.5) | 0.172 | 112 (42.6) | 0.189 |
| Neutropenia | 39 (21.5) | 0.091 | 79 (30.0) | 0.115 |
| Thrombocytopenia | 23 (12.7) | 0.047 | 38 (14.4) | 0.046 |
| Anaemia | 16 (8.8) | 0.032 | 15 (5.7) | 0.017 |
| Metabolism and nutrition disorders | 66 (36.5) | 0.180 | 79 (30.0) | 0.110 |
| Decreased appetite | 30 (16.6) | 0.065 | 34 (12.9) | 0.041 |
| Dehydration | 12 (6.6) | 0.023 | 4 (1.5) | 0.004 |
| Psychiatric disorders | 65 (35.9) | 0.170 | 94 (35.7) | 0.150 |
| Insomnia | 44 (24.3) | 0.104 | 59 (22.4) | 0.082 |
| Depression | 8 (4.4) | 0.015 | 16 (6.1) | 0.018 |
| Anxiety | 12 (6.6) | 0.023 | 13 (4.9) | 0.015 |
| Nervous system disorders | 148 (81.8) | 1.190 | 212 (80.6) | 1.004 |
| Peripheral sensory neuropathy | 110 (60.8) | 0.523 | 143 (54.4) | 0.352 |
| Dizziness | 22 (12.2) | 0.046 | 33 (12.5) | 0.040 |
| Paraesthesia | 13 (7.2) | 0.026 | 26 (9.9) | 0.031 |
| Headache | 14 (7.7) | 0.028 | 22 (8.4) | 0.025 |
| Tremor | 16 (8.8) | 0.032 | 21 (8.0) | 0.025 |
| Dysgeusia | 8 (4.4) | 0.016 | 19 (7.2) | 0.022 |
| Syncope | 12 (6.6) | 0.024 | 15 (5.7) | 0.017 |
| Peripheral sensorimotor neuropathy | 14 (7.7) | 0.028 | 14 (5.3) | 0.016 |
| Eye disorders | 66 (36.5) | 0.183 | 135 (51.3) | 0.246 |
| Cataract | 46 (25.4) | 0.110 | 100 (38.0) | 0.152 |

| Primary System Organ Class<br>Preferred Term | VRd (N=181) | | IVRd (N=263) | |
|---|---|---|---|---|
| | n (%) | Event rate per patient year*a* | n (%) | Event rate per patient year*a* |
| Ear and labyrinth disorders | 23 (12.7) | 0.049 | 38 (14.4) | 0.047 |
| Vertigo | 10 (5.5) | 0.020 | 14 (5.3) | 0.016 |
| Cardiac disorders | 42 (23.2) | 0.093 | 59 (22.4) | 0.075 |
| Atrial fibrillation | 16 (8.8) | 0.032 | 21 (8.0) | 0.024 |
| Vascular disorders | 64 (35.4) | 0.170 | 80 (30.4) | 0.115 |
| Deep vein thrombosis | 20 (11.0) | 0.041 | 23 (8.7) | 0.026 |
| Hypertension | 15 (8.3) | 0.030 | 20 (7.6) | 0.023 |
| Hypotension | 19 (10.5) | 0.039 | 18 (6.8) | 0.021 |
| Orthostatic hypotension | 10 (5.5) | 0.020 | 9 (3.4) | 0.010 |
| Respiratory, thoracic and mediastinal disorders | 88 (48.6) | 0.254 | 103 (39.2) | 0.166 |
| Cough | 24 (13.3) | 0.050 | 43 (16.3) | 0.055 |
| Dyspnoea | 25 (13.8) | 0.052 | 29 (11.0) | 0.034 |
| Productive cough | 4 (2.2) | 0.008 | 15 (5.7) | 0.017 |
| Pulmonary embolism | 13 (7.2) | 0.026 | 13 (4.9) | 0.015 |
| Gastrointestinal disorders | 143 (79.0) | 0.928 | 207 (78.7) | 0.735 |
| Diarrhoea | 88 (48.6) | 0.280 | 144 (54.8) | 0.278 |
| Constipation | 74 (40.9) | 0.210 | 94 (35.7) | 0.159 |
| Nausea | 29 (16.0) | 0.063 | 42 (16.0) | 0.053 |
| Vomiting | 14 (7.7) | 0.028 | 28 (10.6) | 0.033 |
| Abdominal pain | 16 (8.8) | 0.032 | 20 (7.6) | 0.023 |
| Abdominal pain upper | 10 (5.5) | 0.020 | 16 (6.1) | 0.018 |
| Dyspepsia | 10 (5.5) | 0.020 | 15 (5.7) | 0.017 |
| Skin and subcutaneous tissue disorders | 91 (50.3) | 0.326 | 129 (49.0) | 0.247 |
| Rash | 36 (19.9) | 0.086 | 52 (19.8) | 0.071 |
| Pruritus | 12 (6.6) | 0.024 | 15 (5.7) | 0.017 |
| Rash maculo-papular | 6 (3.3) | 0.012 | 15 (5.7) | 0.017 |
| Musculoskeletal and connective tissue disorders | 113 (62.4) | 0.467 | 158 (60.1) | 0.364 |
| Back pain | 31 (17.1) | 0.068 | 58 (22.1) | 0.075 |
| Arthralgia | 36 (19.9) | 0.076 | 50 (19.0) | 0.063 |
| Muscle spasms | 22 (12.2) | 0.045 | 38 (14.4) | 0.048 |
| Pain in extremity | 21 (11.6) | 0.044 | 27 (10.3) | 0.032 |
| Muscular weakness | 17 (9.4) | 0.035 | 25 (9.5) | 0.030 |
| Musculoskeletal chest pain | 10 (5.5) | 0.020 | 16 (6.1) | 0.018 |
| Myalgia | 11 (6.1) | 0.022 | 16 (6.1) | 0.018 |
| Bone pain | 17 (9.4) | 0.035 | 10 (3.8) | 0.011 |
| Osteoarthritis | 13 (7.2) | 0.026 | 10 (3.8) | 0.011 |
| Pathological fracture | 12 (6.6) | 0.024 | 10 (3.8) | 0.011 |
| General disorders and administration site conditions | 131 (72.4) | 0.744 | 193 (73.4) | 0.581 |
| Fatigue | 48 (26.5) | 0.119 | 91 (34.6) | 0.138 |
| Oedema peripheral | 59 (32.6) | 0.155 | 86 (32.7) | 0.130 |
| Asthenia | 44 (24.3) | 0.103 | 57 (21.7) | 0.073 |
| Pyrexia | 21 (11.6) | 0.043 | 42 (16.0) | 0.052 |
| Peripheral swelling | 10 (5.5) | 0.019 | 22 (8.4) | 0.025 |
| Influenza like illness | 11 (6.1) | 0.021 | 14 (5.3) | 0.016 |
| Investigations | 37 (20.4) | 0.086 | 56 (21.3) | 0.074 |
| Weight decreased | 15 (8.3) | 0.031 | 17 (6.5) | 0.020 |
| Injury, poisoning and procedural complications | 53 (29.3) | 0.124 | 133 (50.6) | 0.243 |
| Infusion related reaction | 2 (1.1) | 0.004 | 62 (23.6) | 0.085 |
| Fall | 29 (16.0) | 0.059 | 50 (19.0) | 0.061 |
| Accidental overdose | 5 (2.8) | 0.010 | 14 (5.3) | 0.016 |
| Contusion | 11 (6.1) | 0.021 | 13 (4.9) | 0.015 |

TEAE: Treatment emergent adverse event, SOC: System organ class, PT: Preferred term
MedDRA 26.0
n(%) = number and percentage of patients with at least one event
*a* Calculated as number of patients with an event divided by total patient years.
Note: For patients with event, patient year is censored at time of first event; for patient without event, it corresponds to length of treatment period.
Table sorted by SOC internationally agreed order and by decreasing frequency of PT in IVRd group
Only SOC with at least one PT ≥ 5% in at least one treatment group are presented.

*Supportive studies*

In the study TCD13983 the safety data were largely comparable to the pivotal study, though AEs were generally observed at slightly lower rates.

In the All-Isa group, a similar safety profile was observed compared to the Study EFC12522 safety population, though the frequencies of TEAEs were generally lower, as exemplified below.
In the All-Isa group, the most frequently reported TEAEs (≥20% for all grades) in either the VRd and IVRd groups were: diarrhoea (110 [21.1%] participants and 218 [31.5%] participants, respectively), peripheral sensory neuropathy (140 [26.9%] and 218 [31.5%], respectively), constipation (84 [16.1%] and 162 [23.4%], respectively), neutropenia (52 [10.0%] and 151 [21.8%], respectively), and infusion related reaction (2 [0.4%] and 145 [21.0%], respectively).

The most frequently reported TEAEs ≥20% for all grades) in the All-Isa group were infusion related reaction (642 [35.9%] participants), diarrhoea (531 [29.7%]), upper respiratory tract infection (437 [24.5%), and fatigue (421 [23.6%]).

## *Serious adverse event/deaths/other significant events*

### Serious adverse events

Serious TEAEs were reported in 122 (67.4%) participants in the VRd group and 186 (70.7%) participants in the IVRd group (**Table 24**).

**Table 24.** Treatment emergent SAEs with an incidence ≥ 2% in any treatment group by SOC and PT (worst grade by patient) with groupings used in most common TEAEs - Safety population Study EFC12522

| | **VRd (N=181)** | | | | **IVRd (N=263)** | | | |
|---|---|---|---|---|---|---|---|---|
| **Primary System Organ Class Preferred Term [n(%)]** | **All grades** | **Grade 3** | **≥ Grade 3** | **Grade 4** | **All grades** | **Grade 3** | **≥ Grade 3** | **Grade 4** |
| Infections and infestations | | | | | | | | |
| Bronchitis | 3 (1.7) | 2 (1.1) | 1 (0.6) | 0 | 7 (2.7) | 5 (1.9) | 5 (1.9) | 0 |
| Pneumonia*b* | 38 (21.0) | 33 (18.2) | 25 (13.8) | 7 (3.9) | 78 (29.7) | 74 (28.1) | 61 (23.2) | 6 (2.3) |
| Sepsis | 6 (3.3) | 6 (3.3) | 1 (0.6) | 4 (2.2) | 6 (2.3) | 6 (2.3) | 0 | 4 (1.5) |
| Upper respiratory tract infections*a* | 7 (3.9) | 5 (2.8) | 5 (2.8) | 0 | 5 (1.9) | 2 (0.8) | 2 (0.8) | 0 |
| Urinary tract infection | 5 (2.8) | 5 (2.8) | 4 (2.2) | 1 (0.6) | 5 (1.9) | 5 (1.9) | 5 (1.9) | 0 |
| Nervous system disorders | | | | | | | | |
| Syncope | 6 (3.3) | 6 (3.3) | 6 (3.3) | 0 | 6 (2.3) | 6 (2.3) | 6 (2.3) | 0 |
| Transient ischaemic attack | 5 (2.8) | 1 (0.6) | 1 (0.6) | 0 | 3 (1.1) | 1 (0.4) | 1 (0.4) | 0 |
| Eye disorders | | | | | | | | |
| Cataract | 2 (1.1) | 2 (1.1) | 2 (1.1) | 0 | 6 (2.3) | 4 (1.5) | 4 (1.5) | 0 |
| Cardiac disorders | | | | | | | | |
| Atrial fibrillation | 8 (4.4) | 6 (3.3) | 4 (2.2) | 2 (1.1) | 8 (3.0) | 6 (2.3) | 4 (1.5) | 2 (0.8) |
| Cardiac failure | 6 (3.3) | 5 (2.8) | 4 (2.2) | 1 (0.6) | 1 (0.4) | 1 (0.4) | 1 (0.4) | 0 |
| Respiratory, thoracic and mediastinal disorders | | | | | | | | |
| Pulmonary embolism | 6 (3.3) | 6 (3.3) | 4 (2.2) | 1 (0.6) | 11 (4.2) | 11 (4.2) | 7 (2.7) | 3 (1.1) |
| Gastrointestinal disorders | | | | | | | | |
| Diarrhoea | 9 (5.0) | 8 (4.4) | 8 (4.4) | 0 | 5 (1.9) | 4 (1.5) | 3 (1.1) | 1 (0.4) |
| Musculoskeletal and connective tissue disorders | | | | | | | | |
| Pathological fracture | 7 (3.9) | 5 (2.8) | 5 (2.8) | 0 | 3 (1.1) | 3 (1.1) | 3 (1.1) | 0 |
| Renal and urinary disorders | | | | | | | | |
| Acute kidney injury | 4 (2.2) | 4 (2.2) | 3 (1.7) | 1 (0.6) | 4 (1.5) | 3 (1.1) | 3 (1.1) | 0 |
| General disorders and administration site conditions | | | | | | | | |
| General physical health deterioration | 4 (2.2) | 3 (1.7) | 3 (1.7) | 0 | 1 (0.4) | 1 (0.4) | 1 (0.4) | 0 |

| | VRd (N=181) | | | | IVRd (N=263) | | | |
|---|---|---|---|---|---|---|---|---|
| **Primary System Organ Class Preferred Term [n(%)]** | **All grades** | **Grade 3** | **≥ Grade 3** | **Grade 4** | **All grades** | **Grade 3** | **≥ Grade 3** | **Grade 4** |
| Pyrexia | 3 (1.7) | 1 (0.6) | 1 (0.6) | 0 | 6 (2.3) | 2 (0.8) | 2 (0.8) | 0 |
| Injury, poisoning and procedural complications | | | | | | | | |
| Femur fracture | 1 (0.6) | 1 (0.6) | 1 (0.6) | 0 | 6 (2.3) | 5 (1.9) | 5 (1.9) | 0 |

