NCT03275285

STATISTICAL ANALYSIS PLAN

Randomized, open label, multicenter study assessing the clinical benefit of isatuximab combined with carfilzomib (Kyprolis®) and dexamethasone versus carfilzomib with dexamethasone in patients with relapsed and/or refractory multiple myeloma previously treated with 1 to 3 prior lines

SAR650984-EFC15246

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DATE OF ISSUE: 16-Feb-2023

Total number of pages: 99

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ADA:	anti-drug antibody
ADI:	actual dose intensity
AE:	adverse event
AESI:	adverse event of special interest
ATC:	atonomical therapeutic chemical
AUC:	area under the curve
BOR:	best overall response
BSA:	body surface area
CA:	cytogenetic (chromosomal) abnormalities
CEOI:	concentration at end of infusion
CI:	confidence interval
CR:	complete response
CV:	coefficient of variation
DMC:	data monitoring committee
DOR:	duration of response
ECOG:	eastern cooperative oncology group
eCRF:	electronic case report form
eGFR:	estimated glomerular filtration rate
EORTC:	European organization for Research and Treatment of Cancer
EQ:	EuroQol
FLC:	free light chain
HLGT:	high level group term
HLT:	high-level term
HRQL:	health-related quality of life
IMP:	investigational medicinal product
IMWG:	International Myeloma Working Group
IR:	infusion reaction
IRC:	independent response committee
IRT:	Interactive Response Technology
ISS:	International staging system
ITT:	intent-to-treat
LLT:	lower-level term
MDRD:	modification of diet in renal disease
MedDRA:	medical dictionary for regulatory activities
MM:	multiple myeloma
MR:	minimal response
MRD:	minimal residual disease
MY:	myeloma specific module
NCI-CTCAE:	national cancer institute common terminology criteria for adverse events
NE:	non-evaluable
ORR:	overall response rate

OS:	overall survival
PCSA:	potentially clinically significant abnormality
PD:	progressive disease
PDy:	pharmacodynamics
PFS:	progression free survival
PK:	pharmacokinetic(s)
PR:	partial response
PS:	performance status
PT:	preferred term
QLQ:	quality of life questionnaire
RDI:	relative dose intensity
R-ISS:	revised international staging system
RS:	raw score
SAE:	serious adverse event
sCR:	stringent complete response
SD:	stable disease
SEM:	standard error of the mean
SOC:	system organ class
SPD:	sum of the products of the maximal perpendicular diameters of measured lesions
TEAE:	treatment-emergent adverse event
TT1R:	time to first response
TTBR:	time to best response
TTP:	time to progression
VAS:	visual analogue scale
VGPR:	very good partial response
WHO-DD:	World Health Organization-Drug Dictionary

1 OVERVIEW AND INVESTIGATIONAL PLAN

1.1 STUDY DESIGN AND RANDOMIZATION

This is a prospective multicenter, multinational, randomized, open label, parallel group, 2-arm study assessing the clinical benefit of isatuximab at 10 mg/kg weekly in the first cycle (4 weeks) and then biweekly combined with carfilzomib (at 20 mg/m^2 for the 2 first infusions and then at 56 mg/m^2 for the subsequent infusions) administered twice weekly 3 out of 4 weeks and dexamethasone (20 mg) administered twice weekly versus carfilzomib at 20/56 mg/m^2 twice weekly 3 out of 4 weeks and dexamethasone (20 mg) twice weekly in patients with relapsed and/or refractory multiple myeloma (MM) previously treated with 1 to 3 prior lines.

After confirmation of eligibility criteria, patients will be randomly assigned to one of the two following arms in a 3:2 ratio using an Interactive Response Technology (IRT):

- Isatuximab in combination with carfilzomib and low-dose dexamethasone (IKd [experimental] arm).
- Carfilzomib and low-dose dexamethasone (Kd [control] arm).

The duration of the study for a patient will include a period for screening of up to 3 weeks. The cycle duration is 28 days. Patients will be treated until disease progression, unacceptable adverse event (AE), or patient decision to stop the study treatment.

Randomization will be stratified according to:

- number of prior lines (1 vs. >1).
- Revised International Staging System (R-ISS) stage (I or II vs. III vs. not classified).

Approximately 300 patients (180 patients in IKd arm and 120 patients in Kd arm) will be randomized from approximately 73 sites.

1.2 OBJECTIVES

1.2.1 Primary objectives

The primary objective of this study is to demonstrate the benefit of IKd arm in the prolongation of progression free survival (PFS) using the International Myeloma Working Group (IMWG) criteria (see Appendix E) as compared to Kd arm in patients with relapsed and/or refractory MM previously treated with 1 to 3 lines of therapy.

1.2.2 Secondary objectives

The key efficacy objectives are as follows:

1. To evaluate overall response rate (ORR).
2. To evaluate rate of very good partial response (VGPR) or better.
3. To evaluate rate of VGPR or better (IMWG criteria) with minimal residual disease (MRD) negativity in both arms.

4. To evaluate complete response (CR) rate in both arms (IMWG criteria).
5. To evaluate overall survival (OS) in both arms.

Other secondary objectives are as follows:

1. To evaluate safety in both arms.
2. To evaluate duration of response (DOR) in both arms.
3. To evaluate time to progression (TTP) in both arms.
4. To evaluate PFS2 (see definition in Section 2.1.3.2.2) in both arms.
5. To evaluate time to first response (TT1R) in both arms.
6. To evaluate time to best response (TTBR) in both arms.
7. To determine the pharmacokinetic (PK) profile of isatuximab and carfilzomib when combined together.
8. To evaluate immunogenicity of isatuximab in isatuximab arm.
9. To evaluate generic and disease- and treatment-specific health-related quality of life (HRQL), and changes in HRQL, health state utility, and health status in both arms.

1.2.3 Exploratory objectives

Exploratory objectives are as follows:

1. To explore PK and pharmacodynamics (PDy) relationship.
2. To explore the relationship between immune genetic determinants and efficacy endpoints.
3. To explore relationship between chromosomal abnormalities not part of R-ISS including but not limited to del (1p) and 1q21+ and efficacy endpoints.
4. To explore the impact of M-protein measurement without isatuximab interference on best overall response assessment.

1.3 DETERMINATION OF SAMPLE SIZE

The sample size calculation is based on the primary efficacy endpoint (ie, PFS). The following assumptions were used:

- Kd arm has a median PFS of 19 months.
- IKd arm will have 41% risk reduction in hazard rate in comparison to Kd arm. The targeted hazard ratio is 0.59. Assuming proportional hazards, this is expected to correspond to an improvement in the true median PFS time from 19 months to 32 months.
- Log-rank test at an overall 1-sided 2.5% significance level.
- 3:2 randomization ratio (IKd:Kd).
- An interim analysis for efficacy assessment of PFS is planned when 65% of the PFS events will be observed. An O'Brien and Fleming α-spending function will be used to obtain the nominal significance levels for the interim and final analyses of PFS (see Section 3 for details).

Based on the above assumptions, a total of 159 PFS events are needed to achieve a 90% power for the study.

Three hundred patients (180 patients in IKd arm and 120 patients in Kd arm) would be adequate to achieve the targeted number of events for PFS. Assuming a uniform accrual rate of 19 patients per month, the final PFS analysis cut-off date is expected to be approximately 36 months after first patient in.

Calculations were made using East 6.4 software.

1.4 STUDY PLAN

The complete study plan is presented in Section 1 of the protocol.

1.5 MODIFICATIONS TO THE STATISTICAL SECTION OF THE PROTOCOL

The protocol amendment history table below gives the timing, rationale, and key details of major changes to the protocol statistical section. All changes were performed after the first patient randomized (15-Nov-2017) and before the planned interim analysis (early 2020).

Table 1 - Protocol amendment statistical changes

Amendment Number	Date Approved	Rationale	Description of statistical changes
10	24-Nov-2022	Median PFS was reached at the final PFS analysis; therefore, additional descriptive PFS analysis is no longer necessary.	Text related to additional descriptive PFS analysis was removed.
8	11-Mar-2021	To better characterize the distribution of PFS in a descriptive way for the IKd arm, including the increased possibility of observing median PFS	An additional PFS analysis will be performed when approximately 180 events assessed by the IRC have been observed to better characterize the distribution of PFS in the IKd arm in a descriptive way. This analysis will be performed at the latest 15 months after the 159 PFS event analysis cut-off date in case of the approximately 180 PFS events are not observed at that time
		This analysis has been requested by United States Food and Drug Administration as post-hoc PFS analysis	A sensitivity analysis has been added to evaluate the impact of late progressions and deaths. In this sensitivity analysis, progressions or deaths occurring more than 8 weeks after the last disease assessment (corresponding to two consecutive missed assessments) will be censored at the earliest of the date of last valid disease assessment without evidence of progression before initiation of new anti-myeloma treatment and the cutoff date.
7	13-Nov-2019	Health authorities (FDA) feedback	Change in censoring rules for the primary PFS analysis to consider the initiation of further anti-myeloma therapy. Update of PFS2 definition related to this change.
		Update of statistical sections in order to reflect the changes made in the SAP amendment 1 of July 2019	Please refer to table 2 in Section 1.6

Amendment Number	Date Approved	Rationale	Description of statistical changes
3	08-Feb-2018	Error in number of PFS events	Modification of the number of events required for the final PFS analysis: 159 instead of 158 events
		Recent data strongly suggests MRD negativity is a prognostic factor for PFS and OS not only in patients with CR. Patients who were MRD-negative despite a persistent M-protein component showed similar PFS and OS to patients who were MRD-negative with CR	To add MRD assessment in patients with VGPR
		The order of key secondary endpoints was revised after the addition of MRD assessment in patients with VPGR	Modification of the order of key secondary endpoints: MRD negativity rate in patients with VGPR or better will be tested prior to CR rate
		Updates related to the statistical section of the protocol made in the initial version of the SAP were included in the statistical section of the protocol	Clarifications of infusion/dose delay and dose reduction Confidence interval of primary and key secondary endpoints: replace 95% by (1-2α)% Quality of life: replace 95% confidence intervals by SEM in the graph of mean of EQ-5D-5L VAS and the mean of index utility score over time. Corrections of typos

1.6 STATISTICAL MODIFICATIONS MADE IN THE STATISTICAL ANALYSIS PLAN

The statistical analysis plan history table below gives the timing, rationale, and key details for major changes to the statistical analysis features in the statistical analysis plan.

The initial SAP was approved on 20-Nov-2017. The cutoff date of interim analysis with 103 PFS events (65% information fraction) was on 07-Feb-2020 and the cutoff date of final analysis with 163 PFS events was on 14-Jan-2022. This version of SAP is for the planned analyses at OS final analysis and to remove the additional PFS analysis (at approximately 180 PFS events) added in amended protocol #10 due to uncertainty that median PFS would be reached at the time of the final PFS analysis.

Table 2 - Statistical analysis plan statistical changes

SAP version number	Date approved	Rationale	Description of statistical changes
5	16-Feb-2023	"Cytogenetic abnormality" was replaced by the right term "chromosomal abnormality"	"Cytogenetic abnormality" was replaced by "chromosomal abnormality"
		Description of IR medications by infusion mode	Description of IR medications depending on the mode of administration (initial mode of administration and fixed volume administration mode).
		Description of Prior anti-myeloma treatments by regimen	Description of Prior anti-myeloma treatments by treatment arm and by regimen.
		Description of patients still on study was added	In patient disposition, Addition of the number of patients who ended the study and the reason
		Overall response after the initiation of further therapy	Description of overall response after the initiation of anti-CD38 therapy and other selected drugs class as further anti-myeloma therapy Description of overall response after the initiation of further anti-myeloma therapy by treatment arm and by line
		Description of the follow-up duration regardless of deaths	Addition of the time from randomization to efficacy cut-off date (months).
		Analyses for OS was added	Addition of OS in patients with high-risk chromosomal abnormalities Addition of OS by further therapy with daratumumab Addition of OS by BOR as per IRC and MRD status Addition of OS by chromosomal abnormality at study entry Addition of OS by lenalidomide and bortezomib
		Change as per protocol amendment 10 Median PFS was reached at the final PFS analysis; therefore, additional descriptive PFS analysis is no longer necessary.	Deleting of the additional PFS analysis planned when approximately 180 events assessed by the IRC.
4	07-Mar-2022	Descriptive analyses by second primary malignancies	Addition of demographic characteristic, exposure, disease characteristic at study entry will be described by SPM status. Efficacy data (PFS and OS) will be presented also by SPM status
		Descriptive analyses and new population defined to assess the impact of Covid-19 and the contingency measures related to the pandemic in case of regional or national emergency declared by a governmental agency	In safety, analysis of TEAEs related to Covid-19 has been added. In disposition, premature and definitive treatment discontinuation related to Covid-19 (AE and other, other = link to pandemic situation) will be identified. Critical and major protocol deviations related to Covid-19 pandemic situation will be identified Definition for population without trial impact (disruption) due to Covid-19 pandemic situation has been added In exposure, cycles delayed and dose omissions due to Covid-19 pandemic situation will be identified.

SAP version number	Date approved	Rationale	Description of statistical changes
4	07-Mar-2022	MRD negativity rate in CR patients is a relevant prognostic marker for PFS and OS outcomes and has been added as post-hoc PFS analysis.	Addition of MRD negativity rate in patients with CR. In addition, sensitivity analyses to assess the impact of missing data could be performed (tipping point analysis, multiple imputation).
		PFS by MRD status has been added as post-hoc PFS analysis at interim analysis.	Addition of PFS analysis by MRD status Addition of PFS analysis by MRD status censoring death event due to Covid-19 infections
		Description of PFS2 by daratumumab intake	Addition of PFS2 analysis by daratumumab intake
		Change of statistical method for the sensitivity analysis of OS	Sensitivity analyses to account for possibly informative censoring due to initiation of further anti-myeloma treatment could be performed (eg, Rank Preserving Structural Failure Time (RPSFT) model and inverse probability of censoring weighting (IPCW) method). The same analyses could be performed to account for possibly informative censoring due to initiation of daratumumab. In addition, sensitivity analyses to assess the impact of Covid-19 on the study could be performed (ie, Analysis of OS on the population without trial impact (disruption) due to Covid-19 and analysis of OS censoring the death event due to Covid-19 infections)
		Sensitivity analyses of PFS to assess the impact of Covid-19 on the study could be performed	Addition of • Analysis of PFS on the population without trial impact (disruption) due to Covid-19 and • Analysis of PFS censoring the death event due to Covid-19 infections)
		Since the PFS endpoint met its statistical significance at the planned interim analysis of 103 PFS events (65% information fraction), all future analyses of PFS endpoint are non-inferential. All observed PFS events up to the final PFS analysis cut-off date will be used for PFS final analysis and PFS additional analysis.	This sensitivity analysis #6 is not applicable because all observed PFS event will be conserved in the analyses.
		Subgroup analyses was added to further evaluate the efficacy in specific subgroup	The following subgroup analyses have been added: • Chromosomal abnormality (1q21+) • Chromosomal abnormality (gain 1q21) • Chromosomal abnormality (amplification 1q21)
		Subgroup analyses were added to further evaluate the overall response by new antimyeloma therapy	Description of overall response after the initiation of daratumumab as further anti-myeloma therapy by treatment arm

SAP version number	Date approved	Rationale	Description of statistical changes
4	07-Mar-2022	*Change as per protocol amendment 8* To better characterize the distribution of PFS in a descriptive way for the IKd arm, including the increased possibility of observing median PFS	An additional PFS analysis will be performed when approximately 180 events assessed by the IRC have been observed to better characterize the distribution of PFS in the IKd arm in a descriptive way. This analysis will be performed at the latest 15 months after the 159 PFS event analysis cut-off date in case of the approximately 180 PFS events are not observed at that time
		Change as per protocol amendment 8 This analysis has been requested by United States Food and Drug Administration as post-hoc PFS analysis	A sensitivity analysis has been added to evaluate the impact of late progressions and deaths. In this sensitivity analysis, progressions or deaths occurring more than 8 weeks after the last disease assessment (corresponding to two consecutive missed assessments) will be censored at the earliest of the date of last valid disease assessment without evidence of progression before initiation of new anti-myeloma treatment and the cutoff date.
		For patients with suspected isatuximab interference on serum M-protein IFE, the SEBIA HYDRASHIFT 2/4 isatuximab IFE test will be used by the central lab to specifically measure the endogenous M-protein. It is the new test.	Addition of the number (%) of patients who changed their response with the new test. The time to first CR/sCR in patients with SEBIA HYDRASHIFT 2/4 isatuximab IFE test will be described. In addition, sensitivity analysis has been added using *hybrid BOR* based on the IRC's assessment available for the interim analysis plus the IRC's assessment for the newly collected response data after the interim analysis.
		1q21 gain corresponds to 3 copies only. The right term for the chromosomal abnormalities including at least 3 copies is 1q21+.	Gain 1q was replaced by 1q21+ including gain 1q (3 copies only) and amplification (at least 4 copies)
3	05-Mar-2020	*Change per protocol amendment 7:* Health authorities (FDA) feedback	Change in censoring rules for the primary PFS analysis to consider the initiation of further anti-myeloma therapy. This new censoring rule has been also applied for time to progression. Update of PFS2 definition related to this change.
		Efficacy: to clarify some analyses	Descriptive statistics on patients who achieved a confirmed response will be also provided to summarize time to first response and time to best response. Clarify that sensibility analysis #6 will be performed only for final analysis
		Safety analyses added to better characterize the safety profile	The following analysis has been added: most frequent (≥10% of patients in IKd arm and ≥5% higher in IKd arm compared to Kd arm) TEAEs
		EPRO is considered as an efficacy endpoint	Change the analysis population for EPRO from safety population to ITT population
		Correction	Correct the definition of hepatic mild impairment in Section 2.5.1

SAP version number	Date approved	Rationale	Description of statistical changes
2	22-Jul-2019	*Change as per protocol amendment 3:* error in number of PFS events	Modification of the number of events required for the final PFS analysis: 159 instead of 158 events
		Change as per protocol amendment 3: Recent data strongly suggests MRD negativity is a prognostic factor for PFS and OS not only in patients with CR. Patients who were MRD-negative despite a persistent M-protein component showed similar PFS and OS to patients who were MRD-negative with CR	To add MRD assessment in patients with VGPR
		Change as per protocol amendment 3: The order of key secondary endpoints was revised after the addition of MRD assessment in patients with VPGR	Modification of the order of key secondary endpoints: MRD negativity rate in patients with VGPR or better will be tested prior to CR rate
		Change as per protocol amendment 4: include the possibility for Independent Response Committee (IRC) to consider clinical progression as PD event	In section 2.1.3.1, symptomatic deterioration (as assessed by the investigator) can be considered as progression in the primary analysis of PFS if IRC considers clinical data reported supports clinical progression.
		Efficacy: based on clinical consideration, death due to PD occurring within 45 days after first documentation of PD will be used to confirm PD	Death due to PD occurring within 45 days after a first documentation of PD based on M-protein is considered as confirmation of PD
		Sensitivity analysis for PFS was added to further evaluate the efficacy of study treatments	The following sensitivity analysis has been added: Analysis of PFS as per investigator assessment, ignoring symptomatic deterioration
		Subgroup analysis was added to further evaluate the efficacy in specific subgroup	The following subgroup analysis has been added: • Regulatory region
		Efficacy: some subgroup analyses were removed because not deemed relevant based on number of patients and/or further clinical evaluation	The following subgroup analyses have been removed: • Ethnicity • Chromosomal abnormality del(17p) • Existing plasmacytoma • Previous therapy with anti-CD38 mAb
		Efficacy: some subgroup analyses were modified based on number of patients	The following subgroup analyses have been modified: • Geographical regions • ECOG-PS • Chromosomal abnormality (del(17p), t(4;14), t(14;16)) • eGFR at baseline • MM type at study entry

SAP version number	Date approved	Rationale	Description of statistical changes
2	22-Jul-2019	Efficacy: to clarify some definitions and analyses	The following definitions have been updated: • MRD negativity rate • CR rate The following analyses have been updated: • Evaluation of confounding for primary analysis • Analysis of MRD negativity rate (will be performed on ITT population for key secondary endpoint and on ITT population with VGPR or better as exploratory analysis) • Analysis of CR rate (CR rate will only be tested for comparison when the antibody-capture interference assay will be available). • Further details on the handling of multiplicity and spending functions for secondary endpoints
		Subcategories of VGPR were added to further characterize the efficacy of study treatments	The following subcategories were added: • Biochemical CR • Near CR
		Additional exploratory endpoints were added to further characterize the efficacy of study treatments	The following endpoints were added: • Time to first response • Time to best response • Overall response rate based on investigator assessment • Best overall response based on investigator assessment • Renal response
		Safety analyses added to better characterize the safety profile	The following analyses have been added: • Cumulative exposure to treatment in patient-years • Infusions without IR medication • Indirect Coombs test • Subgroup analyses on TEAEs • Some additional exposure-adjusted analyses of TEAEs • Cardiac AEs: SMQs ”Ischaemic heart disease”, “Cardiomyopathy”, “Embolic and thrombotic events” (venous and arterial), HLGT “Vascular hypertensive disorders” • Hemolytic disorders • Tumor lysis syndrome • Autoimmune disorders • Second primary malignancies • More specifications on analyses of neutropenic complications and thrombocytopenia and hemorrhages
		The following data handling conventions were updated to give the formulas in standard unit	• eGFR formula (MDRD) • Corrected calcium formula

SAP version number	Date approved	Rationale	Description of statistical changes
2	22-Jul-2019	To clarify some definitions and analyses other than for efficacy	The following definitions have been updated: • Baseline value • Type of measurable paraprotein • Overall number of cycles started • Planned dose intensity of carfilzomib • Number of prior lines The following analyses have been updated: • Dose modification of carfilzomib • Analysis of chromosomal abnormalities • Analysis of PK parameters • Analyses of ePROs • Analyses of prior/concomitant medications and IR medications • Analyses of vital signs (addition of plots) • Analyses of laboratory parameters (deletion of analyses according to bone marrow involvement category at baseline) • Analysis of all treatment-emergent adverse event(s) leading to dose modification • Description of IRs • Analysis of medical/surgical history

2 STATISTICAL AND ANALYTICAL PROCEDURES

2.1 ANALYSIS ENDPOINTS

2.1.1 Demographic and baseline characteristics

The baseline value is defined as the last available value or measurement before or on the date of first dose of study treatment (earliest date of isatuximab, carfilzomib and dexamethasone).

For M-protein (serum and urine), an unscheduled assessment performed on the date of first study treatment administration (cycle 1 day 1) will be considered as baseline value. For other parameters, unscheduled assessments or repeated tests (eg, vital signs) performed on the day of first study treatment administration will be considered as post baseline. This definition applies to all variables unless otherwise specified. For patients randomized and not treated, the baseline value is defined as the last available value obtained before or on the date of the randomization.

All baseline safety and efficacy parameters (apart from those listed below) are presented along with the on-treatment summary statistics in the safety and efficacy sections (Section 2.4.5 and Section 2.4.4).

Demographic characteristics

Demographic variables are gender (Male, Female), race (White, Black, Asian, American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, Not reported, Unknown), ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not reported, Unknown), geographical region (Europe, America, Asia, Other countries, see definition in Appendix H), regulatory region (Western countries, Other countries, see definition in Appendix H) and age in years (quantitative and qualitative variable : <65, [65 - 75[and ≥75 years).

Medical or surgical history

Medical or surgical history includes relevant history of previous or associated pathologies other than MM including respiratory medical history. This information will be coded using the version of Medical Dictionary for Regulatory Activities (MedDRA) currently in effect at Sanofi at the time of database lock or one version down.

