STATISTICAL ANALYSIS PLAN

A Phase 1/2 study to evaluate safety, pharmacokinetics and efficacy of isatuximab in combination with cemiplimab in patients with relapsed/refractory multiple myeloma

SAR650984-TCD14906

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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
ALT:	alanine aminotransferase
AST:	aspartate aminotransferase
AT:	all treated
ATC:	anatomic category class
BOR:	best overall response
BUN:	blood urea nitrogen
CBR:	clinical benefit rate
CR:	complete response
CTCAE:	common terminology criteria for adverse events
DFU:	duration of follow-up
DLT:	dose limiting toxicity
DOR:	duration of response
ECOG:	eastern cooperative oncology group, eastern cooperative oncology group
eCRF:	electronic case report form
EOT:	end of treatment
FCGR:	fc gamma receptor
FIH:	first in human
GFR:	glomerular filtration rate
HDAC:	histone deacetylase
HLA:	human leukocyte antigen
HLGT:	high-level group term
HLT:	high-level term
HRQL:	health related quality-of-life
IAC:	independent adjudication committee
IAR:	infusion associated reaction
IFN-γ:	interferon-gamma
IL:	interleukin
IMP:	investigational medicinal product
IMWG:	international myeloma working group
irAE:	immune-related AE
IRT:	interactive response technology
ISS:	international staging system
ITT:	intent to treat
KIR:	killer-cell immunoglobulin-like receptor
KPS:	karnofsky performance status
LLT:	lower level term
MDRD:	modified diet in renal disease

MedDRA:	medical dictionary of regulatory activities
MR:	minimal response
MRD:	minimal residual disease
NCI:	national cancer institue
NIMP:	non investigational medicinal product
ORR:	overall respnse rate
OS:	overall survival
PCSA:	potentially clinically significant abnormalities
PFS:	progression free survival
PK:	pharmacokinetic
PR:	partial response
PS:	performance status
PT:	preferred term
Q2W:	once every two weeks
QW:	once weekly
RDI:	relative dose intensity
RRMM:	relapsed/refractory multiple myeloma
SAE:	serious adverse event
SAP:	statistical analysis plan
SD:	standard deviation
SOC:	system organ class
TEAE:	treatment-emergent adverse event
TLS:	tumor lysis syndrome
TNF-α:	tumor necrosis factor alpha
TTR:	time to response
VGPR:	very good partial response

1 OVERVIEW AND INVESTIGATIONAL PLAN

TCD14906 is the first in human study of isatuximab (SAR650984) in combination with cemiplimab (REGN2810) in patients with relapsed/refractory multiple meyloma. The study was originally designed as a dose de-escalation and expansion study (original protocol 12-Apr-2017). However, following comments from the FDA, the study design was subsequently modified, prior to enrollment of any patients, to evaluate the safety and clinical activity in relapsed/refractory multiple myeloma (RRMM) in 2 parts: dose de-escalation in Phase 1, followed by a three arm randomized Phase 2. This statistical analysis plan (SAP) describes the statistical methods to be used for the analyses of data collected during both Phase 1 and Phase 2 parts of the study. This SAP should be read in conjunction with the amended study protocol (Version 03 - 06-Aug-2018) and electronic case report form (eCRF).

1.1 STUDY DESIGN AND RANDOMIZATION

The study is conducted in 2 parts:

- The Phase 1 (lead in) part was to confirm the feasibility of the isatuximab/cemiplimab combination using 3 + 3 dose de-escalation design. The Phase 1 part of the study was completed at time of writing of this SAP. Three patients were enrolled at DL1 (isatuximab 10 mg/kg once weekly (QW) for four weeks followed by once every two weeks (Q2W) + cemiplimab 250 mg (Q2W) and no patient had DLT.
- The Phase 2 part is to further evaluate the safety, efficacy and PK of the combination versus isatuximab monotherapy. Based on the evaluation of the results from the Phase 1 part of the study, patients are randomized in the Phase 2 part of the study in 1 of the 3 arms using an interactive response technology (IRT) in a 1:1:1 ratio:
  - Arm 1 (control): isatuximab 10 mg/kg QWx4 followed by Q2W (QW/Q2W),
  - Arm 2 (DL1): isatuximab 10 mg/kg QW/Q2W + cemiplimab 250 mg Q2W,
  - Arm 3 (DL-1): isatuximab 10 mg/kg QW/Q2W + cemiplimab 250 mg Q4W.

The duration of the study for a patient will include a period for screening of up to 21 days. Patients will continue treatment until disease progression, unacceptable adverse events, consent withdrawal, or any other reason. After the last dose of study treatment (isatuximab or cemiplimab), the post-treatment follow up period include an extended safety follow-up period of 90 days, and further follow up beyond 90 days after last treatment until death or study cutoff date, whichever occur first.

A maximum of 105 patients (35 patients per arm) will be randomized in the Phase 2 randomization part. Details on study design can be found in Protocol Section 6.

1.2 OBJECTIVES

1.2.1 Primary objectives

The primary objectives are:

- To determine the safety and tolerability of the combination of isatuximab and cemiplimab.
- Phase 2 only: to compare the overall response rate (ORR, defined as complete response[CR] + very good partial response[VGPR] + partial response [PR]) of the combination of isatuximab and cemiplimab versus isatuximab alone in patients with RRMM based on International Myeloma Working Group (IMWG) criteria.

1.2.2 Secondary objectives

The secondary objectives are:

- To determine the following efficacy measurements (Phase 2 part only):
  - Clinical benefit rate (CBR, CR + VGPR + PR + Minimal response[MR]),
  - Duration of response (DOR),
  - Time to response (TTR),
  - Progression free survival (PFS),
  - Overall survival (OS).
- To determine the pharmacokinetic (PK) profile of isatuximab and cemiplimab when given in combination.
- To assess the immunogenicity of isatuximab and cemiplimab when given in combination.

1.2.3 Exploratory objectives

- To explore the minimal residual disease (MRD) in patients achieving a CR.
- To assess the relationship between immune phenotypes, immune regulatory marker expression, adaptive immune response and parameters of clinical response.
- To explore central/effector memory T cell proliferation.

1.3 DETERMINATION OF SAMPLE SIZE

In Phase 1 part, the objective is to determine the recommended Phase 2 Dose (RP2D) based on DLT occurrence. The actual sample size will depend on DLTs observed and number of dose levels actually explored. It is anticipated that 3 to 18 DLT-evaluable patients will be treated in the Phase 1 part of the study.

In Phase 2 randomization part, the objective is to evaluate the efficacy and safety of the combination therapy. Assuming ORR=20% in control arm (isa alone arm) and ORR=50% in combination arms, using Fisher's exact test to compare the ORR in control vs combination arms and an overall 1-sided type I error of 5% for each combination arm, 35 patients per arm is required to achieve a 79% power for each combination arm. EAST 6.0 was used in the sample size calculation. The total expected number of patients treated in Phase 2 randomization part is 105.

1.4 STUDY PLAN

Safety evaluations will be performed continuously throughout the study and will include the following:

- DLT at first cycle as defined in the protocol (Phase 1 only).
- Adverse events (AEs) evaluation including immune related AEs. Severity grade determined according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03.
- Laboratory tests in blood and urine.
- Vital signs and physical exam.
- Eastern Cooperative Oncology Group (ECOG) performance status (PS).
- Cytokines (tumor necrosis factor alpha [TNF-α], interleukin [IL]-1-β, IL-6, interferon-gamma [IFN-γ]), markers of complement (C3, C4, CH50), serum tryptase, lactate dehydrogenase [LDH].
- Chest X-ray and ECG (baseline only).

Disease response evaluation will be performed at screening and Day 1 of every cycle, starting from Cycle 1 unless otherwise stated in the protocol, and include:

- M-protein quantification (serum and/or 24-hour urine), serum free light chain levels.
- Immunoglobulins including IgG, IgA, IgD, IgE and IgM (except Cycle 1 Day 1).
- Bone marrow biopsy/aspiration (at baseline, and to be performed to confirm a CR and as clinically indicated, and at the end of treatment (EOT) visit as clinically indicated).
- Radiologic imaging of plasmacytoma (at baseline, and during the trial as clinically indicated and to confirm response according to IMWG criteria).
- Bone skeletal survey (at baseline, and during the trial as clinically indicated and to confirm response according to IMWG criteria).

The following additional evaluations will also be performed:

- Serum β2-microglobulin (except Cycle 1 Day 1).
- Pregnancy test (except Cycle 1 Day 1).
- Blood typing interference test (at baseline and Cycle 2 Day 1).
- Adaptive immune response in blood and bone marrow aspirate (at baseline, Cycle 3 Day 1 for blood only, and in case of CR).
- Adaptive immune response (humoral and cellular response) (Prior to pre-medication and IMP administration on Day 1 of Cycle 1, Cycle 2, Cycle 4, Cycle 7 and Cycle 10 and in disease progression patients at EOT).
- PD1-PDL1 expression in bone marrow biopsy (at baseline, at Cycle 3 Day 1, and at EOT).
- MRD assessment in bone marrow aspirate (at baseline, and during the trial in case of CR).
- Level of human anti-drug antibodies (ADA).
- Immune phenotyping and molecular analysis on blood and bone marrow.
- FISH bone marrow aspirate (at baseline).

PK samples will be collected in all patients receiving isatuximab and cemiplimab as depicted in the PK study flowcharts included in the protocol.

1.5 MODIFICATIONS TO THE STATISTICAL SECTION OF THE PROTOCOL

- Change from first dose date to randomization date.

Secondary efficacy endpoints (Section 2.1.3.2) including progression free survival (PFS), time to response (TTR) and overall survival (OS) were defined starting from the first treatment date in the protocol, this is updated to the date of randomization in the analysis plan. The associated censoring rules are also updated.

This change is also applied to disease characteristics variables (Section 2.1.1), including time from diagnosis to randomization, time from last regimen to randomization, time from last transplant to randomization and time from last radiotherapy to randomization.

1.6 STATISTICAL MODIFICATIONS MADE IN THE STATISTICAL ANALYSIS PLAN

Not applicable, as this is the 1st version.

2 STATISTICAL AND ANALYTICAL PROCEDURES

2.1 ANALYSIS ENDPOINTS

Unless otherwise specified, analyses endpoints are defined for both Phase 1 and Phase 2 patients and will be analyzed separately based on the analysis population defined in Section 2.3.

The reference date is defined as the date of first dose for Phase 1 and date of randomization for Phase 2.

2.1.1 Demographic and baseline characteristics

The baseline value is defined as the last value or measurement taken up to the date and time of the first dose of study treatment. For efficacy laboratory parameters (eg, serum and urine M-protein), unscheduled assessment performed on the date of first study treatment administration (Cycle 1 Day 1) will be considered as baseline value; for other laboratory tests, unscheduled assessment performed on the date of first study treatment administration will be considered as post baseline. For patients randomized and not treated (Phase 2 only), the baseline value is defined as the last available value obtained up to the date and time of randomization.

All baseline safety and efficacy parameters (apart from those listed below) will be 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 include gender (Male, Female), race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Not Reported, Unknown), ethnicity (Hispanic or Latino, Not-Hispanic or Latino, Not reported, Unknown), age in years (quantitative and qualitative variable : <65, [65 - 75[and ≥75 years), weight (kg) and ECOG performance status.

Medical or surgical history

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

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

Disease characteristics at initial diagnosis

The following MM characteristics at initial diagnosis will be summarized: time from initial diagnosis to reference date (in years) and by category (<5 years and ≥5 years), International Staging System (ISS) stage, and subtype (heavy and light chain component as collected in the eCRF), biclonal status.

Disease characteristics at study entry

The following MM characteristics at study entry will be summarized:

- ISS stage (Table 1), β2-microglobulin level in mg/L (quantitatively and by category: <3.5 mg/L, [3.5-5.5[mg/L and ≥5.5 mg/L), albumin in g/L (quantitatively and by category: <35 g/L and ≥35 g/L).
- Cytogenetic abnormalities from central FISH assessment:
  - Number and percentage of patients with cytogenetic abnormality for del (17p), t(4;14), and t(14;16). Abnormality is defined as at least 15% of abnormal plasma cells for t(4;14), and t(14;16), and at least 10% of abnormal plasma cells for del(17p13),
  - Type of risk: Standard risk, high-risk (defined as presence of del(17p) and/or translocation t(4;14) and /or translocation t(14;16) abnormality) and unknown/missing,
  - Number of patients with 2 abnormalities: del(17p) and t(4,14); and, del(17p) and t(14,16).
- 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 or better at some point previously to 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.
- Measurable paraprotein at baseline (Table 2).
- % of plasma cells in bone marrow at baseline (quantitatively and by category: 0,]0-5%[, [5-20%[, [20-50%[, and ≥50%).
- Patients with plasmacytomas.
- Patients with bone lesions and number of lesion.