*a* Upper respiratory tract infection includes TEAEs in the CMQ "Upper respiratory tract infection". Observed preferred terms are: Influenza, Laryngopharyngitis, Nasopharyngitis, Respiratory syncytial virus infection, Sinusitis, Upper respiratory tract infection, Viral upper respiratory tract infection

*b* Pneumonia includes TEAEs in the narrow SMQ Infective pneumonia. Observed preferred terms are: COVID-19 pneumonia, Pneumocystis jirovecii pneumonia, Pneumonia, Pneumonia bacterial, Pneumonia haemophilus, Pneumonia influenzal, Pneumonia klebsiella, Pneumonia legionella, Pneumonia parainfluenzae viral, Pneumonia pneumococcal, Pneumonia pseudomonal, Pneumonia respiratory syncytial viral, Pneumonia viral, Pulmonary sepsis, Pulmonary tuberculosis, Tuberculosis

*Supportive studies*

In study TCD13983 serious TEAEs in the IVRd group were observed in Part A in 55.6% and in Part B in 52.2% of the participants.

In the All-Isa pool treatment-emergent SAEs were reported 250 (48.0%) participants in the VRd arm, 362 (52.3%) participants in the IVRd arm and 963 (53.9%) participants in All-Isa arm. The most frequently reported treatment-emergent SAEs (≥10% of participants in any treatment arm) (all grades) by primary SOC were: Infections and infestations (110 [21.1%] participants in the VRd arm; 195 [28.2%] participants in the IVRd arm; and 519 [29.0%] participants in the All Isa arm. Within that SOC, the most frequently reported PT (all grades) was pneumonia (36 [6.9%] participants, 78 [11.3%] participants, and 225 [12.6%] participants, respectively.

**Deaths**

The number of deaths reported in study EFC12522 are described in **Table 25**. Grade 5 TEAEs during treatment period by Primary SOC and PT are summarised in **Table 26**.

**Table 25**. Deaths by observation periods and cause of death - Safety population Study EFC12522

| | VRd (N=181) | IVRd (N=263) |
|---|---|---|
| Deaths during the TEAE or CO TEAE or post-treatment period | 59 (32.6) | 69 (26.2) |
| Disease progression | 22 (12.2) | 13 (4.9) |
| Adverse Event | 11 (6.1) | 29 (11.0) |
| Other | 26 (14.4) | 27 (10.3) |
| Deaths during the TEAE period[a] | 9 (5.0) | 29 (11.0) |
| Disease progression | 0 | 0 |
| Adverse Event | 8 (4.4) | 24 (9.1) |
| Other | 1 (0.6) | 5 (1.9) |
| Deaths during the CO TEAE period[b] | 2 (1.1) | NA |
| Disease progression | 0 | NA |
| Adverse Event | 2 (1.1) | NA |
| Other | 0 | NA |
| Deaths during post-treatment period[c] | 48 (26.5) | 40 (15.2) |
| Disease progression | 22 (12.2) | 13 (4.9) |
| Adverse Event | 1 (0.6) | 5 (1.9) |
| Other | 25 (13.8) | 22 (8.4) |
| Deaths within 60 days of first dose | 1 (0.6) | 4 (1.5) |
| Disease progression | 0 | 0 |
| Adverse Event | 1 (0.6) | 3 (1.1) |
| Other | 0 | 1 (0.4) |
| Deaths within 60 days of first dose in CO period | 0 | NA |
| Disease progression | 0 | NA |

| | VRd (N=181) | IVRd (N=263) |
|---|---|---|
| Adverse Event | 0 | NA |
| Other | 0 | NA |

TEAE: Treatment emergent adverse event; CO TEAE: Crossover treatment emergent adverse event

*a* Includes all deaths occurring from the first dose of study drugs up to the last dose of study drugs + 30 days

*b* Includes all deaths occurring from the first dose of Isatuximab during crossover part up to the last dose of study drugs + 30 days. Events are displayed in the VRd arm column, but received IRd before death.

*c* Includes all deaths occurring >30 days after the last dose of study drugs

Deaths that occurred after the operational Cut-off date are excluded from this analysis except for deaths occurring within 30 days from last IMP due to a TEAE starting before the operational Cut-off date

NA: Not Applicable

Among the deaths classified as "Other" in the post treatment period (often occurring during subsequent therapy), 17 were in relation with unknown cause of death (7 in the VRd group and 10 in the IVRd group). For 2 patients in the IVRd group, "Overall deterioration in health" and "Total exhaustion" were reported as "Other" reasons. The remaining events were in relation to identified adverse events occurring in the post treatment period and not related to study treatment: 18 in the VRd group and 10 in the IVRd group. Most of these events were infections (8 in the VRd group and 6 in the IVRd group).

The majority of the deaths occurred during the post-treatment period for both groups. There were 2 deaths reported during the crossover treatment period due to an adverse event (including one who died from COVID-19 pneumonia). During the treatment period and follow up period 3 (1.7%) deaths in the VRd arm were considered related to treatment versus 7 (2.7%) deaths in the IVRd arm. In the VRd arm deaths were due to pneumonia (N=2) and pneumonia aspiration (N=1) and in the IVRd arm due to sepsis, malignant melanoma stage IV, colorectal cancer and rectal adenocarcinoma (in one patient), squamous cell carcinoma of lung, tumour lysis syndrome, chronic inflammatory demyelinating polyradiculoneuropathy and renal tubular acidosis (all N=1).

**Table 26.** Grade 5 TEAEs during treatment period by Primary SOC and PT - Safety population

| Primary System Organ Class<br>Preferred Term [n(%)] | VRd<br>(N=181) | IVRd<br>(N=263) |
|---|---|---|
| Any class | 10 (5.5) | 29 (11.0) |
| Infections and infestations | 7 (3.9) | 17 (6.5) |
| Covid-19 pneumonia | 0 | 8 (3.0) |
| Pneumonia | 2 (1.1) | 4 (1.5) |
| Sepsis | 1 (0.6) | 2 (0.8) |
| Candida sepsis | 0 | 1 (0.4) |
| Pneumonia klebsiella | 0 | 1 (0.4) |
| Pneumonia pseudomonal | 0 | 1 (0.4) |
| Septic shock | 0 | 1 (0.4) |
| Bronchitis | 1 (0.6) | 0 |
| Covid-19 | 2 (1.1) | 0 |
| Pneumonia aspiration | 1 (0.6) | 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | 0 | 1 (0.4) |
| Neuroendocrine carcinoma of the skin | 0 | 1 (0.4) |
| Blood and lymphatic system disorders | 0 | 1 (0.4) |
| Febrile neutropenia | 0 | 1 (0.4) |
| Metabolism and nutrition disorders | 0 | 1 (0.4) |
| Tumour lysis syndrome | 0 | 1 (0.4) |
| Respiratory, thoracic and mediastinal disorders | 2 (1.1) | 3 (1.1) |
| Dyspnoea | 0 | 1 (0.4) |
| Pulmonary embolism | 1 (0.6) | 1 (0.4) |
| Respiratory failure | 0 | 1 (0.4) |
| Pleural effusion | 1 (0.6) | 0 |
| Hepatobiliary disorders | 0 | 1 (0.4) |
| Hepatic cirrhosis | 0 | 1 (0.4) |
| Renal and urinary disorders | 0 | 1 (0.4) |
| Renal tubular acidosis | 0 | 1 (0.4) |
| General disorders and administration site conditions | 1 (0.6) | 6 (2.3) |
| Sudden death | 0 | 4 (1.5) |
| Death | 1 (0.6) | 1 (0.4) |
| Multiple organ dysfunction syndrome | 0 | 1 (0.4) |

*Supportive studies*

In study TCD13983 Part A, a total of 2 participants died between the start of the study and the cut-off date for the CSR analysis. One patient died during the on-treatment period and 1 patient died during the post treatment period (105 days after last dose).

In Part B, 7 participants died between the start of the study and the cut-off date for the CSR analysis. Four (4) participants died during the on-treatment period and 3 participants died during the post-treatment period.

In the All-Isa pool during the treatment period, deaths were reported for 13 (2.5%) participants in the VRd group, 40 (5.8%) participants in the IVRd group, and 131 (7.3%) participants in the All-Isa group (**Table 27**).

**Table 27.** Number (%) of deaths by study period and cause of death - All-Isa - Safety population

| n(%) | NDMM VRd[a] (N=521) | IVRd[b] (N=692) | RRMM and NDMM All-Isa[c] (N=1787) |
|---|---|---|---|
| Death during the treatment period[d] | 13 (2.5) | 40 (5.8) | 131 (7.3) |
| Disease progression | 0 | 1 (0.1) | 41 (2.3) |
| Adverse Event | 10 (1.9) | 34 (4.9) | 80 (4.5) |
| Other | 3 (0.6) | 5 (0.7) | 10 (0.6) |
| Death during post-treatment period | 60 (11.5) | 49 (7.1) | 401 (22.4) |
| Disease progression | 24 (4.6) | 15 (2.2) | 278 (15.6) |
| Adverse Event | 9 (1.7) | 9 (1.3) | 13 (0.7) |
| Other | 27 (5.2) | 25 (3.6) | 110 (6.2) |
| Death within 60 days from first dose | 5 (1.0) | 6 (0.9) | 47 (2.6) |
| Disease progression | 0 | 0 | 28 (1.6) |
| Adverse Event | 3 (0.6) | 5 (0.7) | 15 (0.8) |
| Other | 2 (0.4) | 1 (0.1) | 4 (0.2) |

IVRd: isatuximab in combination with bortezomib, lenalidomide and dexamethasone; VRd: bortezomib, lenalidomide and dexamethasone.
[a] Include VRd treated NDMM patients from EFC12522 (both global portion and China expansion) and IIT15403 (induction period only).