In addition, smoking habits including smoking status at study entry will be collected in a specific eCRF page.

MM characteristics at initial diagnosis

The following MM characteristics at initial diagnosis will be described:

- Cancer diagnosis (as collected in eCRF).
- Time from initial diagnosis of MM to randomization (in years).
- MM type (heavy and light chain component, as collected in eCRF).
- Bi-clonal status (as collected in eCRF).
- International staging system (ISS) stage (as collected in eCRF).

MM characteristics at study entry (before randomization unless otherwise specified)

The following MM characteristics at study entry will be described:

- ISS stage derived from β2-microglobulin level in mg/L and albumin in g/L (Table 3). In addition, β2-microglobulin level in mg/L (quantitative results and by category: <3.5 mg/L, [3.5-5.5 mg/L[and ≥5.5 mg/L) and albumin in g/L (quantitative results and by category: <35 g/L and ≥35 g/L) will be provided.
- R-ISS stage derived as defined in Table 4 from β2-microglobulin, albumin, serum LDH and chromosomal abnormalities [CA] as described below. In addition, serum LDH (quantitative results and by category: ≤ULN, >ULN) will be provided.
- CA determined from central FISH assessment: number and percentage of patients
  - by chromosomal abnormality such as del(17p), t(4;14), t(14;16) as well as 1q21+. Abnormality is defined as at least 30% of abnormal plasma cells with t(4;14), t(14;16) or ≥3 copies of 1q and at least 50% of abnormal plasma cells for del(17p), 1q21+ abnormality includes gain 1q21 (only 3 copies) and amplification 1q21 (≥4 copies of 1q)
  - by type of risk as defined for R-ISS (standard risk vs high-risk [defined as presence of del(17p) and /or translocation t(4;14) and /or translocation t(14;16) abnormality] vs unknown/missing),
  - by number of abnormalities (no chromosomal abnormality vs only 1 chromosomal abnormality vs 2 chromosomal abnormalities vs 3 chromosomal abnormalities vs unknown/missing).
  - by multiple chromosomal abnormalities:
    - del(17p) and t(4,14)
    - del(17p) and t(14,16)
    - 1q21+ and del(17p)
    - 1q21+ and t(4,14)
    - 1q21+ and t(14,16)
    - 1q21+, del(17p) and t(4;14)
    - 1q21+, del(17p) and t(14;16)
- M protein at baseline: serum M protein level in g/dL (quantitative results and by category: <0.5 g/dL and ≥0.5g/dL), urine M protein level in mg/24 hours (quantitative results and by category: <200 mg/24 hours and ≥200 mg/24 hours), serum M protein and urine M protein by category (serum M protein <0.5 g/dL and urine M protein <200 mg/24 hours vs serum M protein ≥0.5 g/dL and urine M protein ≥200 mg/24 hours).
- MM type (heavy and light chain components, as collected in eCRF).
- Bi-clonal status (as collected in eCRF).
- Refractory status.
  - Relapsed and refractory: non-responsive while on salvage therapy or progresses within 60 days of last therapy in patients who have achieved minimal response (MR) or better at some point previously before then progressing in their disease course,
  - Primary refractory: never achieve MR or better in any prior therapies,
  - Relapse: all cases not meeting the relapse and refractory or primary refractory definition.

- % of plasma cells in bone marrow at baseline (quantitative and qualitative variables: 0%,]0-5%[, [5-20%[, [20-50%[and ≥50%).
- Patients with plasmacytoma (as per investigator and independent response committee (IRC)).
- Patients with bone lesions (and number of lesions) (as per investigator and IRC).

Table 3 - ISS staging definition

Stage	Definition
Stage I	β2-microglobulin <3.5 mg/L and albumin ≥35 g/L
Stage II	[β2-microglobulin <3.5 mg/L and albumin <35 g/L] or [β2-microglobulin 3.5 - <5.5 mg/L]
Stage III	β2-microglobulin ≥5.5 mg/L

Table 4 - R-ISS staging definition

Stage	Definition
Stage I	β2-microglobulin <3.5 mg/L and albumin ≥35 g/L and no high-risk CA and LDH ≤ULN
Stage II	Not R-ISS Stage I or III
Stage III	β2-microglobulin ≥5.5 mg/L and either high-risk CA by iFISH or LDH >ULN
Not classified	inconclusive iFISH unless stage III can be determined on LDH and β2 microglobulin only

High-risk CA by iFISH: Presence of del(17p) and /or translocation t(4;14) and /or translocation t(14;16) abnormality
CA: Chromosomal abnormalities
iFISH: interphase fluorescent in situ hybridization

Prior anti-myeloma therapies

- *Prior anti-myeloma treatments:*

  Prior anti-myeloma treatments are collected by regimen in the eCRF. The following variables will be summarized/derived from eCRF data:
  - Number of prior regimens (quantitative and qualitative variable: 1, 2, 3, 4, 5, 6, >6),
  - Number of prior lines (a line of therapy consists of ≥1 complete cycle of a single agent or a regimen consisting of a combination of several drugs, or a planned sequential therapy of various regimens) (quantitative and qualitative variable: 1, 2, 3, >3),
  - Main anti-myeloma therapies by class and agent:
    - Alkylating agents: such as cyclophosphamide, melphalan, bendamustine,
    - Proteasome inhibitors: such as bortezomib, carfilzomib, ixazomib,
    - Immunomodulators: such as lenalidomide, thalidomide, pomalidomide,
    - Monoclonal antibodies: such as elotuzumab (anti SLAMF7 agent), daratumumab (anti CD 38 agent) and anti CD38 agents other than daratumumab (including MOR202),
    - Anthracyclines,
    - Vinca alkaloids,
    - Corticosteroids,
    - HDAC inhibitors.

- The refractory status to immunomodulators, proteasome inhibitors and to both immunomodulators and proteasome inhibitors will be derived. A patient will be considered to be refractory to a drug if any of the following conditions is met:
  - Progression date and end date are complete and progression is before drug end date or within (≤) 60 days of drug end date. If only the day is missing for either date or both dates, the 2 dates should be separated by no more than 1 month,
  - Best overall response is stable disease (SD) or PD,
  - Reason for treatment discontinuation is "Progressive disease".
- Description of last regimen given prior to study entry:
  - Time from completion of last line of treatment to first study treatment administration (months),
  - Main treatments,
  - Best response to last regimen,
  - Duration of last regimen of therapy,
  - Refractory status as defined above,
  - Reason for treatment discontinuation.

- *Prior transplant*: number (%) of patients with at least one transplant, number (%) of patients with at least two transplants, type of transplant (autologous, allogenic).
- *Prior surgery*: number (%) of patients with any prior surgery related to MM, type of procedure and time from last surgery to first study treatment administration (months).
- *Prior radiotherapy*: number (%) of patients with any prior radiotherapy related to MM, intent and time from last radiotherapy to first study treatment administration (months).

Other baseline characteristics

Other baseline characteristics include weight, body surface area (BSA), eastern cooperative oncology group (ECOG) performance status (PS) and left ventricular ejection fraction at baseline as well as randomization strata (as defined in Section 1.1) as per IRT.

Any technical details related to computation described in Section 2.5.

2.1.2 Prior or concomitant medications (other than anticancer therapies)

All medications taken within 21 days before randomization and up to 30 days after the last study treatment administration are to be reported in the case report form pages.

All medications will be coded using the World Health Organization-Drug Dictionary (WHO-DD) using the version currently in effect at Sanofi at the time of database lock.

- Prior medications are those the patient used prior to the first dose of study treatments. Prior medications can be discontinued before first administration or can be ongoing during treatment phase.
- Concomitant medications are any treatments received by the patient concomitantly to any investigational medicinal product (IMP), from first dose to last dose of study treatments + 30 days. A given medication can be classified both as a prior medication and as a concomitant medication. Any anti-cancer treatment administered after the date of the last study treatment administration will not be considered as a concomitant medication and

will be regarded as a further anti-myeloma therapy (see Section 2.1.9). The analysis of concomitant medications will include the infusion reaction (IR) medications.

IR medications

As defined in Section 8.2.2 of the study protocol, patients will routinely receive premedications prior to isatuximab and carfilzomib infusions to reduce the risk and severity of infusion reactions (IRs) commonly observed with monoclonal antibodies and carfilzomib. Several premedications including dexamethasone are recommended prior to isatuximab infusions whereas dexamethasone is the single premedication when carfilzomib is administered without isatuximab. Premedications are defined in the protocol as non-investigational medicinal product(s) and should be reported in a specific form of the eCRF. Dexamethasone being part of both the premedication (for isatuximab and carfilzomib) and the study treatment, dexamethasone administration data will be reported only in the IMP administration page and will not be summarized as IR premedication, unless if additional dexamethasone is given as IR premedication. In case of dexamethasone is prematurely stopped and other study treatment are continued, it could be replaced by other premedication if still needed as defined in the protocol.

Analysis of premedications will focus on those given for prophylactic intent on the days of isatuximab administrations in IKd arm as no or very few premedications will be recorded when carfilzomib is administered without isatuximab.

Medications given in curative intent of IR will be analyzed for both arms.

Any technical details related to computation, dates, imputation for missing dates are described in Section 2.5.

2.1.3 Efficacy endpoints

2.1.3.1 Primary efficacy endpoint(s)

The primary endpoint is PFS defined as the time from the date of randomization to the first documented date of PD (as determined by the IRC) or the date of death from any cause, whichever comes first.

If PD and death are not observed before the analysis cut-off date or the date of initiation of further anti-myeloma treatment, PFS will be censored at the date of the last valid disease assessment not showing PD performed prior to initiation of a further anti-myeloma treatment (if any) or the analysis cut-off date, whichever comes first. A patient without an event (death or PD) and without any valid post-baseline disease assessments will be censored at the day of randomization (Day 1).

An IRC blinded to the randomization arm will evaluate disease assessments at each time point and determine disease response including progression status per IMWG criteria (1) (Appendix E). The full details regarding the determination of the PD are provided in the protocol and the IRC charter. Disease assessments performed after the final PFS analysis will not be reviewed by the IRC. The date of disease progression as determined by the IRC will be used for primary PFS analysis.

Additional details regarding the definition of PFS and handling of events and censoring are given in Appendix F.

Other censoring rules used for sensitivity analyses are provided in Section 2.4.4.1.1. Any technical details, related to computation, dates, and imputation for partial/missing dates, are described in Section 2.5.

The cut-off date for the final analysis of PFS (if not previously stopped at interim analysis) is expected to be the date when the 159th event (first occurrence of either disease progression (assessed by the IRC) or death due to any cause) has been observed. If the final number of events is higher than planned, a sensitivity analysis including these additional events may be performed (See Section 2.4.4.1.1) for details).

Since the PFS endpoint met its statistical significance at the planned interim analysis of 103 PFS events (65% information fraction), all future analyses of PFS endpoint are non-inferential. All observed PFS events up to the PFS analysis data cut-off date will be used for analysis.

Assessment of progression

Response and progression as per IRC will be determined on the basis of central laboratory findings, radiological evaluation if any and investigator information (bone marrow biopsy/aspiration if any) according to IMWG criteria. In addition, IRC can consider clinical progression if clinical data supports it (including new lesions based on physical exam).

Progression based on paraprotein will have to be confirmed based on 2 consecutive assessments. A M protein assessment performed after the initiation of a further anti-myeloma treatment will be used to confirm progressive disease. Death due to progressive disease occurring within 45 days of the first documentation of progression on M protein (regardless initiation of further therapies) is considered as a confirmation of the progression.

Symptomatic deterioration (as assessed by the investigator) will not be considered as progression in the primary analysis of PFS, except if IRC considers clinical data reported supports clinical progression.

Progression cannot be diagnosed on free light chain (FLC) increase only. Disease response for patients with non-measurable M-Protein on Cycle 1 Day 1 is detailed in Appendix E.

Efficacy assessment will be performed on Day 1 of every cycle during treatment. After treatment discontinuation, for patients who discontinued study treatment for reasons other than progression, disease assessments will be performed every month for laboratory disease assessment (central laboratory), every 12 weeks (±1 week) for radiological assessment in case of extramedullary disease (plasmacytoma) at baseline and once a year and as clinically indicated for bone lytic disease assessment (skeletal survey or whole body CT-scan) until confirmation of PD (including patients who initiated further anti-myeloma therapy without PD).

Date of disease progression

The date of the disease progression is the earliest date that indicates disease progression (provided that the progression is subsequently confirmed in case of progression requiring confirmation) according to IMWG criteria as assessed by IRC. Details are provided in the Independent Review Charter.

Determination of the PFS status for the primary analysis

The following rules will be applied to determine if a patient has an event or is censored for the PFS primary analysis for all regions excluding US:

- For a patient who did not die and did not reach progressive disease before the cut-off date, the patient is censored, and the censoring date is determined as follows:
  - If the patient received any further anti-myeloma treatment, then the censoring date is the date of last valid disease assessment without evidence of PD before the start of further anti-myeloma treatment, or the cut-off date, whichever comes first,
  - If the patient did not take any further anti-myeloma treatment then the censoring date is the date of last valid disease assessment without evidence of PD or the cut-off date, whichever comes first.
- For a patient who died or reached progressive disease before the cut-off date:
  - If the patient received any further anti-myeloma treatment before death or progression is documented, then the censoring date is the date of last valid disease assessment without evidence of PD before the start of further anti-myeloma treatment,
  - If the patient reached the PFS endpoint before initiation of further anti-myeloma treatment, the date of the event will be the date of progressive disease or death if no progression occurred.

Following FDA's request to update the primary PFS analysis, the primary PFS analysis for US includes an additional censoring rule for late progressions and deaths. For US, the following rules will be applied to determine if a patient has an event or is censored for the PFS primary analysis:

- For a patient who did not die and did not reach progressive disease before the cut-off date, the patient is censored, and the censoring date is determined as follows:
  - If the patient received any further anti-myeloma treatment, then the censoring date is the date of last valid disease assessment without evidence of PD before the start of further anti-myeloma treatment, or the cut-off date, whichever comes first,
  - If the patient did not take any further anti-myeloma treatment, then the censoring date is the date of last valid disease assessment without evidence of PD or the cut-off date, whichever comes first.
- For a patient who died or reached progressive disease before the cut-off date:
  - If the patient received any further anti-myeloma treatment before death or progression is documented, then the censoring date is the date of last valid disease assessment without evidence of PD before the start of further anti-myeloma treatment,
  - If the patient reached the PFS endpoint before initiation of further anti-myeloma treatment, the date of the event will be the date of progressive disease or death if no progression occurred.
  - Progressions or deaths occurring more than 8 weeks after the last disease assessment (corresponding to two consecutive missed assessments) will be censored at the earliest of the date of last valid disease assessment without evidence of progression before initiation of new anti-myeloma treatment and the cut-off date.

Valid disease assessment

A valid post-baseline disease assessment is one for which the "time point response" is not "non-evaluable" (NE). In addition, disease assessment with missing date will not be considered valid.

Within a time point, if several exams are performed at different dates for a time point not showing disease progression, the date of last valid disease assessment is the date of latest exam.

Non-evaluable cases

Missing exams: if one protocol planned examination is missing for a given disease assessment, the overall response should generally be NE unless there is clear evidence of progression (independently of the missing examination) or response assessment should be downgraded to the IMWG response criteria when the missing exam is not required. Specific rules applying to missing serum or urine M-protein are described in the IRC charter.

For the primary analysis of PFS, progression or death occurring after a disease evaluation with an overall time point response(s) equal to NE will be considered as an event in the analysis.
Such progression or death will be censored in the PFS sensitivity analysis #5 if occurring more than 8 weeks after the last valid disease assessment without progression.

2.1.3.2 Secondary efficacy endpoint(s)

2.1.3.2.1 Key secondary efficacy endpoints

The key secondary efficacy endpoints are:

- ORR, as per IMWG criteria
- Rate of VGPR or better, as per IMWG criteria
- MRD negativity rate in patients with VGPR or better, as per IMWG criteria
- CR rate, as per IMWG criteria
- OS

Best Overall Response (BOR)

BOR is defined as the best response, using the IRC's assessment of response, from the start of treatment until disease progression (as defined in Section 2.1.3.1), death, initiation of further anti-myeloma treatment or cutoff date, whichever occurs first. The ordering of evaluations from best to worse is: stringent complete response (sCR), CR, VGPR, partial response (PR), MR, SD, PD, NE.

Moreover, for patients with VGPR as BOR, the following subcategories will be assessed by the IRC: biochemical CR and near CR.

- Biochemical CR: negative immunofixation of both serum and urine M-protein, with missing bone marrow data.
- Near CR: serum and/or urine M-component detectable by immunofixation but not on electrophoresis.

A confirmation assessment for disease response is required in this study (either MR or better, or PD, except PD diagnosed on radiological assessment).

In addition, BOR according to investigator assessment will be provided.

Hybrid BOR

For the analysis after interim analysis when the SEBIA HYDRASHIFT 2/4 isatuximab IFE test is available, the derivation of this item will be based on the IRC's assessment available for the interim analysis (ie, using conventional IFE test) plus the IRC's assessment for the newly collected response data after the interim analysis (ie, adjusted by SEBIA HYDRASHIFT 2/4 isatuximab IFE test). The response results determined by IRC at time of the interim analysis will remain as it is for the hybrid BOR derivation.

ORR:

Defined as the proportion of patients with sCR, CR, VGPR and PR as BOR as assessed by the IRC using the IMWG response criteria. For patients with non-measurable M-protein on Cycle 1 Day1, only the following overall responses are possible: CR, non-PD and PD (see Appendix E).

In addition, ORR according to investigator assessment will be provided.

Rate of VGPR or better:

Defined as the proportion of patients with sCR, CR and VGPR as BOR.

MRD negativity rate in patients with VGPR or better:

Defined as the proportion of patients for whom MRD is negative at any timepoint after first dose of study treatment. The percentage will be calculated using the number of patients in ITT population as denominator. MRD status will be assessed among patients with VGPR or better by next-generation sequencing. Threshold for negativity will be 10^{-5}. MRD status in a patient will be negative if at least one result of the assessment is negative in this patient otherwise MRD will be considered as positive (MRD status reported as positive, indeterminate, missing or unevaluable). For analysis purpose, patients in the ITT population without MRD assessment will be considered as having positive MRD.

CR rate:

Defined as the proportion of patients with sCR and CR as BOR.

Patients with demonstrated isatuximab interference will be considered in the BOR category corresponding to the M protein assessment obtained without interference, when the antibody-capture interference assay will be available.

M-protein follow-up by serum immunofixation electrophoresis (IFE) is part of the International Myeloma Working Group (IMWG) criteria to assess treatment response. Therefore, it is crucial that the isatuximab band is not confused with the endogenous M-protein of the patient during IFE

interpretation. For patients with suspected isatuximab interference on serum M-protein IFE, the SEBIA HYDRASHIFT 2/4 isatuximab IFE test will be used by the central lab to specifically measure the endogenous M-protein. This will be applied retrospectively for samples collected prior to the interim analysis and samples collected after interim analysis. At time of this retrospective analysis, an analysis with the conventional IFE test will also be performed on the same banked samples, permitting to compare with the original results reported at time of interim analysis. This will be used to demonstrate the sample stability and that retrospectively measurement of M protein without isatuximab interference with banked samples is valid. Patients with updated M protein results following the use of SEBIA HYDRASHIFT 2/4 isatuximab IFE will be reviewed by IRC to determine the response at the time points with updated IFE test results. The CR rate at time of final PFS analysis will be based IRC determined response based on the updated IFE test results using SEBIA HYDRASHIFT 2/4 isatuximab IFE test.

MRD negativity rate in patients with CR or better:

Defined as the proportion of patients with CR or better and for whom MRD is negative by next-generation sequencing at any timepoint after first dose of study treatment. The percentage will be calculated using the number of patients in ITT population as denominator.

PFS in Minimal Residual Disease negative and positive patients

Progression-free survival (as defined in Section 2.1.3.1) by MRD status will be assessed. The same definition of progression, and same censoring rules as for the PFS endpoint will be used.

PFS by SPM status

Progression-free survival (as defined in Section 2.1.3.1) by SPM status will be assessed. The same definition of progression, and same censoring rules as for the PFS endpoint will be used.

OS:

Defined as the time from the date of randomization to death from any cause. If death is not observed before the analysis cut-off date, OS will be censored at the last date the patient is known to be alive or at the cut-off date, whichever comes first.

2.1.3.2.2 Other secondary efficacy endpoints

Other secondary efficacy endpoints will be evaluated as follows:

- **TTP:** defined as time from randomization to the date of first documentation of PD (as determined by the IRC). If progression is not observed before the analysis cut-off date or the date of initiation of further anti-myeloma treatment, TTP will be censored at the date of the last valid disease assessment not showing disease progression performed prior to initiation of a further anti-myeloma treatment (if any) or the analysis cut-off date, whichever comes first.

  For the US only, this parameter will be updated by adding an additional censoring rule for late progressions and deaths. Progressions or deaths occurring more than 8 weeks after the

last valid disease assessment (ie, after >2 consecutive missed scheduled disease assessments) will be censored at the date of last valid disease assessment without evidence of progression before initiation of new anti-myeloma treatment (if any) or the PFS analysis cut-off date, whichever comes first.

- **PFS2:** defined as time from the date of randomization to the date of first documentation of PD (as reported by the investigator) after initiation of further anti-myeloma treatment or death from any cause, whichever happens first. For patients alive without a progression after initiation of further anti-myeloma treatment before the analysis cut-off date, PFS2 will be censored at the date of the last follow-up visit not showing disease progression after initiation of further anti-myeloma treatment or the analysis cut-off date, whichever comes first. Additional details regarding the definition of PFS2 and handling of events and censoring are given in Appendix I.
- **DOR:** defined as the time from the date of the first IRC determined response that is subsequently confirmed for patients achieving PR or better to the date of first documented PD determined by IRC or death, whichever happens first. DOR will be censored at the date of the last valid disease assessment not showing PD performed prior to initiation of a new anti-myeloma treatment (if any) or the analysis cut-off date, whichever occurs first.

  For the US only, this parameter will be also updated by adding an additional censoring rule for late progressions and deaths.
- **TT1R:** defined as the time from randomization to the date of first IRC determined response (PR or better) that is subsequently confirmed. In the absence of response, patients will be censored at the earliest of the date of the last valid disease assessment before disease progression or death, the date of the last valid disease assessment before initiation of a further anti-myeloma treatment (if any) or the analysis cut-off date, whichever comes first.
- **TTBR:** defined as the time from randomization to the date of first occurrence of IRC determined best overall response (PR or better) that is subsequently confirmed. In the absence of response, patients will be censored at the earliest of the date of the last valid disease assessment before disease progression or death, the date of the last valid disease assessment before initiation of a further anti-myeloma treatment (if any) or the analysis cut-off date, whichever comes first.
- **Renal response:**
  - ***A complete renal response*** is defined as an improvement in eGFR from <50 mL/min/1.73m^2 at baseline to ≥60 mL/min/1.73m^2 in at least 1 assessment during the on-treatment period.
  - ***A partial response*** is defined as an improvement in eGFR from <15 mL/min/1.73m^2 at baseline to at least 1 assessment in the range [30 to 60[mL/min/1.73m^2 during the on-treatment-period.
  - ***A minor response*** is defined as an improvement in eGFR from <15 mL/min/1.73m^2 at baseline to at least 1 assessment in the range [15 to 30[mL/min/1.73m^2 during the on-treatment-period or from [15 to 30[mL/min/1.73m^2 at baseline to at least 1 assessment in the range [30 to 60[mL/min/1.73m^2 during the on-treatment-period.
  - ***A durable renal response*** is defined as a response that lasted ≥60 days.

