A Phase 1/2 open-label, multi-center, safety, preliminary efficacy and pharmacokinetic (PK) study of isatuximab (SAR650984) in combination with atezolizumab or isatuximab alone in patients with advanced malignancies

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AMENDED CLINICAL TRIAL PROTOCOL 05

Protocol title:	A Phase 1/2 open-label, multi-center, safety, preliminary efficacy and pharmacokinetic (PK) study of isatuximab (SAR650984) in combination with atezolizumab or isatuximab alone in patients with advanced malignancies
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reason, in any form whatsoever without the prior written

consent of Sanofi (or the concerned affiliated company); 'affiliated company' means any corporation, partnership or other entity which at the date of communication or afterwards (i) controls directly or indirectly Sanofi, (ii) is directly or indirectly controlled by Sanofi, with 'control' meaning direct or indirect ownership of more than 50% of the capital stock or the voting rights in such corporation, partnership or other entity

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Sponsor signatory:

Please refer to the last page of this document for electronic signatures including date and time

Monitoring Team's Representative Name and Contact Information:

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

Document	Country/countries impacted by amendment	Date, Version
Amended Protocol 04	All	11-Jun-2019, Version 1 (electronic 4.0)
Amended Protocol 03	All	07-Dec-2018, Version number: 1 (electronic 3.0)
Amended Protocol 02	All	09-Aug-2018, Version number: 1 (electronic 2.0)
Amended Protocol 01	All	06-Apr-2018, Version number: 1 (electronic 1.0)
Original Protocol		16-Feb-2018, Version number: 1

(electronic 1.0)

Amendment 05 (23 November 2020)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union

Based on the Dear Investigator Letter (DIL) that Sanofi has received from Roche, the newly identified potential risk of Severe Cutaneous Adverse Reactions (SCARs) with atezolizumab use and the associated guidelines for these dermatological events have been added.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
2.3.2.2 Potential and identified risks for atezolizumab	New identified risk of SCARs with atezolizumab use.	based on the DIL that Sanofi has received from Roche regarding the use of atezolizumab
10.21 Management of atezolizumabspecific adverse events – dermatologic events	Recommendations with specifc details regarding SCARs	based on the Dil that Sanofi has received from Roche regarding the use of atezolizumab

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1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Protocol title: A Phase 1/2 open-label, multi-center, safety, preliminary efficacy and pharmacokinetic (PK) study of isatuximab (SAR650984) in combination with atezolizumab or isatuximab alone in patients with advanced malignancies

Short title: Safety, preliminary efficacy and PK of isatuximab (SAR650984) alone or in combination with atezolizumab in patients with advanced malignancies

Rationale:

Monoclonal antibodies (mAbs) that block the programmed cell death-1/programmed cell death-ligand 1 (PD-1/PD-L1) alone or in combination with others mAbs have changed the landscape of cancer immunotherapy. Isatuximab, an anti-CD38 mAb, has shown clinical response in relapsed/refractory multiple myeloma (MM) patients as a single agent and in combination with immuno-modulatory agents. Although isatuximab has not been tested in solid tumors, this study is designed to explore whether isatuximab may contribute to reshaping the tumor immune-environment and will enhance the activity of established anti-PD-L1 therapy.

- Phase 1: To characterize the safety and tolerability of isatuximab in combination with atezolizumab in participants with unresectable hepatocellular carcinoma (HCC), platinum-refractory recurrent/metastatic squamous cell carcinoma of the head and neck (SCCHN),

platinum-resistant/refractory epithelial ovarian cancer (EOC), or recurrent glioblastoma multiforme (GBM), and to determine the recommended Phase 2 dose (RP2D).

- Dose limiting toxicities (DLTs) (in Cycle 1), adverse events (AEs)/serious adverse events (SAEs), and laboratory abnormalities.
- Maximum tolerated dose (MTD) defined as the highest dose level (DL) at which no more than 1 out of 6 participants (starting dose or DL-1) or 2 out of 12 participants (starting dose) experience an investigational medicinal product (IMP)-related DLT.

• Phase 2: To assess response rate (RR) of isatuximab • in combination with atezolizumab in participants with HCC or SCCHN or EOC.	RR defined as the proportion of patients with complete response and partial response as best overall response (assessed by Investigators using Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 see Appendix 11 Section 10.11).

• • Phase 2: To assess the progression free survival rate • at 6 months (PFS-6) of isatuximab in combination with atezolizumab, or as a single agent in participants with GBM.	PFS-6 defined as the PFS rate at 6 months (assessed by Investigators using Response Assessment for Neuro-Oncology [RANO] criteria).
• Recommended Phase 2 dose (RP2D) defined as the dose selected for the Phase 2 portion.	
Objectives	Endpoints
Secondary	
• To evaluate the safety (in Phase 2) profile of • isatuximab monotherapy (GBM only), or in combination with atezolizumab.	Adverse events (AE)/serious AEs and laboratory abnormalities (in Phase 2).
• • To evaluate the immunogenicity of isatuximab and • atezolizumab.	Incidence rate of anti-drug antibodies development (ADA: antiisatuximab and anti-atezolizumab antibodies).
• • To characterize the pharmacokinetic (PK) profile of • isatuximab single agent (GBM only) and atezolizumab in combination with isatuximab.	PK assessed from concentrations of isatuximab (non-compartmental analysis and population PK approach) and atezolizumab (population PK approach).
• To assess overall efficacy of isatuximab in •	Best percent-change from baseline in tumor burden change, disease control rate (DCR) defined as the sum of the complete

combination with atezolizumab, or single agent (GBM only).	response, partial response and stable disease rates, duration of response (DoR), progression free survival (PFS) (HCC, SCCHN, EOC per RECIST 1.1 and GBM per RANO criteria), RR (GBM only, per RANO criteria).