[a]

**Table 28.** Description of infusion reactions - Safety population Study EFC12522

| | IVRd (N=263) |
|---|---|
| Number of patients with at least one IR | 63 (24.0) |
| Worst grade of IR [n(%)] | |
| Grade 1 | 5 (1.9) |
| Grade 2 | 56 (21.3) |
| Grade 3 | 1 (0.4) |
| Grade 4 | 1 (0.4) |
| Grade 5 | 0 |
| Action taken with Isatuximab by patient [n(%)] | |
| Dose not changed | 7 (2.7) |
| Drug interrupted | 54 (20.5) |
| Drug withdrawn | 2 (0.8) |
| Corrective treatment given [n(%)] | 48 (18.3) |
| Episodes by patient [n(%)] | |
| Only 1 episode | 53 (20.2) |
| ≥ 1 episode | 63 (24.0) |
| ≥ 2 episodes | 10 (3.8) |
| ≥ 3 episodes | 1 (0.4) |
| Onset of the first IR at [n(%)] | |
| Number | 63 |
| First infusion | 57 (21.7) |
| Subsequent infusions | 6 (2.3) |
| Occurrence of IR leading to permanent discontinuation at [n(%)] | |
| Occurrence of IR leading to isatuximab withdrawal [n(%)] | |
| First day of study treatment | 2 (0.8) |
| Subsequent days of infusion | 0 |
| IR duration [n(%)] | |
| 1 day | 72 (97.3) |
| 2 days | 0 |
| > 2 days | 2 (2.7) |
| Not recovered | 0 |

| | IVRd (N=263) |
|---|---|

IR: Infusion reaction

The most common symptoms of an IR included dyspnoea and chills (both 4.6%). The most common severe sign and symptom was hypertension (1.1%). On the total number of Isatuximab infusions received by the participants, 92.1% (14311/15543) were associated with IR medications, and only 52 (0.4%) of the isatuximab infusions had IR medications reported as curative intent.

Within 24 hours of the infusion: hypersensitivity TEAEs occurring within 24 hours of isatuximab administration were reported in 38.4% in the IVRd group, primarily infusion related reaction (23.6%) and rash (7.6%): it also included 2 (0.8%) events of drug hypersensitivity, 1 (0.4%) event of anaphylactic reaction, and 1 (0.4%) event of infusion-related hypersensitivity reaction. Grade ≥3 events included 1 event of anaphylactic reaction, 3 events of rash, 1 event of dermatitis acneiform, and 1 event of infusion related reaction. These hypersensitivity events occurring within 24 hours were mostly assessed as related to treatment in these participants in the IVRd group. No cases of cytokine release syndrome were reported.

*Supportive studies*: In the TCD13983 study, in Part A, of the 27 treated participants, IR of any grade occurred in 17 (63.0%) participants. One (5.9%) participant had a Grade 3 IR. In Part B, of the 46 treated participants, IR of any grade occurred in 13 (28.3%) participants.
In the All-Isa pool the number (%) of participants who experienced at least 1 IR was 147 (21.2%) participants in the IVRd group and 643 (36.0%) participants in the All-Isa group. Grade ≥3 IR symptoms were experienced by 9 (2.5%) and 53 (3.6%) participants, respectively.

*Secondary primary malignancies (SPM)*

Secondary primary malignancies (SPM) occurred on treatment and post-treatment periods and were reported in 16 (8.8%) participants in the VRd group and in 42 (16.0%) participants in the IVRd group. The relative risk (95% CI) of IVRd vs VRd was 1.81 (1.05 to 3.11). In the exposure-adjusted analyses, treatment-emergent second primary malignancies occurred at 0.026 event per patient-year in the VRd group, and 0.041 event per patient-year in the IVRd group.

SPMs were skin cancers in 7 (3.9%) participants in the VRd group and in 22 (8.4%) participants in the IVRd group; solid tumors other than skin cancers occurred in 7 (3.9%) and 17 (6.5%) participants, respectively. Hematological second primary malignancies occurred infrequently with the same frequency in each group (1.1%).

Among the 29 participants with SPMs of skin cancer, a medical history of skin cancer(s) was reported in none of the 7 participants in the VRd group and in 6 of the 22 (27.3%) participants in the IVRd group. Second primary malignancy skin cancers led to treatment termination in one participant in each treatment group. All cases were resected and all other participants continued study treatment.

Nine participants discontinued all study intervention or the last ongoing study drug due to second primary malignancy (3 participants (1.7%) in the VRd group [1 for non-skin solid tumors, 1 for skin cancer, 1 for hematological malignancy] and 6 participants (2.3%) in the IVRd group [4 for non-skin solid tumors, 1 for skin cancer, 1 for hematological malignancy).

SPMs with fatal outcome were reported in 2 participants (1.1%) in the VRd group (metastases to peritoneum and adenocarcinoma of colon), and in 6 participants (2.3%) in the IVRd group (neuroendocrine carcinoma of the skin, malignant melanoma, squamous cell carcinoma of the skin, squamous cell carcinoma of lung, colorectal cancer, and rectal adenocarcinoma).

*Supportive studies:* In study TCD13983, in Part A, there were 2 (7.4%) participants with SPMs reported. One participant had a basal cell carcinoma (Cycle 13 and Cycle 26) and Grade 3 squamous cell carcinoma of skin (Cycle 30 and Cycle 37). One participant had a squamous cell carcinoma (Cycle 14) and metastatic squamous cell carcinoma (metastasized to right atrial pavilion Cycle 32). In Part B, there were 4 (8.7%) participants with SPMs reported, including 2 with fatal events (breast cancer metastatic and metastatic malignant melanoma). The other 2 SPMs were skin cancers (squamous cell carcinoma of skin and Bowen's disease).

In the All-Isa pool SPMs that occurred on treatment and in post-treatment periods were reported in 17 (3.3%) participants in the VRd group, 50 (7.2%) participants in the IVRd group, and 107 (6.0%) participants in All-Isa group. Among participants who had SPM, the median time (in months) from the 1st dose of study treatment to the onset of SPMs was 19.68, 25.15, and 18.27 months, respectively. Second primary malignancies were skin cancers in 7 (1.3%) participants in the VRd group. 27 (3.9%) participants in the IVRd group, and 62 (3.5%) of participants in the All-Isa group. Solid tumors other than skin cancers occurred in 8 (1.5%) participants, 20 (2.9%) participants, and 43 (2.4%) participants, respectively.

*Other significant adverse events*

*Haemolytic disorders*

In the IVRd group, a positive indirect Coombs test was reported during study treatment in 136 of 207 (65.7%) participants with both a negative test at baseline and at least one test during study treatment. No cases of hemolytic disorders, including transfusion reactions occurred within 8 days after blood cell transfusion. There were no reports of red blood cell transfusion reactions at any timepoint in the study.

*Supportive studies*: There were no PTs for haemolytic disorders in the NDMM VRd or IVRd groups. In the All-Isa group, 1 (<0.1%) participant had an event of transfusion reaction (Grade 2). The transfusion reaction (non-serious) started at Cycle 14 /Day 401 during a blood transfusion. The duration of the event was 1 day. The AE outcome was recovered/resolved. The indirect Coombs test results was negative on Day 401. The interval from the last study treatment to onset was 10 days. However, this transfusion reaction was not considered to be related to interference with a Coombs test.

*Tumour lysis syndrome (TLS)*

In the VRd group, no participants had TEAEs of TLS. In the IVRd group, 1 participant had a TEAE of TLS, which occurred at Cycle 01 Day 15 and was fatal.

In the All-Isa pool 7 participants with tumour lysis syndrome were observed.

*Infections/neutropenia*

Overall, TEAEs in the SOC infections and infestations were reported in 157 (86.7%) and 240 (91.3%) of participants in the VRd and IVRd groups, respectively.

Respiratory infections were the most frequent infections in the 2 groups. The frequency and severity of respiratory infections in the IVRd group (84.8%, Grade ≥3: 34.2%) were greater when compared with the VRd group (72.4%, Grade ≥3: 26.0%). The most frequently reported respiratory infections TEAEs (≥10% of participants in any treatment group) by PT were: upper respiratory tract infection (33.7% [Grade ≥3: 1.1%] in the VRd group and 34.2% [Grade≥3: 0.8%] in the IVRd group), pneumonia (19.3% [Grade ≥3: 12.7%], 30.0% [Grade ≥3: 20.2%]), COVID-19 (16.6% [Grade ≥3: 2.8%], 22.4% [Grade ≥3: 0.8%]), bronchitis (17.7% [Grade ≥3: 1.7%], 22.1% [Grade ≥3: 2.7%]), and nasopharyngitis (13.8% [with no Grade ≥3], 17.5% [with no Grade ≥3]).

Among 142 (78.5%) participants in the IVRd group and 214 (81.4%) participants in the VRd group who took prophylactic antibiotics, the incidence of TEAEs in the SOC infections and infestations was 83.8% and 90.7%, respectively. For the 39 participants the VRd group and 49 participants the IVRd group who did not take prophylactic antibiotics, the incidence of these TEAEs was 97.4% and 93.9%, respectively. The incidence of Grade ≥3 was lower in both groups for the participants who received antibiotic prophylaxis (35.2% versus 48.7%) in the VRd group and (43.5% versus 51.0%) in the IVRd group versus those not receiving antibiotic prophylaxis.

Neutropenia as AE was reported in 21.5% vs. 30.0%. As abnormal laboratory value neutropenia was reported in 80.1% vs. 87.5% of the participants and Grade 3 or 4 neutropenia was reported in 37.0% of VRd participants and 54.4% of IVRd participants. A total of 37 (20.4%) and 98 (37.3%) participants in the VRd and IVRd groups, respectively, received GCSF/GMCSF for prophylactic and/or curative intent. It was given in prophylactic intent in 7 (18.9%) participants in the VRd and 28 (28.6% of participants receiving GCSF/GMCSF) in the IVRd groups, respectively, and for curative intent in 37 (100%) and 94 (94.9%) participants, respectively).

Complicated neutropenia was derived from infections and laboratory values. It was observed in 15 (8.3%) and 33 (12.5%) participants in the VRd and IVRd groups, respectively. Febrile neutropenia was reported in 4 (2.2%) and 6 (2.3%) participants in the VRd and IVRd groups, respectively. Neutropenic infection was reported in 12 (6.6%) and 28 (10.6%) participants in the VRD and IVRd groups, respectively.

*Supportive studies:* In study TCD13983, in Part A, TEAEs of infections of any grade occurred in 22 (81.5%) participants and infection Grade ≥3 in 11 participants (40.7%). Grade 3 infections in >1 participant included bronchitis in 3 participants and cellulitis in 2 participants. In Part B, TEAEs of infections of any grade occurred (38 [82.6%] participants) and infection Grade ≥3 in 6 participants (2 participants with COVID-19 and 1 participant with Clostridium difficile colitis, pneumonia Hemophilus, Cytomegalovirus colitis, viral lower respiratory tract infection, and superinfection bacterial each).

In the All-Isa pool, in the VRd, IVRd, and All-Isa groups, 178 (34.2%) participants, 302 (43.6%) participants, and 875 (49.0%) participants, respectively, experienced at least 1 severe TEAE (all grades). For Grade ≥3 events, the number (%) of participants was 112 (21.5%), 199 (28.8%), and 542 (30.3%). The most frequently reported PTs (all grades) were: upper respiratory tract infection (13.2%, 16.6%, and 22.2%, respectively), pneumonia (9.6%, 17.1%, and 17.7%, respectively), bronchitis (8.1%, 11.8%, and 12.1%, respectively).

For Grade ≥3 events, the most frequently reported PT was pneumonia (6.7%, 11.6%, and 12.7%, respectively). In the All-Ia pool, in the VRd, IVRd, and All-Isa groups neutropenic complications (All grades) were experienced by 18 (3.5%) participants, 46 (6.6%) participants, and 120 (6.7%) participants, respectively.

*Viral re-activation*

In the EFC12522 (IMROZ) trial, the incidence of viral infections or reactivations was less in the IVRd group than in the VRd group (7.6% in IVRd group and 8.8% in VRd group; Table 61). All except one case of adenoviral infection in IVRd arm were due to Herpes viral infections or reactivations (7.2 vs 8.8%), There were no cases of Hepatitis B virus (HBV) reactivation.

*Cardiac events*

A total of 42 (23.2%) participants in the VRd group and 59 (22.4%) participants in the IVRd group experienced TEAEs (all grades) in the Cardiac disorders SOC. The most frequently reported TEAE in this SOC was atrial fibrillation (16 [8.8%] participants and 21 [8.0%] participants, respectively).

*Supportive studies*: In the All-Isa pool a total of 70 (13.4%) participants in the VRd group, 125 (18.1%) participants in the IVRd group, and 373 (20.9%) participants in the All-Isa group experienced any cardiac event during the treatment period; most events were not severe (Grade ≥3: 6.7%, 8.8%, and 9.5%, respectively).