2.1.4 Safety endpoints

The safety analysis will be based on the AEs and other safety information, such as clinical laboratory data, vital signs, weight and ECOG PS.

Observation period

The observation period starts from the time when the patient gives informed consent and is divided into 3 periods:

- The **pre-treatment** period is defined as the time from the signed informed consent date up to the first dose of study treatments.
- The **treatment** period is defined as the time from the first dose of study treatments administration to the last dose of study treatments + 30 days.
- The **post treatment** period is defined as the period of time starting the day after the end of the treatment period up to the end of the study (as defined in the protocol).

2.1.4.1 Adverse events variables

AEs (including serious adverse events [SAE] and AEs of special interest [AESIs]) will be collected from the time of signed informed consent until the end of study treatment. After end of study treatment, all ongoing SAEs, all ongoing related AEs and all new AEs (serious or not) related to study treatment will be reported and followed up until resolution or stabilization.

Adverse event observation period:

- Pre-treatment AEs are defined as any AE reported during the pre-treatment period.
- Treatment-emergent adverse events (TEAEs) are defined as AEs that developed or worsened or became serious during the treatment period.
- Post-treatment AEs are defined as AEs that developed or worsened or become serious during the post-treatment period.

All AEs (including SAEs and AESI) will be graded according to National cancer institute common terminology for adverse events (NCI-CTCAE) v4.03 and coded to a lower-level term (LLT), preferred term (PT), high-level term (HLT), high-level group term (HLGT) and associated primary system organ class (SOC) using the version of Medical Dictionary for Regulatory Activities (MedDRA) currently in effect at Sanofi at the time of database lock or one version down.

Other significant adverse events

Other significant adverse events will include AESIs, IRs, respiratory AEs, cardiac AEs, hemolytic disorders, tumor lysis syndrome, autoimmune disorders and second primary malignancies. Specific hematological analyses will be also provided.

Adverse events of special interest

AESIs include the following events:

- IRs of Grade ≥3.
- Pregnancy of female patient entered in this study as well as pregnancy occurring in a female partner of a male entered in this study.
- Symptomatic overdose (serious or non-serious) with study treatment (isatuximab or carfilzomib or dexamethasone) or NIMP.

Infusion reactions

IRs are commonly observed with monoclonal antibodies and carfilzomib and typically occur within 24 hours from the start of the infusion.

Whenever possible, a diagnosis of the IR (eg, cytokine release syndrome, infusion related reaction, anaphylactic reaction, or any other term chosen by the investigator) will be reported by the investigator in a specific AE page instead of individual symptoms. In addition, symptoms of the IRs will be reported on a separate eCRF form.

Analysis of IRs will be performed based on the investigator's reporting of IRs (using investigator reported term collected in the specific AE forms).

In addition, an analysis based on any TEAEs (both regardless of relationship and related TEAEs) occurring within 24 hours from the start of any isatuximab or any carfilzomib infusion (ie, TEAEs with onset on the same calendar day of the infusion or on the following day) will be performed.

A similar analysis including TEAEs occurring within 24 hours from the start of any isatuximab or any carfilzomib infusion and within the "Hypersensitivity and CRS" CMQ will be also performed.

Moreover, all TEAEs (not only limited to those occurring within 24h of any isatuximab and any carfilzomib administration) from the above listed CMQ will also be analyzed.

Respiratory AEs

Analysis of selected respiratory TEAEs will focus particularly on the following groupings:

- Lower Respiratory adverse events, selected using CMQ "Lower respiratory events".
- Respiratory infections, selected using CMQ "Respiratory infections".

Late respiratory adverse events (ie, occurring, worsening or becoming serious more than 30 days after last dose) will be analyzed as part of the post-TEAEs analysis.

Cardiac AEs

Analysis of cardiac events will focus on:

- SMQ "Cardiac failure" (narrow).
- CMQ "Cardiac".
- SMQ "Ischaemic heart disease" (narrow).
- SMQ "Cardiomyopathy" (narrow).

- SMQ "Embolic and thrombotic events, venous" (narrow).
- SMQ "Embolic and thrombotic events, arterial" (narrow).
- HLGT "Vascular hypertensive disorders".

Hemolytic disorders

Hemolytic disorders will be selected using the TEAEs from the SMQ 'Haemolytic disorders' (broad+narrow).

Moreover, hemolytic disorders that occurred within 8 days after the blood cell transfusion (red blood cells or platelets) will be displayed.

Tumor lysis syndrome

Tumor lysis syndrome will be identified using the TEAEs from the CMQ 'Tumor lysis syndrome'.

Autoimmune disorders

Autoimmune disorders will be selected using the TEAEs from the CMQ 'GLB_HLGT Autoimmune disorders'

Second primary malignancies

Second primary malignancies will be selected using the CMQ 'Second primary malignancies' and will be sub-categorized as 'haematological', 'non-hematological skin tumors', 'non-hematological non-skin tumors' and "other tumors".

The time to first SPM onset is defined as the date of first SPM AE date – date of first treatment +1. If a patient does not have SPM event, it will be censored at death date, last contact date or cut-off date, whichever comes first.

Neutropenia and neutropenic complications

Neutropenia (from laboratory abnormalities) will be displayed along with neutropenic complications (neutropenic infections, febrile neutropenia).

Neutropenic complications will be analyzed using the following data source:

- Febrile neutropenia selected using CMQ 'Febrile neutropenia'.
- Neutropenic infections: defined as NCI-CTCAE Grade ≥2 infections from SOC 'Infections and Infestations' (selected using CMQ 'GLB_SOC infections and infestations') concomitant with NCI-CTCAE Grade 3-4 neutropenia from laboratory results. Infection and Grade 3-4 neutropenia will be considered as concomitant if one of the following conditions is met:
  - Neutrophils count value measured the day of the start of the AE infection,
  - The last neutrophils count value measured before the start date of the AE infection is within 7 days before the start of the AE infection,
  - The first neutrophils count value measured after the start date of the AE infection is within 2 days after the start of the AE infection.

Thrombocytopenia and hemorrhages

- Thrombocytopenia will be analyzed based on laboratory results.
- Hemorrhages will be selected using the TEAEs from the SMQ 'Haemorrhage terms (excl laboratory terms)' (narrow).
- Severe thrombocytopenia (ie, ≥Grade 4) will be displayed with concomitant hemorrhage if relevant (ie, in case of imbalance between treatment arms). The first hemorrhagic event occurring within 8 days after any occurrence of the thrombocytopenia (laboratory) will be used for this analysis.

Covid-19 infection

Covid-19 infection will be identified using the TEAEs from the CMQ 'COVID19 specific list'.

2.1.4.2 Deaths

The deaths observation periods are per the observation periods defined above.

- Death on-treatment: deaths occurring during the treatment period.
- Death post-treatment: deaths occurring during the post-treatment period.

2.1.4.3 Laboratory safety variables

Clinical laboratory data that will be analyzed consists of blood analyses (including hematology and biochemistry). Clinical laboratory values will be converted into standard international units that will be used in all listings and tables.

Blood samples for clinical laboratories will be taken as defined in the study flowchart and as clinically indicated. The laboratory parameters (excluding those used for disease assessment) will be classified as follows:

- Hematology
  - **Red blood cells and platelets**: hemoglobin and platelet count,
  - **White blood cells:** white blood cell count, neutrophils and lymphocytes.
- Biochemistry
  - **Metabolism:** fasting glucose and albumin,
  - **Electrolytes**: sodium, potassium, chloride, corrected serum calcium, magnesium and phosphate,
  - **Renal function**: serum creatinine, estimated glomerular filtration rate (eGFR) by modification in diet in renal disease (MDRD) formula, blood urea nitrogen and uric acid,
  - **Liver parameters**: alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase and total bilirubin.

Technical formulas are described in Section 2.5.1.

2.1.4.4 Vital signs variables

Vital signs include: heart rate, systolic and diastolic blood pressure and weight.

2.1.4.5 Electrocardiogram variables

Electrocardiogram assessments will be described as normal or abnormal. An interpretation of the results (normal/abnormal) is to be entered in the eCRF. In case of abnormal result, a description of the finding should be reported.

2.1.4.6 Other safety endpoints

Other safety endpoints will include ECOG PS and indirect Coombs test.

2.1.5 Pharmacokinetic variables

2.1.5.1 Population approach for isatuximab

The population PK parameters of isatuximab and their inter-patient PK variability will be estimated.

Empirical Bayesian estimation of individual parameters and of individual exposure (Area Under the Curve [AUC], Cmax and Ctrough) will also be performed.

In addition, $Ctrough_{obs}$ defined as plasma concentration observed before treatment administration during repeated dosing and concentrations at end of infusion (CEOI) will be provided.

Analysis of PK variables except $Ctrough_{obs}$ and concentrations at end of infusion (CEOI) for isatuximab could be presented in a separate report.

2.1.5.2 Non-compartmental analysis for carfilzomib

The following PK parameters will be calculated with PKDMS software (Pharsight) using non-compartmental methods from plasma of carfilzomib concentrations. The parameters will include, but may not be limited to, the following:

Table 5 - List of pharmacokinetic parameters and definitions

Parameters	Definition
C_{eoi}	Concentration observed at the end of IV infusion
C_{max}	Maximum concentration observed after the first infusion
t_{max}	Time to reach C_{max}
C_{last}	Last concentration observed above the lower limit of quantification
t_{last}	Time of C_{last}
C_{trough}	Plasma concentration observed just before treatment administration during repeated dosing
AUC_{last}	Area under the plasma concentration versus time curve calculated using the trapezoidal method from time 0 to t_{last}
AUC	Area under the plasma concentration versus time curve extrapolated to infinity according to the following equation: $AUC = AUC_{last} + C_{last/\lambda z}$

2.1.6 Immunogenicity endpoints

Human anti-drug antibodies (ADAs) to isatuximab will be assessed during the study as described in the protocol for the IKd arm only and will be analyzed using the ADA population (see Section 2.3.4).

Periods of observation:

- ADA pre-treatment period: The ADA pre-treatment period is defined as the time from signed informed consent to the first isatuximab administration.
- ADA on-study observation period: the ADA on-study observation period is defined as the time from first isatuximab administration until the end of the study.

ADA attributes:

- **Pre-existing ADAs** are defined as ADAs that are present in samples drawn during the ADA pre-treatment period.
- **Treatment boosted ADAs** are defined as pre-existing ADA with an increase in titer value during the ADA on-study observation period of at least two titer steps. Assuming a 2-fold serial dilution schema is used for the study, this means that the post-treatment sample titer value is at least (≥) 4-fold of pre-treatment titer value.
- **Treatment induced ADAs** are defined as ADAs that developed at any time during the ADA on-study observation period in patients without pre-existing ADA (including patients without pre-treatment samples).
- **Transient ADA response** is defined by:
  - Treatment-induced ADA detected only at one sampling time point during the ADA on-study observation period (excluding the last sampling time point, which ought to be considered persistent unless shown to be undetectable at a later time) OR,
  - Treatment-induced ADA detected at two or more sampling time points during the on-study observation period, where the first and last ADA-positive samples (irrespective of any negative samples in between) are separated by a period less than 16 weeks and the subject's last sampling time point is ADA-negative.
- **Persistent ADA response** is defined by treatment-induced ADA detected at two or more sampling time points during the ADA on-study observation period, where the first and last ADA-positive samples (irrespective of any negative samples in between) are separated by a period of at least 16 weeks.
- **Indeterminate ADA response** is defined by:
  - Treatment induced ADA detected only in the last sampling time point OR,
  - Treatment-induced ADA detected in the last two sampling time points (both positive), separated by a period of less than 16 weeks.

ADA response endpoints:

- **ADA positive patients** are defined as patients with at least one treatment-induced or treatment-boosted ADA positive sample at any time during the ADA on-study observation period.
- **ADA prevalence** is defined as the sum of the number of patients with pre-existing ADA and the number of patients with treatment induced ADAs, divided by the number of patients in the ADA population.

- **ADA incidence** is defined as the number of ADA positive patients divided by the number of patients in the ADA population.

2.1.7 Health-related quality-of-life endpoints

Health-related quality of life (HRQL) will be assessed using:

- The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Cancer specific module with 30 items (EORTC QLQ-C30) (2, 3).
- The EORTC QLQ myeloma-specific module with 20 items (MY20) (4, 5).
- The EuroQol measure with 5-dimensions and 5-levels per dimension EQ-5D-5L (6, 7).

EORTC QLQ-C30 and EORTC QLQ-MY20

The QLQ-C30 incorporates a Global Health Status/QoL scale, five functional scales (Physical functioning [PF2], Role functioning [RF2], Cognitive functioning [CF], Emotional functioning [EF] and Social functioning [SF]), three symptom scales (Fatigue [FA], Pain [PA] and Nausea/Vomiting [NV]) and six additional single items (Dyspnea [DY], Insomnia [SL], Appetite Loss [AP], Constipation [CO], Diarrhea [DI] and Financial Difficulties [FI]) as symptoms commonly reported by cancer patients and the perceived financial impact of the disease.

A higher score for a global health status/functional scale represents a higher/healthy level of HRQL, whereas a higher score for symptoms/ items represents a higher level of symptomatology/problems.

The EORTC QLQ-MY20 (MY20) is meant for use among patients with MM cancer. It is comprised of:

- 2 functional scales (body image, future perspective).
- 2 symptoms scales (disease symptoms and side-effects of treatment).

Higher scores for “disease symptoms” and “side effects of treatment” indicate more symptoms and side effects and lower HRQL, whereas a high score for “future perspective” and “body image” represents better outcomes.

Raw scores (RS) for the EORTC are calculated using EORTC QLQ-C30 and EORTC QLQ-MY20 scoring formulas (detailed in Appendix G):

- RS is the mean of the component items.
- For functional scales: Score = [1− ((RS− 1)/range)] x 100.
- For symptom scales/single items scales and the Global health status/QoL scale: Score = [(RS − 1)/ range] x 100.

The range is the difference between the maximum and the minimum response to individual items.

EQ-5D-5L

The EQ-5D-5L comprises the EQ-5D 5 dimensions (mobility, self-care, usual activities, paint/discomfort and anxiety/depression) and a visual analogue scale (VAS).

Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems and extreme problems. Overall health state is then defined as a 5-digit number. The health utility index value will be calculated using the crosswalk value sets provided in the EQ-5D-5L Index Value Calculator created by the EuroQol Group and using mapping function developed by Van Hout et al.(8). The value sets based on UK population will be used for all countries.

The EQ VAS records the respondent's self-rated health on a 20 cm vertical VAS with endpoints labelled 0 ('the worst health you can imagine') to 100 ('the best health you can imagine'). This information can be used as a quantitative measure of health as judged by the individual respondents. EQ VAS will be described as given by patient.

Rules of handling with missing items are detailed in Appendix G for the EORTC questionnaires. For the EQ-5D-5L, the health utility score will be missing if response to one or more dimension is missing.

2.1.8 Exploratory biomarker endpoints

A blood sample will be collected on Day 1 of Cycle 1. Leukocyte DNA will be extracted and analyzed for immune genetic determinants (such as Fcγ receptor polymorphisms). Parameters of clinical response will be evaluated in each type of immune genetic determinants.

In IKd arm only, an additional blood sample will be collected at all time-points to evaluate the potential interference of isatuximab in the M protein assessment (central laboratory) up to Cycle 30. This sample will be collected beyond Cycle 30 and until disease progression for patients who reach at least VGPR at cycle 30. In case of isatuximab is discontinued before progression, sample interference assay will be collected up to 3 months after last isatuximab administration or PD, whichever comes first.

In addition to the 3 chromosomal abnormalities (del(17p), t(4:14) and t(14:16)) assessed by FISH at baseline to determine R-ISS stage which is stratification factor, other chromosomal abnormalities such as but not limited to del (1p) and 1q21+ deletion will be assessed by central laboratory. Parameters of clinical response will be evaluated in each of these chromosomal abnormalities.

2.1.9 Further therapy after discontinuation of investigational medicinal product administration during the study

Further therapies after discontinuation of IMP include further anti-myeloma treatments.

Time to Next Treatment

Time to next treatment is defined as the time from randomization to the start of further anti-myeloma treatment. Patients who do not receive any further anti-myeloma treatment before the cut-off date will be censored at the date of their last follow-up visit or the cut-off date, whichever comes first. Patients with no follow-up visit will be censored at their last study treatment administration or the cut-off date whichever comes first.

2.2 DISPOSITION OF PATIENTS

This section describes patient disposition for both patient study status and the patient analysis populations.

Screened patients are defined as any patients who signed the study informed consent.

Randomized patients consist of all patients with a signed informed consent form who have been allocated a randomization number by the IRT, regardless of whether the patient was treated or not.

For patient study status, the total number of patients in each of the following categories will be presented in the clinical study report using a flowchart diagram or summary table:

- Screened patients.
- Screen failure patients and reasons for screen failure (if any).
- Randomized patients.
- Randomized but not treated patients.
- Randomized and treated patients.
- Patients who discontinued study treatment.
- Patients still on treatment.
- Patients still on study
- Status at last study contact.
- Patients with date of last contact obtained before the cut-off date and duration from last contact to cut-off date (0-2weeks, 2-4 weeks, 4-8 weeks, >8 weeks).

A summary of the reasons for definitive and premature treatment discontinuation by treatment group will be provided. Definitive treatment discontinuation is defined as the discontinuation of all the study drugs. Premature treatment discontinuation is defined as the discontinuation of at least one of the study drugs but at least one is continued. Reasons for definitive and premature treatment discontinuation as “adverse event” (Covid-19 infection (AE)) and “Other” related to Covid-19 pandemic situation will be also displayed, when applicable. Listing of the reasons for treatment discontinuation and patients still on treatment at time of the analysis will be provided, when applicable.

A summary of the reasons for end of study by treatment group will be provided. Reasons for end of study as “Death” will be also displayed, when applicable. Listing of patients who ended the study for other reason will be provided.

For all categories of patients (except for the screened and non-randomized categories) percentages will be calculated using the number of randomized patients as the denominator.

In addition, the number and percentage of randomized patients will be presented for each of the 6 stratification levels (number of prior lines = 1 and R-ISS stage = I or II;
number of prior lines = 1 and R-ISS stage = III …) and by treatment group.

All critical or major deviations potentially impacting efficacy analyses, randomization, and drug-dispensing irregularities and other major or critical deviations will be summarized in tables giving numbers and percentages of deviations by treatment group. Critical and major protocol

deviations will be also displayed separately as related versus not related to Covid-19 pandemic situation if applicable.

Additionally, the following analysis populations will be summarized by treatment group:

- Randomized population.
- Efficacy population: intent-to-treat (ITT) population.
- Population without trial impact (disruption) due to Covid-19 infection (AE) and/or pandemic situation.
- Safety population.
- Pharmacokinetics population.
- ADA population.

Definitions of study populations are provided in Section 2.3. Reasons for exclusion from the population without trial impact (disruption) due to Covid-19 infection (AE) and/or pandemic situation will be summarized.

2.2.1 Randomization and drug dispensing irregularities

Randomization and drug-dispensing irregularities occur whenever:

1. A randomization is not in accordance with the protocol-defined randomization method, such as a) a patient is randomized based on an incorrect stratum or b) a patient is randomized twice.

   OR

2. A patient is dispensed an IMP kit not allocated by the protocol-defined randomization, such as a) a patient at any time in the study is dispensed a different IMP than as allocated or b) a non-randomized patient is treated with IMP reserved for randomized patients.

Randomization and drug-dispensing irregularities will be monitored throughout the study and reviewed on an ongoing basis. The following irregularities are prospectively defined:

- IMP dispensation without IRT transaction.
- Erroneous therapy dispensation (ie, patient is dispensed a combination of drugs that does not correspond to the randomization arm).
- Patient randomized twice.
- Stratification error.

All randomization and drug-dispensing irregularities will be documented in the clinical study report and will be summarized by treatment group on the randomized population (number and percentages). Non-randomized but treated patients will be described separately.

2.3 ANALYSIS POPULATIONS

The randomized population includes all randomized patients as defined in Section 2.2.

For any patient randomized more than once, only the data associated with the first randomization will be used in any analysis population. The safety experience associated with any later randomization will be assessed separately.

2.3.1 Efficacy populations

2.3.1.1 Intent–to-treat population

The ITT population is the randomized population. Patients will be analyzed according to the treatment group allocated by IRT, regardless of whether the patients receive any study treatment or receive a different study treatment from that to which they were randomized.

This population is the primary population for all efficacy analyses.

2.3.1.2 Population without trial impact (disruption) due to Covid-19

This population will include all randomized patients:

- without any critical or major deviation related to Covid-19
- and who did not definitively discontinue treatment due to Covid-19 (infection (AE) and/or pandemic situation).
- and who did not definitively discontinue study due to Covid-19 (infection (AE) and/or pandemic situation).

This population could be used for additional analyses to assess the impact of Covid-19 on the study.

2.3.2 Safety population

The safety population will include ITT patients who received at least 1 dose or a part of a dose of the study treatments. This population is the primary population for the analysis of all safety parameters. All analyses using this population will be based on the treatment actually received.

In addition:

- Non-randomized but treated patients will not be part of the safety population; however, their safety data will be presented separately.
- Randomized patients for whom it is unclear whether they took the IMP will be included in the safety population as randomized.
- Patients receiving at least one isatuximab dose (even incomplete or by error at one cycle) during the trial, will be analyzed in the IKd arm.

2.3.3 Pharmacokinetics population

The PK population will include safety population patients from the IKd arm who receive at least one dose of isatuximab, even if incomplete, with data for at least one PK concentration available post-baseline.

2.3.4 ADA population

The ADA population will include safety population patients from the IKd arm with a least one ADA assessment during the ADA on-study observation period with a reportable result.

2.4 STATISTICAL METHODS

Continuous data will be summarized using the number of available data, mean, standard deviation, median, minimum and maximum for each treatment group. Categorical and ordinal data will be summarized using the number and percentage of patients in each treatment group.

2.4.1 Demographics and baseline characteristics

Parameters described in Section 2.1.1 will be summarized on the randomized population by treatment group (as allocated by IRT) and overall using descriptive statistics. Analyses for the safety population will be included in the appendices if the size of the safety population is different (>10%) from the size of the randomized population for any treatment group. Analyses for the population without trial impact (disruption) due to Covid-19 will be included in the appendices if the size of this population is different (>10%) from the size of the randomized population for any treatment group.

Medical or surgical history will be summarized by SOC and PT (SOC will be sorted according to the internationally agreed order and PT by decreasing frequency). In addition, smoking habits will be summarized separately.

Demographic characteristics, MM characteristics at study entry and Prior anti-myeloma treatments will be also described by treatment arm and SPM categories (solid tumor [skin or non-skin cancer], hematology malignancies, or other non-specified). Prior anti-myeloma treatments will be also described by treatment arm and by regimen.

2.4.2 Prior or concomitant medications (other than anticancer therapies)

The prior and concomitant medications will be presented for the randomized population.

Medications will be summarized by treatment group according to the WHO-DD, considering the first digit of the anatomical therapeutic chemical (ATC) class (anatomic category) and the first 3 digits of the ATC class (therapeutic category). All ATC codes corresponding to a medication will be summarized, and patients will be counted once in each ATC category (anatomic or therapeutic) linked to the medication. Therefore, patients may be counted several times for the same medication.