Table 1 - 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

ISS=International Staging System

Table 2 - Derivation of measurable paraprotein at study entry

Measurable paraprotein	Criteria
Serum M-Protein	Serum M-protein ≥1 g/dL (or 0.5 g/dL in case of IgA disease)
Urine M-Protein	Urine M-protein ≥200 mg/24hours
Serum and urine M-protein	Serum M-protein ≥1 g/dL (or 0.5 g/dL in case of IgA disease) and urine M-protein ≥200 mg/24hours
Light chain	Serum immunoglobulin free light chain ≥10 mg/dL and abnormal serum immunoglobulin kappa lambda free light chain ratio <0.26 or >1.65
Not evaluable (neither serum neither urine)	Missing or not evaluable

Prior anti-myeloma therapies

Prior anti-myeloma treatment:

Prior anti-myeloma treatments are collected by regimens on eCRF. A line of therapy consists of ≥1 complete cycle of a single agent, a regimen consisting of a combination of several drugs, or a planned sequential therapy of various regimens (eg, 3-6 cycles of initial therapy with bortezomib-dexamethasone followed by stem cell transplantation consolidation, and lenalidomide maintenance is considered 1 line; Amended protocol Version 3.0, Appendix E). An algorithm will be used to determine number of prior lines: a new line of therapy starts if:

- There is an evidence of progression/relapse. OR,
- A planned course of therapy is modified as a result of toxicity, progression/relapse, lack of response, inadequate response, or any other reasons indicative of incomplete treatment or change of plan.

The following analysis of prior anticancer treatment will be performed.

- Prior anticancer treatments:
  - Number of prior lines (quantitatively and by category: 1, 2… 7 and ≥8),
  - Number of prior regimens (quantitatively and by category: 1, 2… 7 and ≥8),

- Main anticancer treatments:
  - Alkylating agents: including cyclophosphamide, melphalan, bendamustine, cisplatin,
  - Proteasome inhibitors: including bortezomib, carfilzomib, ixazomib,
  - Immunomodulators: including lenalidomide, thalidomide, pomalidomide,
  - Histone deacetylase (HDAC) inhibitors: panobinostat,
  - Corticosteroids: dexamethasone, prednisone,
  - Anthracyclines,
  - Vinca alkaloids,
  - Monoclonal antibodies: including elotuzumab, daratumumab and other anti CD38 agents,
- Description of last regimen prior to study entry:
  - Time from completion of last regimen of treatment to reference date (months),
  - Main treatments,
  - Best response to last regimen,
  - Duration of last regimen of therapy (months).

In addition, the refractory status to main anticancer treatment (as listed above) and refractory status of the last prior anticancer treatment received before enrollment will be derived. A patient is considered to be refractory if any of the following conditions are met:

Progression date and anticancer treatment end date are complete and progression date is within (≤) 60 days of anticancer treatment end date (Progression date - anticancer treatment end date ≤60 days). If only the day is missing for either date or both dates, and the progression date and anticancer treatment end date corresponds to two consecutive months within the same year, then, the patient will be considered refractory, otherwise they will be considered not refractory.

Best overall response (BOR) is SD or PD.

Reason for treatment discontinuation is “progressive disease”.

- Prior transplant: patients with transplant, type of transplant, number of transplant by patient, time from last transplant to reference date (months).
- Prior surgery: patients with any prior surgery related to cancer, type of surgery and time from last surgery to reference date (months).
- Prior radiotherapy: number (%) of patients with any prior radiotherapy related to cancer, intent, and time from last radiotherapy to reference date (months).

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

Vital signs

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

Renal status

Creatinine clearance, ie, glomerular filtration rate (GFR) in mL/min/1.73 m^2 (qualitative variable: <15, [15-30[, [30-60[, [60-90[, ≥90) will be calculated from serum creatinine concentration measured at baseline using Modified Diet in Renal Disease (MDRD) formula (Section 2.5.1).

2.1.2 Prior or concomitant medications (other than anticancer therapies)

All medications taken by the patient within 21 days prior to first study treatment, at any time during the study in addition to IMP will be reported in the eCRF.

The following information will be collected in the medication eCRF page: drug/medication (brand or generic name), reason (eg, curative, prophylaxis, etc), dose and unit, route, start date and end date (if applicable)/ongoing (otherwise).

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

- Prior medications are those the patient used prior (<) to first study treatment administration. Prior medications can be those discontinued before first administration or those ongoing during the treatment phase.
- Concomitant medications are any treatments received by the patient concomitantly to study treatment, from first dose to the date of last administration + 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 further anti-myeloma therapy regardless of the date of initiation (see Section 2.4.10). The analysis of concomitant medications will include premedication (see below).
- Post-treatment medications (excluding post anticancer treatments) are those the patient took from 31 days after last study treatment administration up to the end of the study.

IR medications

As defined in Section 8.2 of the study protocol, patients were to routinely receive premedications prior to isatuximab infusion to reduce the risk and severity of hypersensitivity reactions commonly associated with monoclonal antibodies. Premedications are defined in the protocol as non-investigational medicinal product(s). Premedications are reported on a specific eCRF page.

Analysis of premedications will focus on those given for prophylaxis reason. Medication given in curative intent of IR will be also analyzed.

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

2.1.3 Efficacy endpoints

Response assessments were to be performed on Day 1 of every cycle during treatment by investigators using the International Myeloma Working Group (IMWG) response criteria (1) and by considering the assessment included in Section 1.4.

Biological responses (≥PR) and progression should be confirmed on 2 consecutive biological (serum and/or urine M protein) disease assessments. No confirmation is required for radiological assessment.

For Phase 1, best overall response, duration of response, progression free survival and overall survival will be derived and listed by patient.

2.1.3.1 Primary efficacy endpoint (Phase 2 only)

The primary efficacy endpoint is ORR, defined as the proportion of patients with CR (including sCR), VGPR or PR as BOR as assessed by the investigator. BOR will be derived using disease assessments (overall response CRF page) from the start of treatment through the entire study excluding any assessments performed after disease progression (that is confirmed), the cutoff date or following the start of further therapies for MM (see Figure 1). The ordering of evaluations from best to worse is: sCR, CR, VGPR, PR, MR, stable disease (SD), progressive disease (PD), not evaluable (NE). BOR for patients without response assessment will be 'Not evaluable'. BOR will be the best sequential response based on the investigator's disease assessments as determined by the criteria in Table 3. In addition, the following rules will be applied:

- BOR will be NE for patients who received at most 2 isatuximab administrations with investigator assessment of response of SD or better at Cycle 1 or end of treatment.
- BOR will be PD for patients without response assessment who received 1 cycle of treatment and died due to PD or had symptomatic deterioration within 30 days of last study treatment administration.

Symptomatic deterioration will not be considered as progression in the primary analysis of ORR.

Table 3 - Sequential response determination for investigator response assessment

Overall response at Cycle n	Overall response at Cycle n+1[a]	Sequential response
sCR	sCR	sCR
CR	sCR	CR
sCR	CR	CR
CR	CR	CR
sCR/CR	VGPR	VGPR[b]
sCR/CR	PR	PR
VGPR	sCR/CR/VGPR	VGPR[b]
VGPR	PR	PR

Overall response at Cycle n	Overall response at Cycle n+1[a]	Sequential response
PR	sCR/CR/VGPR/CR/PR	PR
sCR/CR/VGPR/PR	NE/No further evaluation/SD/PD	MR[c]
MR	Any	MR
Any	MR	MR
NE/SD/PD	sCR/CR/VGPR/PR	MR[c]
NE/PD/SD	SD	SD
SD	No further evaluation/NE/PD	SD
NE	SD	SD
PD	No further evaluation/NE	unPD[e]
PD	PD	PD
NE	PD	unPD[e]
NE	No further evaluation	NE
No evaluation[d]		PD[d]

a Disease assessment are planned to be performed every cycle. Disease assessment performed after the start of new anticancer treatment will be excluded from the derivation of BOR.

b Sequence provided for programming purpose.

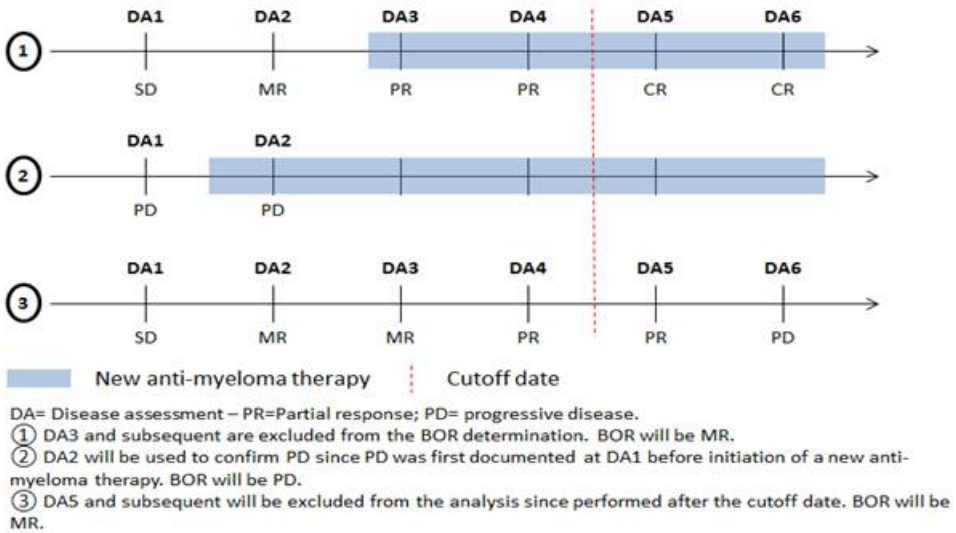
c Unconfirmed PR or CR will be considered MR.

d Only for analysis based on investigator assessment, BOR will be PD for patients without response assessment who received 1 cycle of treatment and died due to PD or had symptomatic deterioration within 30 days of last study treatment administration.

e Unconfirmed PD, unless PD is based on radiological assessment that does not need confirmation.

BOR=best overall response; sCR=stringent complete response; CR=complete response; MR=minor response; NE=not evaluable; PD=progressive disease; PR=partial response; SD=stable disease; VGPR=very good partial response.

Figure 1 - Determination of BOR when disease assessments are performed after new anti-myeloma therapies are started or performed after the cutoff date



DA= Disease assessment – PR=Partial response; PD= progressive disease.
① DA3 and subsequent are excluded from the BOR determination. BOR will be MR.
② DA2 will be used to confirm PD since PD was first documented at DA1 before initiation of a new anti-myeloma therapy. BOR will be PD.
③ DA5 and subsequent will be excluded from the analysis since performed after the cutoff date. BOR will be MR.

Subgroup analyses of BOR will be performed for the variables listed in Table 4.

Table 4 - List of variables for subgroup analyses

Variable	Description
Age	<70 years vs ≥70 years
Gender	Male vs female
Number of previous lines of therapy	≤3 vs >3
ISS staging at study entry	I vs II vs III
High risk cytogenetic	Yes vs No
Baseline creatinine clearance (MDRD)	<60 ml/min/1.73m^2 vs ≥60 ml/min/1.73m^2
Refractory to IMiD	Yes vs No
Refractory to PI	Yes vs No
Refractory to IMiD and PI	Yes vs No
Refractory to daratumumab	Yes vs No
Baseline PD-L1 level	≥50% vs <50%

2.1.3.2 Secondary efficacy endpoints

Secondary efficacy endpoints are defined below.