The most frequently reported events (all grades by PT) in the VRd, IVRd, and All-Isa groups were: atrial fibrillation (4.0%, 4.6%, and 3.6%, respectively) in the Cardiac disorders SOC, and hypertension (3.5%, 5.3%, and 9.4%, respectively) in the Vascular disorders SOC.

## *Laboratory findings*

Severe haematological laboratory abnormalities are shown in **Table 29** and the most frequent (≥5%) severe electrolytes abnormalities are shown in **Table 30**.

**Table 29.** Haematology – Severe abnormalities during the on-treatment period (worst grade per patient) in Study EFC12522 - Safety population Study EFC12522

| **Laboratory parameter n/N1 (%)** | **VRd (N=181)** | **IVRd (N=263)** |
|---|---|---|
| Anemia | | |
| Grade 3 | 29/181 (16.0) | 46/263 (17.5) |
| Grade 4 | 0/181 | 0/263 |
| Lymphocyte count decreased | | |
| Grade 3 | 68/181 (37.6) | 118/263 (44.9) |
| Grade 4 | 28/181 (15.5) | 40/263 (15.2) |
| Neutrophil count decreased | | |
| Grade 3 | 51/181 (28.2) | 94/263 (35.7) |
| Grade 4 | 16/181 (8.8) | 49/263 (18.6) |
| White blood cell decreased | | |
| Grade 3 | 26/181 (14.4) | 72/263 (27.4) |
| Grade 4 | 4/181 (2.2) | 11/263 (4.2) |
| Platelet count decreased | | |
| Grade 3 | 35/181 (19.3) | 39/263 (14.8) |
| Grade 4 | 15/181 (8.3) | 40/263 (15.2) |

Note: % calculated using the number of patients with at least one event (n) over the number of patients assessed for each parameter (N1) during the on-treatment period.
The laboratory toxicity grades are derived based on NCI CTCAE version 4.03

**Table 30.** Electrolytes – Most frequent (≥5%) severe abnormalities during the on-treatment period (worst grade per patient) - Safety population Study EFC12522

| **Laboratory parameter n/N1 (%)** | **VRd (N=181)** | **IVRd (N=263)** |
|---|---|---|
| Hyponatremia | | |
| Grade 3 | 25/181 (13.8) | 38/263 (14.4) |
| Grade 4 | 2/181 (1.1) | 1/263 (0.4) |
| Hypokalemia | | |
| Grade 3 | 16/181 (8.8) | 38/263 (14.4) |
| Grade 4 | 1/181 (0.6) | 9/263 (3.4) |
| Hypermagnesemia | | |
| Grade 3 | 9/181 (5.0) | 13/262 (5.0) |
| Grade 4 | 1/181 (0.6) | 2/262 (0.8) |
| Hypophosphatemia | | |
| Grade 3 | 34/181 (18.8) | 52/262 (19.8) |
| Grade 4 | 3/181 (1.7) | 1/262 (0.4) |

Note: % calculated using the number of patients with at least one event (n) over the number of patients assessed for each parameter (N1) during the on-treatment period.
The laboratory toxicity grades are derived based on NCI CTCAE version 4.03

During the treatment period, Grade 3 hyperglycaemia was reported in 5 (3.2%) participants (with no Grade 4) in the VRd group and 11 (4.6%) participants (with no Grade 4) in the IVRd group, Grade 3 hypoalbuminemia was reported in 2 (1.1%) participants (with no Grade 4) in the VRd group and 2 (0.8%) participants (with no Grade 4) in the IVRd group.

During the treatment period, Grade 3 and 4 alanine aminotransferase increased was reported in 12 (6.6%) and 1 (0.6%) participants in the VRd group and 14 (5.3%) and 2 (0.8%) participants in the IVRd group; Grade 3 and 4 aspartate aminotransferase increased was reported in 6 (3.3%) and 1 (0.6%) participants in the VRd group and 5 (1.9%) and 3 (1.1%) participants in the IVRd group. Grade 3 hyperbilirubinaemia was reported in 1 (0.6%) participant in the VRd group and 7 (2.7%) participants in the IVRd group. No Grade 4 was reported in either group.

A single case with possible Hy's law was identified in which elevations of ALT, AST, and total bilirubin that satisfied Hy's Law criteria occurred on the same day. In this patient the event occurred on the day of death due to sepsis so drug induced liver injury could be ruled out.

Grade 3 and 4 creatinine increased was reported in 5 (2.8%) and 1 (0.6%) participant in the VRd group and 12 (4.6%) and 1 (0.4%) participants in the IVRd group, respectively.

Potentially clinically significant abnormal systolic blood pressure (mmHg) decreases were reported in 50 (27.6%) participants in the VRd group and 95 (36.1%) participants in the IVRd group, and increases in 47 (26.0%) in the VRd group and in 89 (33.8%) in the IVRd group, respectively.

Potentially clinically significant abnormal diastolic blood pressure (mmHg) decreases were reported in 18 (9.9%) participants in the VRd group and 51 (19.4%) participants in the IVRd group, and increases in 3 (1.7%) in the VRd group and in 7 (2.7%) in the IVRd group, respectively.

At baseline, 22 participants in the VRd group and 41 participants in the IVRd group had abnormal ECGs. A total of 31 (42.5%) participants in the VRd group and 36 (50.7%) participants in the IVRd group had ECGs that were normal at baseline and abnormal on treatment, and a total of 5 (22.7%) participants and 11 (26.8%) participants, respectively, had ECGs that were abnormal at baseline and normal on treatment.

In the All-Isa pool comparable or numerically slightly lower rates of haematological, metabolic, electrolyte laboratory abnormalities were observed.

**Immunogenicity**

A total of 253 of the 263 patients in the IVRd group and 25 patients in the crossover part were evaluable for ADA assessment. Twenty-two of 253 evaluable patients had treatment-induced ADA response, resulting in an ADA incidence of 8.7%. Among the 22 patients with treatment-induced ADA, 21 were considered to have a transient ADA response and 1 was considered to have an indeterminate ADA response. In addition, among those with treatment-induced ADA, 13 had a neutralizing response resulting in an NAb incidence of 5.1% (12 transient and 1 indeterminate NAb responses) and 5 had an inconclusive response. No apparent effect of positive ADA was observed on efficacy. No apparent effect of ADA positive was observed on safety. Although there was a higher incidence of serious adverse events (18 (81.8%) vs. 159 (68.8%)), all-grade neutropenic complications (7 (31.8%) vs. 24 (10.4%)), neutropenic complications Grade ≥3 (4 (18.2%) vs. 9 (3.9%)), and thrombocytopenia Grade ≥ 3 (10 (45.5%) vs. 66 (28.6%)) in the ADA positive cohort (**Table 31**).

**Table 31.** Summary of impact of treatment-emergent ADA on clinical safety by ADA status (Positive vs Negative) - ADA population

| n(%) | IVRd (N=253) | |
|---|---|---|
| | Positive (N=22) | Negative (N=231) |
| IRs | 6 (27.3) | 54 (23.4) |
| Grade ≥3 IRs | 0 | 0 |
| TEAEs | 21 (95.5) | 231 (100) |
| Grade ≥3 TEAEs | 20 (90.9) | 211 (91.3) |
| SAEs | 18 (81.8) | 159 (68.8) |
| Grade ≥3 SAEs | 17 (77.3) | 145 (62.8) |
| TEAEs leading to permanent discontinuation of study treatment | 5 (22.7) | 51 (22.1) |
| Grade ≥3 TEAEs leading to permanent discontinuation of study treatment | 5 (22.7) | 47 (20.3) |
| Neutropenia | 22 (100) | 202 (87.4) |
| Grade ≥3 Neutropenia | 11 (50.0) | 128 (55.4) |
| Neutropenic complications | 7 (31.8) | 24 (10.4) |
| Grade ≥3 Neutropenic complications | 4 (18.2) | 9 (3.9) |
| Thrombocytopenia | 19 (86.4) | 223 (96.5) |
| Grade ≥3 Thrombocytopenia | 10 (45.5) | 66 (28.6) |
| Hemorrhages | 5 (22.7) | 53 (22.9) |
| Grade ≥3 Hemorrhages | 1 (4.5) | 6 (2.6) |

IVRd: isatuximab in combination with bortezomib, lenalidomide and dexamethasone
The permanent discontinuation includes the definitive treatment discontinuation and the premature treatment discontinuation of isatuximab. Only safety events that occurred during treatment period were summarized.
MedDRA 26.0

*Supportive studies:* The results in the All-Isa pool were consistent with those reported in Study EFC12522(data not shown).

## *Safety in special populations*

### *Age*

Subgroup analyses per age are shown in **Table 32**.

**Table 32.** Overview of TEAEs by age - Safety population Study EFC12522

| | Age <70 (N=136) | | Age ≥70 to <75 (N=183) | | Age ≥75 (N=125) | |
|---|---|---|---|---|---|---|
| | VRd (N=56) | IVRd (N=80) | VRd (N=68) | IVRd (N=115) | VRd (N=57) | IVRd (N=68) |
| Patients with any TEAE | 54 (96.4) | 80 (100) | 68 (100) | 114 (99.1) | 56 (98.2) | 68 (100) |
| Patients with any grade ≥ 3 TEAE | 45 (80.4) | 76 (95.0) | 59 (86.8) | 101 (87.8) | 48 (84.2) | 64 (94.1) |
| Patients with any grade 3-4 TEAE | 45 (80.4) | 76 (95.0) | 58 (85.3) | 97 (84.3) | 48 (84.2) | 63 (92.6) |
| Patients with any grade 5 TEAE | 3 (5.4) | 5 (6.3) | 5 (7.4) | 15 (13.0) | 2 (3.5) | 9 (13.2) |
| Patients with any treatment emergent SAE*b* | 31 (55.4) | 55 (68.8) | 52 (76.5) | 82 (71.3) | 39 (68.4) | 49 (72.1) |
| Patients with any TEAE leading to definitive treatment discontinuation | 13 (23.2) | 15 (18.8) | 20 (29.4) | 29 (25.2) | 14 (24.6) | 16 (23.5) |
| Patients with any TEAE leading to premature discontinuation of Isatuximab | NA | 3 (3.8) | NA | 3 (2.6) | NA | 0 |
| Patients with any TEAE leading to premature discontinuation of Bortezomib | 5 (8.9) | 8 (10.0) | 9 (13.2) | 10 (8.7) | 3 (5.3) | 14 (20.6) |
| Patients with any TEAE leading to premature discontinuation of Lenalidomide | 2 (3.6) | 13 (16.3) | 0 | 13 (11.3) | 2 (3.5) | 8 (11.8) |
| Patients with any TEAE leading to premature discontinuation of Dexamethasone | 14 (25.0) | 8 (10.0) | 11 (16.2) | 6 (5.2) | 6 (10.5) | 4 (5.9) |

| | Age <70 (N=136) | | Age ≥70 to <75 (N=183) | | Age ≥75 (N=125) | |
|---|---|---|---|---|---|---|
| | VRd (N=56) | IVRd (N=80) | VRd (N=68) | IVRd (N=115) | VRd (N=57) | IVRd (N=68) |
| Patients with any AESI*c* | 2 (3.6) | 11 (13.8) | 9 (13.2) | 17 (14.8) | 2 (3.5) | 8 (11.8) |
| Patients with any treatment-related TEAE*d* (any grade) | 52 (92.9) | 79 (98.8) | 68 (100) | 111 (96.5) | 55 (96.5) | 67 (98.5) |
| Patients with any treatment-related grade ≥ 3 TEAE | 36 (64.3) | 66 (82.5) | 48 (70.6) | 81 (70.4) | 39 (68.4) | 55 (80.9) |
| Patients with any serious treatment-related TEAE | 12 (21.4) | 31 (38.8) | 25 (36.8) | 35 (30.4) | 21 (36.8) | 21 (30.9) |

TEAE: Treatment emergent adverse event, AESI: Adverse event of special interest, SAE: serious adverse event, IR: infusion reaction

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

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

*c* AESIs include IR of grade ≥3, pregnancy (female patient or female partner), symptomatic overdose with study treatment or NIMP and second primary malignancy

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

In the All-Isa pool, in both the VRd and IVRd groups, incidences for any (treatment-related) TEAEs, Grade ≥3 (treatment-related) TEAEs, treatment emergent SAEs, and definitive treatment discontinuations all increased in participants who were >65 years of age, with incidences highest in the ≤75 years /71- 80 years of age category.