The table for prior medications will be sorted by decreasing frequency of ATC followed by all other therapeutic classes based on the overall incidence across treatment groups. In case of equal frequency regarding ATCs (anatomic or therapeutic categories), alphabetical order will be used.

The tables for concomitant medications will be sorted by decreasing frequency of ATC followed by all other therapeutic classes based on the incidence in the IKd arm. In case of equal frequency regarding ATCs (anatomic or therapeutic categories), alphabetical order will be used.

In addition, other analyses including number (%) of patients with concomitant red blood cells transfusions, with concomitant platelets transfusions and with concomitant use of granulocyte colony stimulating factor/ granulocyte-macrophage colony stimulating factor (prophylaxis and curative intent) will be provided for the safety population.

IR medications

Number (%) of patients with IR medications (prophylaxis and curative intent) including diphenhydramine (or equivalent), paracetamol and steroids as defined in Section 2.1.2 will be provided and will be also displayed depending on the mode of administration (initial mode of administration and fixed volume administration mode).ss Number (%) of patients with IR medications for prophylaxis intent will be described by infusion number. Number of infusions with prophylactic IR medications, number of infusions with curative IR medications and number of infusions without any IR medication will also be summarized. Further analyses on cumulative steroids exposure may be performed as needed.

2.4.3 Extent of investigational medicinal product exposure

The extent of IMP exposure will be assessed and summarized by actual treatment within the safety population (Section 2.3.2).

2.4.3.1 Overall study treatment exposure

The following variables will be summarized with descriptive statistics to describe the overall study treatment exposure (all study treatments together):

- Overall number of cycles started, defined by the total number of cycles in which at least one dose of any study treatments is administered.
- Cumulative exposure to treatment (in patient-years), derived by summing the duration of exposure for all patients by treatment group.
- Overall duration of exposure in weeks defined as [(last day of last cycle – first day of first cycle)/7].

The first day of the first cycle is defined as the date of the first dose of study treatment at Cycle 1.

The last day of last cycle is defined as the last date among the following:

- Date of last dose of isatuximab + 7 days if last cycle is Cycle 1 or date of last dose of isatuximab + 14 days if last cycle is Cycle 2 or later.
- Date of last dose of carfilzomib + 7 days if the last dose is administered on Day 1 or 8; or date of last dose of carfilzomib + 6 days if the last dose is administered on Day 2 or 9; or

date of last dose of carfilzomib + 14 days if the last dose is administered on Day 15; or date of last dose of carfilzomib + 13 days is the last dose is administered on Day 16.

- Date of last dose of dexamethasone + 7 days if the last dose is administered on Days 1, 8, 15, or 22; or date of last dose of dexamethasone + 6 days if the last dose is administered on Days 2, 9, 16, or 23.

Number of cycles started by patient will be also summarized as a quantitative variable and by category (ie, number (%) of patients receiving at least 1 cycle, at least 2 cycles, etc.).

Cycle delay will be computed to describe overall dose modification. A cycle is deemed to have been delayed if the start date of the current cycle is >28 + 3 days beyond the start date of the previous cycle (planned cycle duration is 28 days). Cycle start date is defined by the earliest date of isatuximab, carfilzomib or dexamethasone administration within a cycle. Cycle delay is not defined for the first cycle.

Cycle delay will be analyzed at the patient and cycle levels by treatment group as follows:

- Patient level:
  - Number of patients treated (used for % calculation for this level),
  - Number (%) of patients with at least one cycle delay,
    - Between 4 and 7 days,
    - More than 7 days.
  - Number (%) of patients with at least one cycle delay due to Covid-19 pandemic situation
    - Between 4 and 7 days,
    - Between 7 and 14 days,
    - Between 14 and 28 days,
    - More than 28 days.
  - Number (%) of patients with at least one cycle partially done due to Covid-19 pandemic situation (cycle with at least one dose omission of one study drug due to COVID-19 ie, at a visit not done, partially done on site or partially done by phone due to COVID-19)
- Cycle level:
  - Number of cycles administered (used for % calculation for this level),
  - Number (%) of cycles delayed.
    - Between 4 and 7 days,
    - More than 7 days.
  - Number (%) of patients with at least one cycle delay due to Covid-19 pandemic situation
    - Between 4 and 7 days,
    - Between 7 and 14 days,
    - Between 14 and 28 days,
    - More than 28 days.
  - Number (%) of patients with at least one cycle partially done due to Covid-19 pandemic situation

Overall extent of exposure will be also described by treatment arm and SPM categories (solid tumor [skin or non-skin cancer], hematology malignancies, or other non-specified).

2.4.3.2 Isatuximab, carfilzomib or dexamethasone exposure

The following variables will be summarized with descriptive statistics for isatuximab, carfilzomib, and dexamethasone separately to describe exposure to each drug:

- Number of cycles started with each drug.
- Number of cycles started with each drug by patient (as a quantitative variable and by category (ie, number (%) of patients receiving at least 1 cycle, at least 2 cycles, etc.).
- Duration of exposure in weeks, defined as:
  - For isatuximab:
    [date of last dose of isatuximab + 7 days - first dose of isatuximab] / 7 if last cycle is Cycle 1 or [date of last dose of isatuximab + 14 days - first dose of isatuximab] / 7 if last cycle is Cycle 2 or later,
  - For carfilzomib:
    [date of last dose of carfilzomib + 7 days - first dose of carfilzomib] / 7 if the last dose is administered on Day 1 or 8; or [date of last dose of carfilzomib + 6 days - first dose of carfilzomib] / 7 if the last dose is administered on Day 2 or 9; or
    [date of last dose of carfilzomib + 14 days - first dose of carfilzomib] / 7 if the last dose is administered on Day 15; or
    [date of last dose of carfilzomib + 13 days - first dose of carfilzomib] / 7 if the last dose is administered on Day 16,For dexamethasone:
  - [date of last dose of dexamethasone + 7 days - first dose of dexamethasone] / 7 if the last dose is administered on Days 1, 8, 15, and 22; or
    [date of last dose of dexamethasone + 6 days - first dose of dexamethasone] / 7 if the last dose is administered on Days 2, 9, 16, and 23.
- Cumulative dose: the cumulative dose is the sum of all doses administered from first to last dose.
- Actual dose intensity (ADI) per week: defined as the cumulative dose divided by the duration of exposure in weeks.
- Planned dose intensity per week: corresponds to the sum of the theoretical planned doses during the started cycles divided by the theoretical cycle duration expressed in weeks (ie, 4 weeks per cycle started). The sum of the theoretical planned doses corresponds to:
  - The planned dose at C1D1, regardless of dose changes, multiplied by the theoretical total number of doses during the started cycles (4 for cycle 1, 2 for subsequent cycles) for isatuximab
  - The planned dose at C1D1 (ie, 20 mg/m^2), regardless of dose changes, multiplied by 2 + the planned dose at C1D8 (ie, 56 mg/m^2), regardless of dose changes, multiplied by 4 for cycle 1 and the planned dose at C1D8 (ie, 56 mg/m^2), regardless of dose changes, multiplied by 6 for subsequent cycles for carfilzomib
  - The planned dose at C1D1, regardless of dose changes, multiplied by the theoretical total number of doses (equal to 8) during the started cycles for dexamethasone.
- Relative dose intensity (RDI) in %: defined as the ratio of the ADI to the planned dose intensity x 100.

These analyses will be also provided by treatment arm and SPM categories (solid tumor [skin or non-skin cancer], hematology malignancies, or other non-specified).

The following variables will be summarized with descriptive statistics for isatuximab, carfilzomib, and dexamethasone separately to describe dose modifications for each drug:

- Infusion interruption (excluding dexamethasone): an infusion is considered to be interrupted if the administration is stopped during an infusion before it is completed regardless it is further restarted or not.
- Infusion/dose delay within cycle: an infusion/dose is deemed to have been delayed if the actual start date is >1 day beyond the theoretical day of treatment. Infusion/dose delay does not apply to the first infusion/dose of each cycle, in which case it is considered as cycle delay.
- Dose reduction: a dose is considered to be administered at a reduced dose if the actual dose administered at the current administration is at least one level below the prior administration. In addition, if the dose of carfilzomib is not increased to 56 mg/m^2 from C1D8 as planned per protocol, this will be also considered as a dose reduction. Dose reductions will be determined by using the dose intervals defined in Table 6 for carfilzomib and Table 7 for dexamethasone. Although not allowed in the study protocol for isatuximab, potential dose reduction as defined in Table 8 will be screened and reported in the clinical study report. The first administration will not be counted as a dose reduction.
- Dose omission: a dose is considered omitted if the dose is not administered for the scheduled visit and there are positive dose(s) afterwards.

Table 6 - Carfilzomib - Dose reduction criteria

Starting dose 20 mg/m²		Starting dose 56 mg/m²	
Actual dose level	**Dose level interval**	**Actual dose level**	**Dose level interval**
		Dose level -4 (low dose)	>0 mg/m² and ≤22.5 mg/m²
Dose level -3 (low dose)	>0 mg/m² and ≤9 mg/m²	Dose level -3 (27 mg/m²)	>22.5 mg/m² and ≤31.5 mg/m²
Dose level -2 (11 mg/m²)	>9 mg/m² and ≤13 mg/m²	Dose level -2 (36 mg/m²)	>31.5 mg/m² and ≤40.5 mg/m²
Dose level -1 (15 mg/m²)	>13 mg/m² and ≤17.5 mg/m²	Dose level -1 (45 mg/m²)	>40.5 mg/m² and ≤50.5 mg/m²
Initial dose (20 mg/m²)	>17.5 mg/m²	Initial dose (56 mg/m²)	>50.5 mg/m²

Note: if dose is not increased to 56 mg/m² from the third infusion, dose level interval defined for starting dose 56 mg/m^2 will be used to determine dose reduction at the first administration observed from C1D8 and then dose level interval defined for starting dose 20 mg/m^2 will be used for subsequent administrations. In case of delayed dose escalation, dose level interval defined for starting dose 56 mg/m^2 will be used again from the first infusion with planned dose equal to 56 mg/m^2.

Table 7 - Dexamethasone - Dose reduction criteria

Actual dose level	Dose level interval
Dose level -4 (low dose)	>0 mg and ≤2 mg
Dose level -3 (4 mg)	>2 mg and ≤6 mg
Dose level -2 (8 mg)	>6 mg and ≤10 mg
Dose level -1 (12 mg)	>10 mg and ≤16 mg
Initial dose (20 mg)	>16 mg

Table 8 - Isatuximab - Dose reduction criteria

Actual dose level	Dose level interval
Dose level -2 (low dose)	>0 mg and ≤2.5 mg
Dose level -1 (5 mg)	>2.5 mg and ≤7.5 mg
Initial dose (10 mg/kg)	>7.5 mg

Dose modification will be analyzed at the patient and total number of infusions levels as follows separately for isatuximab and carfilzomib:

- Patient level:
  - Number of patients treated (used for % calculation for this level),
  - Number (%) of patients with at least one infusion delay,
  - Number (%) of patients who did not escalate the carfilzomib dose to 56 mg/m² on the third infusion (for patients who have received at least one dose of carfilzomib at or after C1D8, carfilzomib table only)
    - Number (%) of patients who never escalate the carfilzomib dose to 56 mg/m²
    - Number (%) of patients with a delayed carfilzomib dose escalation to 56 mg/m²
  - Number of patients who discontinued carfilzomib before C1D8 (carfilzomib table only),
  - Number (%) of patients with at least one dose reduction,
  - Number (%) of patients with at least one dose omission,
  - Number (%) of patients with at least 1, 2, 3 or more than 3 dose omission(s) due to Covid-19 pandemic situation
  - Number (%) of patients with at least 2 consecutive or more than 2 consecutive dose omissions due to Covid-19 pandemic situation
  - Number (%) patients with a least one infusion interruption
    - Number (%) of patients with a least one infusion interrupted and re-started
    - Number (%) of patients with a least one infusion interrupted and not completed (not re-started)
- Total number of infusions level:
  - Total number of infusions (used for % calculation for this level),
  - Number of infusions interrupted,
    - Number of infusions interrupted and re-started
    - Number of infusions interrupted and not completed (not re-started)
  - Number of infusions interrupted more than once,
  - Number (%, calculated using the total number of infusions interrupted) of administrations interrupted at:
    - 1st infusion,
    - 2nd infusion,
    - Subsequent infusions.
  - Time from infusion start to first interruption in minutes (quantitative and qualitative: <5, 5-10, 11-30, 31-60, 61-90, 91-120, >120)

Moreover, duration of infusion defined as the time from the start (date/time) of infusion to the end (date/time) of infusion will be summarized for first and subsequent infusions separately for isatuximab and carfilzomib. In addition, exposure data for isatuximab will be also displayed depending on the mode of administration (initial mode of administration and fixed volume administration mode).

For dexamethasone, dose modification will be analyzed at the patient level only:

- Number of patients treated (used for % calculation for this level),
- Number (%) of patients with at least one dose delay,
- Number (%) of patients with at least one dose reduction,
- Number (%) patients with a least one dose omission.
- Number (%) of patients with at least 1, 2, 3 or more than 3 dose omission(s) due to Covid-19 pandemic situation
- Number (%) of patients with at least 2 consecutive or more than 2 consecutive dose omissions due to Covid-19 pandemic situation

2.4.4 Analyses of efficacy endpoints

All efficacy analyses will be performed on the ITT population. All analyses using the stratification factors will be performed using the stratification factor as per IRT.

2.4.4.1 Analysis of primary efficacy endpoint(s)

Primary analysis will consist of PFS comparison between IKd arm versus Kd arm through a log-rank test procedure stratified by stratification factors as entered in the IRT (ie, number of previous lines of therapy and R-ISS). The nominal significance levels at the interim and final analyses will be determined using alpha-spending function (see Section 3) in order to control the overall one-sided type 1 error at 2.5%.

In addition, the following estimates will be provided:

- The hazard ratio and corresponding confidence interval (CI) at (1-2α) % level (α being the one-sided nominal significance level: α=0.023 at final analysis, α=0.005 at PFS interim analysis) will be estimated using the Cox proportional hazards model stratified by the same stratification factors as those used for the log-rank test described above. Underlying assumptions of the Cox proportional hazards model will be assessed by graphical methods (ie, log-log graphical methods).
- PFS data will be analyzed using the Kaplan-Meier method by treatment group in the ITT population:
  - Kaplan-Meier estimates of the 25th, 50th and 75th percentiles and their associated 2-sided 95% CIs will be provided. The confidence intervals will be constructed using a log-log transformation of the survival function and the methods of Brookmeyer and Crowley,
  - Number of patients at risk as well as the probabilities of surviving without disease progression at least 6, 12, 18, 24 and 36 months (if possible, depending on the time of the analysis) with 2-sided 95% CIs will be estimated for each treatment group using the Kaplan-Meier method,

  - Kaplan-Meier curves will be plotted. These plots will include the number of patients at risk at key time points by treatment group.
- For patients with events, the type of event (confirmed disease progression or death) will be summarized by treatment group using counts and percentages. The type of disease progression will also be presented (progression diagnosed on M-protein or radiological progression).
- For patients who died without evidence of disease progression, the time from the last valid disease assessment to the death will be summarized by treatment group using number, mean, standard deviation, median and range.
- The number (%) of censored patients, the reason and timing of their censoring (ie, censored at randomization, censored at the last valid disease assessment before the initiation of further anti-myeloma treatment, censored at last valid disease assessment before the cut-off date, censored at the cut-off date), and the time from the last disease assessment to the cut-off date will be summarized by treatment group. For each censoring reason, when applicable, distinction will be made between cases where no event was observed and cases where an event was observed after the censoring.
- Follow-up duration (months) will be defined as the time interval from the date of randomization to the date of last contact with the patient. Patients who have died will be censored on their date of death. Median follow-up duration (months) will be estimated using the Kaplan-Meier method.

2.4.4.1.1 Sensitivity analyses

Sensitivity analyses of PFS will be performed at a 1-sided α level unless otherwise specified. The same statistical methods used in the primary analysis will be applied to the PFS data using different censoring and event rules or stratification rules as defined below. Additional details are provided in Appendix F.

Sensitivity analysis on PFS endpoints for US only and ex-US will be performed separately.

The sensitivity analyses for all regions excluding US will include:

- 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.
- Analysis based on scheduled assessment dates instead of actual assessment dates and late PFS events censored (analysis done if lack of adherence to the protocol-defined schedule of disease assessments between the treatment groups has been detected).
- PFS analysis using the date of the last observed event as cut-off date (analysis done if some events are observed after the PFS analysis cut-off date due to operational aspects).
- Unstratified PFS analysis.
- PFS analysis using stratification factors as per eCRF (if relevant).

- PFS analysis on the population without trial impact (disruption) due to Covid-19
- PFS analysis censoring death event due to Covid-19 infections (Covid-19 grade 5 TEAEs + death due to other (Covid-19))

For US, as the primary analysis of PFS includes an additional censoring rule for late progressions and deaths, this additional censoring rule will be applied for all sensitivity PFS analyses same as used in ex-US except sensitivity analysis #5 (Analysis based on scheduled assessment dates instead of actual assessment dates and late PFS events censored) that already included this censoring rule. For sensitivity analysis #2 (PFS analysis using Investigator assessment of response including symptomatic deterioration) and #4 (Initiation of further anti-myeloma treatment considered as PFS event), this additional censoring rule will be applied to all types of events (PD, death and either symptomatic deterioration or initiation of further anti-myeloma therapy).

Sensitivity analysis #1 (progression based on blinded IRC disease assessment, regardless of further anti-myeloma treatment)

Patients with documented PD or death after the start of further anti-myeloma treatment will not be censored at the date of the last valid disease assessment not showing disease progression performed prior to initiation of a further anti-myeloma treatment. Progression or deaths occurring after any further anti-myeloma treatment will be considered as PFS events in this analysis.

Sensitivity analysis #2(progression based on investigator's disease assessment and including symptomatic deterioration)

PFS will be derived using the investigator's disease assessment (as reported in the eCRF) using the censoring and event rules from the primary analysis. In addition, in this analysis, symptomatic deterioration will be considered as an event. If symptomatic deterioration is observed in the absence of documented disease progression per IMWG criteria or prior to documented disease progression or death, the date of the PFS event will be the date of symptomatic deterioration.

Sensitivity analysis #3 (progression based on investigator's disease assessment and ignoring symptomatic deterioration)

PFS will be derived using the investigator's disease assessment (as reported in the eCRF), ignoring symptomatic deterioration and using the censoring and event rules from the primary analysis.

The concordance/discordance between the IRC and the investigator assessment of PD will be summarized by treatment group using counts and percentages. For patients with PD per both the IRC and the investigator, the concordance of the timing of the events will be summarized by treatment group using counts and percentages.

Sensitivity analysis #4 (progression based on blinded IRC disease assessment and considering initiation of further anti-myeloma treatment as an event)

PFS endpoint will be analyzed based on IRC disease assessment, including initiation of further anti-myeloma treatment as an event. If further anti-myeloma treatment is initiated in absence or before disease progression is documented per IMWG criteria, the start date of the further anti-myeloma treatment will be used as the date of PFS event.

Sensitivity analysis #5 (progression based on blinded IRC disease assessment, analysis based on scheduled assessment dates instead of actual assessment dates and censoring late progressions and deaths)

Adherence to the protocol-defined schedule of disease assessments will be assessed by comparing the timing of disease assessments between the treatment groups (the day of the disease assessment relative to the date of C1D1). If an imbalance is observed between the treatment groups, the PFS endpoint based on the IRC disease assessments will be calculated using nominal assessments days instead of the actual assessment days as the progression dates and last valid disease assessment dates in the censoring and event rules used for the primary analysis. The visit windows for defining uniform progression and assessment dates are provided in Table 9.

In this sensitivity analysis, progression or death occurring more than 8 weeks after the last valid disease assessment without progression will be censored.

Table 9 - Visit windows for uniform progression and assessments days

#Window	Nominal day	Window for disease progression assessment
	Baseline	No window
1	Day 29	Day 2 – Day 43
2	Day 57	Day 44 – Day 71
3	Day 85	Day 72 – Day 99
4	…	…

In general, the window for the time point of Day 28*n+1 (where n>1) is [Day 28*n – 12, Day 28*n + 15]. Day is determined relative to the date of C1D1. For example, progression occurring from Day 72 up to Day 99 will be assigned to the nominal day, Day 85.

Sensitivity analysis #6 (sensitivity to number of events observed at the cut-off date)

The cut-off date for the final PFS analysis is the actual date when the 159th event (first occurrence of either disease progression or death due to any cause) has been observed. Due to operational aspects some events could be observed after the cut-off date. If appropriate, a sensitivity analysis may be performed using the date of the last observed event as cut-off date at the exact nominal significance level based on the actual number of events.

Since the PFS endpoint met its statistical significance at the planned interim analysis of 103 PFS events (65% information fraction), all future analyses of PFS endpoint are non-inferential. All observed PFS events up to the analysis cut-off date will be used for PFS final analysis. Hence this sensitivity analysis #6 is not applicable for the PFS final analysis.

Sensitivity analysis #7 (sensitivity to stratification)

In order to assess the robustness of the primary analysis to stratification factors, analysis of PFS by using unstratified log-rank test procedure and unstratified Cox's regression model will be performed.

Sensitivity analysis #8 (sensitivity to randomization strata)

In order to assess the robustness of the primary analysis to randomization stratum mistakes (ie, the stratum recorded in IRT differs from the actual one), a sensitivity analysis of PFS will be performed using the stratification factors as derived from eCRF data, if relevant.

Sensitivity analysis #9 (sensitivity to assess the impact of Covid-19)

In order to assess the impact of Covid-19 on the study, a sensitivity analysis of PFS will be performed on the population without trial impact (disruption) due to Covid-19 (as defined in Section 2.3.1.2).

Sensitivity analysis #10 (progression based on blinded IRC disease assessment and censoring death event due to Covid-19 infections)

In order to assess the impact of Covid-19, PFS endpoint will be analyzed based on IRC disease assessments, censoring death event due to Covid-19 infections (Covid-19 grade 5 TEAEs + death due to other (Covid-19)). If patient died from Covid-19 infections (and no progressive disease confirmed before), then the patient is censored and the censoring date is the date of last valid disease assessment without evidence of PD.

Other potential sensitivity analyses

In addition, the following two sensitivity analyses (9) could be performed to account for possibly informative censoring due to initiation of further anti-myeloma treatment:

- Delta-adjusted method that specifies that the hazard of having an event for experimental subjects who switched to further anti-myeloma treatment is multiplicatively increased relative to the hazard for experimental subjects who have not switched.
- Reference-based method that specifies that the hazard for experimental subjects who switched to further anti-myeloma treatment lies between the hazard for experimental subjects who have not switched and the hazard for the reference control subjects.

Both methods are suitable for a tipping point analysis by varying the sensitivity parameter (or penalty) and examining the resulting treatment effect estimates, confidence intervals and p values. In particular, the amount of penalty which overturns the primary analysis results will be looked for.

2.4.4.1.2 Subgroup analyses

Evaluation of consistency:

The consistency of the results from the primary analysis will be evaluated across pre-defined subgroups in patients with available results. The definition of each subgroup is defined in Table 10. Depending upon the study results, additional subgroups may be examined, and subgroups with small sample sizes may be combined to create a larger meaningful subgroup. For each subgroup, the treatment effect hazard ratio and its associated 2-sided 95% confidence interval will be estimated. A forest plot summarizing the results for each subgroup will be provided.

Evaluation of interactions:

For each pre-defined factor defined in Table 10, PFS will be analyzed using a non-stratified Cox proportional hazards model with terms for the factor, treatment and their interaction. The test of the interaction will be performed at the 10% alpha level.