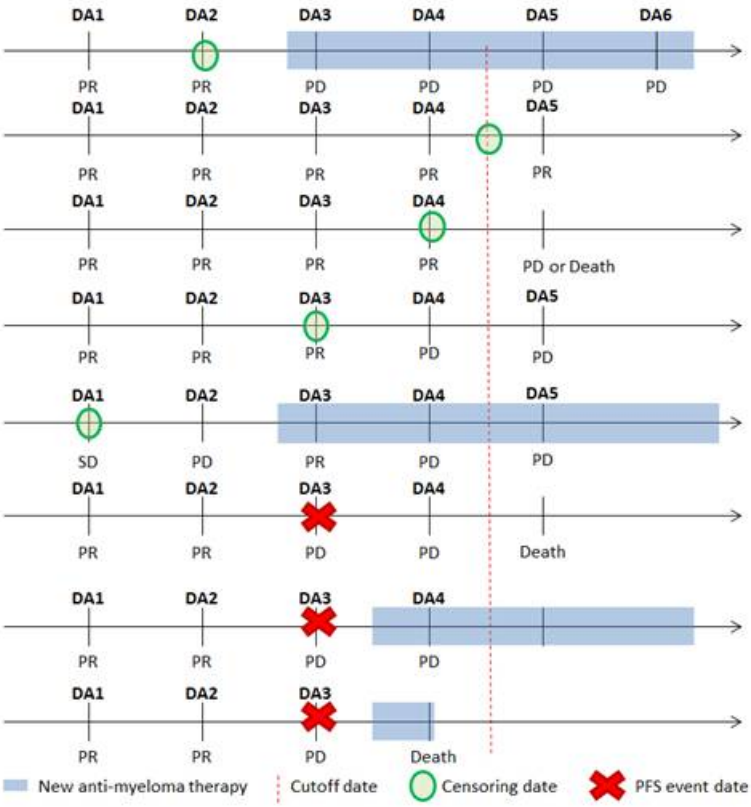
- CBR: defined as the proportion of patients with CR (including sCR), VGPR, PR or MR as assessed by investigators using the IMWG response criteria.
- DOR: DOR is defined as the time from the date of the first response (≥PR) that is subsequently confirmed, to the date of first documented PD or death (if reported before the analysis cutoff date or the date of initiation of a new anticancer treatment), whichever happens earlier. In the absence of the confirmation of subsequent disease progression or death before the analysis cut-off date or the date of initiation of a further anticancer treatment, the DOR will be censored at the date of the last valid disease assessment not showing disease progression performed prior to initiation of a further anticancer treatment and the analysis cut-off date, whichever is earlier. DOR will not be calculated for patients that do not achieve a PR or better.
- TTR: defined as time from randomization to first response (PR or better) that is subsequently confirmed.
- PFS: defined as the time interval from the randomization date to the date of the first documented disease progression that is subsequently confirmed or the date of death due to any cause, whichever comes first. For patients who did not experience documented disease progression or death before the analysis cut-off date or the date of initiation of new anticancer treatment, PFS will be censored at the date of the last valid disease assessment not showing disease progression performed prior to initiation of a further anticancer treatment or the analysis cut-off date, whichever comes first. Date of PFS event/censoring relative to date of further anti-myeloma therapies and cutoff date are illustrated in Figure 2. In addition, patient without PFS event (death or documented disease progression) and without any valid post-baseline disease assessments will be censored at the randomization date. Patients with death and time between the last post-baseline assessment and death >2 cycles will be censored at the date of last valid assessment (ie, not equal to NE). Subgroup analysis for variables defined in Table 4 will be performed.

- OS: defined as the time interval from the date of randomization to death from any cause. Patients without death prior to the analysis cutoff date will be censored at the last date the patient is known to be alive or the cut-off date whichever comes first.

Other efficacy endpoints include:

- Best percent change in paraprotein: Best percent change in paraprotein will be calculated for the measurable paraprotein parameter defined at baseline (Section 2.1.1). In case that both serum and urine M proteins are measurable, change in serum M protein will be calculated. The calculation will exclude anytime point following the start of other anticancer therapy or cutoff date.
- Duration of follow-up (DFU) (in months): DFU is defined as the time from randomization to last disease assessment before start of other therapy or cut-off date or death, whichever comes first.
- MRD: MRD will be assessed by sequencing and/or flow cytometry in bone marrow samples from CR patients. Method to measure MRD include multi-parametric flow cytometry (MFC) and more recently next generation sequencing to amplify and sequence immunoglobulin gene segments present in myeloma clone is a quantitative method for MRD detection. Bone marrow samples will be collected at CR.

Figure 2 - Date of PFS event/censoring relative to the date of further anti-myeloma therapies and the cutoff date using investigator's assessment



2.1.4 Safety endpoints

The safety analysis will be based on the reported AEs and other safety information, such as clinical laboratory data, vital signs, ECG and ECOG performance status (Section 1.4).

Observation period

The observation period will be divided into 3 periods: pre-treatment, on-treatment, and post-treatment including the extended safety follow-up period.

- The **pre-treatment period** is defined as the time from when the patient gave informed consent and the start of study treatment administration.
- The **on-treatment period** is defined as the time from the first dose of study treatment up to 30 days after the last dose of study treatment.
- The **post-treatment period** is defined as the time starting the day after the end of the on-treatment period up to the end of the study (as defined in the protocol).
    - The **extended safety follow-up period** is defined as the time period from 31 days after the last dose of study treatments to 90 days after the last dose of study treatments.

2.1.4.1 Adverse events variables

Adverse events occurring from signature of informed consent form up to 30 days after the last study treatment administration will be recorded in the eCRF. In addition, all study treatment related AEs and serious AEs (SAEs) ongoing at time of study treatment discontinuation will be followed during the follow-up period until resolution or stabilization.

All AEs (including SAEs) will be 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 MedDRA in effect at Sanofi at the time of database lock.

The severity of AEs will be assessed according to NCI-CTCAE Version 4.03.

The following AEs will be described:

- **Pre-treatment AEs**: defined as any AE reported during the pre-treatment period.
- **Treatment-emergent AEs (TEAEs):** defined as any AE developed, worsened (according to the Investigator's opinion), or became serious during the on-treatment period.
- **Post-treatment AEs:** defined as any AE developed, worsened (according to the Investigator's opinion), or became serious during the post-treatment period.
    - **Extended safety follow-up period AEs:** defined as any AE developed, worsened (according to the Investigator's opinion), or became serious during the extended safety follow-up period.

In addition, deaths (Section 2.1.4.2), SAEs, AEs leading to withdrawal, and other significant AEs will be analyzed. Other significant events will include:

Adverse events of special interest (AESIs):

- Grade ≥2 acute infusion reactions (IRs).
- Grade ≥3 immune-related TEAEs.
- Any grade of treatment emergent immune-related AEs (irAE) in a patient previously treated with a Pi3K inhibitor.
- DLTs (for Phase 1 part only).
- Symptomatic overdose with IMP/NIMP.
- Pregnancy occurring in a female patient or in a female partner of a male patient.

Infusion reactions

Infusion reactions typically occur within 24 hours from the start of each cemiplimab/isatuximab infusion. As described above, Grade ≥2 IRs are AESIs.

Whenever possible, a diagnosis of the IR (eg, Cytokine release syndrome, infusion related reaction, anaphylactic reaction, or any other teams chosen by the investigator) will be reported by the investigator on a specific AE page instead of individual symptoms. Each IR diagnosis will be reported as related to isatuximab, cemiplimab or NIMP (eg, premedication). In addition, symptoms of the IRs will be reported on a separate eCRF form.

The primary analysis of IR will include all events regardless of the relationship to isatuximab, cemiplimab or NIMP.

One type of IR analysis will be performed based on the investigator's reporting of IR (diagnosis or symptoms).

Another type of IR analysis will include TEAEs (one table including related TEAEs, one table including all TEAEs regardless of relationship) occurring within 24 hours from the start of each infusion of isatuximab and/or cemiplimab (ie, TEAEs with onset on the same calendar day of the cemiplimab/isatuximab infusion or on the following day).

A similar type of analysis including TEAEs occurring within 24 hours from the start of each infusion and within the within 24 hours in the "Hypersensitivity and CRS" CMQ will also be performed.

Moreover, all the TEAEs (not only limited to those occurring within 24h of each infusion) from the above listed CMQ will also be analyzed.

If relevant (see Section 2.4.5.2), additional analyses of IR will be performed separately for IRs related to isatuximab or to cemiplimab.

IRs related to NIMP (if any) will be reported in a listing.

Immune-related AEs

Immune-related AEs are typically associated with immune checkpoint inhibitors (2). The symptoms of irAEs may be subtle (Amended Protocol Version 3.0, Section 6.5.4) and may include, but not limited to, colitis, endocrine AE, pneumonitis, renal AE, dermatologic AE, hepatitis, ophthalmologic AE (Uveitis), nausea and vomiting. Because irAEs could occur long after exposure with immune checkpoint inhibitors, the irAE analysis will not be limited to the on-treatment period, but also include the extended safety follow up period.

Different types of irAE analysis will be performed.

- Grade ≥3 irAEs reported as AESIs: include all AESIs and exclude IRs, pregnancy, symptomatic overdose and DLT (if any).
- TEAEs plus extended safety follow-up AEs (related to cemiplimab; regardless of relationship).
- TEAEs plus extended safety follow-up AEs from sponsor selected grouping of PTs (related to cemiplimab; regardless of relationship).

Respiratory AEs

Analysis of 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'.

In addition, respiratory adverse events with late onset (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 adverse events will focus particularly on SMQ "Cardiac failure" (narrow).

Neutropenia and neutropenic complications

Neutropenia, febrile neutropenia and neutropenic infections will be analyzed using the following data source:

- Neutropenia based on laboratory results.
- 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 condition 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)'.
- Moreover, severe thrombocytopenia (ie, ≥Grade 4) with concomitant hemorrhage will be displayed if relevant. The first hemorrhages event occurring within 8 days after any occurrence of the thrombocytopenia (Lab) will be used for this analysis.

Hemolytic disorders

Hemolytic disorders will be selected using the TEAEs from the CMQ 'Haemolytic disorders Broad'.

Tumor lysis syndrome

Tumor lysis syndrome will be identified using CMQ 'Tumour lysis syndrome'.

Second primary malignancies

Second primary malignancies will be selected using CMQ 'Second primary malignancies'

2.1.4.2 Deaths

The deaths observation periods are per the observation periods defined in Section 2.1.4.

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

2.1.4.3 Laboratory safety variables

Clinical laboratory data consists of blood and urine analysis, including hematology, biochemistry, and urinalysis. Clinical laboratory values will be converted into standard international units and these international units will be used in all listings and tables.

The laboratory parameters will be classified as follows:

- Hematology
  - **Red blood cells, platelets, and white blood cells:** hemoglobin, hematocrit, red blood cell count, white blood cell with differential, and platelet count,
  - **Coagulation**: prothrombin time (expressed as international normalized ratio [INR]), activated partial thromboplastin time (aPTT).
- Biochemistry
  - **Metabolism:** fasting glucose, total protein, albumin**,**
  - **Electrolytes:** sodium, potassium, chloride, bicarbonate/carbon dioxide, calcium, corrected calcium (formula included in Section 2.5.1), magnesium, phosphate,

- **Renal function:** uric acid, creatinine, creatinine clearance (eGFR), urea or blood urea nitrogen (BUN),
- **Liver parameters:** aspartate aminotransferase (AST), alanine aminotransferase (ALT), bilirubin (total and direct), alkaline phosphatase, LDH,
- **Hormonal:** thyroid stimulating hormore (TSH), and free T4.

- Urinalysis
  - Qualitative analyses (dipstick),
  - Quantitative analyses: sodium, potassium, calcium, chloride, red blood cell, leukocytes, protein, glucose, ketone, pH, bilirubin, nitrate, and specific gravity.

Technical formulas are described in Section 2.5.1.

2.1.4.4 Vital signs variables

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

2.1.4.5 R code for conditional power and stopping boundary calculation Electrocardiogram variables

Twelve-lead ECG will be performed at screening and as clinically indicated.

2.1.4.6 Other safety endpoints

Other safety endpoints include:

- Chest X-ray at screening and as clinically indicated.
- Cytokines (TNF-α, IL-1-β, IL-6, IFN-γ), markers of complement (C3a, C4, CH50), serum tryptase.
- Indirect antiglobuline test (IAT).

2.1.5 Immunogenicity variables

Anti-drug antibodies (ADA) against isatuximab and cemiplimab were collected according to the PK/PD flowcharts of the protocol.

Observation period

The observation period will be defined for isatuximab and cemiplimab separately, which are divided into 2 periods: ADA pre-treatment and ADA on-study observation.

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

ADA attributes

Pre-existing ADA is defined as ADA that are present in samples drawn during the pre-treatment period.

Treatment boosted ADA is defined defined as pre-existing ADA with a significant increase in the ADA titer during the study compared to the baseline titer. A low serial dilution schema (2-fold or 3-fold) should be applied during titration. A difference in titer values of two titer steps between treatment or follow-up sample and its baseline sample is considered significant. For examples, at least a 4-fold increase in titers for 2-fold serial dilution schema (or 9-fold increase in titers for 3-fold serial dilution schema). If no titer could be determined for a positive sample, the titer will be reported as the minimal required dilution of the assay.