*Gender*

Males in the IVRd group (but not in the VRd group) had a higher incidence of AESIs (18.2%, compared to 8.3% for females in the IVRd group), due to a difference in SPMs; TEAEs in the SOC neoplasms benign, malignant and unspecified were reported in 24.5% of males in the IVRd group and 12.5% of females in the IVRd group, with the difference driven by the PTs of squamous cell carcinoma of skin, basal cell carcinoma, Bowen's disease, and colorectal adenoma. Aside from this, no consistent trends by gender were observed.

In the All-Isa pool no consistent trends by gender were observed, however data on AESIs were not provided.

*Race, renal function, hepatic function*

In general, there did not appear to be any trends in the incidence of TEAEs by race, renal function, hepatic function for IVRd subgroups.

In the All-Isa pool Non-Caucasians had a higher incidence of any treatment-related TEAE, any grade ≥3 TEAE, any serious TEAE, any treatment-related serious TEAE in the NDMM VRd (N=521) and IVRd (N=692) group, but not in the RRMM and NDMM All-Isa (N=1787) group. There did not appear to be any trends in the incidence of TEAEs by renal function and hepatic function for IVRd subgroups.

## Discontinuation due to adverse events

Overall, 47 (26.0%) and 60 (22.8%) participants in the VRd and IVRd groups, respectively, had TEAEs leading to definitive treatment discontinuation (discontinuation of all study intervention or the last ongoing study drug; **Table 33**).

**Table 33.** TEAEs leading to definitive treatment discontinuation by Primary SOC and PT - Safety population Study EFC12522

| | VRd (N=181) | | IVRd (N=263) | |
|---|---|---|---|---|
| **Primary System Organ Class Preferred Term [n(%)]** | **All grades** | **Grade ≥ 3** | **All grades** | **Grade ≥ 3** |
| Any class | 47 (26.0) | 37 (20.4) | 60 (22.8) | 57 (21.7) |
| Infections and infestations | 17 (9.4) | 16 (8.8) | 22 (8.4) | 22 (8.4) |
| Covid-19 pneumonia | 1 (0.6) | 1 (0.6) | 8 (3.0) | 8 (3.0) |
| Pneumonia | 4 (2.2) | 4 (2.2) | 6 (2.3) | 6 (2.3) |
| Sepsis | 1 (0.6) | 1 (0.6) | 2 (0.8) | 2 (0.8) |
| Bronchitis fungal | 0 | 0 | 1 (0.4) | 1 (0.4) |
| Candida sepsis | 0 | 0 | 1 (0.4) | 1 (0.4) |
| Diarrhoea infectious | 0 | 0 | 1 (0.4) | 1 (0.4) |
| Lower respiratory tract infection viral | 0 | 0 | 1 (0.4) | 1 (0.4) |
| Pneumonia klebsiella | 0 | 0 | 1 (0.4) | 1 (0.4) |
| Pneumonia pseudomonal | 1 (0.6) | 1 (0.6) | 1 (0.4) | 1 (0.4) |
| Septic shock | 1 (0.6) | 1 (0.6) | 1 (0.4) | 1 (0.4) |
| Bronchitis | 1 (0.6) | 1 (0.6) | 0 | 0 |
| Clostridium difficile colitis | 1 (0.6) | 1 (0.6) | 0 | 0 |
| Covid-19 | 3 (1.7) | 3 (1.7) | 0 | 0 |
| Escherichia sepsis | 1 (0.6) | 1 (0.6) | 0 | 0 |
| Meningitis cryptococcal | 1 (0.6) | 1 (0.6) | 0 | 0 |
| Osteomyelitis | 1 (0.6) | 0 | 0 | 0 |
| Pneumonia aspiration | 1 (0.6) | 1 (0.6) | 0 | 0 |
| Respiratory syncytial virus infection | 1 (0.6) | 1 (0.6) | 0 | 0 |
| Urinary tract infection | 2 (1.1) | 2 (1.1) | 0 | 0 |
| Urosepsis | 1 (0.6) | 1 (0.6) | 0 | 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | 6 (3.3) | 4 (2.2) | 11 (4.2) | 11 (4.2) |
| Rectal adenocarcinoma | 0 | 0 | 2 (0.8) | 2 (0.8) |
| Colorectal cancer | 0 | 0 | 1 (0.4) | 1 (0.4) |
| Lung neoplasm malignant | 0 | 0 | 1 (0.4) | 1 (0.4) |
| Malignant melanoma stage iv | 0 | 0 | 1 (0.4) | 1 (0.4) |
| Myelodysplastic syndrome | 1 (0.6) | 1 (0.6) | 1 (0.4) | 1 (0.4) |
| Neuroendocrine carcinoma of the skin | 0 | 0 | 1 (0.4) | 1 (0.4) |
| Prostate cancer | 0 | 0 | 1 (0.4) | 1 (0.4) |
| Small cell lung cancer | 0 | 0 | 1 (0.4) | 1 (0.4) |
| Squamous cell carcinoma of lung | 0 | 0 | 1 (0.4) | 1 (0.4) |
| Squamous cell carcinoma of skin | 0 | 0 | 1 (0.4) | 1 (0.4) |
| Adenocarcinoma of colon | 2 (1.1) | 2 (1.1) | 0 | 0 |
| Bladder transitional cell carcinoma | 1 (0.6) | 0 | 0 | 0 |
| Invasive ductal breast carcinoma | 1 (0.6) | 1 (0.6) | 0 | 0 |
| Skin cancer | 1 (0.6) | 0 | 0 | 0 |
| Blood and lymphatic system disorders | 3 (1.7) | 3 (1.7) | 1 (0.4) | 1 (0.4) |
| Febrile neutropenia | 0 | 0 | 1 (0.4) | 1 (0.4) |
| Anaemia | 1 (0.6) | 1 (0.6) | 0 | 0 |
| Aplasia pure red cell | 1 (0.6) | 1 (0.6) | 0 | 0 |
| Thrombocytopenia | 1 (0.6) | 1 (0.6) | 0 | 0 |
| Metabolism and nutrition disorders | 0 | 0 | 1 (0.4) | 1 (0.4) |
| Tumour lysis syndrome | 0 | 0 | 1 (0.4) | 1 (0.4) |
| Nervous system disorders | 4 (2.2) | 3 (1.7) | 8 (3.0) | 6 (2.3) |
| Chronic inflammatory demyelinating polyradiculoneuropathy | 0 | 0 | 2 (0.8) | 2 (0.8) |
| Dementia | 1 (0.6) | 0 | 1 (0.4) | 1 (0.4) |
| Hypersomnia | 0 | 0 | 1 (0.4) | 1 (0.4) |
| Ischaemic stroke | 0 | 0 | 1 (0.4) | 1 (0.4) |
| Memory impairment | 0 | 0 | 1 (0.4) | 0 |
| Neuralgia | 0 | 0 | 1 (0.4) | 0 |
| Parkinson's disease | 0 | 0 | 1 (0.4) | 1 (0.4) |
| Peripheral sensory neuropathy | 0 | 0 | 1 (0.4) | 0 |
| Guillain-barre syndrome | 1 (0.6) | 1 (0.6) | 0 | 0 |
| Loss of consciousness | 1 (0.6) | 1 (0.6) | 0 | 0 |
| Peripheral sensorimotor neuropathy | 1 (0.6) | 1 (0.6) | 0 | 0 |
| Cardiac disorders | 4 (2.2) | 3 (1.7) | 1 (0.4) | 1 (0.4) |
| Atrial fibrillation | 1 (0.6) | 1 (0.6) | 1 (0.4) | 1 (0.4) |
| Atrial flutter | 1 (0.6) | 0 | 0 | 0 |
| Cardiac failure | 1 (0.6) | 1 (0.6) | 0 | 0 |
| Cardiac failure acute | 1 (0.6) | 1 (0.6) | 0 | 0 |
| Vascular disorders | 2 (1.1) | 2 (1.1) | 0 | 0 |
| Hypotension | 1 (0.6) | 1 (0.6) | 0 | 0 |
| Orthostatic hypotension | 1 (0.6) | 1 (0.6) | 0 | 0 |

| Primary System Organ Class<br>Preferred Term [n(%)] | VRd (N=181)<br>All grades | Grade ≥ 3 | IVRd (N=263)<br>All grades | Grade ≥ 3 |
|---|---|---|---|---|
| Respiratory, thoracic and mediastinal disorders | 4 (2.2) | 2 (1.1) | 2 (0.8) | 2 (0.8) |
| Dyspnoea | 2 (1.1) | 0 | 1 (0.4) | 1 (0.4) |
| Pulmonary embolism | 1 (0.6) | 1 (0.6) | 1 (0.4) | 1 (0.4) |
| Chronic obstructive pulmonary disease | 1 (0.6) | 1 (0.6) | 0 | 0 |
| Gastrointestinal disorders | 5 (2.8) | 1 (0.6) | 0 | 0 |
| Diarrhoea | 5 (2.8) | 1 (0.6) | 0 | 0 |
| Hepatobiliary disorders | 0 | 0 | 3 (1.1) | 3 (1.1) |
| Congestive hepatopathy | 0 | 0 | 1 (0.4) | 1 (0.4) |
| Hepatic cirrhosis | 0 | 0 | 1 (0.4) | 1 (0.4) |
| Hepatitis cholestatic | 0 | 0 | 1 (0.4) | 1 (0.4) |
| Skin and subcutaneous tissue disorders | 1 (0.6) | 1 (0.6) | 2 (0.8) | 1 (0.4) |
| Drug eruption | 0 | 0 | 1 (0.4) | 0 |
| Rash | 0 | 0 | 1 (0.4) | 1 (0.4) |
| Erythema multiforme | 1 (0.6) | 1 (0.6) | 0 | 0 |
| Musculoskeletal and connective tissue disorders | 1 (0.6) | 1 (0.6) | 1 (0.4) | 1 (0.4) |
| Spinal osteoarthritis | 0 | 0 | 1 (0.4) | 1 (0.4) |
| Muscular weakness | 1 (0.6) | 1 (0.6) | 0 | 0 |
| Renal and urinary disorders | 2 (1.1) | 2 (1.1) | 2 (0.8) | 2 (0.8) |
| Renal impairment | 0 | 0 | 1 (0.4) | 1 (0.4) |
| Renal tubular acidosis | 0 | 0 | 1 (0.4) | 1 (0.4) |
| Acute kidney injury | 1 (0.6) | 1 (0.6) | 0 | 0 |
| Chronic kidney disease | 1 (0.6) | 1 (0.6) | 0 | 0 |
| General disorders and administration site conditions | 5 (2.8) | 4 (2.2) | 7 (2.7) | 7 (2.7) |
| Sudden death | 0 | 0 | 4 (1.5) | 4 (1.5) |
| Asthenia | 1 (0.6) | 0 | 1 (0.4) | 1 (0.4) |
| Death | 1 (0.6) | 1 (0.6) | 1 (0.4) | 1 (0.4) |
| Multiple organ dysfunction syndrome | 0 | 0 | 1 (0.4) | 1 (0.4) |
| Fatigue | 1 (0.6) | 1 (0.6) | 0 | 0 |
| General physical health deterioration | 1 (0.6) | 1 (0.6) | 0 | 0 |
| Generalised oedema | 1 (0.6) | 1 (0.6) | 0 | 0 |
| Investigations | 0 | 0 | 1 (0.4) | 1 (0.4) |
| Amylase increased | 0 | 0 | 1 (0.4) | 1 (0.4) |
| Injury, poisoning and procedural complications | 0 | 0 | 3 (1.1) | 3 (1.1) |
| Fall | 0 | 0 | 2 (0.8) | 2 (0.8) |
| Femur fracture | 0 | 0 | 2 (0.8) | 2 (0.8) |

TEAE: Treatment emergent adverse event, SOC: System organ class, PT: Preferred term
MedDRA 26.0
n(%) = number and percentage of patients with at least one TEAE leading to definitive treatment discontinuation

Treatment-emergent AEs leading to isatuximab premature treatment discontinuation were reported in 6 (2.3%) participants in the IVRd group. The TEAEs leading to isatuximab (N=6) premature treatment discontinuation were anaphylactic reaction, confusional state, pneumonitis, pulmonary fibrosis, rash, and infusion-related reaction (1 [0.4%] each).