Table 10 - PFS subgroups analyses: covariates investigated

Prognostic factor	Description
Age	<65 vs ≥65 years
Gender	Male vs female
Race	Caucasian vs other
Region of the world (geographical)	Europe vs America vs Asia vs Other countries
Region of the world (regulatory)	Western countries vs Other countries
ECOG PS at baseline	0 or 1 vs >1
ISS staging at study entry	I vs II vs III
R-ISS staging at study entry (IRT)	I or II vs III vs not classified
Number of previous lines of therapy (IRT)	1 vs >1
Chromosomal abnormality (del(17p), t(4;14), t(14;16))	At least one vs. none
Chromosomal abnormality (1q21+)	Yes vs No
Chromosomal abnormality (gain 1q21)	Yes vs No
Chromosomal abnormality (amplification 1q21)	Yes vs No
MM type at study entry	IgG vs non IgG
Previous autologous stem-cell transplantation	Yes vs No
Baseline eGFR (MDRD formula)	<60 vs ≥60 mL/min/1.73 m^2
Previous treatment with proteasome inhibitor	Yes vs No
Previous treatment with IMiD [a]	Yes vs No
Previous treatment with proteasome inhibitor and IMiD	Yes vs No

Subgroup analyses will be conducted when at least 10 patients will be included in each treatment arm within each subgroup.
[a] IMiD: Immunomodulatory imide drugs

Evaluation of confounding:

Since the results from the primary analysis could be impacted by confounding factors, any potential issues will be examined and, if confirmed, an exploratory analysis of the primary endpoint will be done accordingly. A multivariate Cox proportional hazards model will be used to identify prognostic factors among the demographic and baseline characteristics factors described in the table (except for gain 1q21/ amplification 1q21) above using a stepwise selection procedure with a 15% significance level for removing effects. For significant prognostic factors identified in the multivariate model, the balance between treatment groups will be assessed. If major confounding is identified through screening for treatment group imbalances in a prognostic factor at baseline, an exploratory analysis of PFS will be done after adjusting for the prognostic factors in the multivariate Cox proportional hazards model. Differences between the adjusted and unadjusted models will be discussed in the clinical study report.

2.4.4.2 Analyses of secondary efficacy endpoints

2.4.4.2.1 Analysis of key secondary efficacy endpoints

ORR, rate of VGPR or better, CR rate and MRD negativity rate

Key secondary endpoints other than OS will be analyzed in the ITT population and tested at the time of the primary and/or the final analysis of PFS analysis. CR rate will only be tested for comparison when the antibody-capture interference assay will be available.

The primary PFS analysis corresponds either to the positive interim PFS analysis (when 103 events are observed) or the final PFS analysis (when 159 events are observed). In case of positive interim PFS analysis, key secondary endpoints will be tested sequentially up to the null hypothesis failed to be rejected for a key secondary endpoint (see Section 2.4.4.3). At final PFS analysis, the testing procedure will resume where it stopped at interim analysis (if applicable). OS will be analyzed and tested only at the final OS analysis cut-off date that is approximately 3 years after the primary PFS analysis. The significance levels of binary secondary endpoints at the interim and final analyses will be determined using spending functions, except if the information fraction is 100% at the interim analysis of PFS (see Section 3). BOR, ORR, rate of VGPR or better, CR/sCR rate and MRD negativity rate will be summarized with descriptive statistics per treatment arm. Confidence intervals at (1-2α) % level (α being the adjusted one-sided nominal significance level using alpha-spending function specific to each endpoint at final and interim analyses) will be computed for ORR, rate of VGPR or better, CR rate (including sCR), MRD negativity rate and MRD negativity rate in patients with CR or better using the Clopper-Pearson method. These endpoints will be compared between treatment arms using Cochran Mantel Haenszel test stratified by stratification factors as entered in the IRT. The stratified odds ratio and its associated 95% CI will be also provided.

A shift table matching the BOR at the interim analysis and at final analysis will be provided for each arm. The BOR at final analysis is based on the SEBIA HYDRASHIFT 2/4 isatuximab IFE test, while the BOR at the interim analysis is based on the conventional IFE test.

For analysis purpose, subjects in the ITT population without MRD assessment will be considered as having positive MRD. In addition, analyses on MRD negativity rate will be also performed on the ITT population but restricted to patients with VGPR or better as per investigator and restricted to patients with CR or better as per investigator, as exploratory analyses.

A sensitivity analysis of key secondary endpoints described above will be performed using investigator's assessment of response.

Sensitivity analyses will be conducted to assess the impact of missing data in the analysis of MRD negativity rate in patients with CR or better (ie: multiple imputation, tipping point analysis).

A tipping point analysis that will consider all combinations of the values of missing MRD data in the IKd arm and in Kd arm. This will range all the missing value being imputed as negative MRD or positive MRD. Following Liublinska and Rubin (10), graphical displays (heat maps) will be used to indicate the tipping point analysis results for each combination of imputed missing values. Respectively, the stratified odds ratio will be displayed on the heat map for each combination.

In addition, MRD negativity in patients with CR or better will be analyzed using multiple imputation for CR or better patients who have a missing MRD status. The rate of MRD negativity in patients with CR or better will be derived from observed and imputed values. Missing MRD status in patients with CR or better will be imputed 50 times to generate 50 complete datasets by using the SAS MI procedure based on Fully Conditional Specification (FCS) logistic regression method. The logistics regression method will include treatment group as main effect, the baseline characteristics values (such as ECOG, age) and stratification factors as entered in the IRT (ie, number of previous lines of therapy and R-ISS) as covariate. Each imputed dataset will be analyzed with the Cochran Mantel Haenszel test stratified on stratification factors to compare treatment arms. Combined estimates of stratified odds ratio and its associated 95% CI from the 50 imputed datasets will be obtained through the SAS MIANALYZE procedure using Rubin's formulae. The normalizing transformations will be applied to the statistics estimated from each imputed dataset before the Rubin's combination rules. The common odds ratio estimates will be log-transformed before combining process and back-transformed after.

The overall response after the initiation of daratumumab as further anti-myeloma therapy will be described by treatment arm with at least the following items:

- Daratumumab regimens overall
- Daratumumab with IMiD and PI
- Daratumumab with IMiD
- Daratumumab with PI
- Daratumumab monotherapy plus or minus steroids
- Daratumumab with Alkyl. Agents

At time of OS analyses, the overall response after the initiation of anti-CD38 therapies (daratumumab or other anti-CD38 agents) and other selected drugs class as further anti-myeloma therapy will be described by treatment arm with at least the following items:

- anti-CD38 therapies regimens overall
- anti-CD38 therapies with IMiD and PI
- anti-CD38 therapies with IMiD
- anti-CD38 therapies with PI
- anti-CD38 therapies monotherapy plus or minus steroids
- anti-CD38 therapies with Alkyl. Agents
- anti-BCMA antibodies

The overall response after the initiation of further anti-myeloma therapy will be described by treatment arm and by line.

PFS in Minimal Residual Disease negative and positive patients

PFS by MRD status (negative and positive) will be analyzed using the Kaplan-Meier method by treatment group. The Kaplan-Meier curves of PFS for MRD negative and positive patients will be provided.

In addition, sensitivity analyses of PFS by MRD status to assess the impact of Covid-19 on the study may be performed similarly to the sensitivity analyses #10 described for the primary

efficacy endpoint (ie, analysis of PFS by MRD status censoring the death event due to Covid-19 infections (Covid-19 grade 5 TEAEs + death due to other (Covid-19)).

PFS by SPM status

PFS by SPM status (At least one SPM versus No SPM) will be analyzed using the Kaplan-Meier method by treatment group. The Kaplan-Meier curves of PFS for patients with at least one SPM and without SPM) will be provided.

OS

The OS analysis will be performed approximately 3 years after the primary PFS analysis cut-off date using the ITT population.

The analysis of OS will consist of comparison between the IKd arm versus Kd arm through a log-rank test procedure stratified by stratification factors as entered in the IRT (ie, number of previous lines of therapy and R-ISS) at the 1-sided level of 0.025.

In addition,

- The estimates of the hazard ratio and corresponding 95% CI will be provided using a Cox proportional hazard model stratified by the stratification factors as entered in the IRT. Underlying assumptions of the Cox proportional hazard model will be assessed by graphical methods (ie, log-log graphical methods)
- OS data will be analyzed using the Kaplan-Meier method by treatment group:
  - Kaplan-Meier estimates of the 25^{th}, 50^{th} and 75^{th} percentiles and their associated 95% CIs will be provided,
  - Number of patients at risk as well as the probabilities of surviving at least 12, 24, 36 and 48 months (if possible, depending on the time of the analysis) with 95% CI will be estimated for each treatment group using the Kaplan-Meier method.
- The number of censored patients, the reasons for their censoring (ie, alive at the cut-off date, alive at the last contact before the cut-off date, and lost to follow-up) and the time between the date of last contact and the cut-off date will be summarized by treatment group.
- Kaplan-Meier curves will be plotted.

OS - Sensitivity analyses

A sensitivity analysis of OS by using unstratified log-rank test procedure and unstratified Cox's regression model will be performed. In addition, sensitivity analyses to account for possibly informative censoring due to initiation of further anti-myeloma treatment (eg: daratumumab, anti-CD38 therapies) could be performed (eg, Rank Preserving Structural Failure Time (RPSFT) model and inverse probability of censoring weighting (IPCW) method). The same analyses could be performed to account for possibly informative censoring due to initiation of anti-CD38 therapies.

In addition, sensitivity analyses of OS to assess the impact of Covid-19 on the study may be performed similarly to the sensitivity analyses #9 and #10 described for the primary efficacy

endpoint (ie, Analysis of OS on the population without trial impact (disruption) due to Covid-19 and analysis of OS censoring the death event due to Covid-19 infections (Covid-19 Grade 5 TEAEs + death due to other (Covid-19)). For the analysis of OS censoring the death event due to Covid-19 infections, if a patient died due to Covid-19 infections, then the patient is censored at the last known alive date, which is one day before date of death.

OS by SPM status

OS by SPM status (At least one SPM versus No SPM) will be analyzed using the Kaplan-Meier method by treatment group. The Kaplan-Meier curves of OS for patients with at least one SPM and without SPM) will be provided.

Subgroup analyses

Subgroup analyses on main prognostic factors defined in Table 10 may be performed for the key secondary endpoints based on the findings, as exploratory analyses. In addition, supplementary subgroup analyses will be added as:

- Previous treatment with lenalidomide
- Refractory to lenalidomide
- Refractory to lenalidomide at last prior regimen
- Previous treatment with bortezomib
- Refractory to bortezomib
- Refractory to bortezomib at last prior regimen
- Chromosomal abnormality del(17p)
- Chromosomal abnormality t(4,14)
- Chromosomal abnormality t(14,16)
- At least one chromosomal abnormality (del(17p), t(4,14), t(14,16), 1q21+)
- Isolated 1q21+ (Present 1q21+ and standard risk CA versus Absent 1q21+ and standard risk CA)

OS by baseline eGFR (MDRD formula) (<60 mL/min/1.73m^2 versus ≥60 mL/min/1.73m^2) will be analyzed using the Kaplan-Meier method by treatment group. The Kaplan-Meier curves will be displayed.

OS will be presented using the Kaplan-Meier method by treatment group in patients with high-risk chromosomal abnormalities. The Kaplan-Meier curves of OS for these patients will be provided.

Kaplan-Meier curves will be displayed using at least the following categories

- 1q21+ status (present versus absent)
- Chromosomal abnormality including 1q21+ status (At least one chromosomal abnormality including 1q21+ versus None)
- Number of prior lines of therapy as per IRT (1 versus >1)
- R-ISS stage at study entry as per IRT (I or II versus III versus Not classified)
- Age (<65 years versus ≥65 years)
- Refractory to lenalidomide

- Previous treatment with lenalidomide
- 1q21+ (Present 1q21+ versus Absent 1q21+ versus Present gain 1q21 versus Present amplification 1q21)

OS – other analyses

OS will be analyzed using the Kaplan-Meier method by further therapy with anti-CD38 therapy (Kd - No further therapy with anti-CD38 therapy vs Kd - Further therapy with anti-CD38 therapy vs IKd). The associated Kaplan-Meier will be provided.

In addition, Kaplan-Meier curves will be displayed by BOR as per IRC at time of PFS final analysis and MRD in patients (less than PR vs PR vs MRD + and VGPR or better vs MRD –) and by treatment arm. Kaplan-Meier curves will be also displayed using the following categories:

- Complete response (sCR or CR) (yes versus no)
- MRD status (MRD negativity versus MRD positivity)
- MRD negativity and complete response (sCR or CR) versus Other

The time from randomization to efficacy cut-off date (months) will be summarized.

2.4.4.2.2 Analysis of other secondary efficacy endpoints

Other secondary endpoints will be analyzed at the time of the primary analysis and/or the final PFS analysis in the ITT population.

The time-to-event endpoints will be analyzed using Kaplan-Meier methods.

In addition, for patients who achieve a confirmed response, descriptive statistics (n, mean, standard deviation, median, range) will also be provided to summarize time to first response and time to best response.

For investigation of renal response, the incidence of PCSAs defined for eGFR (see Section 2.4.5.3 and Appendix C) during the treatment period will be summarized by treatment group according to the following baseline categories:

- Normal
- Abnormal according to PCSA criterion

The number of patients with complete, partial and minor renal response will be provided by treatment group.

Analysis of other secondary endpoints will be descriptive only. Any testing procedure carried out on these endpoints will be considered as exploratory.

PFS2 by daratumumab intake

PFS2 by daratumumab intake (Yes versus No) will be analyzed using the Kaplan-Meier method by treatment group. The Kaplan-Meier curves of PFS2 for patients with daratumumab intake and without daratumumab intake will be provided.

PFS2 by anti-CD38 therapy

At time of OS analyses, in patients with at least one line of further therapy, PFS2 on first line with anti-CD38 therapy will be analyzed using the Kaplan-Meier method by treatment group. The Kaplan-Meier curves will be provided.

Moreover, PFS2 by anti-CD38 therapy (Yes versus No) will be analyzed using the Kaplan-Meier method by treatment group. The associated Kaplan-Meier curves will be provided.

2.4.4.3 Multiplicity issues

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

- ORR at the time of the primary PFS analysis and/or the final PFS analysis
- Rate of VGPR or better at the time of the primary PFS analysis and/or the final PFS analysis
- MRD negativity rate at the time of the primary PFS analysis and/or the final PFS analysis
- CR rate will only be tested at the PFS final analysis for comparison when the antibody-capture interference assay will be available (ie, the SEBIA HYDRASHIFT 2/4 isatuximab IFE test is available)
- OS tested only at end-of-study.

The significance levels at the interim and final PFS analyses will be determined using alpha-spending function specific to each endpoint (see Section 3). The primary analysis of PFS corresponds either to the positive interim analysis or the final PFS analysis, whichever is first.

No update of PFS, ORR, rate of VGPR or better, MRD negativity rate and CR rate will be provided at the time of OS analysis.

If the actual number of PFS events in interim analysis is different from the number planned, the significance level for the final analysis of the PFS endpoint will be adjusted using the actual total number of PFS events at interim analysis and according to the pre-specified alpha-spending function.

2.4.5 Analyses of safety data

The summary of safety results will be presented by treatment group by using actual treatment.

General common rules

All safety analyses will be performed on the safety population as defined in Section 2.3.2, unless otherwise specified.

The analysis of the safety variables will be essentially descriptive, and no systematic testing is planned. Relative risks versus control arm and their 95% confidence intervals may be provided, if relevant.

2.4.5.1 Analyses of adverse events

Generalities

The primary focus of adverse event reporting will be on TEAEs. Pre-treatment and post-treatment adverse events will be described separately.

If an adverse event date of onset (occurrence, worsening, or becoming serious) is incomplete, an imputation algorithm will be used to classify the adverse event as pre-treatment, treatment-emergent, or post-treatment. The algorithm for imputing date of onset will be conservative and will classify an adverse event as treatment emergent unless there is definitive information to determine it is pre-treatment or post-treatment. Details on classification of adverse events with missing or partial onset dates are provided in Section 2.5.3.

Regarding treatment discontinuation, the following definitions will be used:

- **Premature** treatment discontinuation is defined as the discontinuation of at least one of the study drugs but at least one is continued
- **Definitive** treatment discontinuation is defined as the discontinuation of all the study drugs.

The grade will be taken into account in the summary. For patients with multiple occurrences of the same event, the maximum (worst) grade by period of observation is used. Summaries will be provided for all grades combined and for Grade ≥3 (including Grade 5). Missing grades, if any, will be included in the "all grades" category (see Section 2.5.3).

Sorting within tables ensures the same presentation for the set of all adverse events within the observation period (pre-treatment, treatment-emergent, and post-treatment). For that purpose, the table of all TEAEs presented by SOC and PT sorted by the internationally agreed SOC order (see Appendix A) and decreasing frequency of PTs within SOCs will define the presentation order for all other tables unless otherwise specified. Sorting will be based on results for the IKd arm.

The AE incidence tables presented by primary SOC, HLGT, HLT and PT will present the number (n) and percentage (%) of patients experiencing an AE sorted by SOC internationally agreed order, then by alphabetic order of HLGT, HLT and PT.

A summary of tables provided for analyses of adverse events is provided in Appendix B.

Overview of TEAEs

An overview of TEAEs including the number (%) of patients with the following events will be provided for the safety population:

- TEAE of any grade.
- Grade ≥3 TEAE.
- Grade 3-4 TEAE.
- Grade 5 TEAE (any TEAE with a fatal outcome during the treatment period).
- Treatment-related TEAE.

- Treatment-related TEAE of Grade ≥3.
- Serious TEAE.
- Serious treatment-related TEAE.
- TEAE leading to definitive (all study drugs) treatment discontinuation.
- TEAE leading to premature treatment discontinuation of isatuximab.
- TEAE leading to premature treatment discontinuation of carfilzomib.
- TEAE leading to premature treatment discontinuation of dexamethasone.
- AESI: IRs of Grade ≥3 (pregnancy and overdose, if any, will be presented separately).

Treatment-related TEAEs are TEAEs reported as related to the study regimen in the eCRF.

Analysis of all treatment-emergent adverse events

The following frequency distributions of TEAEs (incidence tables) will be provided for the safety population, for all grades combined and Grade ≥3:

- All TEAEs by primary SOC, HLGT, HLT, and PT.
- All TEAEs by primary SOC and PT.
- Most frequent (≥5% of patients in any group) TEAEs by primary SOC and PT.
- Most frequent (≥5% of patients in any group) TEAEs by PT.
- Most frequent (≥10% of patients in IKd arm and ≥5% higher in IKd arm compared to Kd arm) TEAEs by primary SOC and PT.
- All treatment-related TEAEs by primary SOC and PT.
- Most frequent (≥5% of patients in any group) treatment-related TEAEs by primary SOC and PT.
- Most frequent (≥5% of patients in any group) treatment-related TEAEs by PT.

Analysis of all serious treatment emergent adverse event(s)

The following frequency distributions of serious TEAEs (incidence tables) will be provided for the safety population, for all grades combined and Grade ≥3:

- All serious TEAEs by primary SOC, HLGT, HLT, and PT.
- All serious TEAEs by primary SOC and PT.
- Most frequent (≥2% of patients in any group) serious TEAEs by primary SOC and PT.
- Most frequent (≥2% of patients in any group) serious TEAEs by PT.
- All serious treatment-related TEAEs, by primary SOC and PT.
- Most frequent (≥2% of patients in any group) serious treatment-related TEAEs by primary SOC and PT.
- Most frequent (≥2% of patients in any group) serious treatment-related TEAEs by PT.

Analysis of all treatment-emergent adverse event(s) leading to treatment discontinuation

The following frequency distributions of TEAEs leading to treatment discontinuation (incidence tables) will be provided for the safety population, for all grades combined and Grade ≥3:

- All TEAEs leading to definitive treatment discontinuation, by primary SOC, HLGT, HLT, and PT.
- All TEAEs leading to definitive treatment discontinuation, by primary SOC and PT.
- All TEAEs leading to premature treatment discontinuation of isatuximab, by primary SOC, HLGT, HLT, and PT.
- All TEAEs leading to premature treatment discontinuation of isatuximab, by primary SOC and PT.
- All TEAEs leading to premature treatment discontinuation of carfilzomib, by primary SOC, HLGT, HLT, and PT.
- All TEAEs leading to premature treatment discontinuation of carfilzomib, by primary SOC and PT.
- All TEAEs leading to premature treatment discontinuation of dexamethasone, by primary SOC, HLGT, HLT, and PT.
- All TEAEs leading to premature treatment discontinuation of dexamethasone, by primary SOC and PT.

Analysis of all treatment-emergent adverse event(s) leading to dose modification

The following summary tables are based on the investigator's intent reported in the AE page ("action taken"):

- All TEAEs leading to dose reduction of any drug by primary SOC and PT.
- All TEAEs leading to dose reduction of isatuximab by primary SOC and PT.
- All TEAEs leading to dose reduction of carfilzomib by primary SOC and PT.
- All TEAEs leading to dose reduction of dexamethasone by primary SOC and PT.
- All TEAEs leading to dose interruption of any drug by primary SOC and PT.
- All TEAEs leading to dose interruption of isatuximab by primary SOC and PT.
- All TEAEs leading to dose interruption of carfilzomib by primary SOC and PT.
- All TEAEs leading to any dose delay of any drug by primary SOC and PT.

Of note, as per eCRF completion guideline, action taken for a TEAE leading to dose omission was to be reported as dose reduction in the AE page of the eCRF.

Analysis of other significant adverse events

Analysis of infusion reactions

The following summaries will be provided:

- Number (%) of patients experiencing IRs with isatuximab and/or with carfilzomib according to investigator reported AEs presented by primary SOC and PT (both sorted by decreasing order of frequency) will be summarized by treatment groups and by grades (all grades and by grade).

- Description of the IRs with isatuximab and/or carfilzomib (according to investigator reporting) will be summarized by treatment groups:
  - Number (%) of patients with at least one IR,
  - Number (%) of patients by worst grade of IR,
  - Number (%) of patients by action taken,
  - Number (%) of patients with corrective treatment given,
  - Number (%) of patients with only 1, ≥1, ≥2, ≥3, ≥4 and ≥5 episodes,
  - Number (%) of patients with first occurrence of IRs during the first "two days" of infusion (C1D1 and C1D2) and subsequent "two days" of infusion (eg, C1D8 and C1D9, C1D15 and C1D15),
  - Number (%) of patients with occurrence of IR leading to permanent treatment discontinuation, isatuximab withdrawal and carfilzomib withdrawal the first day of study treatment and subsequent days of infusion if any
  - Number (%) of patients with IR during the first "two days" of infusion, the second "two days of infusion", the third "two days" of infusion, the fourth set of infusion (1 day for IKD arm only) and subsequent "two days" of infusion,
  - Number (%) of patients with at least two episodes of IRs within the same "two days" of infusion,
  - Total number of IR episodes,
  - Grade of IR,
  - Day of onset from the first infusion given within the "two days",
  - IR duration (in days).
- Similar description will be also provided depending on the mode of administration (initial mode of administration and fixed volume administration)
- Number (%) of patients experiencing TEAEs (related and regardless of relationship) within 24 hours from the start of any isatuximab and any carfilzomib infusion presented by primary SOC and PT (both sorted by decreasing order of frequency) will be summarized by treatment groups and by grades (all grades and Grades ≥3).
- Similar table including all TEAEs (related and regardless of relationship) within 24 hours from the start of any isatuximab and any carfilzomib infusion from the selected CMQ (see Section 2.1.4.1) will also be performed and presented by SOC and PT (both decreasing order of frequency).
- Number (%) of patients experiencing TEAEs (related and regardless of relationship) not limited to those occurring within 24hours of any isatuximab and any carfilzomib administration from the selected CMQ (see Section 2.1.4.1) will be summarized by treatment groups and by grades (all grades and Grades ≥3) and presented by SOC and PT (both decreasing order of frequency).
- Number of patients with symptoms of IRs with isatuximab and/or with carfilzomib presented by primary SOC and PT (both sorted by decreasing order of frequency) will be summarized by treatment groups and by grades (all grades and by grade).