Treatment-induced ADA is defined as defined as ADA that developed at any time during the ADA on-study observation period in patients without pre-existing ADA (including patients without pretreatment samples). If the baseline ADA sample is missing or non-reportable and at least one reportable ADA sample is available during the treatment (including follow-up period) the baseline sample will be considered as "negative" for data analysis. This is considered being a conservative approach for ADA assessment.

Subject status

Among evaluable population for immunogenicity (described in Section 2.3.5), following patient status will be defined:

- ADA-positive subject: A subject with at least one treatment induced or treatment boosted ADA-positive sample at any time following the first study treatment administration.
- ADA-negative subject: Subject without any treatment induced or treatment boosted ADA-positive sample during the on-study observation period.
- ADA-inconclusive subject: A subject who cannot irrefutably be classified as ADA-negative (eg, all post baseline samples inconclusive).

Overview of the ADA response

Two main categories can be reported for the epidemiology of an ADA immune response: ADA prevalence and ADA incidence:

- ADA prevalence is defined as the proportion of all patients tested positive for ADAs (including preexisting antibodies, treatment boosted ADAs and treatment induced ADAs) at any point.
- ADA incidence is defined as the proportion of subjects found to either have seroconverted (treatment induced ADAs) or boosted their pre-existing ADA response during the on-study observation period. Only evaluable subjects (described in Section 2.3.5) are considered for computing ADA incidence.

Kinetics of the immune response

- **Onset of ADA:** refers to the time period between the initial drug administration and the first instance of treatment induced ADAs (in days). The "median time to ADA development" and the quartiles Q1 and Q3 will be reported.
- **Duration of ADA:** ADA duration will be calculated as the date of last treatment induced.
- ADA sample minus date of first treatment induced or treatment boosted ADA sample + 1.
- ADA duration will be calculated only for patients with at least two ADA positive samples. Median duration of an induced ADA response and the quartiles Q1 and Q3 should be reported.
- **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), OR
  - Treatment induced ADA detected at two or more sampling time points during the treatment (including follow-up period if any), where the first and last ADA-positive samples (irrespective of any negative samples in between) are separated by a period less than 16 weeks, and the patient'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 are separated by at least 16 weeks (irrespective of any negative samples in between).
- Indeterminate ADA is defined by:
  - Treatment induced ADA detected only at the last sampling time point, OR
  - The last two samples being ADA-positive and separated by a period of less than 16 weeks.

Treatment-boosted ADAs are excluded from the analysis of ADA kinetics.

2.1.6 Pharmacokinetic variables

The PK sampling times for isatuximab and cemiplimab were provided in the PK/PD flowcharts of the protocol.

The following PK parameters (listed in Table 5) will be calculated with pharmacokinetic data management system (PKDMS) software (Pharsight) V3.0; using non-compartmental analysis (NCA) from isatuximab and cemiplimab concentrations after the first administration on Cycle 1. The parameters will include, but may not be limited to the following:

Table 5 - List of pharmacokinetic parameters and definitions after the first administration

Parameters	Analyte		Definition
	Cemiplimab	Isatuximab	
C_{eoi}	•	•	Concentration observed at the end of intravenous (IV) infusion
C_{max}	•	•	Maximum concentration observed
t_{max}	•	•	Time to reach C_{max}
C_{last}	•	•	Last concentration observed above the lower limit of quantitation
t_{last}	•	•	Time of C_{last}
AUC_{0-14d} or AUC_{0-28d}	•		Area under the concentration versus time curve calculated using the trapezoidal method over the dosing interval (DL1=14 days and DL-1=28 days)
AUC_{0-7d}		•	Area under the plasma concentration versus time curve calculated using the trapezoidal method over the dosing interval (7 days)

C_{trough} are defined as sample collected just before treatment administration during repeated dosing.

In addition, Populations PK approaches may be used for both compounds and PK estimates may be used to conduct exploratory exposure-response analyses for safety and efficacy and PK/PD analyses for relevant biomarkers. If done, the data generated will be reported in stand-alone report(s).

2.1.7 Biomarker endpoints

2.1.7.1 Immune Genetic Determinants

Germline genetic data of Fc gamma receptor (FCGR), human leukocyte antigen (HLA) and killer-cell immunoglobulin-like receptor (KIR) genes will be analyzed on blood samples collected on Day 1 of Cycle 1:

- FCGR polymorphisms (FCGR2A and FCGR3A): For each gene, the results will be of the form AA, Aa or aa with A and a-alleles, the major and minor allele, respectively.
- HLA genotypes: HLA-A, HLA-B and HLA-C have been typed for each gene. The results will be epitope genotypes (Table 6) and allele genotypes.

Table 6 - Epitopes of HLA Class I recognized by KIR

		Amino-acid at position[a]					
HLA class I	**Epitope**	**77**	**80**	**81**	**82**	**83**	
HLA-B	Bw6	Ser	Asn	Leu	Arg	Gly	
	Bw4	Asn	Thr	Ala	Leu	Arg	
	Bw4	Asn	Ile	Ala	Leu	Arg	
	Bw4	Asp	Thr	Leu	Leu	Arg	
	Bw4	Ser	Thr	Leu	Leu	Arg	
	Bw4	Ser	Thr	Ala	Leu	Arg	
HLA class I	Epitope	77	80	81	82	83	Associated allotypes
HLA-A	Aw4	Asn	Ile	Ala	Leu	Arg	A*23; A*24
	Aw4	Ser	Ile	Ala	Leu	Arg	A*32
	A3		Key residues not yet published				A*03
	A11		Key residues not yet published				A*11
HLA class I	Epitope	77	80				
HLA-C	C1	Ser	Asn				
	C2	Asn	Lys				

a Numbering from the first codon of the mature protein

- KIR genotypes: The presence or absence of 16 KIR genes will be screened. A KIR gene will be defined as present if at least one assay gives positive results; otherwise it will be defined as negative.

2.1.7.2 Immune phenotyping

Immune phenotyping in bone marrow (baseline, D1 of Cycle 3) and/or peripheral blood (baseline, D1 of Cycle 3 and EOT) will be assessed. The blast cells and immune cell populations include MDSC cell, B-cell, T-cell and NK-cell subsets and regulatory T cells (Treg)/CD8 effector ratio will be determined by multiparametric flow cytometry based on the expression of different cell surface markers.

2.1.7.3 Adaptive immune response

Adaptive immune response (TCR repertoire profiling) will be assessed in blood and bone marrow samples, which are collected at screening, D1 of Cycle 3 (blood only) and at CR.

Adaptive immune response (humoral and cellular immune responses to myeloma-related tumor antigens) will be assessed in blood prior to pre-medication and IMP administration on D1 of Cycle 1, Cycle 2, Cycle 4, Cycle 7 and Cycle 10 and in disease progression patients at EOT. Humoral response will be assessed in all sites. Cellular response will be assessed in patients at selected sites.

2.1.7.4 PD1-PDL1 expression

PD1-PDL1 expression will be assessed using archival bone marrow biopsy.

2.1.7.5 Blood typing interference test

Blood typing interference test will be done on blood sample.

2.1.8 Health related quality-of-life (HRQL) endpoints

Not applicable following Protocol Amendment 3.

2.1.9 Health economic endpoints

Not applicable.

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

Further therapies after discontinuation of study treatment will be collected on a specific eCRF page. The following information will be collected: relapse/progression date, best response, drug/medication (brand or generic name), start date and end date (if available)/ongoing (otherwise).

2.2 DISPOSITION OF PATIENTS

This section describes patient disposition for both patient study status and the patient analysis populations. Disposition will be described separately for Phase 1 and Phase 2 patients, based on the analysis population defined in Section 2.3.

Screened patients are defined as any patients who signed the informed consent. Randomized patients and all treated/safety patients are defined in Section 2.3.

For patient study status, patients in each of the following categories will be provided in a summary table or a flowchart diagram:

- Screened patients.
- Screen failure patients and reasons for screen failure (if any).
- Randomized patients (Phase 2 only).
- Randomized but not treated patients (Phase 2 only).
- Randomized and treated patients (Phase 2)/treated (Phase 1).
- Patients who discontinued study treatment.
- Patients still on treatment.
- Status at last study contact.

A summary of the reasons for definitive and premature treatment discontinuation for any compound by arm will be provided. Definitive treatment discontinuation is defined as the discontinuation of all the study drugs. Premature treatment discontinuation (only for the combination arms) is defined as the discontinuation of at least one of the study drugs but at least one is continued. Listing of the reasons for treatment discontinuation at time of the analysis will be provided.

Patients in each country and center will be summarized using the randomized population.

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 arm.

Additionally, the following analysis populations will be summarized:

- ITT/randomized population.
- Safety population.
- Pharmacokinetics population.
- ADA evaluable population.

Definition of study populations are provided in Section 2.3.

2.2.1 Randomization and drug dispensing irregularities

For the Phase 2, randomization and drug-dispensing irregularities occur whenever:

- A randomization is not in accordance with the protocol-defined randomization method, such as a) an ineligible patient is randomized, b) a patient is randomized twice. OR,
- A patient is dispensed an IMP not allocated by the protocol-defined randomization, such as a) a patient at any time in the study is dispensed a different treatment IMP than as randomized (which may or may not contain the correct-as-randomized IMP), or b) a non-randomized patient is treated with IMP reserved for randomized patients.

All randomization and drug-dispensing irregularities will be documented in the clinical study report. The irregularities will be categorized and summarized among randomized patients (number and percentages). Non randomized and treated patients in Phase 2 (if any) will be described separately.

Randomization and drug-dispensing irregularities to be prospectively identified include but are not limited to:

- Study treatment administration without IRT transaction.
- Patient randomized twice.
- Treatment taken or schedule different from randomized treatment/schedule.

2.3 ANALYSIS POPULATIONS

Unless otherwise specified, analysis population will be defined separately for Phase 1 and Phase 2 patients.

2.3.1 Intent to treat (ITT)/Randomized population (Phase 2 only)

The intent to treat/randomized population includes all patients from Phase 2 who gave their informed consent and were assigned a randomization number by the IRT, regardless of whether the patient was treated or not. In this population, patients will be analyzed according to the arm allocated by IRT, regardless of whether patients received any study drug or receive a different study drug from which they were randomized.

For any patient randomized more than once, only the data associated with the first randomization will be used for analysis.

This population is the primary population for all efficacy analyses.

2.3.2 All treated (AT)/safety population

The all treated/safety population is defined by phases.

For Phase 1, the all treated/safety population is defined as all screened patients who received at least one dose or a part of a dose of the study treatments (isatuximab or cemiplimab), regardless of the amount of treatment administered.

For Phase 2, the all treated/safety population is defined as all randomized patients who received at least one dose or a part of a dose of the study treatments (isatuximab or cemiplimab), regardless of the amount of treatment administered.

- Patients who receive at least 1 cemiplimab dose (even incomplete) during the trial will be analyzed in the combination arms:
  - Patient who receive at least 1 cemiplimab dose at Day 15 of any cycle will be analyzed in Q2W arm. Patient without any cemiplimab dose at Day 15 of any cycle will be analyzed in Q4W arm.
- Patients who receive isatuximab only throughout the trial will be analyzed in isatuximab control arm.

Randomized patients from whom it is unclear whether they took the IMP will be included in the safety population, and included in the treatment arms as randomized.

Non-randomized but treated patients will not be part of the safety population; however, their safety data will be presented separately.

This population is the primary population for the analysis of all exposure and safety parameters (except for DLT evaluation). Phase 1 and Phase 2 patients will be analyzed separately.

2.3.3 Patients evaluable for DLT assessment (Phase 1 only)

The DLT evaluable population is defined as patients in the Phase 1 part receiving the planned doses of isatuximab and cemiplimab during Cycle 1, and who completed the DLT observation period of Cycle 1 after the first IMP administration, unless they discontinue the study treatment(s) due to DLT. Dose-limiting toxicity will be validated by the Study Committee. Patients not evaluable for DLT will be replaced.

2.3.4 Pharmacokinetic population

The PK population will be defined independently for isatuximab and cemiplimab, and includes patients from the all treated population with at least one reportable concentration after the study drug administration (whatever the cycle and even if dosing is incomplete).

2.3.5 ADA evaluable population

The ADA evaluable population will be defined independently for isatuximab and cemiplimab, and includes subjects with at least one sample, taken post-baseline after drug administration during the treatment or follow-up observation period, that is appropriate for ADA testing with a reportable result (positive, negative or inconclusive).