Overall design:

This is a Phase 1/2 open-label, non-randomized, multi-center, safety, preliminary efficacy, and PK study of isatuximab in combination with atezolizumab, or isatuximab alone in participants with advanced malignancies. The study will be conducted in 2 phases (see Section 1.2 for study design schema):

Phase 1 (safety run-in):

Patients with HCC, or SCCHN, or EOC, or GBM will be enrolled in Phase 1.

Starting dose is 1200 mg once every 3 weeks (Q3W) for atezolizumab with isatuximab given 10 mg/kg once weekly (QW) for 3 weeks followed by Q3W as described in the table below:

Dose level (DL)	Isatuximab	Atezolizumab
Starting dose	10 mg/kg QW × 3 →Q3W	1200 mg Q3W
Minus -1 (DL-1)	5 mg/kg QW × 3 →Q3W	1200 mg Q3W

The DLT observation period is the first cycle (21 days). The totality of the safety findings, including all the AEs occurring during treatment, unless due to disease progression or an obviously unrelated cause, will be taken into consideration by a Study Committee for the determination of the maximum tolerated dose and RP2D for the isatuximab and atezolizumab combination.

The selection of the RP2D will be based on the observation of the DLTs rules, as illustrated in the table below:

Isatuximab dose	DLTs	Dose
Starting dose:	If ≤1/6 participant	Starting dose will be RP2D
	If 2/6 participants	+6 participants at starting dose

	If a total of 2/12 participants	Starting dose will be RP2D
	If a total ≥3/6 participants or a total of ≥3/12 participants	+6 participants at DL-1
DL-1:	If ≤1/6 participant	DL-1 will be the RP2D
	If 2/6 participants	+6 participants at DL-1
	If a total of 2/12 participants	DL-1 will be the RP2D
	If a total ≥3/6 participants or a total of ≥3/12 participants	Alternative dose/schedule will need to be sought

The first administration of the IMP in each participant in Phase 1 is to be staggered by at least a 3-days interval. Following the identification of the RP2D, Phase 2 will be initiated.

The National Cancer Institute (NCI) common terminology criteria for adverse events

(CTCAEversion 4.03 will be used to assess the severity of the AEs. Causal relationships are to be determined by the Investigator on the basis of the combination regimen actually administered.

Phase 2 (efficacy signal search with a 2-stage design):

The combination dose for Phase 2 will be determined based on safety data from Phase 1. For the combination cohorts, atezolizumab will be administered first, followed by isatuximab on Day 1 of each cycle. Monotherapy dose for GBM (Cohort D-2) for Phase 2 will be determined based on results from Cohort D-1.

Phase 2 may include up to 6 cohorts conducted with a 2-stage design as shown in below tables.

Enrollment in Cohort A, B, C, and D-1 will be performed in parallel. Then enrollment in Cohort D-2and E will be performed sequentially at the end of each respective Stage 2 of previous cohorts depending on results observed.

Cohort A	Cohort B	Cohort C	Cohort D-1	Cohort D-2
HCC	SCCHN	EOC	GBM	if positive benefit from Cohort D-1 Phase 2 Stage 2
Stage 1 then	Stage 1 then Stage 2	Stage 1 then Stage 2	Stage 1 then Stage 2	GBM Stage 1 then Stage 2

Stage 2

Isatuximab weekly for 3 weeks then Q3W + atezolizumab Q3W combination	Isatuximab monotherapy weekly for 3 weeks then Q3W
Cohort E If positive results in Phase 2 Stage 2 one of the above cohorts	

Isatuximab and atezolizumab Q3W combination, without initial isatuximab weekly dosing

Number of participants:

In Phase 1, approximately 6 to 24 DLT evaluable participants are expected to be enrolled.

In Phase 2, sufficient participants will be screened to achieve 285 treated participants with study intervention in cohorts A, B, C, D-1, and D-2. All treated participants will be included in the primary efficacy population. Section 9.2 gives details of the sample size determination.

Additional participants may be enrolled up to a total of 350 participants.

Intervention groups and duration:

The duration of the study for a participant will include a screening period (up to 28 days), a treatment period (up to 2 years), a safety follow-up period up to 90 days and every 90 days follow-up visits or phone calls (until death or study cut-off). The study cut-off is planned at 12 months after the last participant enters the study, or when all participants have had the opportunity to complete the end of treatment (EOT) visit 30 days after the last study treatment administration, whichever is the latest.

Treatment period: The cycle duration is 21 days. Participants will continue treatment until disease progression confirmed by imaging performed no less than 4 weeks after initial evidence of progression, unacceptable AE, participant’s decision to stop the treatment, 2 years of uninterrupted delivery of IMP(s) without documented progressive disease (PD).

Safety follow-up period: After treatment discontinuation, participants will return to the study site

30 days (±7 days) after the last dose of IMP(s), or when the participant receives another anti-cancer therapy, whichever is earlier, for EOT assessments. In addition, there will be an

extended safety follow-up period for 90 days after the last dose of IMPs for ADA assessment and for safety assessment.

Participants who discontinue the study treatment without PD will be followed at 90 days (±7 days) for disease assessment.

Survival follow-up period: The further follow-up schedule beyond 90 days after last dose of IMP(s) is according to the disease progression status:

- Participants who discontinue study treatment due to PD: phone call follow-up will be done every 90 days from the date of last IMP(s) administration until death or study cut-off date.
- Participants who discontinue the study treatment without PD: will be followed every 90 days for disease assessment until confirmation of PD or start treatment with another anti-cancer therapy, or until study cut-off date whichever comes first. After PD, participant will be followed by phone call until death or study cut-off date.
- Participants who are still on study treatment after study cut-off date: will continue to receive study treatment if they benefit, and will undergo planned study procedures (except PK and ADA) until confirmation of PD, or start with another anti-cancer therapy, or treatment period ended, whichever comes first.

All SAEs still ongoing at the end of the study treatment, and all AEs considered related to study treatment still ongoing or occurring after the end of study treatment, which will be followed until resolution/stabilization.