Analysis of adverse events of special interest

The analysis of IRs of Grade ≥3 will be part of the analyses described above for IRs.

A listing of patients who reported overdose during the study will be provided. This listing will include drug with overdose and type of overdose (accidental or intentional, symptomatic or not). Moreover, a listing of pregnancies (pregnancy as well as pregnancy of partner) will be provided.

Respiratory AEs

Respiratory TEAEs will be analyzed using selections defined in Section 2.1.4.1 and will be presented by PT, sorted by decreasing incidence. Post-treatment respiratory AEs will be analyzed separately using the post-TEAEs analysis.

Cardiac TEAEs

Cardiac TEAEs will be analyzed using selections defined in Section 2.1.4.1.

TEAEs in the SMQs “Cardiac failure”, Ischaemic heart disease” and “Cardiomyopathy” will be presented by primary SOC and PT, sorted by decreasing incidence.

TEAEs in the SMQs “Embolic and thrombotic events, venous” and “Embolic and thrombotic events, arterial” will be presented by SMQ and by decreasing incidence of PT.

In addition, TEAEs in the SMQ “Cardiac failure” will be presented by PT and by cardiac medical history (prior medical history vs no prior medical history) as well as by PT and by LVEF at baseline (LVEF [40-50 [%, LVEF [50-60[% and LVEF ≥60%).

TEAEs in CMQ “Cardiac” will be presented by PT and by cardiac medical history.

TEAEs in HLGT “Vascular hypertensive disorders” will be presented by PT and by hypertension medical history (prior medical history vs no prior medical history).

Hemolytic disorders

Hemolytic disorders that occurred within 8 days after the blood cell transfusion will be analyzed using selection defined in Section 2.1.4.1 and will be presented by PT.

A listing of patients with hemolytic disorders will be provided. This listing will include the PT, the study day of diagnosis (from first dose of study treatment), the interval to onset from the last study treatment before the diagnosis (last drug administered), the duration of AE, the cycle of occurrence, the grade, the seriousness, the outcome, the action taken on study treatment, the study day of the blood transfusion, and results and sampling date of indirect Coombs test.

TLS

A listing of patients with TLS (selected using definition in Section 2.1.4.1) will be provided.

Autoimmune disorders

A listing of patients with autoimmune disorders (selected using definition in Section 2.1.4.1) will be provided. This listing will include the PT, the study day of diagnosis (from first dose of study treatment), the interval to onset from the last study treatment before the diagnosis (last drug administered), the duration of AE, the cycle of occurrence, the grade, the seriousness, the action taken on study treatment, and the outcome.

Second primary malignancies (SPM)

A listing of patients who reported second primary malignancies (selected using definition in Section 2.1.4.1) during the study will be provided. This listing will include at least the following items: the PT, the study day of diagnosis (from first dose of study treatment), the number of days from last study treatment to diagnosis, prior exposure to anti-myeloma treatments, days from initiation of further myeloma treatment to onset, cycle of occurrence, outcome, action taken, grade, causal relationship to isatuximab, seriousness and whether or not patient received subsequent anti-cancer treatment. Listing of deaths on patients with SPM will be also provided.

The following summaries will be provided by sub-category ('haematological', 'non-hematological skin tumors', 'non-hematological non-skin tumors' and 'other tumors'):

- Time from 1st dose of study treatment to second primary malignancy (quantitative and qualitative, <3, 3 - <6, 6 - 12, >12 months)
- Number of patients experiencing second primary malignancies (worst grade) during the following periods:
  - Treatment period,
    - ≥3 months after first study treatment
  - Post-treatment period,
    - Before further anti-multiple myeloma therapy
    - After further anti-multiple myeloma therapy,
      - ≥3 months after further anti-multiple myeloma therapy,

In addition, the description of AEs in the CMQ 'Second primary malignancies' CMQ (worst grade) will be provided by sub-category ('haematological', 'non-hematological skin tumors', 'non-hematological non-skin tumors' and 'other tumors') and by decreasing incidence of PT for:

- All treatment-emergent and post-treatment AEs
- All TEAEs

These analyses will be also performed by medical history of SPM (yes or no).

Figure of cumulative incidence rate for time to first SPM will be provided using a Fine and Gray method considering death as a competing risk.

For patients treated with IKd, a multivariate Cox proportional hazards model will be used to identify prognostic factors among the demographic and baseline characteristics factors described below using a stepwise selection procedure with a 15% significance level for entering effects and a 15% significance level for removing effects.

Table 11 - Risk factor analyses on time to first SPM : covariates investigated

Prognostic factor	Description (*if relevant)*
Age	<75 vs ≥75 years
Gender	Male vs female
Race	Caucasian vs other
ISS staging at study entry	I vs II vs III
R-ISS staging at study entry (IRT)	I or II vs III vs not classified
Number of previous lines of therapy (IRT)	1 vs >1
Chromosomal abnormality (del(17p), t(4;14), t(14;16))	At least one vs. none
ECOG PS at baseline	0 or 1 vs >1
Neutrophil count (10^9/L) at baseline	
Hemoglobin (g/L) at baseline	
Platelets count (10^9/L) at baseline	
Lymphocytes (10^9/L) at baseline	
Beta 2-microglobulin (mg/L) at baseline	
Serum LDH (IU/L) at baseline	
Albumin (g/L) at baseline	
Previous treatment with IMiD [a]	Yes vs No
Previous treatment with Melphalan	Yes vs No
Prior history of SPM	Yes vs No
Type of region	Sunny [Australia / Brazil / Spain / Greece / Italy / Turkey] vs Non-sunny [Canada / Czech Republic / France / United Kingdom / Hungary / Japan / Korea, Republic of / New Zealand / Russian Federation / United States]

[a] IMiD: Immunomodulatory imide drugs

Neutropenia and neutropenic complications

Neutropenia (from laboratory abnormalities) will be displayed along with neutropenic complications (febrile neutropenia and neutropenic infections, see Section 2.1.4.1).

If relevant, duration of Grade 3/4 neutropenia episode, cumulative duration of Grade 3/4 neutropenia by patient and time to first Grade 3/4 neutropenia will be analyzed using laboratory data.

The start date of a Grade 3/4 laboratory neutropenia episode is defined as the date of first Grade 3/4 assessments for that episode. The end date of a Grade 3/4 neutropenia episode is defined as the first date of neutropenia assessment afterwards of Grade 1/2 or with no abnormality for that episode assuming there will be at least 3 days between the first Grade ≤2 neutropenia and the next Grade≥3 assessment (if any). If the start date of a new episode is within 3 days of the previous episode, then the two episodes will be considered as one episode. The worst grade of an episode is the worst grade of all assessments included in that episode.

Duration of a Grade 3/4 neutropenia episode (in days) is defined as end date of an episode – start date of an episode +1. If a patient does not have an end date of an episode before the cutoff date

then the duration of the episode will be censored at the last neutrophil assessment of Grade 3/4 or the cutoff date, whichever comes first.

Time to first Grade 3/4 neutropenia (in days) is defined as: date of the first on-treatment Grade 3/4 neutropenia assessment – date of first treatment +1. If a patient does not have Grade 3/4 neutropenia, time to first Grade 3/4 neutropenia will be censored at the last assessment of neutropenia of Grade 1/2 or with no abnormality or the cutoff date, whichever comes first. If a patient does not have any on-treatment assessment of neutropenia, then the patient will be censored at Cycle 1 Day 1.

Thrombocytopenia and hemorrhages

The number (%) of patients will be provided for:

- On-treatment thrombocytopenia (laboratory data) identified through grading of laboratory data per the NCI-CTCAE 4.03, by grade.
- Hemorrhages as defined in Section 2.1.4.1 by grade.
- Hemorrhages following Grades 4 thrombocytopenia (Lab). The first hemorrhages event occurring within 8 days after any occurrence of the thrombocytopenia (Lab) will be used for this analysis.

Covid-19 infection

TEAEs Covid-19 infection will be analyzed using selections defined in Section 2.1.4.1 and will be presented by SOC and PT, sorted by decreasing incidence (all TEAEs, serious TEAE and fatal TEAEs). Table or listing of patients with Covid-19 infection after vaccination will be presented. Number (%) of patients with Covid-19 vaccination will be presented.

Subgroup analyses of TEAEs

The effect of patient baseline characteristics on the incidence of patients with any TEAE (overview table) and any TEAE by primary SOC and PT (all grades and Grade ≥3) will be summarized by treatment group according to each of the below intrinsic factors, separately:

- Age group: <65, [65 - 75[and ≥75 years.
- Gender: Male, Female.
- Race: Caucasian, Non-Caucasian.
- Renal status: eGFR ≥60 mL/min/1.73m^2 and <60 mL/min/1.73m^2.
- Hepatic status: normal and abnormal (defined as mild impairment or moderate impairment or severe impairment, see definition in Section 2.5.1).

Exposure-adjusted analyses of TEAEs

The event rate per patient-year (the number of patients with an event in question divided by total patient-years) will be provided for:

- Overview table (patients with any TEAE, with any Grade ≥3 TEAE, with Grade 5 TEAE, with any serious TEAE, with any TEAE leading to definitive treatment discontinuation).

- Most frequent (≥5% of patients in any group) TEAEs, most frequent (≥5% of patients in any group) Grade ≥3 TEAEs by SOC and PT.
- All TEAEs, all Grade ≥3 TEAEs, all serious TEAEs, all Grade ≥3 serious TEAEs by SOC.
- All TEAEs in the Second Primary Malignancies CMQ (worst grade) during the treatment period and during the study period by decreasing PT, and by tumor type (solid tumor [skin or non-skin cancer], hematology malignancies, or other non-specified).

For a patient with event, patient year is censored at time of first event; for patient without event, it corresponds to length of treatment period as defined in Section 2.1.4.

Analysis of pre-treatment and post-treatment adverse events

The following frequency distributions of AEs (incidence tables) will be provided for the safety population, for all grades combined and Grade ≥3:

- All pre-treatment AEs by primary SOC and PT, showing the number (%) of patients with at least 1 pre-treatment AE, sorted by the internationally agreed SOC order and decreasing incidence of PTs within each SOC.
- All pre-treatment SAEs by primary SOC and PT, showing the number (%) of patients with at least 1 pre-treatment SAE, sorted by the internationally agreed SOC order and decreasing incidence of PTs within each SOC.
- All post-treatment AEs by primary SOC and PT, showing the number (%) of patients with at least 1 post-treatment AE, sorted by the internationally agreed SOC order and decreasing incidence of PTs within each SOC.
- All post-treatment SAEs by primary SOC and PT, showing the number (%) of patients with at least 1 post-treatment SAE, sorted by the internationally agreed SOC order and decreasing incidence of PTs within each SOC
- All post-treatment AEs in the CMQ ‘Second primary malignancies’ (worst grade) by decreasing PT, and by tumor type (solid tumor [skin or non-skin cancer], hematology malignancies, or other non-specified).

2.4.5.2 Deaths

An overview of Grade 5 AEs (excluding pre-treatment ones) will be provided summarizing the number (%) of patients with any:

- Grade 5 AE (TEAE and post-treatment).
- Fatal TEAE (regardless date of death/period).
  - Grade 5 TEAE (TEAE with a fatal outcome during the treatment period),
  - Any grade TEAE with a fatal outcome during the post-treatment period (worsened to Grade 5 in the post-treatment period).
- Post-treatment Grade 5 AE (excluding a TEAE that worsened to Grade 5 during the post-treatment period).

The following summaries of deaths will be generated for the safety population:

- Number (%) of patients who died by study period (treatment period and post-treatment period) and within 60 days from first dose of study treatment and reasons for death (disease progression, AE, other) by treatment received.
- All TEAEs leading to death by primary SOC and PT, sorted by the internationally agreed SOC order and by decreasing incidence of PTs.
- All TEAEs related to treatment and leading to death by primary SOC and PT sorted by the internationally agreed SOC order and by decreasing incidence of PTs.
- Number (%) of patients with TEAE(s) leading to death regardless of relationship and related to study treatment by primary SOC, HLGT, HLT, and PT.
- Summary of AEs leading to death, by primary SOC and PT:
  - In context of disease progression (death within 30 days from last study treatment administration and the cause of death is disease progression),
  - In context other than disease progression (death within 30 days from last study treatment administration and for whom cause of death is not disease progression, or the death occurred more than 30 days from last study treatment administration and the cause of death is AE).

In addition, a listing of deaths in non-randomized patients or randomized but not treated patients will be provided on the screened patients.

2.4.5.3 Analyses of laboratory variables

Laboratory (hematology and biochemistry) values will be analyzed after conversion into standard international units.

International units will be used in all listings and tables. Hematological and biochemistry results will be graded according to NCI-CTCAE v4.03, when applicable. For patients with multiple occurrences of the same laboratory variable during the treatment period, the maximum grade (worst) per patient will be used.

For hematological parameters and for some selected biochemistry parameters, sanofi generic ranges (lower limit of normal, upper limit of normal) are defined (see list of parameters in Appendix D) and will be used for grading. For other biochemistry parameters (eg, for hepatic enzymes ALT, AST, alkaline phosphatase, total bilirubin), grading will be derived using local laboratory normal ranges.

The number and proportion of patients with abnormal laboratory tests at baseline will be presented by grade and all grades together. A similar table showing abnormalities during the treatment period will be provided. The denominator used for percentage calculation is the number of patients with at least one evaluation of the laboratory test during the considered observation period.

When appropriate, the summary table will present the frequency of patients with any grade of abnormal laboratory tests and with Grade 3-4 abnormal laboratory tests.

For eGFR, uric acid, blood urea nitrogen and chloride, potentially clinically significant abnormality (PCSA) values will be derived. PCSA values are defined as abnormal values considered medically important by the Sponsor according to predefined criteria/thresholds based on literature review (see Appendix C). The PCSA criteria will determine which patients had a PCSA at baseline and which patients had at least 1 PCSA during the treatment period, taking into account all evaluations performed during the treatment period, including non-scheduled or repeated evaluations. The incidence of PCSA will be summarized by treatment group at baseline as well as at any time during the treatment period irrespective of the baseline level.

Shift tables showing the number of patients by worst grade during the treatment period will be provided according to the grade at baseline of selected parameters (eg, thrombocytopenia, neutropenia, lymphopenia, anemia and other tests as appropriate) by treatment group.

Further analyses including summary of cycle of onset (all grades and Grade ≥3), duration and concomitance with other hematological abnormalities may also be provided.

2.4.5.4 Analyses of vital sign variables

For blood pressure/heart rate parameters, the incidence of PCSAs taken into account assessments done prior to study treatment administration at any cycle during the treatment period will be summarized by treatment group whatever the baseline level and/or according to the following baseline categories:

- Normal/missing
- Abnormal according to PCSA criterion or criteria

In IKd arm, as vital signs are measured several times on Cycle 1 Day 1 (just before starting infusion, 1 hour after starting infusion, and at end of infusion), only the values corresponding to assessments done before starting infusion will be considered for the definition of baseline.

The incidence of PCSA taken into account assessments done during and after isatuximab administration at any cycle during the treatment period will also be summarized in the IKd arm.

In addition, for heart rate, systolic and diastolic blood pressure, mean with the corresponding standard deviation could be plotted over time (at predose of any visit) by treatment group.

2.4.5.5 Analyses of electrocardiogram variables

The incidence of patients with at least 1 abnormal ECG at any time during the treatment period will be summarized by treatment group irrespective of the baseline level and/or according to the following baseline status categories:

- Normal/missing
- Abnormal

A listing of abnormalities and analysis of AEs in appropriate SMQs (eg, Cardiac) will be provided if relevant.

2.4.5.6 Analyses of other safety endpoints

A shift table of baseline ECOG PS versus best and worst ECOG PS on treatment will be provided.

For indirect Coombs test, a summary of patients in experimental arm with indirect Coombs test performed during the on-treatment period will be provided, including the number (%) of patients with:

- All tests negative
- At least one positive test

And among patients with at least one positive test during study treatment, number (%) of patients with:

- Negative indirect Coombs test at baseline
- Missing indirect Coombs test at baseline
- Panagglutination (resolved by DTT and not resolved by DTT)

2.4.6 Exploratory analyses of biomarker variables

Biomarker endpoints will be analyzed using patients from the ITT population who have at least 1 evaluable assessment on the biomarker of interest.

2.4.6.1 Genetic variables (immune genetic determinant)

2.4.6.2 Descriptive analysis

Each genetic biomarker will be summarized with descriptive statistics by treatment group and overall. Hardy-Weinberg equilibrium will be tested for each genetic biomarker. If there is a strong disequilibrium, the genetic biomarker may be removed from the following analyses.

2.4.6.2.1 Univariate analysis

Each genetic biomarker will be tested for a potential prognostic and/or predictive effect for PFS.

A Cox regression model will be conducted separately for each genetic biomarker with a treatment effect, a biomarker effect and a biomarker×treatment interaction.

Benjamini-Hochberg multiple correction procedure will be used to control the False Discovery Rate (11).

Additional analyses using ORR (by considering logistic regression) or OS might also be performed.

2.4.6.3 Potential interference of isatuximab in the M protein assessment

The following analyses will be performed when the data will be available.

Number (%) of patients with suspected isatuximab interference with serum M protein conventional IFE test and with potential impact on the BOR will be described.

The response available for the interim analysis and for the final analysis (including the impact of interference for the IKd arm) will be described for each arm.

A sensitivity analysis will be performed in the IKd arm using hybrid BOR based on the IRC's assessment at the interim analysis (using conventional IFE test) plus the IRC's assessment for the newly collected response data after the interim analysis (using Hydrashift isatuximab IFE test in IKd arm).

Number (%) of patients who changed their response following the HYDRASHIFT 2/4 isatuximab IFE test results will be described. A shift table matching the BOR at the interim analysis and at final analysis will be provided for patients with Hydrashift isatuximab IFE test in IKd arm. Listing of patients who changed their response following the HYDRASHIFT 2/4 isatuximab IFE test results and their HYDRASHIFT 2/4 isatuximab IFE test results together with the conventional IFE test results will be provided. The patients who had natural improvement in BOR after interim analysis will be also listed.

The concordance/discordance between the conventional test results on the same banked samples performed at time of interim analysis and time of final analysis for patients with suspected isatuximab interference will be summarized by using counts and percentages. Listing will be provided.

The time to first CR or sCR in months will be described in patients with Hydrashift isatuximab IFE test.

2.4.7 Analyses of pharmacokinetic variables

Individual concentrations and PK parameters of carfilzomib will be summarized by descriptive statistics (such as mean, geometric mean, median, standard deviation, standard error of the mean [SEM], coefficient of variation [CV], minimum, and maximum).

Predose concentrations ($Ctrough_{obs}$) and CEOI for isatuximab will be tabulated with standard descriptive statistics by visit. Predose concentrations will be represented graphically as function of sampling time (day/cycle) over the study period to visualize the steady state achievement. A listing of $Ctrough_{obs}$ for individual patients will also be provided. $Ctrough_{obs}$ will be kept for the descriptive statistics if sampling occurs within 7 days ± 1 day after the previous infusion for sampling done during Cycle 1 and within 14 days ± 3 days after the previous infusion for sampling done for subsequent cycle up to Cycle 10.

Accumulation ratio will be calculated with CEOI (C2D1 vs C1D1) and Ctrough (C2D1 vs C1D8 and C4D1 vs C1D8) and will be summarized by descriptive statistics (such as geometric mean, arithmetic mean median, standard deviation, standard error of the mean (SEM), coefficient of variation (CV), minimum and maximum).

The population PK of isatuximab will be characterized in the population of patients in the IKd arm, using a nonlinear mixed effect model based on PK data from Phase I/II studies and III in which intensive and sparse blood sampling protocols were used. The population estimates from this analysis will provide a prior distribution from which individual Bayesian estimates of the PK

parameters for each patient in this study will be derived. Additional details of the analysis plan will be provided in a separate document.

Pharmacokinetic parameters of isatuximab will be summarized by descriptive statistics (such as mean, geometric mean, median, standard deviation, SEM, CV, minimum, and maximum).

2.4.8 Analyses of immunogenicity variables

The immunogenicity for isatuximab will be assessed by summarizing the number (%) of patients with pre-existing ADA and ADA negative at baseline, and by summarizing the number (%) of ADA positive patients (including treatment-induced ADA and treatment boosted ADA) during the on-study observation period. Anti-drug antibody prevalence and ADA incidence will be described. Data listing of each ADA sample results for patients with ADA positive at baseline or on-study will be provided. Further analyses may be performed, such as descriptive statistics on titers, time to onset and duration of ADA.

The impact of positive immune response on efficacy, PK and safety endpoints may be further explored by graphical methods or descriptively, depending on ADA prevalence.

2.4.9 Analyses of quality of life/health economics variables

PRO endpoints for each of the 3 selected HRQL and health utility instruments (EORTC QLQ-C30, QLQ-MY20 and EQ-5D-5L) will be analyzed in patients from ITT population.

For each questionnaire, the compliance profile over time will be summarized on the ITT population (number and percentage of forms received versus expected, and number and percentage of forms evaluable versus expected). A questionnaire is considered received if a least one item on the form is completed. A questionnaire is expected as defined in the study flowchart and based on the number of cycles started by the patient. A questionnaire is evaluable if the overall response rate is greater than 80%. Reasons for non-completion will be summarized on the safety population.

A descriptive summary at each visit (including EOT and assessment done 90 days after last study treatment) and change from baseline will be provided for each group for the following variables:

- EORTC QLQ-C30: global health status/QoL scale, the five functional scales (physical, emotional, cognitive, role and social), the three symptom scales (fatigue, nausea/vomiting and pain) and the six additional single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties).
- MY20: future perspective, body image, disease symptoms and side effects of treatment.
- EQ-5D-5L: health utility index value and VAS score.

2.4.10 Further therapy after discontinuation of investigational medicinal product administration during the study

A summary table will be provided for further anti-myeloma treatments based on WHO-DD coding. A summary table will be also provided by number of subsequent line and drug class.

Time to next treatment

Time to next treatment will be analyzed using Kaplan-Meier methods.

At time of OS analyses, the duration between last dose of IMP and subsequent therapy with anti-CD38 therapy will be described. The duration between last dose of IMP and first subsequent therapy with anti-CD38 therapy will be also described.

2.5 DATA HANDLING CONVENTIONS

2.5.1 General conventions

The following formulas will be used for computation of parameters.

Demographic formula

Body surface area value will be derived using the variation of DuBois and DuBois formula:

$$BSA = 0.0007184 \times Weight\ (kg)^{0.425} \times Height\ (cm)^{0.725}$$

Renal function formula

eGFR will be derived using the equation of MDRD:

*eGFR = 175 × (Serum_creatinine*0.0113)* $^{-1.154}$ *× (Age)* $^{-0.203}$ *× (0.742 if Female) × (1.212 if African American)*

with eGFR in mL/min/1.73 m^2, serum creatinine in µmol/L and age in years.