2.3.6 Biomarker population

There will be no population flag for biomarker. Biomarker endpoints will be analyzed using patients from the all treated population who have one assessment on the biomarker of interest unless otherwise specified.

2.4 STATISTICAL METHODS

Unless otherwise specified, analyses will be descriptive and performed separately for Phase 1 and Phase 2 patients, based on the analysis population defined in Section 2.3.

For Phase 1 part, when the number of treated patient is small (<5), baseline information together with listings on response and adverse events will be provided. Summary tables might be presented if deemed appropriate.

In Phase 2 summary tables (except for demographics and baseline characterastics), treatment arms will be presented as follows:

- Isatuximab 10 mg/kg QW/Q2W (Isa).
- Isatuximab 10 mg/kg QW/Q2W + cemiplimab 250 mg Q2W (Isa + CemQ2W).
- Isatuximab 10 mg/kg QW/Q2W + cemiplimab 250 mg Q4W (Isa + CemQ4W).

Parameters on demographics and baseline characterastics would be provided by treatment arms and overall.

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

2.4.1 Demographics and baseline characteristics

Parameters described in Section 2.1.1 will be summarized using descriptive statistics on the AT/safety population in Phase 1 or ITT/randomized population in Phase 2. For Phase 2, analyses for the AT/safety population will be included in the appendices if the size of the randomized population is different (>10%) from the size of the all treated/safety population for any arm.

Past medical or surgical history will be summarized by primary SOC and PT (SOC will be sorted according to the internationally agreed order and PT by decreasing frequency) for randomized population in Phase 2.

2.4.2 Prior or concomitant medications (other than anticancer therapies)

The prior and concomitant medications will be presented for the AT/safety population in Phase 1 and the randomized population in Phase 2.

Medications will be summarized by arm and overall according to the WHO-DD dictionary, considering the first digit of the anatomic category class (ATC) (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 tables for prior, concomitant and post treatment medications will be sorted by decreasing frequency of ATC followed by all other therapeutic classes based on the incidence in the Isa + CemQ2W column. In case of equal frequency regarding ATCs (anatomic or therapeutic categories), alphabetical order will be used.

IR medications

Number (%) of patients with IR medications (including prophylaxis and curative intent) as defined in Section 2.1.2 will be provided. Number (%) of patients with prophylactic IR medications including acetaminophen, diphenhydramine (or equivalent) and steroids will be provided by infusions. A similar summary will be provided for IR medications of curative intent.

2.4.3 Extent of investigational medicinal product exposure and compliance

The extent of study treatment exposure will be assessed and summarized on the AT/safety populations.

2.4.3.1 Overall exposure

The dose information will be assessed by the following variables to summarize the overall study treatment exposure (all study treatments together):

- Number of cycles started, defined by maximum of isatuximab/cemiplimab cycles started.
- Duration of overall exposure (or time on-treatment) (in weeks) is defined as (last day of last cycle - first day of first cycle)/7. The first day of first cycle is defined by the earliest of isatuximab and cemiplimab administration date. The last day of last cycle is defined by the last date among the following:
  - Date of last dose of isatuximab + 7 days if last cycle is QW cycle, or date of last dose of isatuximab + 14 days if last cycle is Q2W cycle,
  - Date of last dose of cemiplimab + 14 days if last cycle is Q2W cycle or date of last dose of cemiplimab + 28 days if last cycle is Q4W cycle (if applicable).

Total number of cycles started, number of cycles started by patients as a quantitative variable and by category (ie, number (%) of patients receiving at least 1 cycle, at least 2 cycles etc), duration of overall exposure will be summarized by descriptive statistics.

Cycle delay is defined as follows:

- A cycle is deemed as delayed if the start date of the current cycle - 28 - start date of the previous cycle is >3 days. Cycle delay is not defined for the first cycle.

Cycle delayed will be analyzed at the patient and cycle levels, as follows:

- Patient level:
  - Number of patients treated (used for % calculation in this section),
  - Number (%) of patients with a least 1 cycle delayed:
    - Number (%) of patients with a cycle delayed between 4 and 7 days (using maximum delay),
    - Number (%) of patients with a cycle delayed >7 days (using maximum delay).
- Cycle level:
  - Number of cycles (used for % calculation in this section),
  - Number (%) of cycles delayed:
    - Number (%) of cycles delayed between 4 and 7 days,
    - Number (%) of cycles delayed >7 days.

2.4.3.2 Isatuximab exposure

The isatuximab dose information will be assessed by the following:

- Total number of cycles started.
- Number of cycles started by patient.

- Duration of isatuximab exposure (or time on-treatment) (in weeks) is defined depending on the isatuximab administration schedule as follows:
  - If drug is discontinued at a cycle with QW isatuximab administration: [date of last dose of isatuximab + 7 days - date of first dose of isatuximab]/7,
  - If drug is discontinued at a cycle with Q2W isatuximab administration: [date of last dose of isatuximab + 14 days - date of first dose of isatuximab]/7.
- Actual dose (mg/kg): for a given cycle and day of administration, the actual dose in mg/kg corresponds to the actual dose in mg administered at each time point divided by the actual body weight as measured at each time point (cycle and day).
- Cumulative dose (mg/kg): the cumulative dose is the sum of all actual doses of isatuximab, expressed in mg/kg, given from first to last administration.
- Actual dose intensity (ADI) in mg/kg/week: defined as the cumulative dose (in mg/kg) divided by the duration of isatuximab exposure (in weeks).
- Relative dose intensity (RDI) in %:

$$100 \times \frac{\text{ADI (mg/kg/week)}}{\text{Planned Dose Intensity (mg/kg/week)}}$$

Planned dose intensities in mg/kg/week corresponds to the planned dose (10 mg/kg) multiplied by the theoretical total number of doses during the started cycles (count 2 for Q2W cycles, 4 for QW cycles), and divided by the theoretical cycle duration expressed in weeks (ie, 4 weeks per cycle started).

The total number of cycles started, number of cycles started by patients as a quantitative variable and by category (ie, number [%] of patients receiving at least 1 cycle, at least 2 cycles, etc), duration of isatuximab exposure, cumulative dose, ADI and RDI will be summarized by descriptive statistics.

The following variables will be derived to describe dose delays/modifications:

- Dose delay (within a cycle): A dose is deemed as delayed if the actual start date of the infusion - theoretical start date of an infusion is >1 day for weekly administration, is >2 days for Q2W administration. Dose delay does not apply to the first infusion of each cycle.
- Infusion interruption: An infusion will be considered to be interrupted (as collected on CRF) if the isatuximab administration is stopped during an infusion before it is completed regardless of whether it is further restarted or not.
- Dose omission: a dose is considered omitted if the dose is not administered for the scheduled visit and there are positive dose(s) afterwards.

Dose delayed/modification will be analyzed at the patient, cycle and the total number of isatuximab administration levels as follows:

- Patient level (number of all treated patients will be used for % calculation):
  - Number (%) of patients with at least 1 dose delay,
  - Number (%) of patients with at least 1 dose omission,
  - Number (%) of patients with a least 1 infusion interrupted:
    - Number (%) of patients with a least 1 infusion interrupted and re-started,
    - Number (%) of patients with a least 1 infusion interrupted and not re-started,
  - Number (%) of patients with at least 2 infusions interrupted.
- Infusion level
  - Total number of infusions (used for % calculation for this section),
  - Number (%) of infusions interrupted:
    - Number (%) of infusions interrupted and re-started,
    - Number (%) of infusions interrupted and not re-started,
  - Number (%) of infusions interrupted more than once,
  - Number of infusion interrupted at (with % calculated using the total number of infusions interrupted): 1st infusion, 2nd infusion, subsequent infusions,
  - Time from infusion start to first interruption in minutes (quantitative and qualitative: 5-10, 11-30, 31-60, 61-90, 91-120, >120).

Duration of isatuximab infusion (in hours) is defined as the time from the start (date/time) of isatuximab infusion to the end (date/time) of isatuximab infusion in the same visit. It will be summarized for first and subsequent infusions.

2.4.3.3 Cemiplimab exposure

The cemiplimab dose information will be assessed by the following:

- Total number of cycles started.
- Number of cycles started by patient.
- Duration of cemiplimab exposure (or time on-treatment) (in weeks) is defined depending on the cemiplimab administration schedule as follows:
  - Q2W cemiplimab administration: [date of last dose of cemiplimab + 14 days - date of first dose of cemiplimab]/7,
  - Q4W cemiplimab administration: [date of last dose of cemiplimab + 28 days - date of first dose of cemiplimab]/7.
- Actual dose (mg): for a given cycle and day of administration.
- Cumulative dose (mg): the cumulative dose is the sum of all actual cemiplimab doses.

- ADI in mg/week: defined as the cumulative dose (in mg) divided by the duration of cemiplimab exposure (in weeks).
- RDI in %:

$$100 \times \frac{\text{ADI (mg/week)}}{\text{Planned Dose Intensity (mg/week)}}$$

Planned dose intensities in mg/week is 125 mg/week for Q2W schedule, and 62.5 mg/week for Q4W schedule.

The total number of cycles started, number of cycles started by patients as a quantitative variable and by category (ie, number [%] of patients receiving at least 1 cycle, at least 2 cycles, etc), duration of cemiplimab exposure, cumulative dose, ADI and RDI will be summarized by descriptive statistics.

The following variables will be derived to describe dose delays/modifications:

- Dose delay (within a cycle, only applicable to Q2W schedule): A dose is deemed as delayed if the actual start date of the infusion – theoretical start date of an infusion is >2 days for Q2W administration. Dose delay does not apply to the first infusion of each cycle.
- Infusion interruption: An infusion will be considered to be interrupted (as collected on CRF) if the cemiplimab administration is stopped during an infusion before it is completed regardless of whether it is further restarted or not.
- Dose omission: a dose is considered omitted if the dose is not administered for the scheduled visit and there are positive dose(s) afterwards.

Dose delayed/modification will be analyzed at the patient, cycle and the total number of cemiplimab administration levels as follows:

- Patient level (number of all treated patients will be used for % calculation):
  - Number (%) of patients with at least 1 dose delay,
  - Number (%) of patients with at least 1 dose omission,
  - Number (%) of patients with a least 1 infusion interrupted:
    - Number (%) of patients with a least 1 infusion interrupted and re-started,
    - Number (%) of patients with a least 1 infusion interrupted and not re-started,
  - Number (%) of patients with at least 2 infusions interrupted.
- Infusion level
  - Total number of infusions (used for % calculation for this section),
  - Number (%) of infusions interrupted:
    - Number (%) of infusions interrupted and re-started,
    - Number (%) of infusions interrupted and not re-started,

- Number (%) of infusions interrupted more than once,
- Number of infusion interrupted at (with % calculated using the total number of infusions interrupted): 1st infusion, 2nd infusion, subsequent infusions,
- Time from infusion start to first interruption in minutes (quantitative and qualitative: 5-10, 11-30, 31- 60, 61-90, 91-120, >120).

Duration of cemiplimab infusion (in hours) is defined as the time from the start (date/time) of cemiplimab infusion to the end (date/time) of cemiplimab infusion in the same visit. It will be summarized for first and subsequent infusions.

2.4.4 Analyses of efficacy endpoints

All analyses described in this section are applicable to the Phase 2 part of the study only. For Phase 1, a listing of response data including duration of response on the all treated population will be provided instead of summary table.

In Phase 2, all primary, secondary and exploratory analyses will be performed using the randomized population in Phase 2.

The cutoff date for the primary analysis of ORR will be 6 months after the date of the first dose of the last patient. In this analysis, hypothesis test(s) will be performed (Section 2.4.4.1).

Final analysis cutoff date for OS analysis and updated analysis of ORR and other secondary endpoints will be approximately 12 months after the date of the first dose of the last patient.

An interim analysis of response rate (including confirmed and unconfirmed responses) will be conducted when the first 15 randomized patients in each arm have completed 2 cycles of treatment or definitively discontinued the treatment. A combination arm will be stopped early for futility (Section 3).

2.4.4.1 Analysis of primary efficacy endpoint(s)

The ORR will be summarized by treatment arms with descriptive statistics. A 95% two-sided confidence interval(s) will be computed using Clopper-Pearson. BOR will also be summarized descriptively.

The Fisher's exact test will be performed to compare the ORR in control arm vs each of the combination arm, using a 1-sided significance level of 0.10 with Hochberg adjustment (at time of primary analysis of ORR; ie, cutoff date 6 months after last patient first dose). If the maximum p-value (of two p-values) is less than 0.1, the null hypothesis for both combination arms will be rejected; else if minimal p-value is less than 0.05, the null hypothesis will be rejected for this corresponding arm only. If only one combination arm is continued after the interim analysis in addition to the control arm, then ORR will be tested using an 1-sided significant level of 0.05.