Treatment-emergent AEs leading to premature bortezomib treatment discontinuation were reported in 17 (9.4%) participants in the VRd group and 32 (12.2%) participants in the IVRd group. This was mostly due to peripheral sensory neuropathy (7 [3.9%] in the VRd group and 20 [7.6%] in the IVRd group) and peripheral sensorimotor neuropathy (3 [1.7%], 2 [0.8%]), respectively.
Treatment-emergent AEs leading to premature lenalidomide treatment discontinuation were reported in 4 (2.2%) participants in the VRd group and 34 (12.9%) participants in the IVRd group. This was mostly due to peripheral sensory neuropathy (1 [0.6%] in the VRd group and 5 [1.9%] in the IVRd group) and atrial fibrillation (1 [0.6%], 1 [0.4%]), respectively.

Treatment-emergent AEs leading to premature dexamethasone treatment discontinuation were reported in 31 (17.1%) participants in the VRd group and 18 (6.8%) participants in the IVRd group. This was mostly due to fatigue (5 [2.8%] in the VRd group and no participants in the IVRd group) and insomnia (3 [1.7%], 1 [0.4%]), respectively.

*AEs leading to dose modifications*

Overall, 117 (64.6%) participants in the VRd group and 191 (72.6%) participants in the IVRd group had at least 1 TEAE (all grades) leading to dose delay. The most frequently reported TEAEs leading to dose delay (in ≥10% of the participants, all grades) were: neutropenia (33 [18.2%] participants in the VRd group and 58 [22.1%] participants in the IVRd group), COVID-19 (16 [8.8%], 40 [15.2%]), upper respiratory tract infection (16 [8.8%], 31 [11.8%]), and pneumonia (12 [6.6%], 42 [16.0%]).

Treatment-emergent AEs leading to dose interruption of isatuximab were reported in 56 (21.3%) participants in the IVRd group. The most frequently reported TEAE leading to dose interruption (in ≥10% of the participants, all grades) was: infusion-related reaction (55 [20.9%] participants).

Dose reductions and omissions were permitted for lenalidomide, bortezomib, and dexamethasone. Dose reductions were not permitted for isatuximab, and dose omissions were permitted. "Dose reduction" was recorded as the action taken for both dose reductions and dose omissions.

Treatment-emergent AEs led to isatuximab dose reductions/omissions in 137 (52.1%) participants in the IVRd group. The most frequently reported TEAE leading to dose reduction (with an incidence≥10%) was: upper respiratory tract infection.

Treatment-emergent AEs led to bortezomib dose reductions/omissions in 127 (70.2%) participants in the VRd group and 183 (69.6%) participants in the IVRd group. The most frequently reported TEAE leading to dose reduction (with an incidence ≥10% in either group) was: peripheral sensory neuropathy (55 [30.4%] in the VRd group and 74 [28.1%] in the IVRd group).

Treatment-emergent AEs led to lenalidomide dose reductions/omissions in 141 (77.9%) participants in the VRd group and 218 (82.9%) participants in the IVRd group. The most frequently reported TEAEs leading to dose reduction (with an incidence ≥10% in either group) were: diarrhoea (23 [12.7%] in the VRd group and 38 [14.4%] in the IVRd group), neutropenia (21 [11.6%], 49 [18.6%]), pneumonia (18 [9.9%], 27 [10.3%]), and upper respiratory tract infection (17 [9.4%], 29 [11.0%]).

Treatment-emergent AEs led to dexamethasone dose reductions/omissions in 140 (77.3%) participants in the VRd group and 216 (82.1%) participants in the IVRd group. The most frequently reported TEAEs leading to dose reduction (with an incidence ≥10% in either group) were: pneumonia (17 [9.4%] in the VRd group and 32 [12.2%] in the IVRd group) and upper respiratory tract infection (13 [7.2%], 28 [10.6%]).

*Supportive studies*

No data have been provided from study TCD13983.

In the All-Isa group TEAEs leading to any dose modification of isatuximab were observed in 1187 of the participants (66.4%). The most frequently reported TEAEs that led to dose modifications of isatuximab in the All-Isa group were infusion related reaction (27.4%), neutropenia (13.3%), pneumonia (11.2%), upper respiratory tract infection (10.6%), bronchitis (5.1%), thrombocytopenia (4.6%), and COVID-19 (4.5%).

## *Post marketing experience*

*Interference with blood typing*

A total of 4 cases were reported in the in the interval period between the last PBRER and the data lock point of this SCS (02 March 2023 to 26 September 2023).

There was a single clinical trial case from an investigator-initiated study of PT Haemolytic Uraemic Syndrome; and one case each of PTs Haemolysis, Haemolytic Anaemia and Reticulocytosis from unsolicited reports. These cases did not suggest involvement of a blood transfusion.

Cumulatively in the Sanofi PV database there has been one case of PT Transfusion Reaction, however this was a reaction to a platelet transfusion as opposed to red cell transfusion. There have been no case reports in the Sanofi GPV database of red blood cell transfusion reactions to date.

*Infusion related reactions of Grade ≥3*

A total of 151 cases were retrieved for the interval period between the last PBRER and the data lock point of this SCS. Of these cases, there are 47 events of either 'Infusion related hypersensitivity' or 'Infusion related reaction'. After limiting the events to cases that were either non-solicited or from non-Sanofi sponsored trials, new events received within the above interval, and events that were of intensity Grade ≥3, "severe," or "blank" 9 cases were identified. Two additional cases that were classified as serious were also further investigated: one was due to carfilzomib and one was stated to be due to isatuximab for a total of 10. All cases were categorized as recovered resolved. All were considered to be due to isatuximab.

*Anaphylactic reaction*

A total of 9 events in 8 cases were retrieved for the interval period between the last PBRER and the data lock point of this SCS. Latency was not available for 6 of the cases. 5 events were reported as Anaphylactic reaction and 4 as anaphylactic shock. No events were reported to have a fatal outcome.

*Viral reactivation*

A total of 16 events in 16 cases (14 solicited and two unsolicited) were retrieved for the interval period between the last PBRER and the data lock point of this SCS. Herpes Zoster was the most frequent PT (Herpes Zoster 5, Herpes Zoster 1 and Herpes Zoster disseminated 1). There were 2 events of PT: Cytomegalovirus infection, and one event each of PTs: Anogenital warts, Cytomegalovirus infection reactivation, Epstein Barr virus positive mucocutaneous ulcer, Hepatitis B reactivation; Hepatitis E, Herpes Virus Infection, and two of Progressive Multifocal encephalopathy. 8 events were recovered/ resolved, 1 recovering / resolving, 5 cases not recovered / resolved and for two outcome is unknown. There were no fatal cases.

*Secondary primary malignancies*

A total of 73 cases (7 unsolicited and 66 solicited) were retrieved for the interval period between the last PBRER and the data lock point of this SCS. There were 94 events in the 73 cases, twenty four events were directly related to the multiple myeloma (PTs: Plasma cell myeloma 15, Plasma cell myeloma recurrent 3, Plasmacytoma 2, Plasma Cell Leukaemia 3 and Leptomeningeal Myelomatosis 1).

Thirty five (35) of the events were skin cancers, and the remaining non skin cancers. Of the non-skin cancers, there were two events each of acute lymphocytic leukemia and adenocarcinoma of colon, and there was one event each of the other tumors. There were no rare or unusual tumours.

*Tumour Lysis Syndrome*

One case was retrieved for the interval period between the last PBRER and the data lock point of this SCS. A >65-year-old male who had an extensive and serious medical history developed mild Tumor Lysis syndrome the day after commencing isatuximab, carfilzomib and dexamethasone in a Sanofi observational study. The patient developed significant other events over 7 months and died of disease progression.

## 2.5.1. Discussion on clinical safety

Duration of exposure and number of exposed patients in the IVRd arm in the pivotal study are sufficient for the safety assessment of the newly proposed treatment regimen. Supportive studies provide additional information on the safety profile in the new indication. The open label nature of the trial may have influenced reporting of safety.

*AEs*

Overall, the number of (treatment-related) TEAEs, Grade ≥ 3 TEAE, SAEs were numerically slightly higher in the IVRd arm compared to the VRd arm. This could have been influenced by the longer exposure in the IVRd arm (53.2 months) compared to the VRd arm (31.3 months), as the differences between the two treatment arms are less pronounced when comparing exposure-adjusted TEAEs. Any grade ≥3 TEAE and infusion related reactions remained higher in the IVRd arm after adjusting for exposure. The latter was to be expected since isatuximab is the only drug that was administered via infusion. The exposure-adjusted rate for Grade ≥3 TEAEs was 1.171 and 0.986 events per patient-year in the Isa-VRd and VRd groups, respectively, 0.031 and 0.019 for Grade 5 TEAEs, 0.375 and 0.435 for treatment-emergent serious adverse events, and 0.066 and 0.090 for TEAEs leading to treatment discontinuation, respectively.

TEAEs reported more frequently in the IVRd group than in the VRd group (with an difference of ≥5%) were infusion related reaction (23.6% vs. 1.1%), cataract (38.0% vs. 25.4), pneumonia (30.0% vs. 19.3%), fatigue (34.6% vs 26.5%), neutropenia (30.0% vs. 21.5%), diarrhoea (54.8% vs. 48.6%), COVID-19 (22.4% vs. 16.6%), and back pain (22.1% vs 17.1%). The most frequent Grade ≥3 TEAEs were neutropenia (30% vs. 20.4%), pneumonia (20.2% vs. 12.7%), cataract (15.6% vs 11.0%), and thrombocytopenia (11.8% vs 10.5%).

In the supportive studies the safety profile was comparable to that observed in the pivotal study, except for the lower frequencies of AEs, most likely due to the shorter exposure in these studies. Overall, the observed safety is in line with the known safety profile for isatuximab.

Cataract was reported with a slightly higher incidence in the IVRd arm compared to the VRd arm and has been included in section 4.8 as adverse drug reactions reported in patients with multiple myeloma treated with isatuximab in combination with bortezomib, lenalidomide, and dexamethasone.

*SAEs*

Serious TEAEs were observed at a comparable frequency (67.4% vs. 70.7%), also at the exposure adjusted incidence. The most frequently reported serious TEAE pneumonia (29.7% vs. 21.0% in the IVRd group vs. the VRd group). Other SAEs had a frequency of ≤5%. This is in line with the known safety profile for isatuximab.

*Deaths*

During the treatment period, there were more deaths in the IVRd arm compared to the VRd arm (N=29 (11.0%) vs. N=9 (5.0%)). These deaths are of concern as it could relate to the intensity of the IVRd schedule, particularly as most deaths due to AEs are infectious in nature (6.5% vs. 3.9%). On the other hand, there are more deaths in the VRd arm compared to the IVRd arm in the post treatment period (15.2% vs. 26.5%) and overall (26.2% vs. 32.6%), most of which are due to disease progression. It appears that the more intense regimen of IVRd leads to less disease progression.

No dose escalation/finding studies of isatuximab with VRd have been presented. It is unknown whether a different dose of isatuximab/VRd would have resulted in less on-treatment deaths. This is considered to be an uncertainty, however this uncertainty is not pursued as, it is not known whether a similar efficacy would have been observed with a different regimen.

*AESIs and other events of interest*

IRRs were observed in 24% of the IVRd patients. Few severe IRRs were observed (one Grade 3 event and one Grade 4 event). The IRRs were managed with premedication and interruptions. One (0.4%) event of anaphylactic reaction (Grade 3) was observed in the IVRd group. Isatuximab was discontinued in 0.8% of patients due to infusion reactions. The description of IRRs is in line with what is known for these events from previous studies and anaphylactic reaction is included as an ADR in patients treated with isatuximab in combination with bortezomib, lenalidomide, and dexamethasone. In addition, and in line with the protocol of the pivotal study, section 4.2 of the SmPC states that in case of Grade ≥ 3 hypersensitivity reactions or infusion reaction, isatuximab treatment should be permanently discontinued.