Corrected calcium formula

Corrected Calcium (mmol/L) = Serum Calcium (in mmol/L) + 0.8 * 0.25 (4 – (serum albumin [in g/L] * 0.1))

Hepatic function

- *Normal:* Total bilirubin ≤Upper limit of Normal (ULN) and aspartate aminotransferase (AST) ≤ULN.
- *Mild impairment:* ULN <Total Bilirubin ≤1.5 × ULN and AST = Any; or Total bilirubin ≤ULN and AST >ULN.
- *Moderate impairment:* 1.5 × ULN <Total Bilirubin ≤3 × ULN and AST = Any.
- *Severe impairment:* Total Bilirubin >3 × ULN and AST = Any.

Qol formulas

EORTC QLQ-C30 and QLQ-MY20 raw scores and scores calculation:

For all scales, RS = mean of the component items.

For functional scales, Score = (1- ((RS-1)/range)) *100

For symptom scales/items and the global health status, Score = (RS-1)/range *100

The range is the difference between the maximum and the minimum response to individual items.

See Appendix G.

Number of prior lines

If the reason for discontinuation of the last treatment of a regimen is "completed" and there is no date of progression or in case of transplantation with no date of progression, the next regimen is not a new line of therapy. In other cases, the next regimen is a new line of therapy.

2.5.2 Data handling conventions for secondary efficacy variables

Not applicable.

2.5.3 Missing data

The analyses and summaries of continuous and categorical variables will be based on observed data only. Percentages will be calculated using as denominator the number of patients with non-missing observation in the considered population. When relevant, the number of patients with missing data is presented.

Handling of disease characteristics missing/partial dates

- If the day is missing, it will be estimated by 1.
- If the month is missing, it will be estimated by 1 (only for medical history variables).
- If the year is missing, no estimation will be performed.

Handling of medication missing/partial dates

No imputation of medication start/end dates or times will be performed. If a medication date or time is missing or partially missing and it cannot be determined whether it was taken prior or concomitantly, it will be considered a prior, concomitant, and post-treatment medication.

Imputation of incomplete date for further anti-myeloma treatment start date

For further anti-myeloma treatments, if the medication start date is missing, it will be imputed as follows:

- If the medication start day and month are missing and the medication start year is the same as the study treatment end year, the medication start date will be set equal to study treatment end date + 1.
- If the medication start day and month are missing and the medication start year is after the study treatment end year, the medication start day and month will each be set to 01.
- If the medication start day is missing and medication start year and month is the same as the study treatment end year and month, the medication start day will be set equal to the study treatment end day + 1.

- If the medication start day is missing and medication start month is before the study treatment end month and the medication start year is the same as study treatment end year, the medication start day will be set to 01.
- If the medication start day is missing and the medication start month is after the study treatment end month and the medication start year is the same as study treatment end year, the medication start day will be set to 01.
- If the medication start day is missing and the medication start month is not missing and the medication start year is after the study treatment end year, the medication start day will be set to 01.
- If the medication start day, start month and start year is missing, the medication start date will be set equal to the study treatment end date + 1.

Handling of missing/partial death dates

- If the day of the death date is missing, it will be imputed as the first day of the month, except if the date of the patient's last contact is in the same month as the death date. In this case, the death date is imputed as the date of last contact + 1 day.
- If the day and month of the death date is missing, the date of death will be imputed to the first of January of the year, except if the date of the patient's last contact is in the same year as the death date. In this case, the death date will be imputed as the date of last contact + 1 day.
- If the death date is missing, no imputation will be done, and the patient will be censored at the last contact date.

Handling of adverse events with missing or partial date of onset

Missing or partial adverse event onset dates (occurrence or becoming serious) will be imputed so that if the partial adverse event onset date information or visit number does not indicate that the adverse event started prior to treatment or after the treatment-emergent adverse event period, the adverse event will be classified as treatment-emergent. In case of AEs worsening during the study, the emergence will also be based on the cycle of worsening. No imputation of adverse event end dates will be performed. These data imputations are for categorization purpose only and will not be used in listings. No imputation is planned for date of adverse event resolution.

Missing grade

If the grade is missing for one of the treatment emergent occurrences of an AE, the maximal severity on the remaining occurrences will be considered. If the severity is missing for all the occurrences, no imputation will be done, and missing grades will be summarized in the “all grades” category.

Handling of missing assessment of relationship of adverse events to investigational medicinal product

If the assessment of the relationship to the regimen is missing, then the relationship to the regimen has to be assumed and the adverse event considered as such in the frequency tables of possibly related adverse events, but no imputation should be done at the data level.

Handling of potentially clinically significant abnormalities

If a patient has a missing baseline value, he/she will be grouped in the category "normal/missing at baseline."
For PCSAs with 2 conditions, one based on a change from baseline value and the other on a threshold value, with the first condition being missing, the PCSA will be based only on the second condition.

2.5.4 Windows for time points

Laboratory data

An episode occurred during a cycle if the date of sampling is after (>) the first day of the cycle, but prior or equal (≤) to the first day of the next cycle.

2.5.5 Unscheduled visits

Unscheduled visit measurements of laboratory data, vital signs, and ECG will be used for computation worst values and/or grades. They will be also used for computation of baseline except if they are collected on the day of first study administration.

2.5.6 Pooling of centers for statistical analyses

Data from all sites will be pooled together for analyses.

2.5.7 Statistical technical issues

Not applicable.

3 INTERIM ANALYSIS

An interim analysis for efficacy assessment of PFS is planned when 65% of the 159 PFS events have been observed. The interim PFS cut-off date is expected approximately 24 months after the first patient in and all patients are expected to be randomized at the time of the interim PFS analysis.

An O'Brien and Fleming α-spending function will be used to obtain the nominal significance levels for the interim and final analyses of survival on PFS. The 1-sided nominal significance level to declare overwhelming efficacy at 65% information fraction (103 PFS events) is 0.005 (corresponding to a HR of 0.6) and to declare superiority of IKd at the final analysis (159 events) is 0.023 (corresponding to a HR of 0.725). The stopping boundaries on PFS endpoint at interim analysis will be calculated using the actual number of events.

Interim analysis will be performed by an independent statistician under the supervision of the DMC. The DMC will also review secondary efficacy endpoints and safety data available at the time of the interim analysis.

The DMC may declare overwhelming efficacy of the study if the following conditions are met:

- Stopping boundaries are crossed.
- Positive trend observed for key secondary efficacy endpoints.
- Consistency of the treatment effect on the primary efficacy endpoint across subgroups such as: age and stratification factors.

The primary analysis of PFS corresponds either to the positive interim analysis or the final PFS analysis. In case of positive results at interim analysis, disease assessments data will be collected according to the protocol until the final analysis cut-off date (159 PFS events observed) and PFS results will be updated (non-inferential analysis).

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

If the null hypothesis for any key efficacy endpoint fails to be rejected at the interim PFS analysis, then any subsequent key efficacy endpoint(s) will not be tested until the final PFS analysis. If the null hypothesis for an endpoint is rejected at the interim PFS analysis, it will remain being rejected and will not be re-tested at final PFS analysis.

The following examples are provided for illustration purpose regarding IA:

- If PFS is significant at IA, ORR will be subsequently tested at IA based on an overall one-sided α level of 0.025, the prespecified spending function and actual information fraction.
  - If ORR is significant at IA, other key binary secondary endpoints will be tested sequentially in a similar fashion,

  - If ORR is not significant, all other key binary secondary endpoints will not be tested. At final analysis (without retesting PFS), ORR will be tested again taking α spent at IA into consideration. To be specific, the remaining α will be determined by an overall one-sided α level of 0.025, the prespecified spending function and actual IA information fraction. If ORR is significant at final analysis, other key binary secondary endpoints will be tested sequentially in a similar fashion.
- If PFS is not significant at IA and it is significant at final analysis, ORR will be subsequently tested. Both ORR at IA and final analysis may be compared to the rejection boundaries determined by an overall one-sided α level of 0.025, the prespecified spending function and actual IA information fraction. If ORR is significant (crossing boundary at either IA or final analysis or both), other key binary secondary endpoints will be tested sequentially in a similar fashion.

The CR rate will only be tested for comparison when the antibody-capture interference assay will be available.

OS will be analyzed only once at the end-of-study (ie, 3 years after the primary PFS analysis cut-off date).

In addition, close safety monitoring is planned, and DMC will regularly monitor patient safety. More details on formal safety reviews and on interim analysis are given in the DMC charter.

4 DATABASE LOCK

Estimated cut-off date will be approximately 24 months and 36 months after first patient in for the interim PFS analysis and for the final PFS analysis, respectively.

The cut-off date for analysis of OS will be 3 years after the primary PFS analysis cut-off date. The primary PFS analysis corresponds either to the positive interim PFS analysis or the final PFS analysis.

5 SOFTWARE DOCUMENTATION

All summaries and statistical analyses will be generated using SAS version 9.4 or higher.

Biomarkers analyses will be generated using R version 3.4.0 or higher.

6 REFERENCES

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7 LIST OF APPENDICES

Appendix A SOC sorting order

The internationally agreed order (International Conference on Harmonization (ICH)-endorsed guide for MedDRA users on data output) for SOC:

1. Infections and infestations.
2. Neoplasms benign and malignant (including cysts and polyps).
3. Blood and the lymphatic system disorders.
4. Immune system disorders.
5. Endocrine disorders.
6. Metabolism and nutrition disorders.
7. Psychiatric disorders.
8. Nervous system disorders.
9. Eye disorders.
10. Ear and labyrinth disorders.
11. Cardiac disorders.
12. Vascular disorders.
13. Respiratory, thoracic and mediastinal disorders.
14. Gastrointestinal disorders.
15. Hepato-biliary disorders.
16. Skin and subcutaneous tissue disorders.
17. Musculoskeletal, connective tissue and bone disorders.
18. Renal and urinary disorders.
19. Pregnancy, puerperium and perinatal conditions.
20. Reproductive system and breast disorders.
21. Congenital and familial/genetic disorders.
22. General disorders and administration site conditions.
23. Investigations.
24. Injury, poisoning and procedural complications.
25. Surgical and medical procedures.
26. Social circumstances.
27. Product issue.

Appendix B Description of summary tables for the analyses of AEs

In addition to the analyses described in the table below, an overview of TEAEs, a table describing the IRs, specific hematological analyses, cardiac TEAEs by medical history or LVEF at baseline, subgroup and exposure-adjusted analyses of TEAEs will be provided.

MedDRA coding variables	Sorting	Layout	Events
SOC, HLGT, HLT, and PT	• Primary SOC: internationally agreed order • HLGT, HLT, PT: alphabetical order	**Treatment groups:** n (%) of patients with any event (all grades combined) and n (%) of patients with event of Grade ≥3	• All TEAEs • Serious TEAEs • TEAEs leading to treatment definitive discontinuation • TEAEs leading to premature treatment discontinuation of isatuximab • TEAEs leading to premature treatment discontinuation of carfilzomib • TEAEs leading to premature treatment discontinuation of dexamethasone
SOC and PT	• Primary SOC: internationally agreed order • PT: decreasing order of frequency within each SOC defined by the all TEAEs table	**Treatment groups:** n (%) of patients with any event (all grades combined) and n (%) of patients with event of Grade ≥3	• All TEAEs • Most frequent (≥5% of patients in any group) TEAEs • Treatment-related TEAEs • Most frequent (≥5% of patients in any group) treatment-related TEAEs • Serious TEAEs • Most frequent (≥2% of patients in any group) serious TEAEs • Treatment-related serious TEAEs • Most frequent (≥2% of patients in any group) serious treatment-related TEAEs • TEAEs leading to treatment definitive discontinuation • TEAEs leading to premature treatment discontinuation of isatuximab • TEAEs leading to premature treatment discontinuation of carfilzomib • TEAEs leading to premature treatment discontinuation of dexamethasone • TEAEs leading to dose interruption • TEAEs leading to dose delay • TEAEs leading to dose reduction • Pre-treatment AEs • Serious pre-treatment AEs • Post-treatment AEs • Serious post-treatment AEs

MedDRA coding variables	Sorting	Layout	Events
SOC and PT	• Primary SOC: internationally agreed order • PT: alphabetical order	**Treatment groups:** n (%) of patients with any event (all grades combined) and n (%) of patients with event of Grade 3 and Grade 4	• Most frequent (≥10% of patients in IKd arm and ≥5% higher in IKd arm compared to Kd arm) TEAEs
SOC and PT	• Primary SOC: decreasing order of frequency • PT: decreasing order of frequency	**Treatment groups:** n (%) of patients with any event (all grades combined) and n (%) of patients with event by grade	• IRs (according to investigator reported TEAEs) • Covid-19 infection (all TEAEs) • Covid-19 infection (serious TEAEs) • Covid-19 infection (fatal TEAEs)
SOC and PT	• Primary SOC: decreasing order of frequency • PT: decreasing order of frequency	**Treatment groups:** n (%) of patients with any event (all grades combined) and n (%) of patients with event of Grade ≥3	• Symptoms of IRs • TEAEs (related and regardless of relationship) within 24 hours from the start of each isatuximab and each carfilzomib infusion • TEAEs (related and regardless of relationship) from the selected CMQ within 24 hours from the start of each isatuximab and each carfilzomib infusion • TEAEs (related and regardless of relationship) from the selected CMQ (not limited to those occurring within 24 hours from the start of each isatuximab and each carfilzomib infusion) • TEAES in SMQ “Cardiac failure”, SMQ “Ischaemic heart disease” and SMQ “Cardiomyopathy”
SMQ and PT	• SMQ: alphabetical order • PT: decreasing order of frequency within each SMQ	**Treatment groups:** n (%) of patients with any event (all grades combined) and n (%) of patients with event of Grade ≥3	• Embolic and thrombotic events with SMQ “Embolic and thrombotic events, venous” and SMQ “Embolic and thrombotic events, arterial”
PT	• PT: Decreasing order of frequency	**Treatment groups:** n (%) of patients with any event (all grades combined) and n (%) of patients with event of Grade ≥3	• Most frequent (≥5% of patients in any group) TEAEs • Most frequent (≥5% of patients in any group) treatment-related TEAEs • Most frequent (≥2% of patients in any group) serious TEAEs • Most frequent (≥2% of patients in any group) serious treatment-related TEAEs • Respiratory TEAEs • Hemolytic disorders

AE=adverse event; HLGT=high-level group term; HLT=high-level term; IR=infusion reaction; MedDRA=Medical Dictionary for Regulatory Activities; n (%)=number and percentage of patients; PT=preferred term; SOC=system organ class; TEAE=treatment-emergent adverse event.

Appendix C Potentially clinically significant abnormalities criteria

Parameter	PCSA	Comments
Clinical Chemistry		
eGFR (mL/min/1.73m2) (Estimate of GFR based on an MDRD equation)	<15 (end stage renal disease) ≥15 - <30 (severe decrease in GFR) ≥30 - <60 (moderate decrease in GFR) ≥60 - <90 (mild decrease in GFR) ≥90 (normal GFR)	Use is optional. FDA draft Guidance 2010 Pharmacokinetics in patients with impaired renal function-study design, data analysis, and impact on dosing and labeling
Uric Acid Hyperuricemia Hypouricemia	 >408 µmol/L <120 µmol/L	Harrison- Principles of internal Medicine 17th Ed., 2008.
Blood Urea Nitrogen	≥17 mmol/L	
Chloride	<80 mmol/L >115 mmol/L	
Vital signs		
HR	≤50 bpm and decrease from baseline ≥20 bpm ≥120 bpm and increase from baseline≥20 bpm	To be applied for all positions (including missing) except STANDING.
SBP	≤95 mmHg and decrease from baseline ≥20mmHg ≥160 mmHg and increase from baseline ≥20 mmHg	To be applied for all positions (including missing) except STANDING.
DBP	≤45 mmHg and decrease from baseline ≥10 mmHg ≥110 mmHg and increase from baseline ≥10 mmHg	To be applied for all positions (including missing) except STANDING.
Orthostatic Hypotension Orthostatic SDB Orthostatic DBP	 ≤-20 mmHg ≤-10 mmHg	
Weight	≥5% increase from baseline ≥5% decrease from baseline	FDA Feb 2007.

Appendix D Generic ranges for hematology and biochemistry parameters

The current list of generic ranges for hematology parameters (for adults) is provided in the table below:

Table 12 - Generic ranges for hematology parameters

LBTESTCD	LBTEST	GENDER	LBSTRESU	LBGNNRLO
HGB	Hemoglobin	F	g/L	120
HGB	Hemoglobin	M	g/L	135
LYM	Lymphocytes		10^9/L	1
NEUT	Neutrophils		10^9/L	1,8
PLAT	Platelets		10^9/L	150
WBC	Leukocytes		10^9/L	4,5
EOS	Eosinophils		10^9/L	0
BASO	Basophils		10^9/L	0
MONO	Monocytes		10^9/L	0,18
HCT	Hematocrit	F	%	0,36
HCT	Hematocrit	M	%	0,41
RBC	Erythrocytes	F	10^12/L	4
RBC	Erythrocytes	M	10^12/L	4,5
INR	INR		ratio	0,8

Based on NEJM (N Engl J Med 2004;351:1548-63.): “Laboratory Reference Values”, Alexander Kratz, M.D., Ph.D., M.P.H., Maryjane Ferraro, Ph.D., M.P.H., Patrick M. Sluss, Ph.D., and Kent B. Lewandrowski, M.D.

The current list of generic ranges for biochemistry parameters (for adults) is provided in the table below:

Table 13 - Generic ranges for biochemistry parameters

LBTEST	LBSTRESU	LBGNNRLO - LBGNNRHI
Albumin	g/L	35 - 55
Blood Urea Nitrogen (BUN)	mmol/L	3,6-7,1
Calcium	mmol/L	2,2 - 2,6
Corrected calcium	mmol/L	2,2 - 2,6
Glucose	mmol/L	3,9 - 7
Bicarbonate (HCO3)	mmol/L	22 - 29
Carbon dioxide	mmol/L	21 - 30
Potassium	mmol/L	3,5 - 5
Magnesium	mmol/L	0,8 - 1,2
Sodium	mmol/L	136 - 145
Phosphate	mmol/L	1 - 1,4
Protein	g/L	55 - 80
Urea	mmol/L	3,6 - 7,1

Appendix E International Myeloma Working Group Response Criteria

Disease response will be assessed using the updated International Myeloma Working Group Response Criteria (IMWG). A confirmation assessment for disease response within 4 weeks is required in this protocol (either PR or better, or PD).

As a reminder, patients with measurable FLC only at screening are not eligible in the study.

M protein value on Cycle 1 Day 1 will be taken as baseline value for response assessment.

PD cannot not be diagnosed on FLC increase only, even in patients for whom serum and urine M protein become below level of eligibility on efficacy laboratory performed on Cycle 1 Day 1 (see below the table for assessment of overall response and progression diagnosis of these patients).

Adapted from updated International Myeloma Working Group Response Criteria

IMWG MRD criteria (requires CR as defined below)	
Sustained MRD-negative	MRD negativity in the marrow (NGF or NGS, or both) and by imaging as defined below, confirmed minimum of 1 year apart. Subsequent evaluations can be used to further specify the duration of negativity (eg, MRD-negative at 5 years)
Flow MRD-negative	Absence of phenotypically aberrant clonal plasma cells by NGF on BMAs using the EuroFlow standard operation procedure for MRD detection in multiple myeloma (or validated equivalent method) with a minimum sensitivity of 1 in 10^5 nucleated cells or higher
Sequencing MRD-negative	Absence of clonal plasma cells by NGS on BMA in which presence of a clone is defined as less than two identical sequencing reads obtained after DNA sequencing of BMAs using the LymphoSIGHT platform (or validated equivalent method) with a minimum sensitivity of 1 in 10^5 nucleated cells or higher
Imaging-positive MRD-negative	MRD negativity as defined by NGF or NGS plus disappearance of every area of increased tracer uptake found at baseline or a preceding PET/CT or decrease to less mediastinal blood pool SUV or decrease to less than that of surrounding normal tissue
Standard IMWG response criteria	
Response	**IMWG criteria**
CR	• Negative immunofixation on the serum and urine and • Disappearance of any soft tissue plasmacytomas and • <5% plasma cells in BMAs. **Two consecutive assessments are needed. No known evidence of progressive disease or new bone lesions if radiographic studies were performed**
sCR	CR as defined above plus: • Normal FLC ratio (0.26 to 1.65) and • Absence of clonal cells in BM by immunohistochemistry (κ/λ ratio ≤4:1 or ≥1:2 for κ and λ patients, respectively, after counting ≥100 plasma cells). **Two consecutive assessments of laboratory parameters are needed. No known evidence of progressive disease or new bone lesions if radiographic studies were performed**

Response	IMWG criteria
VGPR	• Serum and urine M protein detectable by immunofixation but not on electrophoresis or • ≥90% reduction in serum M protein plus urine M protein level <100 mg/24 hour. • ≥90% decrease in the sum of the products of maximal perpendicular diameter compared to baseline in soft tissue plasmacytoma. **Two consecutive assessments are needed. No known evidence of progressive disease or new bone lesions if radiographic studies were performed.**
PR	• ≥50% reduction of serum M protein and reduction in 24 hours urinary M protein by ≥90% or to <200 mg/24 hour • In addition to the above listed criteria, if present at baseline, a ≥50% reduction in the size (sum of the products of the maximal perpendicular diameters) of soft tissue plasmacytomas is also required **Two consecutive assessments are needed. No known evidence of progressive disease or new bone lesions if radiographic studies were performed.**
MR	≥25% but ≤49% reduction in serum M protein and reduction in 24h urine M protein by 50 to 89%, which still exceed 200 mg/24 hour. In addition to the above listed criteria, if present at baseline, ≥50% reduction in size (SPD) of soft tissue plasmacytomas is also required. **Two consecutive assessments are needed. No known evidence of progressive disease or new bone lesions if radiographic studies were performed.**
Stable Disease	• Not meeting criteria for CR, VGPR, PR, MR or progressive disease. **No known evidence of progressive disease or new bone lesions if radiographic studies were performed.**
Progressive disease	Any 1 or more of the following criteria: Increase of ≥25% from lowest confirmed value in any 1 of the following criteria: • Serum M protein (the absolute increase must be ≥0.5 g/dL). • Serum M protein increase ≥1 g/dL if the lowest M component was ≥5 g/dL. • Urine M-component (the absolute increase must be ≥200 mg/24 hour). Appearance of new lesion(s), ≥50% increase from nadir in SPD of >1 lesion, or ≥50% increase in the longest diameter of a previous lesion >1 cm in short axis. **Two consecutive assessments are needed for PD on M protein.**

Abbreviations: CR = complete response, FLC = free light chain, IMWG = International Myeloma Working Group, M = monoclonal, MRD = minimal residual disease, NGF = next-generation flow, NGS = next-generation sequencing, PD = progressive disease, PET = positron emission tomography, MR = minor response, PR = partial response, sCR = stringent complete response, SD = stable disease, SPD = sum of the products of the maximal perpendicular diameters of measured lesions, SUV = maximum standardized uptake value, VGPR = very good partial response.

Patients with disease only measurable by FLC are not allowed.

A plasmacytoma that has been radiated is not suitable for response assessment; however, it must be monitored to assess for progressive disease.

For patients achieving VGPR by other criteria, a soft tissue plasmacytoma must decrease by more than 90% in the sum of the products of the maximal perpendicular diameters of measured lesions (SPD) compared with baseline.

For IgA and IgD myeloma, quantitative immunoglobulin measurements are preferred for assessments, the same percentage changes apply fornserum M-spike (see table above).