Investigational medicinal products:

- Isatuximab:
  - Formulation: drug product concentrated solution in vials containing 20 mg/mL (500 mg/25 mL) isatuximab in 20 mM histidine, 10% (w/v) sucrose, 0.02% (w/v) polysorbate 80, pH 6.0,
  - Route(s) of administration: solution for intravenous (IV) infusion, - Dose regimen: the starting dose is 10 mg/kg.
- Atezolizumab:
  - Formulation: drug product concentrated solution in a single-dose vial containing 1200 mg/20 mL (60 mg/mL),
  - Route(s) of administration: solution for IV infusion, - Dose regimen: 1200 mg per administration.

Non investigational medicinal products: will be locally sourced and formulations may vary.

All participants will receive the following premedications to prevent or reduce incidence or

severity of infusion-associated reactions (IARs), 30 to 60 minutes prior to isatuximab infusion (no longer than 60 minutes). The standard premedication regimen will include:

- Acetaminophen 650 to 1000 mg oral route (PO) (or equivalent).
- Ranitidine 50 mg IV (or equivalent).
- Diphenhydramine 25 to 50 mg IV (or equivalent).
- Methylprednisolone 100 mg IV (or equivalent).
- Montelukast 10 mg oral route (PO) (or equivalent).

Criteria for optional premedication for IARs:

- For a patient who has no IAR for the first 4 infusions: Premedication for the subsequent infusions is optional at the Investigator's discretion. However, if during the subsequent infusions without premedication the patient experiences an IAR (any grade), premedication must be restarted for all subsequent infusions.
- If a patient develops an IAR Grade ≤2 during their first infusion only and then experiences no further IARs during their next 3 infusions: The Investigator should discuss with the

Sponsor Medical Monitor when considering omitting premedication for the next infusion. If no IAR is observed for the next infusion without premedication, premedication is optional for the subsequent infusions at the Investigator's discretion. However, if during the next infusion without premedication the patient experiences an IAR (any grade), premedication must be restarted for all subsequent infusions.

When isatuximab and atezolizumab are to be administrated on the same day, the administration sequence is: atezolizumab, followed by premedications, followed by isatuximab.

When only isatuximab is to be administrated on a day, the administration sequence is: premedications, followed by isatuximab.

Statistical considerations:

Data from HCC, SCCHN, EOC and GBM cohorts in Phase 2 will be analyzed and reported separately by cohort.

- Analysis of primary efficacy endpoints:
  - For HCC, SCCHN and EOC Phase 2: RR will be summarized with descriptive statistics. A 90% two-sided confidence interval will be computed using

Clopper-Pearson method. The statistical inference will be based on the hypothesis and

alpha level defined in the sample size calculation section,

- ◦ For GBM: PFS-6 will be summarized using Kaplan-Meier method.
- Analysis of secondary efficacy endpoints:
- ◦ Tumor burden change: the best percent-change from baseline in tumor burden will be summarized and presented graphically. In addition, a summary of the area under the curve (AUC) and the time adjusted AUC of percent-change from baseline in tumor burden will also be provided as an exploratory analysis,
- ◦ DOR and PFS will be summarized using Kaplan-Meier method,
- ◦ RR for GBM and DCR (complete response + partial response + stable disease) will be summarized with descriptive statistics.
- Analysis of safety endpoints:

In Phase 1, the DLTs will be listed by participant using the DLT evaluable population.

In Phase 1 and 2, the AEs will be coded according to Medical Dictionary for Regulatory Activities (MedDRA). AEs and laboratory abnormalities will be graded according to the NCI-CTCAE version 4.03.

- ◦ The number (%) of participants experiencing treatment-emergent AEs (TEAEs) by primary system organ class (SOC) and preferred term (PT) will be summarized by CTCAE grade (all grades and Grade ≥3) for the all-treated population. Same table will be prepared for treatment-related TEAEs, AEs of special interest (AESIs), TEAEs leading to treatment discontinuation, serious TEAEs and TEAEs with fatal outcome. The post-treatment AEs will be analyzed separately,
- ◦ The number (%) of participants with laboratory abnormalities (ie, all grades and Grade ≥3) using the worst grade during the on-treatment period will be provided for the all-treated population.
- Pharmacokinetics:
- ◦ Concentrations of both atezolizumab and isatuximab and PK parameters of isatuximab at Cycle 1 Week 1 will be descriptively summarized (mean, geometric mean, median, standard deviation, standard error of the mean, coefficient of variation, and minimum and maximum),
- ◦ Immune response and pharmacodynamic endpoints:
- ◦ Findings from immune markers and pharmacodynamics markers will be descriptively summarized and tabulated.

Planned date for analysis cut-off:

For each cohort, the analysis cut-off date for the primary analysis (RR for HCC, SCCHN, and EOC, PFS-6 for GBM) will be 6 months after the last participant's first treatment in the cohort.

The analysis cut-off date for the secondary efficacy endpoints including DoR and PFS will be 12 months after the last participant's first treatment in the cohort. The primary analysis of RR in the cohort for HCC, SCCHN, and EOC, and of PFS-6 in the cohort for GMB will be updated. In the case of inadequate efficacy for a cohort at interim analyses, the Sponsor may decide not to update primary nor perform secondary analyses for that cohort.

Study Committee:

Composition of the Study Committee will vary based on the matter discussed, but it will generally include Sponsor representatives and at least two investigators responsible for the indication in matter. Sponsor representatives and Investigators who have enrolled at least 1 patient will review clinical data approximately every 2 weeks during the course of the Phase 1 part. Then Study Committee will convene regularly or ad hoc when required, to review data and provide strategic recommendations on study medical decisions such as at the end of the Stage 1 of each cohort and Stage 2 of Cohorts A to D-2.