ORR and BOR will also be summarized descriptively for subgroups variable defined in Table 4.

2.4.4.2 Analyses of secondary efficacy endpoints

No hypothesis testing will be performed on secondary efficacy endpoints. The following analyses will be performed:

- CBR: will be summarized with descriptive statistics.
- VGPR or above rate: will be summarized with descriptive statistics.
- DOR: Kaplan-Meier estimates of the 25th, 50th and 75th percentiles including the 95% confidence interval as well as Kaplan-Meier curves will be provided for patients who achieve a response ≥PR. DOR will be also summarized with statistics in the subset of patients with BO ≥PR.
- PFS and OS: PFS and OS will be analyzed using the Kaplan-Meier method. The Kaplan-Meier estimates of the 25th, 50th and 75th percentiles and their associated 95% confidence interval will be computed. The Kaplan-Meier curves will be plotted.
- DFU and TTR will be summarized with descriptive statistics. Best percent change in paraprotein will be displayed in a waterfall plot. In the waterfall plot, patients with BOR of ≥PR will have negative percentage change. The patients will be ordered from highest positive change to smallest negative change. Percent change >100% will be displayed as 100% increases. A swimmer plot of time on treatment (ie, duration of exposure) will also be provided. The patients will be ordered by BOR and duration of exposure. Patients with the best BOR and longest duration will be presented at the top of the plot.

A listing of response data will be provided for the randomized population and second listing will be provided for patients who are ADA positive (Section 2.1.6), and will include the following variables: high risk status, number of prior lines of anti-myeloma treatment, selected prior treatments given (alkylating agent, IMid, PI, mAb), duration of exposure (weeks), reason for treatment discontinuation, measurable paraprotein at baseline, best percent change in paraprotein, best overall response, date of first response ≥PR, date of first disease progression/last disease assessment, indication of progressive disease, time to first response and DOR.

A listing of best percent change in % plasma cell in bone marrow biopsy will be provided and will include the following variables: measurable paraprotein at baseline, best percent change in paraprotein, BOR, baseline plasma cells count; post baseline plasma cells count and best percent change in plasma cells count.

Number (%) of patients with MRD negative will be provided. This may be replaced by a listing if the number of MRD negative patient is small (≤5).

Subgroup analyses for secondary endpoints may be performed if relevant.

2.4.4.3 Multiplicity issues

For the primary efficacy analysis in Phase 2, one hypothesis is to be tested on each of the 2 dose arms. To control overall type I error, Hochberg procedure will be used. The procedure is described in Section 2.4.4.1. An interim analysis is included to stop a dose arm for futility only, thus the type I error rate is not inflated.

2.4.5 Analyses of safety data

All safety analyses will be performed on the AT/safety population as defined in Section 2.3.2.

2.4.5.1 Dose-limiting toxicities (Phase 1 only)

The DLTs will be listed by patient on the patients evaluable for DLT population for Phase 1.

2.4.5.2 Analyses of adverse events

The primary focus of adverse event analysis will be on treatment-emergent adverse events. Pre-treatment and post-treatment AEs will be described separately.

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

For patients with multiple occurrences of the same AE within the observation period (pre-treatment, on-treatment and post-treatment), the maximum severity grade will be used. Summaries will be provided for all grades and for Grade ≥3 (including Grade 5). Missing grade handling is provided in Section 2.5.3.

The following adverse events analyses will be performed. The presentation strategy (eg, by all grades and Grade ≥3 and by PT etc) are included in Table 7.

- Overview of TEAEs.
- TEAEs (regardless relationship to study treatment).
- Drug related TEAEs.
- Deaths (Section 2.4.5.3).
- SAEs.
- Adverse events leading to withdrawal.
  - Analysis of all treatment-emergent adverse event(s) leading to definitive treatment discontinuation. Analysis of all treatment-emergent adverse event(s) leading to premature isatuximab discontinuation. Analysis of all treatment-emergent adverse event(s) leading to premature cemiplimab discontinuation. If the number of patients who discontinued treatment due to a TEAE is ≤5, no summary table will be provided. Instead, listing(s) will be provided.
- TEAE leading to dose modification
  - Separate analysis for each type of modification: dose reduction of any drug, dose interruption of any drug, dose delay of any drug.

- Other significant adverse events
  - IR and IR symptoms (details are included below),
  - Immune related AEs (details are included below),
  - Respiratory AEs(details are included below),
  - Hematological adverse events(details are included below; not included in Table 7),
  - Second primary malignancies,
  - Other AESIs:
    Pregnancy and symptomatic overdose. Data will be listed if ≤5 patients,
  - Pre- and Post-treatment AE/SAEs.

Sorting within tables will ensure the same presentation for the set of all AEs within the observation period (pre-treatment, on-treatment, and post-treatment). For that purpose, the table of all TEAEs presented by SOC and PT sorted by the internationally agreed SOC order and decreasing frequency of PTs within SOCs will define the presentation order for all other tables unless otherwise specified. Sorting will be based on the incidence of AEs of the isatuximab QW/Q2W plus cemiplimab Q2W arm.

Overview of TEAEs

An overview of TEAEs including the number (%) of patients with the following treatment emergent events will be provided:

- TEAE.
- TEAE of Grade ≥3.
- TEAE of Grade 3-4.
- TEAE of Grade 5 (any TEAE with fatal outcome during the on-treatment period).
- Treatment emergent SAE.
- TEAE leading to definitive study treatment discontinuation, ie, discontinuation of isatuximab in control arm, and discontinuation of isatuximab and cemiplimab in combination arms.
- TEAE leading to premature discontinuation (only applicable to combination arms)
  - TEAE leading to premature isatuximab discontinuation, ie, discontinuation of isatuximab before cemiplimab,
  - TEAE leading to premature cemiplimab discontinuation, ie, discontinuation of cemiplimab before isatuximab.
- AESI
  - IR of Grade ≥2.
- Treatment-related TEAE (related to either isatuximab or cemiplimab).
- Treatment-related TEAE of Grade ≥3.
- Serious treatment-related TEAE.

Other significant adverse events

Infusion reactions

IR analyses will be done by including all the adverse events regardless of relationship to isatuximab, cemiplimab or NIMP. Unless otherwise described, the presentation strategy is described in Table 7.

- Number (%) of patients experiencing IRs (as a diagnosis, no symptoms) according to investigator reported AEs presented by primary SOC and PT (both sorted by decreasing order of frequency) will be summarized by grades (all grades and Grade ≥3).
- Description of the IR diagnoses (using the diagnosis reported and excluding symptoms)
  - Worst grade,
  - Action taken with isatuximab and cemiplimab,
  - Number (%) of patients with only 1, ≥1, ≥2, ≥3, ≥4 and ≥5 episodes,
  - Number (%) of patients with first occurrence of IR at the first infusion and subsequent infusions,
  - Number (%) of patients with IR at the first and subsequent infusions,
  - Number (%) of patients with at least two episodes of IRs at the same infusion,
  - Day of onset from infusion,
  - Duration (in days).
- Number of patients with symptoms of IRs (as reported by investigator).
- Number (%) of patients experiencing TEAEs (related and regardless of causal relationship) within 24 hours from the start of each infusion.
- Similar tables including all TEAEs within 24 hours from the start of each infusion from the selected list of CMQ (see Section 2.1.4.1).
- Number (%) of patients experiencing TEAEs (related and regardless of causality), (not only limited to those occurring within 24h of each infusion) from the selected list of CMQ (see Section 2.1.4.1).

If the IR rate is much higher (≥20%) in combination arms than in the control arm, additional analyses of IR might be performed separately for isatuximab and cemiplimab.

A listing of IRs that are related to NIMP will be provided.

Immune related AEs:

Because irAEs could occur long after exposure with immune checkpoint inhibitors, the irAE analysis will include both on-treatment period and extended safety follow up period. As noted in Table 7, the analysis will include:

- Number (%) of patients experiencing irAEs reported as AESI by investigator: include all AESI and exclude IRs, pregnancy, symptomatic overdose and DLT (if any).
- Number (%) of patients experiencing AEs from selected grouping of PTs occurring during the treatment emergent and extended safety follow up periods (one analysis for events related to cemiplimab; another analysis for regardless of relationship).
- Number (%) of patients experiencing AEs occurring during the treatment emergent and extended safety follow up periods (one analysis for events related to cemiplimab; another analysis for events regardless of relationship).

Respiratory TEAEs:

Respiratory TEAEs will be analyzed using selection defined in Section 2.1.4.1 and will be presented by PT.

Cardiac TEAEs

Cardiac TEAEs will be analyzed using selection defined in Section 2.1.4.1 and will be presented by PT, sorted by decreasing incidence.

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.

Neutropenia and neutropenic complications

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

Thrombocytopenia and hemorrhages

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

- On-treatment thrombocytopenia (Lab) 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.

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, study day of diagnosis (from first dose of study treatment), interval to onset from the last study treatment before the diagnosis (last drug administered), duration of AE, the cycle of occurrence, severity, seriousness, outcome, action taken on study treatment, study day of the blood transfusion, and results and sampling date of indirect anti-globulin test.

Overdose

A listing of patients who reported symptomatic overdose with study treatment during the study will be provided. This listing will include drug with overdose.

Pregnancy

Moreover, a listing of pregnancies (pregnancy as well as pregnancy of partner) will be provided.

Tumor lysis syndrome (TLS)

A listing of patients with TLS reported in eCRF AE forms (using a CMQ: Tumor lysis syndrome) during the study will be provided. The clinical chemistry parameters regarding hyperkalemia, hyperphosphatemia, hypocalcemia, and hyperuricemia might be listed to corroborate any report of TLS identified with the above CMQ.

Second primary malignancies

A listing of patients who reported second primary malignancies during the study will be provided (as per the CMQ).

This listing will include the diagnosis, type of second priamry malignancies, study day of the diagnosis (from the first dose), number of days from the last study treatment to the diagnosis, prior exposure to anti-myeloma treatments, and whether the patient received subsequent anti-cancer treatment.

Table 7 - Description of summary tables to be provided for the analysis of TEAEs

MedDRA variables	Sorting	Layout	Events
PT	• PT: Decreasing order of frequency of Isa + CemQ2W arm	**By treatment arms (and all patients if Phase 1):** n (%) of patients with any event and n (%) of patients with event of Grade ≥3	• TEAEs occurring in ≥5% of the patients (in any group for Phase 2) • Cardiac TEAEs • Respiratory TEAEs
SOC, HLGT, HLT, and PT	• Primary SOC: internationally agreed order • HLGT, HLT, PT: alphabetical order	**By treatment arms(and all patients if Phase 1):** n (%) of patients with any event and n (%) of patients with event of Grade ≥3	• All TEAEs • Serious TEAEs • Drug-related serious TEAEs • TEAEs leading to definitive treatment discontinuation
SOC and PT	• Primary SOC: internationally agreed order • PT: decreasing order of frequency of Isa + CemQ2W arm	**By treatment arms (and all patients if Phase 1):** n (%) of patients with any event and n (%) of patients with event of Grade ≥3	• All TEAEs • TEAEs occurring in ≥5% of the patients (in any group for Phase 2) • Drug-related TEAEs • Serious TEAEs • Drug related serious TEAEs • TEAEs leading to isatuximab discontinuation • TEAEs leading to cemiplimab discontinuation • TEAEs leading to dose interruption of isatuximab • TEAEs leading to dose interruption of cemiplimab • TEAEs leading to dose delay of isatuximab • TEAEs leading to dose delay of cemiplimab • TEAEs leading to dose reduction[a] of isatuximab • TEAEs leading to dose reduction[a] of cemiplimab • Pre-treatment AEs; Serious pre-treatment AEs • Post-treatment AEs; Serious post-treatment AEs

MedDRA variables	Sorting	Layout	Events
SOC and PT	• Primary SOC: internationally agreed order • PT: decreasing order of frequency of Isa + CemQ2W arm	**By treatment arms (and all patients if Phase 1):** n (%) of patients with any event and n (%) of patients with event of Grade ≥3	IR analysis: • IR diagnosis (as reported by investigator) • Symptoms of IR (as reported by investigator) • TEAEs (related; regardless of relationship) within 24 hours from the start of each infusion • TEAEs (related; regardless of relationship) from the selected CMQ within 24 hours from the start of each infusion • TEAEs (related; regardless of relationship) from the selected CMQ (not limited to those occurring within 24 hours from the start of each isatuximab infusion)
SOC and PT	• Primary SOC: internationally agreed order • PT: decreasing order of frequency of Isa + CemQ2W arm	**By treatment arms (and all patients if Phase 1):** n (%) of patients with any event and n (%) of patients with event of Grade ≥3	irAE analysis: • irAE reported as AESI by investigator • AEs as defined by irAE selected grouping of AEs occurring during the treatment emergent and extended safety follow up periods (related to cemiplimab; regardless of relationship) • AEs occurring during the treatment emergent and extended safety follow up periods (related to cemiplimab; regardless of relationship)

a Dose reduction is corresponding to action taken to any study treatment, as “Dose reduced”, “Dose delayed and reduced”.