Definite increase in the size of existing bone lesions or soft tissue plasmacytomas is defined as below:

- ≥50% increase in the size of at least one bidimensionally measurable lesion (in comparison with the measurements at Nadir) or appearance of a new lesion.
- Pathological fracture or collapse of bone are not necessarily evidence of disease progression.

Reminder: definitions of Response and Progression are based on IMWG Uniform Reporting Criteria:

- Any response (sCR, CR, VGPR, PR) or progression needs to be confirmed by two consecutive disease assessments according to the Study Flow Chart. A disease assessment at one time point not matched by the same disease assessment at the next time point will be considered unconfirmed (except for progression by imaging, BM plasma cell counts, where one time point is adequate for confirmed progression).
- Urine M protein is not needed to document PR or minor response if baseline urine M protein was not measurable; however, it is still required for CR and very good PR.
- Documentation of response requires two consecutive readings of the applicable disease parameter (serum M protein, urine M protein), performed at any time (no minimum interval is required, it can be done the same day); however, to confirm response or progressive disease, 2 discrete samples are required; testing cannot be based upon the splitting of a single sample.
- Patients will continue in the last confirmed response category until there is confirmation of progression or improvement to a higher response status; patients cannot move to a lower response category.
- Percent decreases for response calculations are from baseline values (Cycle 1 Day 1).
- Percent increases for progression calculations are from lowest response values or baseline values, whichever is the smaller number. The lowest value does not need to be confirmed.
- The lowest confirmed value before suspected progression will be used as baseline for calculation of progression; if a serum and/or urine spike is considered too low to quantitate, this value can be assigned as 0 as a baseline for documentation of subsequent progressive disease. Patients will be considered to have progressive disease if they meet the criteria for progression by a variable that was not considered measurable at baseline; however, for patients who had a measurable serum or urine M-spike at baseline, progression cannot be defined by increases in serum FLC alone.

Patients with serum and urine M protein below level of eligibility on efficacy laboratory performed on Cycle 1 Day 1 (eg, patients with only FLC measurable disease according to IMWG, M-protein value >0 [or IF positive] and <0.5 g/dL):

- These patients can have only 2 possible overall responses: **CR, non-PD** or **PD**.
- Patients with M-protein (urine and/or serum) below the level of measurability (M protein value >0 [or IF positive] and <0.5 g/dL) can have CR, non-PD, or PD responses only according to the increase or decrease of M protein or extramedullary disease if applicable, following the IMWG criteria.
- Patients with FLC measurable disease only (M protein = 0 and IF negative), can have either non-PD or PD responses (PD will be an absolute increase of >10 mg/dL in the difference between involved and uninvolved FLC).
- Patients with serum M protein value >0 g/dL (or serum IF positive) and <0.5 g/dL, independently of FLC can only be qualified as: CR, non-PD, or PD.

  AND/OR
- Patients with urine M protein value >0 mg/24h (or urine IF positive) and <200 mg/24h, independently of FLC can only be qualified as: CR, non-PD, or PD.

  OR
- Patients with serum M protein value = 0 g/dL and serum IF for intact Ig negative and urine M-protein = 0 mg/24h and urine IF negative, independently of FLC can only be qualified as: non-PD or PD.

Appendix F Description of primary and sensitivity analyses of PFS

General rule for censoring for all sensitivity analyses:

Patient is censored

- at the last valid assessment if this one is done on or before cutoff date,
- at cutoff if the last valid assessment is done after cutoff date,
- at randomization if there is no valid assessment after randomization.

Initiation of further anti-myeloma therapy must be considered or not for the selection of the last valid assessment according to the sensitivity analysis considered.

The following tables 13 to 18 includes the description of PFS primary analysis and sensitivity analyses for all regions except US. The Table 19 includes the description of PFS primary analysis for US. The sensitivity analyses for PFS in US will be similar as the one performed for ex-US by adding the additional censoring rule for late progression and deaths.

Table 14 - PFS Primary analysis (progression based on blinded IRC disease assessment)

Situation	Date of progression or censoring	Outcome
No baseline disease assessments	Date of Randomization	Censored
No valid post-baseline disease assessments	Date of Randomization	Censored
Documented Progression prior to initiation of new anti-myeloma treatment and prior to the cut-off date	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	Date of death	Event
Both documented progression prior to initiation of new anti-myeloma treatment and death prior to the cut-off date	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 without evidence of progression before the initiation of new anti-myeloma treatment and cut-off date	Censored

Table 15 - PFS sensitivity analysis #1 (progression based on blinded IRC disease assessment and ignoring further anti-myeloma treatment)

Situation	Date of progression or censoring	Outcome
No baseline disease assessments	Date of Randomization	Censored
No valid post-baseline disease assessments	Date of Randomization	Censored
Documented Progression prior to the cut-off date	Earliest date among all disease assessments with evidence of progression	Event
Death without documented progression prior to the cut-off date	Date of death	Event
Both documented progression and death prior to the cut-off date	Date of progression	Event
No documented progression according to and no death prior to the cut-off date	Earliest of the date of last valid disease assessment without evidence of progression 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	Ignored	Ignored

Table 16 - PFS sensitivity analysis #2 (progression based on investigator's disease assessment and including symptomatic deterioration)

Situation	Date of progression or censoring	Outcome
No baseline disease assessments	Date of Randomization	Censored
No valid post-baseline disease assessments	Date of Randomization	Censored
Death prior to the cut-off date without initiation of new anti-myeloma treatment or documented progression or symptomatic deterioration	Date of death	Event
Documented progression prior to initiation of new anti-myeloma treatment and prior to the cut-off date with no symptomatic deterioration.	Earliest date among all disease assessments with evidence of progression	Event
Both documented progression according to the investigator prior to initiation of new anti-myeloma treatment and death prior to the cut-off date with no symptomatic deterioration.	Date of documented progression	Event
Symptomatic deterioration prior to initiation of new anti-myeloma treatment and prior to the cut-off date with no documented progression according to the investigator regardless of death occurrence.	Date of symptomatic deterioration	Event
Symptomatic deterioration and documented progression according to the investigator prior to initiation of new anti-myeloma treatment and prior to the cut-off date regardless of death occurrence	Earliest date among symptomatic deterioration and documented progression	Event
Both no symptomatic deterioration and no documented progression according to the investigator prior to initiation of new anti-myeloma treatment and prior to the cut-off date, 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
Initiation of new anti-myeloma treatment before symptomatic deterioration, or before documented progression according to investigator 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

Table 17 - PFS sensitivity analysis #3 (progression based on investigator's disease assessment and ignoring symptomatic deterioration)

Situation	Date of progression or censoring	Outcome
No baseline disease assessments	Date of Randomization	Censored
No valid post-baseline disease assessments	Date of Randomization	Censored
Documented Progression prior to initiation of new anti-myeloma treatment and prior to the cut-off date	Earliest date among all disease assessments with evidence of progression	Event
Death without documented progression and without initiation of new anti-myeloma treatment prior to the cut-off date	Date of death	Event
Both documented progression prior to initiation of new anti-myeloma treatment and death prior to the cut-off date	Date of progression	Event
No documented progression according to investigator 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 investigator and no death	Ignored	Ignored
Initiation of new anti-myeloma treatment before documented progression according to investigator or before death	Earliest of the date of last valid disease assessment without evidence of progression before the initiation of new anti-myeloma treatment and cut-off date	Censored

Table 18 - PFS sensitivity analysis #4 (progression based on blinded IRC disease assessment and including initiation of further anti-myeloma treatment as an event)

Situation	Date of progression or censoring	Outcome
No baseline disease assessments	Date of Randomization	Censored
No valid post-baseline disease assessments	Date of Randomization	Censored
Documented Progression prior to initiation of new anti-myeloma treatment and prior to the cut-off date	Earliest date among all disease assessments with evidence of progression	Event
Death without both documented progression and initiation of new anti-myeloma treatment and prior to the cut-off date	Date of death	Event
Both documented progression prior to initiation of new anti-myeloma treatment and death prior to the cut-off date	Date of progression	Event
No documented progression according to IRC prior to initiation of new anti-myeloma treatment and prior to the cut-off date and no death prior to the cut-off date	Earliest of the date of last valid disease assessment without 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 and before the cut-off date	Start date of new anti-myeloma treatment	Event

Table 19 - PFS sensitivity analysis #5 (progression based on blinded IRC disease assessment, assigning uniform progression and assessment dates and censoring late progressions and deaths)

Situation	Date of progression or censoring	Outcome
No baseline disease assessments	Date of Randomization	Censored
No valid post-baseline disease assessments	Date of Randomization	Censored
Documented progression prior to the cut-off date and within 8 weeks from last previous valid disease assessment	Date of the scheduled visit for this time window	Event
Death without documented progression prior to the cut-off date and within 8 weeks from last valid disease assessment	Date of death	Event
Death or Progression after more than one missed laboratory disease assessment (ie, more than 8 weeks from last valid disease assessment)	Earliest of the date of last valid disease assessment without evidence of progression before initiation of new antimyeloma treatment and cut-off date	Censored
Symptomatic deterioration reported and no documented progression according to IRC and no death	Ignored	Ignored
No documented progression according to IRC and no death	Earliest of the date of last valid disease assessment without evidence of progression before initiation of new antimyeloma treatment and cut-off date	Censored
Initiation of new anti-myeloma treatment before documented progression according to IRC or before death	Earliest of the date of last valid disease assessment without evidence of progression before initiation of new antimyeloma treatment and cut-off date	Censored

Note: 8 weeks corresponds to twice the time between two disease assessments per protocol (every 2*4 weeks)

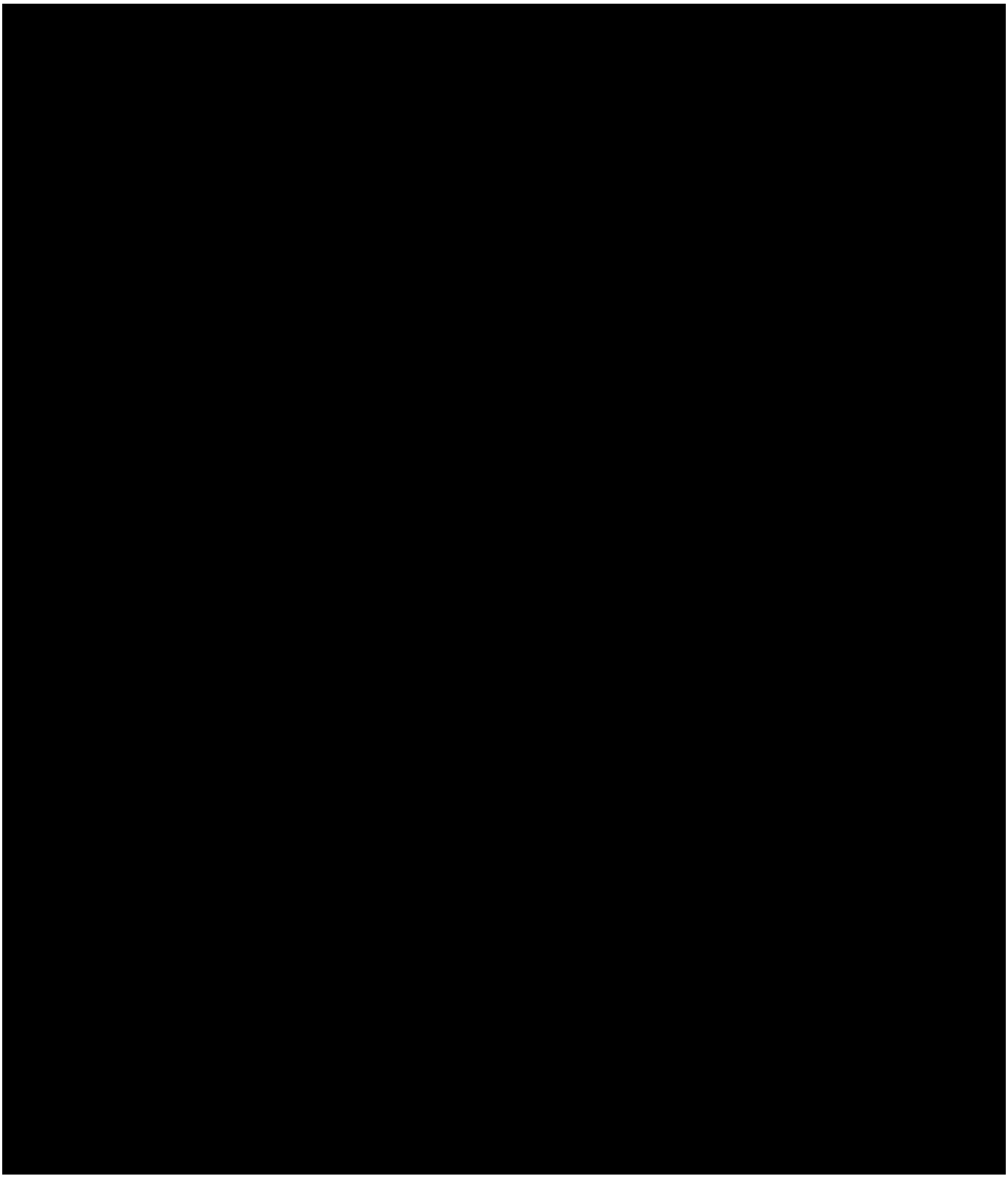
Table 20 - PFS Primary analysis (censoring late progressions and deaths) for US following FDA's request

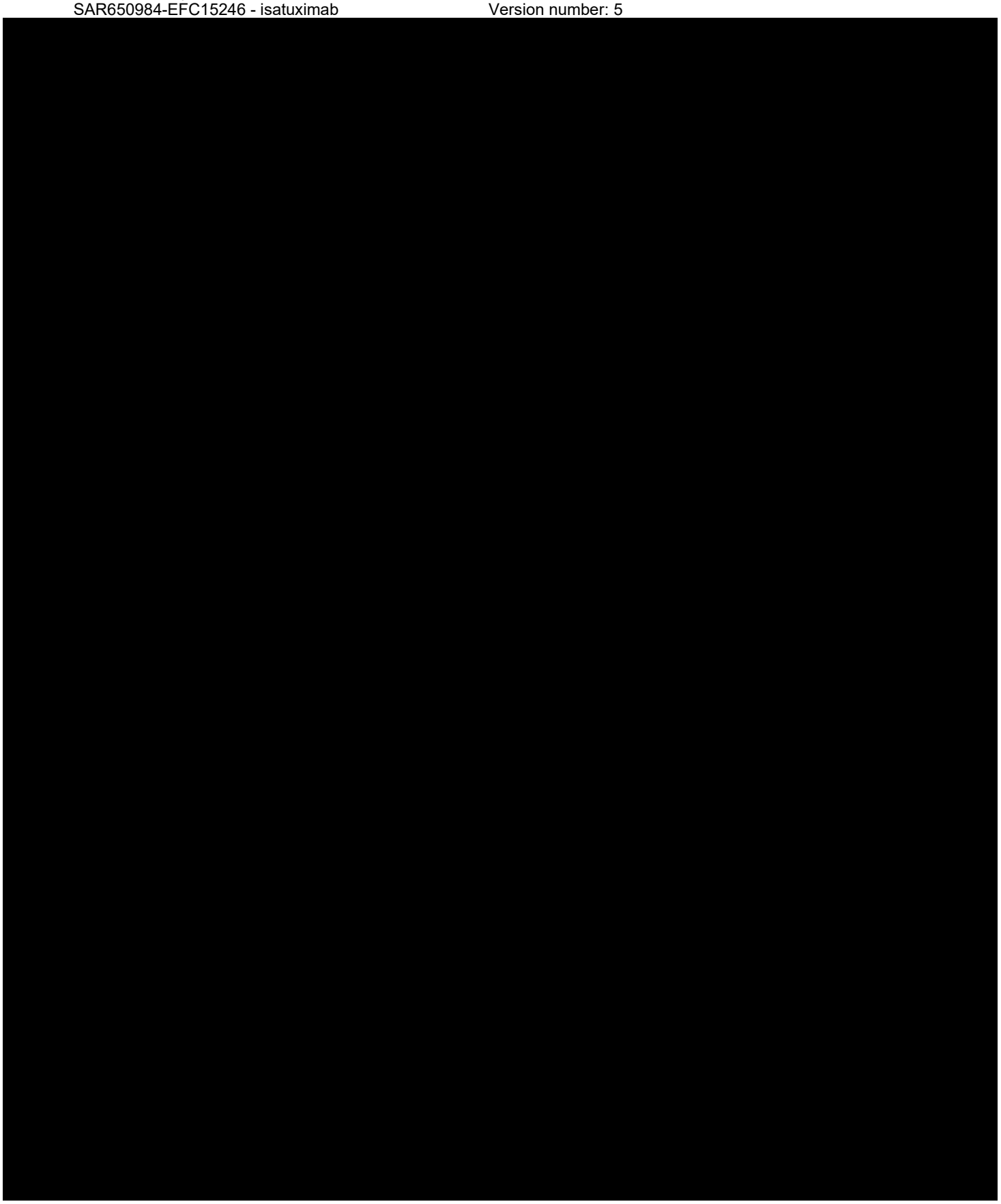
Situation	Date of progression or censoring	Outcome
No baseline disease assessments	Date of Randomization	Censored
No valid post-baseline disease assessments	Date of Randomization	Censored
Documented Progression prior to initiation of new anti-myeloma treatment and prior to the cut-off date and within 8 weeks from last previous 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 8 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 8 weeks from last previous 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 without evidence of progression before the initiation of new anti-myeloma treatment and cut-off date	Censored
Earliest of Death or progression occurring more than 8 weeks 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

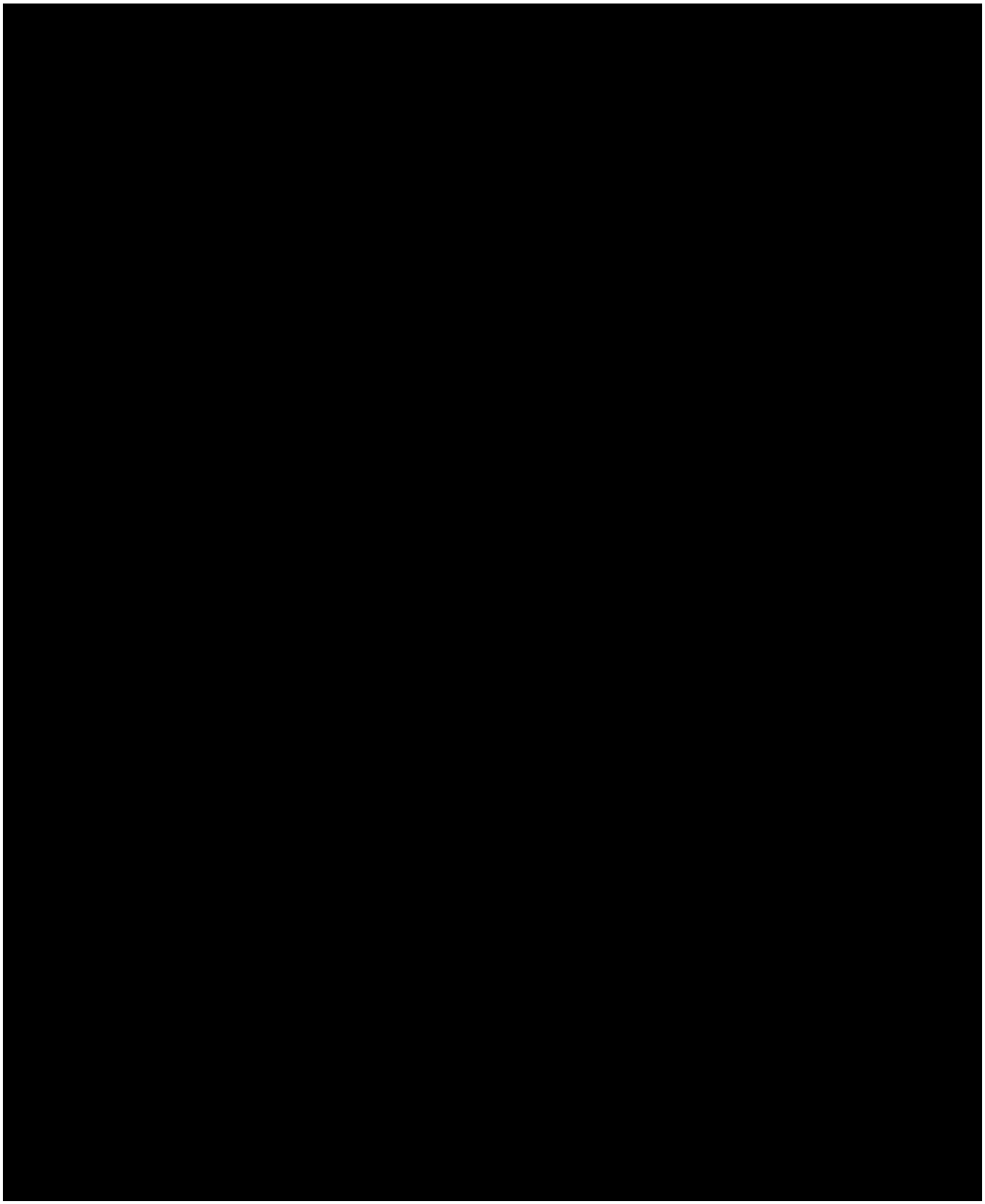
Note: 8 weeks corresponds to twice the time between two disease assessments per protocol (every 2*4 weeks)

Appendix G EORTC QLQ-C30 and QLQ-MY20 items, scales and scores

For QLQ-C30:







Appendix H Definitions of regions

1. Geographical regions

Europe	America	Asia	Other countries
Czech Republic	Brazil	Japan	Australia
France	Canada	Republic of Korea	New Zealand
Greece	United States		Russian Federation
Hungary			Turkey
Italy			
Spain			
United Kingdom			

2. Regulatory regions

Western countries	Other countries
Australia	Brazil
Canada	Czech Republic
France	Hungary
Greece	Japan
Italy	Republic of Korea
New Zealand	Russian Federation
Spain	Turkey
United Kingdom	
United States	

Appendix I Description of PFS2 analysis

Table 21 - PFS2 analysis (progression based on investigator disease assessment)

Situation	Date of progression or censoring	Outcome
No valid post-baseline disease assessments	Date of randomization	Censored
Death when further anti-myeloma treatment not yet started and prior to the cut-off date	Date of death	PFS2 event
No disease progression on study treatment* but disease progression or death after initiation of further anti-myeloma treatment and prior to the cut-off date	First progression date after initiation of further anti-myeloma therapy reported as per investigator or date of death if no progression after initiation of further anti-myeloma treatment	PFS2 event
No disease progression on study treatment*, no disease progression and no death after initiation of further anti-myeloma treatment and prior to the cut-off date	Earliest of the date of the last follow-up visit after initiation of further anti-myeloma treatment and the cut-off date. If no initiation of further anti-myeloma treatment, same date of censoring as for PFS on study treatment	Censored
Disease progression on study treatment*, no disease progression and no death after initiation of further anti-myeloma treatment and prior to the cut-off date	Earliest of the date of the last follow-up visit after initiation of further anti-myeloma treatment and the cut-off date. If no initiation of further anti-myeloma treatment, censor at the date of progression on study treatment	Censored
Disease progression on study treatment*, disease progression or death after initiation of further anti-myeloma treatment and prior to the cut-off date	First progression date after initiation of further anti-myeloma therapy reported as per investigator or date of death if no progression after initiation of further anti-myeloma treatment	PFS2 event

* disease progression on study treatment or in follow-up but before initiation of further anti-myeloma treatment as per investigator including symptomatic deterioration