1.2 SCHEMA

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1.3 SCHEDULE OF ACTIVITIES (SOA)

Evaluation	Screening (up to 28 days before Day 1)		Treatment Phasea		End of Treatment (EOT)	Post Treatment Follow-up Phase		Notes
a A cycle is 21 days								
	Cycle 1		Cycle 2 and Beyond	Safety follow-up Period	Survival follow-up			
D28 to D15	D-14 to D-1	D1 (±1)	D8 (± 1)	D15 (±1)	D1 (± 2) 30 (±7) days after last IMPs admin	At 60 (±7) days after last IMPs admin	At 90 (±7) days after last IMPs admin	Every 90 days (±7) after last safety follow-up
Informed consent/ Inclusion and exclusion criteria	X							Informed Consent: Informed consent may be signed prior to D -28.
Demography, Medical/Surgical and Disease History	X							
Physical examination		X (<7days prior to	Xc	Xc	X	X	X	X	Section 8.2.1

	first dose)									
Height (at baseline only) /Weight/ ECOG (HCC,SCCHN,EOC) or	X		X	Xc	Xc	X	X		X	X	Section 8.2.1
Karnofsky PS (GBM)										
Vital Signs	X		X	Xc	Xc	X	X		X	X	See Section 8.2.2
Resting O2 saturation for SCCHN	X		X	Xc	Xc	X	X				See Section 8.2.2

Evaluation	Screening (up to 28 days before Day 1)	Treatment Phasea				End of Treatment (EOT)	Post Treatment Follow-up Phase		Notes
a A cycle is 21 days									
Cycle 1		Cycle 2 and Beyond		Safety follow-up Period		Survival follow-up			
D28 to D15	D-14 to D-1	D1 (±1)	D8 (± 1)	D15 (±1)	D1 (± 2)	30 (±7) days after last IMPs admin	At 60 (±7) days after last IMPs admin	At 90 (±7) days after last IMPs admin	Every 90 days (±7) after last safety follow-up	

12-Lead ECG	X			As clinically indicated					See Section 8.2.3
Laboratory Assessments									
Pregnancy test (WOCBP only)b	X (within 7 days prior to first dose)			X	X	X	X (every 30±7 days until 5 months after last dose of study treatment)		b Women of child bearing potential must have a negative serum pregnancy test result within 7 days prior to first IMP administration.
Blood Chemistry	X	X	Xc	Xc	X	X	X	X	See Section 10.3 Table 12
Hematology	X	X	Xc	Xc	X	X	X	X	Section 10.3
Coagulation(GBM)	X	X	Xc	Xc	X	X			Section 10.3
Coagulation (for HCC, SCCHN, and EOC)	X			As clinically indicated					Section 10.3

Evaluation	Screening (up to 28 days before Day 1)			Treatment Phasea		End of Treatment (EOT)	Post Treatment Follow-up Phase		Notes
a A cycle is 21 days									
	Cycle 1		Cycle 2 and Beyond	Safety follow-up Period		Survival follow-up			
D28 to D15	D-14 to D-1	D1 (±1)	D8 (± 1)	D15 (±1)	D1 (± 2)	30 (±7) days after last IMPs admin	At 60 (±7) days after last IMPs admin	At 90 (±7) days after last IMPs admin	Every 90 days (±7) after last safety follow-up	
Blood Typing Interference Test		X				Cycle 2 Day 1 only				Section 10.3 Before each transfusion.
Serology HBV and HCV (for HCC only)	X									Section 10.3
Urinalysis (at baseline and if required) /urine dipstick	X		X	As clinically indicated		X	X	X		Section 10.3
Disease Assessment										
CT/MRI (for HCC, SCCHN, and EOC)	X					X (Weeks 9, 18, 27, and then	X (if necessary)		X (until PD is confirmed if no PD documented & confirmed)	Section 8.1

			every 12 weeks)				
Brain MRI (for GBM only)	X (within 14 days prior to first dose)		X (Weeks 6, 12, 18, 24, and then every 9 weeks)	X (if necessary)	X (until PD is confirmed if no PD documented & confirmed)		Section 8.1
AFP (for HCC) / CA125 (for EOC)		X	X (Weeks 9, 18, 27, and then every 12 weeks)	X (if necessary)	X (until PD is confirmed if no PD documented & confirmed)		Section 8.1
Isatuximab Administration		X	Xc	Xc X			c evaluation not applicable for Cohort E
Atezolizumab Administration		X		X			

Evaluation	Screening (up to 28 days before Day 1)	Treatment Phasea	End of Treatment (EOT)	Post Treatment Follow-up Phase	Notes
a	A				

	cycle is 21 days							
	Cycle 1	Cycle 2 and Beyond	Safety follow-up Period		Survival follow-up			
D28 to D15	D-14 to D-1	D1 (±1)	D8 (± 1)	D15 (±1)	D1 (± 2)	30 (±7) days after last IMPs admin	At 60 (±7) days after last IMPs admin	At 90 (±7) days after last IMPs admin	Every 90 days (±7) after last safety follow-up
AE/SAE Assessment	X			Continuously throughout period				X (ongoing related AEs, ongoing SAEs at EOT and new related AE/SAEs)	
Prior/ Concomitant Medication	X (within 14 days prior to first dose)			Continuously throughout period				X (related to AE/SAEs listed above)	
PK				See Pharmacokinetics and immunogenicity Flow Chart					
ADA				See Pharmacokinetics and immunogenicity Flow Chart					
Tumor Biopsy, Archival									
Tumor Tissue Collection, Biomarker				See Biomarker Flow Chart					
Blood Draw									
Subsequent						X	X	X	X