AE=adverse event; AESI=adverse event of special interest; 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.

2.4.5.3 Deaths

Number (%) of patients who died by study period (on-treatment and post-treatment, within 60 days from first dose of study treatment), and cause of death will be summarized. A listing of patients who died while participating in the study including cause of death, death date, days from first and last dose to death, preferred term, and causal relationship to isatuximab/cemiplimab (when applicable) will be provided.

2.4.5.4 Analyses of laboratory variables

Each laboratory test result will be graded by CTCAE criteria (Version 4.03), when applicable. For hematological parameters and for some biochemistry parameters, sanofi sponsor generic normal ranges will be used for the grading of laboratory abnormalities (see list of parameters in Table 11 and Table 12). For other biochemistry parameters (eg, for hepatic parameters), grading will be derived using the local laboratory normal ranges.

The number (%) of patients with abnormal laboratory tests at baseline and during the on-treatment period will be presented by all grades and each grade. For patients with multiple occurrences of the same laboratory variable during the on-treatment period, the maximum grade (worst) per patient will be used.

The denominator used for percentage calculation is the number of patients with at least 1 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, urea acid, chloride and BUN, potentially clinically significant abnormalities (PCSA) values defined as abnormal values considered medically important by the Sponsor according to predefined criteria/thresholds based on literature review (Table 8**)** will be derived. PCSA criteria will determine which patients had at least 1 PCSA during the on-treatment period, taking into account all evaluations performed during the on-treatment period, including nonscheduled or repeated evaluations. The incidence of PCSA any time during the on-treatment period will be summarized by arm and overall, irrespective of the baseline level.

Shift tables showing the number of patients in each grade at baseline by worst grade during the on-treatment period will be provided for selected parameters (eg, anemia, thrombocytopenia, neutropenia and other tests as appropriate).

For creatinine clearance using MDRD formula, the number (%) of patients by category (<15, [15-30[, [30-60[, [60-90[, ≥90 mL/min/1.73m^2) and by period (baseline and on-treatment) as well as a shift table will be provided.

Table 8 - Potentially clinically significant abnormalities criteria for laboratory tests

Parameter	PCSA	Comments
Clinical Chemistry		
eGFR (mL/min/1.73m2) (Estimate of GFR based on an MDRD equation)	≥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		Harrison- Principles of internal Medicine 17th Ed., 2008
Hyperuricemia	>408 µmol/L	
Hypouricemia	<120 µmol/L	
Blood Urea Nitrogen	≥17 mmol/L	
Chloride	<80 mmol/L >115 mmol/L	

2.4.5.5 Analyses of vital sign variables

The incidence of PCSAs prior to study treatment administration at any cycle during the on-treatment period will be summarized by arm whatever the baseline level and/or according to the following baseline categories:

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

The incidence of PCSA during and after study treatment administration at any cycle during the on-treatment period will also be summarized

Table 9 - Potentially clinically significant abnormalities criteria for vital signs

Parameter	PCSA	Comments
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.
Weight	≥5% increase from baseline ≥5% decrease from baseline	FDA Feb 2007

Temperature and respiratory rate will be summarized at baseline and end of treatment, by arm (and all patients for Phase 1).

A listing of patients with at least one PCSA will be provided.

2.4.5.6 Analyses of electrocardiogram variables

The number (%) of patients with normal/abnormal ECG result during the on-treatment period will be summarized by arm (and all treated patients for Phase 1).

2.4.5.7 Analyses of other safety endpoints

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

The summary statistics (including number, mean, median, Q1, Q3, standard deviation, minimum and maximum) of baseline values, peak values, change from baseline and relative change from baseline will be calculated for Cytokines (TNF-α, IL-1-β, IL-4, IL-6, IFN-γ), markers of complement (C3a, C4, CH50) and serum tryptase when available.

For IAT, a summary of patients with indirect Coombs test during the on-treatment period will be provided, including 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.

A listing of chest x-ray results will be provided.

2.4.6 Analyses of immunogenicity variables

Immunogenicity analysis will be done separately for isatuximab and cemiplimab.

Number of evaluable patients, number (%) of pre-existing ADA and negative patients at baseline, number (%) of boosted and induced patients (either transient, persistent or indeterminate) will be reported, along with descriptive statistics of titer, by arm and overall. Prevalence and incidence will also be presented.

In addition, for positive ADA patients, time to onset, duration of ADA response, and the characterization of the immune response (transient, persistent, indeterminate) will be provided.

An individual data listing with ADA samples status (positive, negative or inconclusive), the titer if applicable, date of first/last dose, duration of exposure, study period, cycle/day, time point and date/time of sampling along with C_{trough} value of the drug will be provided for all patients.

The impact on safety and efficacy endpoints may be further explored by graphical methods or descriptively, depending on the ADA prevalence.

2.4.7 Analyses of pharmacokinetic variables

PK analysis will be done separately for isatuximab and cemiplimab.

2.4.7.1 PK parameters

2.4.7.1.1 Cycle 1

Following the first administration, individual concentrations and PK parameters of drug will be listed and summarized by descriptive statistics (such as the number of observations, arithmetic and geometric mean, median, SD, standard error (SE), coefficient of variation (CV)%, minimum, and maximum) by arm and possibly overall.

Individual and mean concentration profiles over time will be plotted by arm and possibly overall under the responsibility of Sanofi, Pharmacokinetic, Dynamic and Metabolism (PKDM), Translational Medicine and Early Development (TMED) department.

A comparison between isatuximab PK parameters (Cmax and $AUC_{0\text{-}7d}$) obtained after monotherapy (control arm) and isatuximab combined treatment with cemiplimab (DL1 and DL-1 arms) based on geometric mean ratio will be provided.

2.4.7.1.2 Overall treatment: C_{trough} and C_{eoi}

C_{trough} defined as a sample collected before dosing, and in a time window of 12 to 16 days after the previous infusion for the Q2W administration, or in a time window of 6 to 8 days after the previous infusion for the QW administration will be included in the descriptive analysis irrespectively of infusion interruption. However C_{trough} drawn outside collection of time window described in the PKPD flowchart of the protocol or collected after dose deviation higher than ±50% from intended dose will be excluded from the analyses.

C_{eoi} collected after significant infusion interruption, drawn outside collection of time window described in the PKPD flowchart of the protocol or collected after dose deviation higher than ±50% from intended dose will be excluded from the analyses.

Individual C_{trough} and C_{eoi} will be listed and summarized with same descriptive statistics as above by arm and possibly overall.

Mean (±SE) of C_{trough} will be plotted over treatment phase by arm and possibly overall.

Individual C_{trough} ratio and C_{eoi} ratio (described in Table 10) will be listed and summarized by descriptive statistics by arm and possibly overall as described above.

Table 10 - C_{trough} and C_{eoi} ratio

Analyte	C_{trough}	C_{eoi}
Isatuximab	C2D1 vs C1D8	C2D1 vs C1D1
	C4D1 vs C1D8	C4D1 vs C1D1
cemiplimab	C4D1 vs C1D15 (DL1)	C4D1 vs C1D1
	C4D1 vs C2D1 (DL-1)	

2.4.7.2 Immunogenicity impact on PK

Immunogenicity impact on PK analysis may be explored, depending on the ADA prevalence.

A descriptive statistics of C_{trough} as described above will be provided at each cycle in the subset of negative patients by arm and possibly overall where positive or inconclusive patients will be observed.

A graphical representation of individual C_{trough} profile will be provided throughout the course of treatment by arm and possibly overall where positive or inconclusive patients will be observed. Positive patients profile will be highlighted (eg, color or bold) and the concentration of the administered drug at the same time as ADA positive result will be notified.

2.4.8 Analyses of Biomarker variables

2.4.8.1 Genetic variables

Summary of BOR will be provided for the following patients:

- High risk cytogenetic markers (del17p and/or t(4;14) and/or t(14;16)).
- FcGR3A types: F/F, F/V, V/V and missing.
- HLA and KIR genotypes including:
  - HLA-B BW4-80Ile+ and KIR3DL1+ vs HLA-B BW4-80Ile- or KIR3DL1-,
  - KIR3DS1- vs KIR3DS1+.

2.4.8.2 Other variables

Graphs showing ORR/non-responder rate by biomarker levels will be provided for the following parameters at baseline:

- CD38 mRNA.
- Immune cell level (B-cell, T-cell and NK-cell subsets respectively in blood and bone marrow samples).

Bone marrow and blood samples will be collected for the following biomarker analyses:

- Correlation of immunophenotype in bone marrow and/or peripheral blood with parameters of clinical response. Blast cells and immune cell populations (including MDSC cell, T-cell, NK-cell subsets and Treg/CD8 effector ratio) will be characterized by multiparametric flow cytometry analysis on the expression of cell surface markers. The proportion of cells positive for a given marker or set of markers (eg, regulatory T cells [Tregs]) will be correlated with response to SAR650984. Bone marrow aspirate and blood will be collected at baseline and Day 1 of Cycle 3 and blood samples only will be collected at EOT.
- Whenever possible, PD-L1 expression in malignant plasma and immune cells will be determined and correlated with clinical response. Access to archival bone marrow biopsy material will be requested at screening and if available, retrospective expression analysis will be performed by IHC assay.
- Correlation of adaptive immune response (TCR repertoire profiling) with parameters of clinical response. Blood and bone marrow samples will be collected at screening, D1 of Cycle 3 (blood only) and at CR.
- Correlation of adaptive immune response (humoral and cellular immune responses to myeloma-related tumor antigens) with parameters of clinical response. Blood will be collected prior to pre-medication and IMP administration on D1 of Cycle 1, Cycle 2, Cycle 4, Cycle 7 and Cycle 10 and in disease progression patients at EOT. Humoral response will be assessed in all sites. Cellular response will be assessed in patients at selected sites.

Additional analysis, not specified in the protocol but related to the drug action and/or effect of isatuximab/cemiplimab, may be conducted on remaining samples pending evolving literature.

2.4.8.3 Potential interference of isatuximab in the M protein assessment

Number (%) of patients with M protein interference and with potential impact on the BOR will be explored.

2.4.9 Analyses of quality of life variables

Not applicable as no quality of life variable is collected.

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

Further therapies will be descriptively summarized by arm and overall.

2.5 DATA HANDLING CONVENTIONS

2.5.1 General conventions

The following formulas will be used for computation of parameters.

Creatinine clearance (eGFR) using the equation of MDRD formula:

$$GFR = 175 \times (Scr)^{-1.154} \times (Age)^{-0.203} \times (0.742 \text{ if Female}) \times (1.212 \text{ if African American})$$

with serum creatinine in mg/dL and age in year.

Corrected calcium formula:

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

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 the denominator the number of patients with a non-missing observation in the considered population. When relevant, the number of patients with missing data will be presented.

When incomplete or missing dates were found in the eCRF, attempts were made to retrieve the complete date, especially for dates within the month prior to first dose. However, if some dates remain incomplete, the following rules will be applied:

Handling of disease characteristics missing/partial dates (if not otherwise specified below)

- If the day is missing, it will be imputed to be 1.
- If the month is missing, it will be imputed to be 1 (only for medical history variables).
- If the year is missing, no imputation will be performed.

Handling of medication (other than anticancer treatment) missing/partial dates

No imputation of medication start/end dates or times will be performed. If a medication date 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.

Handling of post anti-myeloma treatment missing/partial dates

For post anti-myeloma treatments, if the anticancer treatment 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 treatment end year, the medication start date will be set equal to treatment end date + 1.
- If the medication start day and month are missing and the medication start year is after the 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 treatment end year and month, the medication start day will be set equal to the treatment end day + 1.
- If the medication start day is missing and medication start month is before the treatment end month and the medication start year is the same as 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 treatment end month and the medication start year is the same as 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 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 treatment end date + 1.

No imputation will be done for the missing/partial end 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 or after treatment, 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.