Secondary primary malignancies (SPM) were observed in in 42 patients (16.0%, 0.041 events per patient-year)) of the IVRd patients and in 16 patients (8.8%, 0.026 events per patient-year) of the IRd patients. SPMs were skin cancers in the majority of cases (8.4% vs 3.9%), solid tumours other than skin cancers (6.5% vs. 3.9%) and haematological (1.1% in each group) were less frequent. Patients with SPM of skin cancer continued treatment after resection of the skin cancer, except one patient in each treatment group. SPMs with fatal outcome were reported in 6 patients (2.3%) in the IVRd group (neuroendocrine carcinoma of the skin, malignant melanoma, squamous cell carcinoma of the skin, squamous cell carcinoma of lung, colorectal cancer, and rectal adenocarcinoma) and in 2 patients (1.1%) in the VRd group (metastases to peritoneum and adenocarcinoma of colon). A recent study, among 737 patients with NDMM not eligible for ASCT who were randomly assigned to daratumumab plus lenalidomide and dexamethasone or to lenalidomide and dexamethasone has reported a similar incidence of SPMs with those observed in study EFC12522: After a 28 month follow, 8.8% and 7.1% of the patients respectively, had developed a SPM and 20% and 13%, respectively 8 after 56 months of follow up. (Facon T et,al, 2019 and Facon T et,al, 2021). Physicians should carefully evaluate patients before and during treatment as per IMWG guidelines for occurrence of SPM and initiate treatment as indicated.

TLS was observed in one patient in the IVRd arm; on Day 15 of Cycle 1, an AE of Tumour lysis syndrome/ renal tubular acidosis (Grade 5) was reported. The association of TLS with isatuximab has been described in the SmPC and no further updates to the product information are warranted from this new case.

Infections were observed in almost all patients, at similar rates between the study arms (IVRd group, any Grade: 91.3%, Grade ≥3 TEAEs 44.9% vs. VRd group, any Grade: 86.7% Grade ≥3 TEAEs: 38.1%). Infections mostly concerned respiratory infections. Prophylactic antibiotics were given in most patients. The SmPC states that antibacterial and antiviral prophylaxis (such as herpes zoster prophylaxis) according to treatment guidelines should be considered during treatment. Incidence of herpes zoster was 5.7% in the IVRd group compared to 5.5% in the VRd group. Pneumonia was the most commonly reported severe infection with Grade 3 reported in 25.1% of patients in the IVRd group compared to 15.5% in the VRd group, Grade 4 in 2.3% of patients in the IVRd group compared to 3.9% in the VRd group. Grade 5 pneumonia, based on preferred term, occurred in 1.5% of patients in the Isa-VRd group compared to 1.1% in the VRd group. Fatal infections were reported in 6.5% of patients in the Isa-VRd group and 4.4% in the VRd group.

For bronchitis the absolute incidence (22.1% IVRd vs 17.7% VRd) as well as the exposure adjusted incidence (0.075 IVRd vs. 0.071 VRd) of bronchitis was higher in the IVRd group than the VRd group. Similarly, for vomiting the absolute incidence of vomiting was higher in the IVRd group than the VRd group (10.6% vs 7.7%, respectively) as was the incidence adjusted rate (0.033 IVRd vs 0.028 VRd, respectively).

Finally, the occurrence of COVID-19 was reported in study EFC12522 which has not been previously described, as this disease was likely not prevalent at the time of earlier submissions. All have now been included as an ADR in section 4.8 reported in patients treated with isatuximab in combination with bortezomib, lenalidomide, and dexamethasone.

In patients treated with IVRd, neutropenia was reported as a laboratory abnormality in 87.5% of patients and as an adverse reaction in 30% of patients, with Grade 3-4 neutropenia reported as a laboratory abnormality in 54.4% of patients (with 35.7% Grade 3 and 18.6% Grade 4) and as an adverse reaction in 30% of patients. Neutropenic complications have been observed in 12.5% of patients, including 2.3% of febrile neutropenia and 10.6% of neutropenic infection. The guidelines in the EFC12522 study protocol for dose adjustments in response to hematologic toxicities recommends treatment delay for Grade 3 or Grade 4 neutropenia or for febrile neutropenia and/or neutropenic infection until the absolute neutrophil count improves to at least 1 x $10^9$ /L, and until fever and infection recover in case of febrile neutropenia and/or neutropenic infection, and this is now also reflected in the SmPC.

The safety information in the SmPC sections 4.4 and 4.8 reflects the risk for infections, especially respiratory infections. There are also recommendations for their management.

*Laboratory findings*
Severe haematological laboratory abnormalities were very common in both the IVRd and VRd group, however Grade 3-4 neutropenia (54.3% vs. 37.0%) and decreased white blood cells (31.6% vs. 16.6%) were more frequently observed in the IVRd group. Neutropenia has been described for other isatuximab combination regimens. Therefore, the MAH was requested to add thrombocytopenia, anaemia and lymphopenia as ADRs for IVRd.

In total, N=22/253 (8.7%) patients evaluable for ADA assessment. In total 13 patients (5.1%) had a NAbs (12 transient and 1 indeterminate NAb responses) and 5 had an inconclusive response. Subgroups of patients with positive ADA/NAb result are considered too small to evaluate an effect on efficacy or safety in the pivotal study. Supportive data was provided which indicated that (≥ Grade 3) neutropenic complications, ≥ Grade 3 thrombocytopenia and ≥ Grade 3 haemorrhages seem to occur more often in ADA positive NDMM Isa-treated/IVRd patients compared to ADA negative patients. Therefore, the effect of ADA positivity on safety in NDMM patients is considered uncertain, as reflected in the SmPC.

*Special populations*
A sufficient number of patients of ≥70 years of age have been included as is fitting with the epidemiology of MM. In subgroups per age, the safety is general comparable, except for fatal TEAEs, which were not were reported in patients less than 65, but reported in 10.7 % of patients 65-74, and in 13.2% of patients 75 or older and this information has been included in the SmPC.

Safety between males and females was generally comparable except that in the IVRd group AESI were observed more frequently in males compared to females, due to a difference in SPMs (24.5% TEAEs in the SOC neoplasms benign, malignant and unspecified in males versus 12.5% in females). In general, there did not appear to be any trends in the incidence of TEAEs by race, renal function, hepatic function for IVRd subgroups.

*Discontinuations and dose modifications due to AEs*
Discontinuation of all study medication due to AEs was observed in comparable rates between the study arms (IVRd 22.8% vs. VRd 26.0%). Most commonly due to infections (8.4% vs. 9.4%), with the most common PT in the IVRd group being pneumonia (2.3% vs 2.2%). Als discontinuations due to neoplasms (4.2% vs. 3.3%) were relatively frequently observed. AEs leading to isatuximab premature treatment discontinuation were reported in 6 (2.3%) participants in the IVRd group; anaphylactic reaction, confusional state, pneumonitis, pulmonary fibrosis, rash, and infusion-related reaction (1 [0.4%] each). Dose modifications were frequent in both the IVRd and VRd groups (72.6% vs. 64.6%). The most frequently reported TEAEs leading to dose delay were: neutropenia (22.1% vs. 18.2%), COVID-19

(15.2% vs. 8.8%), upper respiratory tract infection (11.8% vs. 8.8%) and pneumonia (16.0% vs. 6.6%). The reasons for TEAEs leading to discontinuation/dose modification are related to the known safety profile for isatuximab or VRd.

*Post marketing experience*
The post marketing safety data provided by the MAH are in line with the known safety concerns.

### 2.5.2. Conclusions on clinical safety

Safety findings from the pivotal study EFC12522 and the supportive TCD13983 study are consistent with the known safety profile of isatuximab as characterised previously.

The addition of isatuximab to VRd leads to a slightly higher toxicity, most notably for infusion related reactions, pneumonia, severe neutropenia and secondary primary malignancies which are known safety concerns from other isatuximab treatment regimes. New ADRs, such as COVID-19 and cataract, which were reported with a higher incidence in patients treated with IVRd compared to VRd have been included in the product information.

Overall, submitted safety information supports the use of isatuximab in combination with bortezomib, lenalidomide and dexamethasone for the treatment of adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant.

### 2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

## *2.6. Risk management plan*

The MAH submitted an updated RMP version 2.1 with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 2.1 is acceptable.

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 2.1 with the following content:

### *Safety concerns*

| **Summary of Safety Concerns** | |
|---|---|
| Important identified risks | Interference for blood typing (minor antigen) (positive indirect Coombs' test) |
| Important potential risks | Viral reactivation |
| Missing information | None |

### *Pharmacovigilance plan*

Not applicable.

### *Risk minimisation measures*

| Safety concern | Risk minimisation measures |
|---|---|
| **Interference for blood typing (minor antigen) (positive indirect Coombs' test)** | **Routine risk minimisation measures:**<br>SmPC sections 4.4 and 4.5.<br>PL section 2.<br>**Legal status:** Available only on prescription. Isatuximab should be administered by a HCP, in an environment where resuscitation facilities are available (SmPC section 4.2).<br>**Additional risk minimisation measures:**<br>Healthcare Professionals and blood banks educational material (brochure) and patient card. |
| **Viral reactivation** | **Routine risk minimisation measures:**<br>SmPC sections 4.2, 4.4 and 4.8.<br>PL section 2.<br>**Legal status:** Available only on prescription. Isatuximab should be administered by a HCP, in an environment where resuscitation facilities are available (SmPC section 4.2).<br>**Additional risk minimisation measures:**<br>None |

## *2.7. Update of the Product information*

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.7, 4.8, 5.1 and 5.2 the SmPC have been updated. The Package Leaflet has been updated accordingly.

## 2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons: There is no need for an additional consultation for adult patients in the proposed indication, considering that the need for this population with multiple myeloma have been identified and addressed throughout the consultation for the initial marketing authorisation application.

# 3. Benefit-Risk Balance

## *3.1. Therapeutic Context*

### 3.1.1. Disease or condition

MM is a cancer of the haemopoietic system that is characterized by uncontrolled clonal expansion of plasma cells in the bone marrow. These plasma cells produce an excess amount of abnormal antibodies (so called M protein) or fragments thereof that cause a range of health issues, including impairment of the immune system and increased blood viscosity. Patients often present with bone lesions, anaemia, hypercalcaemia and renal failure.

The final indication is: "Isatuximab in combination with bortezomib, lenalidomide and dexamethasone is indicated for the treatment of adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplantation."

### 3.1.2. Available therapies and unmet medical need

In transplant ineligible, older/frail patients, a typical first-line treatment strategy would consist of bortezomib-lenalidomide-dexamethasone (VRd). Recently, daratumumab-lenalidomide-dexamethasone (DRd) and daratumumab-bortezomib-melphalan-prednisone (DaraVMP) were approved as first line treatment for transplant ineligible patients.

Even though survival prognosis is good in the standard risk patients, MM remains incurable and there is still need for additional treatment options in order to achieve prolonged disease control.

### 3.1.3. Main clinical studies

The pivotal study is EFC12522 (IMROZ) is a randomized, open-label Phase 3 study in NDMM patients who are not eligible for ASCT. In this study, isatuximab, bortezomib, lenalidomide and dexamethasone (IVRd) was compared to VRd alone. IVRd and VRd were given for an induction period of 24 weeks (four 42-day cycles), followed by continuous treatment in 28-day cycles with the isatuximab, lenalidomide and dexamethasone (IRd) or the lenalidomide and dexamethasone (Rd) intervention.

Patients were randomized in a 2:3 ratio of VRd (N=181) to IVRd (N=265). Randomization was stratified by country (Non-China versus China), age (<70 years versus ≥70 years) and R-ISS (I or II versus III versus not classified). Patients randomized to the VRd group were allowed to crossover to receive isatuximab in combination with lenalidomide and dexamethasone (IRd) in case of confirmed progression.

Efficacy was analysed in the ITT population with a data cut-off date of 26 September 2023, corresponding to the pre-planned PFS interim analysis #2 with 75% information fraction.

Supportive efficacy and safety data was derived from Study TCD13983, which included patients with NDMM not eligible for transplant (Part A; N=27 and Part B; N = 33) or with no intent for immediate transplantation (Part B; N = 13). The primary safety population (N=263) also included the EFC12522 study.