Anticancer Therapy Status																	
Survival Status														X			
Study Phase													Treatment Phase				
Cycle						Cycle 1							Cycle 2			Cycle 3	
Day within the Cycle						D1				D15			D1			D1	
Sample RNT (h) Ref: SOI	SOI	EOI	EOI +30 min				-						SOI	-		SOI	- SO
Atezolizumab																	
Sample time window Atezolizumab	[-24h, SOI]	±5 min	±10 min				-						[-24h, SOI]	-		[-24h, SOI]	- [-2 SO
Sample RNT (h) Ref: SOI Isatuximab	SOI		-	EOI	EOI +4h	72h	168h (SOI of Day 8)	SOI	EOI				SOI	-EOI		SOI	- SO
Sample time window Isatuximab	-		-	±10 min	±30 min	±5 h	[-24h, SOI]	[-24h, SOI]	±10 min				-	-±10 min		-	- -
IMP administration (IV infusion)																	
Atezolizumab	X---------- X												X			X	X
Isatuximab			X----------				X	X----------					X----------				X

			X				X			X		
Pharmacokinetics a,i j												
Atezolizumab Sample ID	S00	-	S01			-			S00c	-	S00c	- S0
Isatuximabi Sample ID	P00b	-	-	P01f	P02	P03P04d,gP05g		P06f	P00b, g	-P01f	P00b, g	- P0 g
Immunogenicity (ADA) a, e ,i												
Atezolizumab c, j	AS00				-				AS00	-	AS00	- AS
Isatuximabg,h i	AP00 b				-				AP00 b	-	AP00b	- AP

a Refer to the laboratory manual for sample collection, processing and shipping. b Isatuximab PK or ADA predose samples should be collected before isatuximab administration and at the same time as atezolizumab predose samples when applicable. c Atezolizumab sample collected strictly before the start of atezolizumab infusion (during treatment phase). d P04 sample must be collected even if the participant withdraws the study without receiving the second administration of isatuximab.

- After start of study treatment, if 1 drug is prematurely discontinued, ADA samples for this drug will be collected and tested on Day 1 of the 2 next cycles. The ADA sample collection for other drug should be done as planned.

- Sample collected just before actual end of infusion of isatuximab. g Isatuximab sample collected strictly before the start of isatuximab infusion (during treatment phase). h After FUP 90(±7) days after last isatuximab administration no further ADA will be sampled even if the status is positive or inconclusive.
- Isatuximab PK and ADA samples to be collected each cycle until the last study treatment for PK and until FUP 90(±7) days after last IMP administration for ADA or at the cut-off date, whichever comes first. However, collection can be reduced or stopped earlier upon notification from the Sponsor based on the updated knowledge of isatuximab on PK/ADA.
- For subsequent cycles, atezolizumab PK and ADA samples (pre-dose) are to be

collected at Cycle 8 Day 1 and Cycle 16 Day 1 only.

Abbreviations: SOI: Start of infusion, EOI: End of infusion, P= Plasma, S= Serum, AP= Antibody-Plasma, AS= Antibody-Serum, IMP= Investigational medicine product, D= Day, EOT= End of treatment, FUP= followup period, RNT= relative nominal time, IV= Intravenous, ID= Identification, ADA= Anti-drug antibody

Sample Collection		Biomarker Analysis	Screening		Treatment Phase			Post-Treatme Phase
Cycle 1	Cycle 2	Cycle 3	Cycle 5 and Beyond	EOT	Follow-up			
D-28 to D-1	D1 (-1 day) a	D1	D1	D1	30 (±7) days after last IMP admin	60 (±7) days after last IMP admin	a. Biomarker blood draw may be performed within 1 working day prior to IMP administration.	
Peripheral Blood		Immune genetic markers		X				
Tumor mutational profile (plasma cell free DNA)		X	X	X		X		
Immunophenotyping		X	X	X	X (odd cycles only)	X	X	Only fo Phase 2 Stage 2 particip
Plasma or serum cytokines	X	X	X	X	X (odd cycles only)	X	X	Only fo Phase 2 Stage 2 particip

Adaptive immunity	X	X (only 1 on-treatment sample, see Study Reference Manual for details)				Only Ph 2 Stage participa if suffici clinical respons observa in Phase and Pha Stage 1
Plasma or serum Metabolites	X	X	X	X (odd cycles only)	X	participa Only Ph 2 Stage participa if suffici clinical respons observa in Phase and Pha Stage 1
Archival Pre-Treatment Tumor Tissue Collection (for HCC, SCCHN, EOC and GBM)	If feasible, biomarker analyses listed below for "Baseline or on treatment tumor biopsy core"	X				participa

Baseline or on treatment tumor biopsy core in order of priority (Biopsy to be performed for HCC, SCCHN, and EOC if adequate archival tissue is not available)	Core 1	CD38 and PD-L1 expression, immune contexture (IHC analyses)	X	X (if clinically feasible)
Core 2	CD38 and PD-L1 expression, immune contexture (IHC analyses)	X		X (if clinically feasible)
Core 3	Transcriptomic analysis	X		X (if clinically feasible)

2 INTRODUCTION

Cluster of differentiation 38 (CD38) is a type II glycosylated 45 kilodalton membrane protein that was identified as a lymphocyte marker (1). CD38 functions as a receptor binding to CD31 and is involved in cell adhesion and signal transduction. CD38 is also an ecto-enzyme catalyzing the synthesis and hydrolysis of cyclic adenosine-diphosphate-ribose from nicotinamide adenine dinucleotide to adenosine diphosphate-ribose (2). Adenosine diphosphate-ribose can be further converted into adenosine, a multifunctional immunosuppressive nucleoside that binds to different specific receptors expressed by immune effector cells (3).

The expression of CD38 in healthy humans can be detected on natural killer (NK) cells, monocytes, dendritic cells, macrophages, granulocytes, activated T and B cells, and plasma

cells. Several hematological malignancies express CD38 including those of B-lymphocyte,

T-lymphocyte and myeloid origin. Moreover, in some solid tumors, such as prostate cancer and glioblastoma, CD38 expression has been shown. See Section 2.1 for additional information on biological functions of CD38 and its role in tumor microenvironment.