Handling of death with missing or partial date of death

The imputation for missing or partial death date will proceed as follows:

- If the death day is missing and the death month and year are the same as the last month and year the patient was last known to be alive, the death day will be set equal to the last day the patient was known to be alive + 1.
- If the death day is missing and the death month is after the month the patient was last known to be alive and the death year is the same as the year the patient was last known to be alive, the death day will be set to 01.

- If the death day and month are missing and the death year is the same as the year the patient was last known to be alive, the death date will be set equal to the date the patient was last known to be alive + 1.
- If the death day and month are missing and the death year is after the year the patient was last known to be alive, the death day and month will both be set to 01.

If the date the patient was last known to be alive is partial or missing, no imputation for missing or partial death date will be performed. The last date the patient was known to be alive is the last of: date of last dose, date of last visit performed (when the patient is known to be alive according to subject vital status), date of last laboratory assessment, date of last vital signs.

Handling of adverse events with 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 study treatment (isatuximab or cemiplimab) is missing, then the relationship to isatuximab/cemiplimab has to be assumed and the AE considered as such in the frequency tables of possibly related AEs, but no imputation will be done at the data level. No imputation will be done for relationship to NMIP.

Handling of parameters expressed as inequality or approximation

For some parameters (such as laboratory parameters), if the value is expressed as "<xx", "≤xx, half of the numeric portion of the entry or limit of quantification will be used in calculations.

Handling of missing date/time in duration of infusion calculation

When both cemiplimab and isatuximab are given to a patient on the same visit:

- Missing cemiplimab end date/time will be imputed by isatuximab start date/time (if available).
- Missing isatuximab start date/time will be imputed by cemiplimab end date/time (if available).

Other types of missing date/time will not be imputed, and data will be excluded from the analysis of duration of infusion.

2.5.4 Windows for time points

Laboratory data

A protocol planned laboratory test is considered to have occurred during a cycle if the date of sampling is after (>) the first day of the cycle, but prior to or equal (≤) to the first day of the next cycle. For unscheduled tests, a test is considered to have occurred during a cycle if the date of sampling is equal to or after (≥) the first day of the cycle, but prior (<) 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 of worst values and/or grades.

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

For Phase 2 part, a formal interim analysis of response rate (including confirmed and unconfirmed responses) will be performed when the first 15 randomized patients in each arm completed 2 cycles of treatment or permanently discontinue treatment. The purpose of the analysis is to stop combination arm early for futility.

The analysis will include the first 15 randomized patients from each arm in the ITT population. Given the observed response rate (including confirmed and unconfirmed responses) from each combination arm, and assuming the numbers of response follow binomial distribution with response rate=20% in control arm, and 50% in combination arm for the remaining 20 patients in each arm, the conditional power can be calculated based on 1-sided Fisher's exact test at 0.05 significance level (for each combination arm vs. control arm separately) at the end of the trial. If the conditional power is <30% for a combination arm, the arm will be stopped early for futility. The detailed decision rule of whether to continue or stop the arm is included in Appendix B. R-code for calculating conditional power is included in Appendix C.

The analysis will include the following parameters/analyses (defined in Section 2): response rate (including confirmed and unconfirmed responses), demographics and baseline characteristics, prior or concomitant medication, AEs (TEAE, death, SAE, TEAE leading to discontinuation and IR), laboratory variables (abnormality of hematological and chemistry test), PK NCA after first adminsitration and ADA based on available data.

In addition, formal safety review by data monitoring committee (DMC) are planned approximately every 3 months to regularly monitor unblinded patient safety data (all meetings), unblinded efficacy data (except the 1st DMC meeting) and quality of trial conduct. More details on formal safety reviews and on interim analyses are given in the DMC charter.

4 DATABASE LOCK

The database will be locked when clinical review of the database has been completed and all critical queries have been resolved.

5 SOFTWARE DOCUMENTATION

All summaries and statistical analyses, except for biomarker analysis, will be generated using SAS® Version 9.4 or higher. Biomarker analyses will be performed using R software Version 3.4.0 or above.

6 REFERENCES

1. Kumar S, Paiva B, Anderson KC, Durie B, Landgren O, Moreau P et al. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. Lancet Oncol. 2016;17(8):328-46.

2. Chen TW, Razak AR, Bedard PL, Siu LL, Hansen AR. A systematic review of immune-related adverse event reporting in clinical trials of immune checkpoint inhibitors. Ann Oncol. 2015;26(9):1824-9.

3. Kratz A, Ferraro M, Sluss PM, Lewandrowski KB. Laboratory reference values.

7 LIST OF APPENDICES

Appendix A: Generic ranges for hematological and biochemistry

Appendix B: Interim analysis decision boundary

Appendix C: R code for conditional power and stopping boundary calculation

Appendix A Generic ranges for hematological and biochemistry

Table 11 - Generic ranges for hematological parameters

Test	Gender	Unit	Lower/Upper limit of normal
Hemoglobin	F	g/L	120 - 160
Hemoglobin	M	g/L	135 - 175
Lymphocytes		10^9/L	1 - 2
Neutrophils		10^9/L	1.8 - 3.15
Platelets		10^9/L	150 - 350
Leukocytes		10^9/L	4.5 - 11
Eosinophils		10^9/L	0 - 0.4
Basophils		10^9/L	0 - 0.15
Monocytes		10^9/L	0.18 - 0.5
Hematocrit	M	ratio	0.41 - 0.53
Hematocrit	F	ratio	0.36 - 0.46
Erythrocytes	F	10^{12}/L	4 - 5.2
Erythrocytes	M	10^{12}/L	4.5 - 5.9
INR		ratio	0.8 -1.2

Based on Kratz et al. (3)

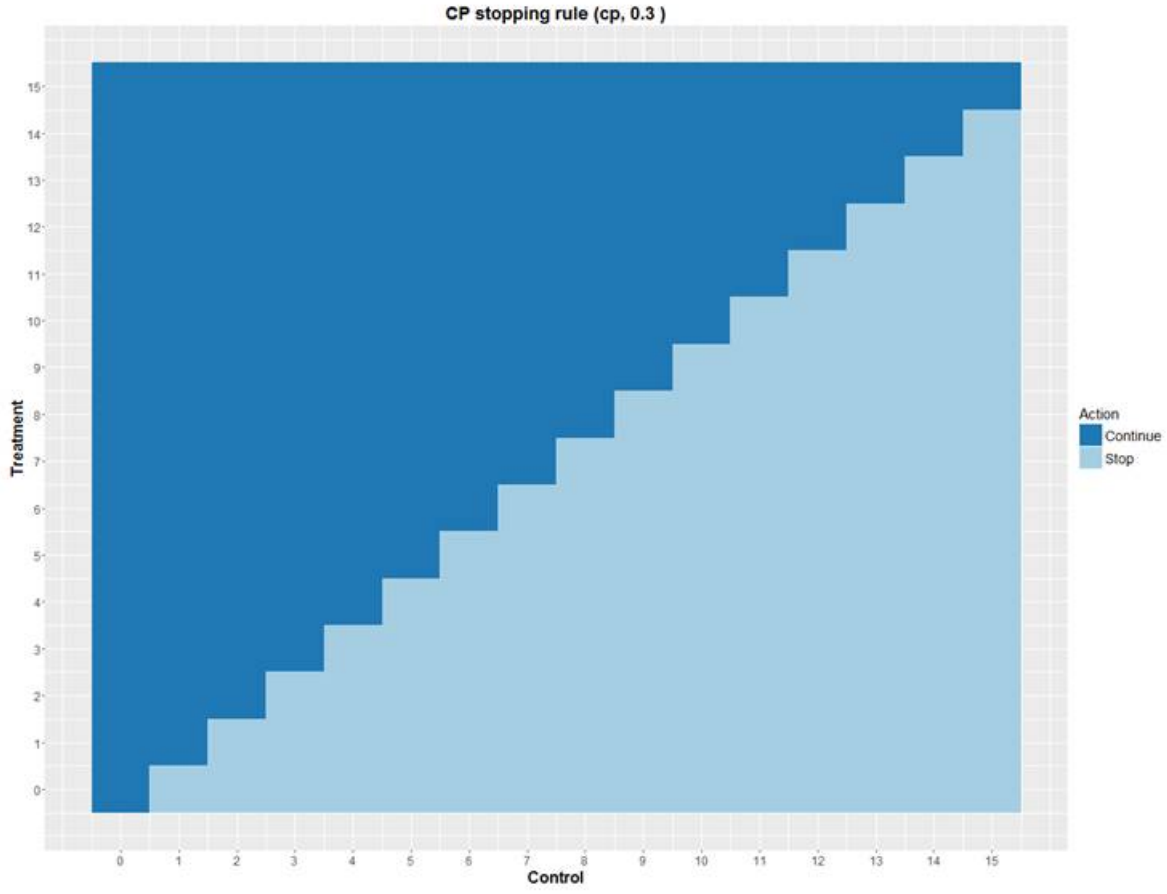
The current list of generic ranges for biochemistry parameters (for adults) is provided in the table below:

Table 12 - Generic ranges for biochemistry parameters

Test	Unit	Lower/Upper limit of normal
Albumin	g/L	35 - 55
Blood Urea Nitrogen (BUN)	mmol/L	3.6 - 7.1
Calcium	mmol/L	2.2 - 2.6
Chloride	mmol/L	80 - 115
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 B Summary of statistical analyses

Assuming there are 15 patients per arm included in the combination and control arms. The action to either continue or stop the combination arm depends on the number of responder in the combination and control arms respectively. The detailed decision is included below. The x axis represents number of responders in the control arm. The y axis represents number of responders in the combination arm. When action="Continue", the combination arm is recommended to continue; otherwise, it is recommended to stop the combination arm due to lack of confidence to achieve a positive results if the arm is continued.



Appendix C R code for conditional power and stopping boundary calculation

```
## conditional power function; output conditional power
getcp = function( r0, r1 ,m0, m1 ,n0=35, n1=35, SIG.LEVEL = 0.05){
# r0, r1 – number of response in control arm and combination arm at IA, respectively;
# m0, m1 - number of randomized patient in control and combination arm at IA, respectively
# n0, n1 - planed final sample size if the trial is continued for control and combination arm;
# SIG.LEVEL - 1-sided significant level for Fisher's exact test
p0 = 0.2 #r0/m0
p1 = 0.5 #r1/m1

ilow <- 0
ihigh <- n0 - m0
jlow <- 0
jhigh <- n1-m1
prob.reject = 0
for (i in ilow:ihigh) {
for (j in jlow:jhigh) {
x <- matrix(c(j+r1, n1-(j+r1),i+r0, n0-(i+r0)), 2, 2)
pval <- fisher.test(x, alternative="greater")$p.value
if (pval <= SIG.LEVEL) {
prob.reject <- prob.reject + dbinom(i, n0-m0, p0) * dbinom(j, n1-m1, p1)
}
}}
prob.reject
}

# Stopping boundary; for each combination of responders, calculation the decision rule.
pcut = 0.3
n1size = 15
n0size=15
type = "CP"
alter = "less"

res = NULL
for(trt.1 in 0:n1size){
for(con.1 in 0:n0size){
trt.data = rep(0, n1size)
con.data = rep(0, n0size)
```

```
if(trt.1) trt.data[1:trt.1] = 1
if(con.1) con.data[1:con.1] = 1

cp = getcp(con.1, trt.1, m0 = n0size, m1 = n1size)
if (alter == "less" & cp< pcut) {action = "Stop"
}else if(alter == "greater" & cp >pcut){
action = "Stop"
}else {
action ="Continue"
}

res.temp = data.frame(type, trt.1, con.1, action)
res = rbind(res, res.temp)
}
}

colnames(res) = c("Type", "Treatment", "Control", "Action")

if (alter == "greater") {direction = 1}else {direction = -1}

# graphic presentation of the stopping rule
library(ggplot2)

txt = paste(type, "stopping rule (cp,", pcut,")")
ggplot(res, aes(x = Control, y = Treatment, fill =Action))  + geom_tile() +
scale_x_continuous(breaks = 0:n0size) +  scale_y_continuous(breaks = 0:n1size) +
theme(axis.text=element_text(size=12),
axis.title=element_text(size=16,face="bold"),
plot.title = element_text(size = 18, face = "bold"),
legend.title=element_text(size=15) , legend.text=element_text(size=12) ) +
ggtitle(txt) +  scale_fill_brewer(palette  = "Paired", direction = direction)
```

TCD14906 16.1.9 Statistical analysis plan

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm)
[redacted]		