## 3.2. Favourable effects

The study met its primary endpoint PFS by IRC; at a median duration of follow-up of 59.73 months, a PFS advantage was observed in the IVRd arm compared to the VRd arm; HR 0.60 (95% CI 0.41- 0.88), p=0.0005. The median PFS is NC (95% CI: NC to NC) in the IVRd arm and 54.34 (95% CI: 45.21 to NC) months in the VRd arm. The PFS effect is robust in sensitivity analyses and consistent across most subgroups.

An hierarchical procedure was carried out for the key secondary endpoints; PFS is supported by secondary endpoints CR rate (CR+sCR) and MRD negativity rate at $10^{-5}$ in participants with CR; CR rate: 74.7% (95%CI: 0.69 to 0.80) vs. 64.1% (95%CI: 0.57 to 0.71) and MRD[-] CR rate: 55.5% (95%CI: 0.49 to 0.62) vs. 40.9% (95%CI: 0.34 to 0.48) in the IVRd and VRd arm respectively. The VGPR or better rate was similar in both treatment groups 89.1% (95% CI: 0.85 to 0.93) in the IVRD arm vs 82.9% (95% CI: 0.77 to 0.88) for the VRd group, and did not show a statistically significant difference. The OS analysis, which was next in the hierarchical testing procedure, is considered descriptive.

The median OS was not reached. In total 26.0% and 32.6% of the events were met in the IVRd and VRd arm (OS information fraction of 63%). The OS HR was 0.78 (99.97% CI: 0.41 to 1.48), nominal p = 0.0760.

ORR and PFS2 were not part of the hierarchical testing strategy. The ORR was 91.3% in the IVRd arm and 92.3% in the VRd arm. PFS2 events were observed in 31.7% for the IVRd group versus 41.4% for VRd. The median PFS2 was not reached in either treatment group; the PFS2 HR was 0.697 (95% CI 0.51 to 0.952).

In supportive study TCD13983 Part A, the sCR/CR rate was 38.5% (sCR 11.5%) and the median DOR was 34.43 months. In Part B the CR/sCR rate was 53.3% (sCR 15.6%) and the median DOR was NC.

## 3.3. Uncertainties and limitations about favourable effects

OS data are still immature, and therefore, the CHMP has recommended that the MAH provides the OS data from the next interim and final analysis, estimated in Q3 2025 and Q4 2027 respectively.

Patients were not re-randomized after the induction treatment. It is therefore not certain whether the favourable effects of isatuximab can be attributed to the induction phase alone, or also to the continuous phase.

Patients with PD in the continuous treatment phase of the VRd arm were allowed to cross over to the isatuximab arm (IRd). Analyses that sought to account for the crossover to the treatment arm suggested that the OS effect would have been weaker if patients had not crossed over to receive IRd.

Protocol amendments were made during study EFC12522. These changes were based on external information and are considered to have minimal impact on assessment of the treatment effect. The changes made to the secondary endpoints are considered to be minor.

## 3.4. Unfavourable effects

The median exposure in the IVRd arm is 53.2 months and 31.3 months in the the VRd arm.

The most frequently reported (treatment-related) TEAEs by PT in the IVRd versus VRd arm occurred in comparable rates in the two study arms. TEAEs reported more frequently in the IVRd arm than in the VRd arm include infusion related reaction (23.6% vs. 1.1%), cataract (38.0% vs. 25.4), pneumonia

(30.0% vs. 19.3%), fatigue (34.6% vs. 26.5%), neutropenia (30.0% vs. 21.5%) and diarrhoea (54.8% vs. 48.6%).

Grade ≥3 TEAEs were observed in 91.6% and 84.0% of the patients. The most frequent Grade ≥3 TEAEs were neutropenia (30% vs. 20.4%), pneumonia (20.2% vs. 12.7%), cataract (15.6% vs. 11.0%), and thrombocytopenia (11.8% vs. 10.5%).

Grade 5 AE during the treatment period were observed in 29 (11.0%) patients in the IVRd arm and in 10 (5.5%) patients in the VRd arm. Most deaths due to AEs are infectious in nature (6.5% vs. 3.9%). Overall (including post-treatment period and crossover period) the number of deaths in the IVRd arm is 26.2% compared to 32.6% the VRd arm, including 4.9% and 12.2% due to disease progression.

Severe IRRs occurred in 2 (0.8%) patients. Secondary primary malignancies were observed in 16.0% of the IVRd patients and 8.8% of the VRd patients; skin cancers in 8.4% vs. 3.9%, solid tumors other than skin cancers in 6.5% vs. 3.9% and haematological in 1.1% in each group.

TLS was observed in one patient in the IVRd arm (Grade 5 event). Infections in the IVRd arm were observed in 91.3% (Grade ≥3: 44.9%) and in the VRd arm in 86.7% (Grade ≥3: 38.1%). Infections were mostly respiratory in nature (84.8% vs. 72.4%). Grade 3 or 4 neutropenia was reported in 54.4% of IVRd patients and in 37.0% of VRd participants. Complicated neutropenia was observed in 12.5% vs. 8.3% of the patients respectively.

Discontinuation of all study medication due to AEs was observed in comparable rates between the study arms (IVRd: 22.8% vs. VRd: 26.0%), most commonly due to infections (8.4% vs. 9.4% respectively).

Exposure-adjusted TEAEs remain to show difference between the IVRd group and VRd group for any Grade ≥3 TEAE (1.171 vs. 0.986 event rate per patient year) and infusion related reactions (0.085 vs. 0.004) and to a lesser extent for pneumonia (0.105 vs 0.078).

The supportive study confirms the types of AEs observed in the pivotal study.

## *3.5. Uncertainties and limitations about unfavourable effects*

No dose escalation/finding studies of isatuximab with VRd were submitted. It is unknown whether a different dose of isatuximab/VRd would have resulted in a more favourable safety profile.

## *3.6. Effects Table*

**Table 34.** Effects Table for Sarclisa in combination with bortezomib, lenalidomide and dexamethasone for the treatment of NDMM in patients not eligible for ASCT (data cut-off: 26 September 2023)

| Effect | Short description | Unit | IVRd | VRd | Uncertainties / Strength of evidence | References |
|---|---|---|---|---|---|---|
| **Favourable Effects** | | | | | | |
| PFS | Time from randomisation to first disease progression (according to the IMWG response | Months (95CI%) | NR (NR-NR) | 54.34 (45.2-NR) | SoE: Multiple PFS sub-group analyses favour IVRD<br><br>SoE: Secondary endpoints, including ORR and CR also favour IVRD | Study EFC12522 |

| Effect | Short description | Unit | IVRd | VRd | Uncertainties / Strength of evidence | References |
|---|---|---|---|---|---|---|
| | criteria) or death | | HR 0.60 (95% CI 0.41 -0.88) | | | |
| OS | Time from date of randomisation to death from any cause | Months (95CI%) | NR (NR to NR) | NR (NR to NR) | Unc: OS immature (26% vs 33% of events met) | |
| | | | HR 0.78 (99.97% CI: 0.41 to 1.48) | | | |
| **Unfavourable Effects** | | | | | | |
| Grade ≥3 AEs | Grade ≥3 TEAEs | % | 91.6% | 84.0% | | Study EFC12522 |
| Grade 5 TEAEs | AE with a fatal outcome during the treatment period | % | 11.0% | 5.5% | Overall (including post-treatment and cross-over period) the number of deaths in the IVRd arm is 26.2% compared to 32.6% in the VRd arm. | |
| SPMs | Secondary primary malignancies | % | 16.0% | 8.8% | Median exposure to IVRd higher compared to VRd | |
| Severe neutropenia | Grade 3-4 neutropenia | % | 54.4% | 37.0% | | |

Abbreviations: AE- adverse event; ASCT: autologous stem cell transplant; CI-confidence interval; CR-complete response rate; HR = Hazard ratio; IMWG= International Myeloma Working Group; IVRd - isatuximab, bortezomib, lenalidomide, and dexamethasone; NDMM- newly diagnosed multiple myeloma; NR- not reached; PFS- Progression free survival; SoE: Strength of Evidence; SPM-secondary primary malignancy; TEAE- treatment-emergent AE; Unc: Uncertainties; VRd - bortezomib, lenalidomide, and dexamethasone.

## *3.7. Benefit-risk assessment and discussion*

### 3.7.1. Importance of favourable and unfavourable effects

Survival for patients with NDMM is lower compared to the general population, and there is an unmet medical need for new treatments which can provide increased responses and reduced toxicity. Addition of isatuximab to the SOC first-line triplet regimen VRd resulted in a statistically significant improvement in PFS. The improvement in PFS appears to be maintained over time and is consistent over the majority of subgroups. Therefore, the treatment effect is considered to be clinically relevant.

The treatment effect is supported by secondary endpoints indicating a deeper response in patients treated with IVRd when compared to VRd. OS data for the current interim analysis are immature, the Kaplan-Meier curves are inconclusive, potentially due to the higher number of on-treatment deaths in the IVRd arm compared to the VRd arm (see below). However, in absence of mature OS data the secondary endpoint PFS2 is supportive of the primary endpoint. The MAH has committed to providing the OS data at the next interim and final analysis, estimated in Q3 2025 and Q4 2027 respectively.

The addition of isatuximab to VRd leads to a higher toxicity, with the exception of a significantly higher number of on-treatment deaths in the IVRd compared to the VRd group. Most of these deaths were due to infections and this could relate to the intensity of the IVRd schedule. On the other side in the post-

treatment period and overall, less fatal events were observed for IVRd compared to VRd due to less disease progression in the IVRd arm. No dose finding studies of isatuximab with VRd have been presented and it is unknown whether a different dose of isatuximab/VRd would have resulted in an optimalisation of the B/R.

The addition of isatuximab to VRd leads to a higher toxicity compared to VRd mainly due to infusion related reactions, pneumonia, severe neutropenia and secondary primary malignancies. These AEs generally reflect the known safety profile of isatuximab and adequate warnings to minimise these risks are already included in the isatuximab product information.

### 3.7.2. Balance of benefits and risks

The benefit of isatuximab in combination with bortezomib, lenalidomide and dexamethasone in NDMM patients who are ineligible for ASCT has been established.

No new safety concerns were identified for isatuximab. The observed clinical activity, i.e., the benefit in PFS with the addition of isatuximab to bortezomib, lenalidomide and dexamethasone is considered to outweigh the additive toxicity of the new proposed treatment regime.

### 3.7.3. Additional considerations on the benefit-risk balance

## *3.8. Conclusions*

The overall B/R of Sarclisa in combination with bortezomib, lenalidomide and dexamethasone for the treatment of adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant is positive.

# 4. Recommendations

## *Outcome*

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends by consensus the variation to the terms of the Marketing Authorisation, concerning the following change:

| **Variation accepted** | | **Type** | **Annexes affected** |
|---|---|---|---|
| C.I.6.a | C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one | Type II | I and IIIB |

Extension of indication to include in combination with bortezomib, lenalidomide, and dexamethasone the treatment of adult patients with newly diagnosed active multiple myeloma who are not eligible for autologous stem cell transplant (ASCT) for Sarclisa, based on results from EFC12522 (IMROZ) pivotal phase III study and the supportive TCD13983 phase 1b/2 study. EFC12522 is an ongoing prospective, multicenter, international, randomized, open-label, 2-arm parallel group study to assess the clinical benefit of VRd (control group) versus IVRd (active group) for the treatment of participants with NDMM who are not eligible for ASCT. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.7, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 2.1 of the RMP has also been

submitted.

### *Amendments to the marketing authorisation*

In view of the data submitted with the variation, amendments to Annexes I and IIIB and to the Risk Management Plan are recommended.

### *Similarity with authorised orphan medicinal products*

The CHMP by consensus is of the opinion that Sarclisa is not similar to Darzalex, Farydak, Kyprolis, Ninlaro and Carvykti, within the meaning of Article 3 of Commission Regulation (EC) No. 847/200. See appendix 1.

## 5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

### *Scope*

Please refer to the Recommendations section above.

### *Summary*

Please refer to Scientific Discussion 'Sarclisa-EMEA/H/C/004977/II/30'.