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades (4). The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control (5). The normal function of PD-1, expressed on the cell surface of activated T cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an immunoglobulin superfamily member related to cluster of differentiation 28 and cytotoxic T-lymphocyte associated protein 4 (CTLA-4), which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (programmed cell death-ligand 1 [PD-L1] and/or programmed cell death-ligand 2 [PD-L2]). The structures of murine PD-1 alone (6) and in complex with its ligands were first resolved (7, 8) and more recently the nuclear magnetic resonance-based structure of the human PD-1 extracellular region and analyses of the interactions with its ligands were also reported (9).

Programmed cell death 1 protein and family members are type I transmembrane glycoproteins containing an immunoglobulin Variable-type domain responsible for ligand binding and a cytoplasmic tail which is responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif and an immunoreceptor tyrosine-based switch motif (ITSM). Following T cell stimulation, PD-1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the ITSM motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules, such as CD3ζ, PKCθ and ZAP70, which are involved in the CD3 T cell signaling cascade (10). The mechanism by which PD-1 down-modulates T cell responses is similar to, but distinct from that of CTLA-4 (11). Programmed cell death 1 protein was shown to be expressed on activated lymphocytes, including peripheral CD4+ and CD8+ T cells, B cells, regulatory T cells and NK cells (12). Expression has also been shown during thymic development on CD4-CD8- (double negative) T cells (13) as well as subsets of macrophages (14) and dendritic cells (15). The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types (16). PD-L1 is expressed at low levels on various non-hematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is only detectably expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments (16). Both ligands are Type I transmembrane receptors containing both immunoglobulin variable- and immunoglobulin constant-like domains in the extracellular region and short cytoplasmic regions with no known signaling motifs. Binding of either PD-1 ligand to PD-1 inhibits T cell activation triggered through the

T cell receptor. Programmed cell death-ligand 2 is thought to control immune T cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T cell function in peripheral tissues. Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T cell inhibitor (17, 18) which, via its interaction with the PD-1 receptor on tumor-specific T cells, plays a critical role in immune evasion by tumors (19). As a consequence, the PD-1/PD-L1 pathway is an attractive target for therapeutic intervention in cancer (20).

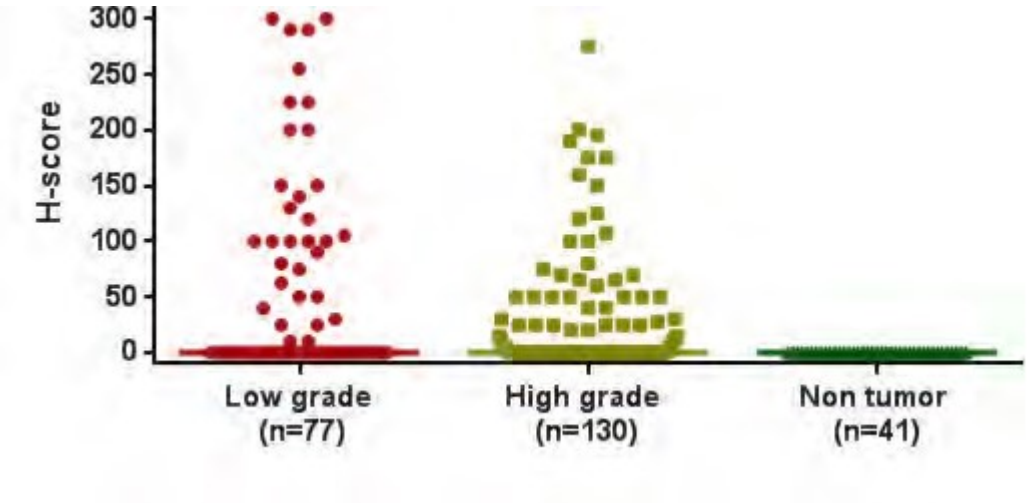
Five anti-PD-1 and anti-PD-L1 antibodies, nivolumab, pembrolizumab, atezolizumab, avelumab and durvalumab, are now approved in multiple indications including HCC and SCCHN (21, 22, 23, 24, 25, 26, 27, 28, 29).

2.1 STUDY RATIONALE

Monoclonal antibodies that block the PD-1/PD-L1 axis have changed the landscape of cancer therapy. Nivolumab, pembrolizumab, atezolizumab, avelumab, and durvalumab were approved by the US Food and Drug Administration (FDA). Despite their success, optimal outcomes for many patients will require combination therapies. Numerous clinical studies are currently evaluating anti-PD-1/PD-L1 antibodies in combination with chemotherapy, targeted therapies and other immunotherapies in patients with solid tumors and hematological malignancies.

CD38 expression is well documented in hematological cancers, including MM, lymphomas and leukemias. In solid tumors, CD38 is found expressed on the tumor cells of treatment naïve prostate adenocarcinoma and glioblastoma biopsies (Sanofi report NCB22V1). Therefore, isatuximab monotherapy cohort will be initiated in patients with glioblastoma upon positive signal of isatuximab and atezolizumab combination Phase 2 Stage 2. The rationale to initiate monotherapy cohort is to evaluate whether the combination treatment would provide additional benefit compared to isatuximab monotherapy in patients with glioblastoma. Figure 2 shows the H-scores for CD38 in tumor tissues from glioblastoma patients with low-grade and high-grade diseases. H-scores in normal non-tumor brain tissues are also shown.

in low and high grade glioblastoma



In other solid tumor types, CD38 is not detected on the tumor cells, although it can be detected within the tumor microenvironment. The role of CD38 in the solid tumor environment is not completely understood, but there are several findings indicating that CD38 can contribute to the immune-suppressive tumor microenvironment:

- CD38 catalyzes the conversion of nicotinamide adenine dinucleotide into immunosuppressive adenosine.
- CD38 expression is highly correlated with the expression of PD-1 and its ligands in solid tumor biopsies.

- CD38 is found upregulated in tumor models that have acquired resistance to anti-PD-L1 (30, 31).
- CD38 expressing myeloid derived suppressor cells promote growth of human tumors in mice (32).
- CD38 expressing mouse tumor cells inhibit the proliferation of autologous T cells (9).

A recent report has shown that the combination of anti-PD-L1 and CD38 antibodies induces a greater anti-tumor immune response than anti-PD-L1 in a mouse lung cancer model (K-rasLA1/+p53R172HΔg/+-derived tumor) (Figure 3) (30, 31).

Figure 3 - Combination of anti-CD38 and anti PD-L1 in a mouse lung cancer model results in enhanced anti-tumor activity, decreases incidence of lung metas

2.2 BACKGROUND

2.2.1 Solid tumors

2.2.1.1 Hepatocellular Carcinoma

Hepatocellular carcinoma is a rising cause of cancer related deaths worldwide (29). The leading cause of HCC is associated with chronic hepatitis B (33%), alcohol (30%) or hepatitis C (21%) (33). The majority of HCC patients are detected at an advanced or end stage (13). Systemic treatment options for advanced disease are limited with sorafenib being the only approved effective standard of care in the first line unresectable advanced setting. The objective RR (1 to 3%) is minimal and survival benefit (6.5 to 10.7 months versus 4.2 to 7.9 months with placebo) is modest in both Caucasian and Asian population (34, 35). Recently, lenvatinib, another vascular endothelial growth factor receptor inhibitor, has demonstrated similar survival benefit to sorafenib (13.6 months versus 12.3 months) in a Phase 3 study (36). The FDA has accepted a supplemental new drug application for lenvatinib as a frontline systemic treatment for patients with advanced hepatocellular carcinoma in September 2017. For patients who were able to tolerate sorafenib but subsequently progressed on sorafenib, regorafenib has been approved based on an overall survival (OS) benefit compared with placebo (10.6 months versus 7.8 months) (3). In September 2017, nivolumab received accelerated approval from the FDA in patients who have been previously treated with sorafenib, supporting the use of immunotherapy for treatment of HCC in the second-line setting.

HCC is an immunogenic tumor in an immunotolerant environment. The chronic inflammatory conditions in the liver (eg, cirrhosis, hepatitis B virus (HBV)/hepatitis C virus (HCV) infection) contribute to the immunosuppressive tumor microenvironment through T cell exhaustion, with presence of PD-1 expressing tumor-infiltrating lymphocytes in HCC lesions, supporting the use of PD-1/PD-L1 immune checkpoint blockade as a therapeutic

strategy (14, 2, 37).

Multiple anti-PD-1/PD-L1 inhibitors (including pembrolizumab, atezolizumab, and durvalumab) are being developed, as a monotherapy or in combination, for treatment of patients with HCC. In the Phase 1/2 study CheckMate040, nivolumab achieved a RR of 14% (central review using RECIST 1.1) in the 145 patients who received sorafenib. More importantly, responses were observed irrespective of HCC etiology or PD-L1 expression. The response was durable

(9.9 months) and most disease stabilizations lasted at least 6 months. The safety profile observed in patients with advanced HCC was generally similar to that observed in patients with other cancers, with the exception of a higher incidence of elevations in transaminases (18% Grade 3/4 aspartate aminotransferase [AST], 11% Grade 3/4 alanine aminotransferase [ALT]) and bilirubin (7% Grade 3/4 bilirubin) levels. Immune-mediated hepatitis requiring systemic corticosteroids occurred in 5% of patients. US FDA accelerated approval was granted based on this study (2).

Durvalumab, a human immunoglobulin G1 antibody targets PD-L1, also demonstrated some clinical activity in patients with HCC (could be positive for HBV or HCV) with a RR of 10% and similar median OS as nivolumab (13.2 months, as of Oct 2016). The most common Grade 3/4 TEAE was elevation in transaminases (7.5% AST and 5.0% ALT). Although the preliminary results are encouraging, most patients with HCC do not respond to PD-1/PD-L1 inhibitors monotherapy.

The current study (ACT15377) will evaluate the safety, tolerability, and RRs of isatuximab in combination with atezolizumab as primary objective, in patients with unresectable HCC who progressed on/after or are intolerant to sorafenib.

2.2.1.2 Squamous cell carcinoma of head and neck

Approximately 60% of patients with SCCHN are diagnosed with locoregionally advanced disease (12). More than 50% of these patients will have recurrence within 3 years with chemotherapy or chemoradiation (5, 6). There is about 10% of patients present with metastatic disease (15). First-line palliative treatment for patients with recurrent or metastatic SCCHN is platinum-based system therapy. Adding cetuximab to cisplatin/ carboplatin plus 5-fluorouracil followed by maintenance cetuximab improves RR from 20% to 36%, and survival from 7.4 months to 10.1 months (16). For the patients who have cancer progression within 6 months after platinum-based chemotherapy administered in the context of primary or recurrent disease, the prognosis is poor. ORRs to second-line chemotherapy or anti-EGFR agent are 6-13%. Median survival is approximately 6 months (8, 11, 17).

Nivolumab and pembrolizumab are the first PD-1 immune checkpoint inhibitors granted

with US FDA approval for treating patients with recurrent/metastatic SCCHN who progress on or after platinum-based chemotherapy. Nivolumab was shown to be superior to standard of care (median OS 7.5 months versus 5.1 months, RR 13% versus 5.8%, respectively) in platinum-refractory population regardless of PD-L1 status in Phase 3 Checkmate 141 (11). Pembrolizumab, which was granted accelerated approval based on RR of 16% to 18% in patients with recurrent and metastatic SCCHN did not meet primary endpoints in a randomized study when compared to standard of care (18, 19, 20). Atezolizumab monotherapy also demonstrated clinical activity in the PD-L1 expression enriched recurrent and metastatic SCCHN population from a Phase 1 study. The overall RR was 22%, and median OS was 6 months (38). Multiple clinical trials are ongoing to evaluate the use of PD-1/PD-L1 immune checkpoint inhibitors in combination with therapies to improve clinical outcomes in patients with recurrent/metastatic SCCHN (9).

The current study (ACT15377) will evaluate the safety, tolerability, and RRs of isatuximab in combination with atezolizumab as primary objective, in patients with recurrent/metastatic

SCCHN who progressed on/after one and no more than two lines of platinum-based therapy.

2.2.1.3 Epithelial ovarian cancer

Epithelial ovarian cancer, which accounts for a majority of diagnoses of ovarian cancer, is further subdivided into various cell types, grades, and anatomic locations. The most common form is high-grade serous ovarian cancer, which accounts for approximately 70% of all EOC (39). More than 60% of patients with ovarian cancer are diagnosed with advanced (stage III–IV) disease, the mainstay of treatment for which is upfront surgical cytoreduction followed by adjuvant platinum-based chemotherapy. Bevacizumab is approved (excluding the United States) as a first-line treatment in combination with standard chemotherapy (40). Platinum-based therapy (plus bevacizumab) continues to be the principal regimen used to treat platinum-sensitive tumors (defined as relapse at least 6 months after completion of last platinum-based therapy). However, platinum resistance eventually occurs in virtually all patients with recurrent EOC, as response usually lasts for only a few months and with each subsequent course of therapy the treatment free interval shortens until the disease is declared “platinum-resistant” (defined as progression within 6 months of platinum-based therapy) or “platinum-refractory” (defined as progression during or within 4 weeks after the last dose) (32).

For the patients who harbor mutations in the genes encoding breast cancer type 1 and 2 susceptibility protein (BRCA1 and BRCA2), which occur in 10–15% of ovarian cancers, poly(ADP ribose) polymerase (PARP) inhibitors are transforming the treatment landscape (41).

The first PARP inhibitor, olaparib is approved as a maintenance therapy in germline

BRCA-mutated patients with platinum-sensitive recurrent disease based on a randomized Phase 3 study (PFS 19.1 months versus 5.5 months) (42).

Commonly used treatments in the setting of recurrent platinum-resistant EOC nowadays include pegylated liposomal doxorubicin (PLD), paclitaxel (weekly) and topotecan (40, 43). These single agent chemotherapies were reported to result in PFS of 3-4 months, OS of about 12 months, and RRs ranging from 10% to 15% (32). Management of recurrent platinum-resistant EOC remains challenging due to toxicities associated with cytotoxic agents and emergent of drug resistance.

Studies have shown that EOC, particularly those of high-grade serous, is most likely associated with pattern of adaptive immune resistance and may be more likely to respond to immune checkpoint inhibitors (44, 45). Immune checkpoint inhibitors are being extensively tested in the clinic for treatment of recurrent EOC. To date, anti-PD-1/PD-L1 monotherapy have demonstrated similar RRs and PFS as single agent chemotherapy in platinum-resistance disease in small Phase 1/2 studies (46, 47, 48). However, durable responses were noted with avelumab, nivolumab and pembrolizumab which created enthusiasm as durable responses are atypical in this setting. A randomized Phase 3 study evaluating avelumab in combination with PLD in patients with platinum-resistant/refractory ovarian cancer is currently underway (49).

The current study (ACT15377) will evaluate the safety, tolerability, and RRs of isatuximab in combination with atezolizumab as primary objective, in patients with platinum-resistant/ refractory recurrent EOC, who received no more than 3 lines of systemic therapy for platinum-sensitive disease and no prior therapy for platinum-resistant/refractory disease (specific to France: see Appendix 8 in Section 10.8.1).

2.2.1.4 Glioblastoma Multiforme

Adult GBM is one of the most aggressive primary cancers of the brain with a 5-year survival rate of 5% (50). Treatment of newly diagnosed GBM consists of maximal safe surgical resection, followed by radiotherapy with concurrent and maintenance temozolomide. Adding temozolomide improves median PFS to 6.9 months and OS to 14.6 months (51). Only 10% of patients survive longer than 5 years. O-6-methylguanine-DNA methyltransferase gene methylation status identifies patients most likely to benefit from the addition of temozolomide (52).

At tumor progression, treatment options are scarce and of poor effectiveness. Lomustine is one of the commonly used treatments for recurrent GBM with an OS of <8.6 months, RRs of 4-5%, and PFS rate at 6 months of 8-19% (median PFS <2 months) (53, 54, 55). Bevacizumab was approved by the US FDA for treatment of recurrent GBM based on RRs of

20-26% in two Phase 2 studies (25, 26). However, the improved RRs of bevacizumab did not translate into meaningful OS (<10 months versus <8.6 months for lomustine). It has been hypothesized that the pseudoresponse of bevacizumab is attributed to its normalization effect as an anti-angiogenic agent which interferes with magnetic resonance imaging (MRI) interpretation during disease assessment (21).

Glioblastoma multiforme is recognized as an immunosuppressive neoplasm due to activation of various immune escape mechanisms including the PD-1/PD-L1 pathway. Upregulation of PD-L1 expression was detected in >70% of recurrent GBM tumor specimens, along with sparse-to-moderate density of tumor infiltrating lymphocytes (22). Contrary to conventional belief where immune responses were limited in the brain due to the blood brain barrier (BBB), the BBB has selective permeability for immune cells regulating the brain microenvironment. Glioblastoma cells are also known to release factors that disrupt the BBB, permitting infiltration of activated macrophages and lymphocytes (23, 24). Tumor-specific immune memory response has been demonstrated in orthotopic immunocompetent murine glioblastoma model where treatment with immune checkpoint inhibitors including anti-PD-1/PD-L1 led to long-term survival. In particular, increased activated CD8+ and natural killer cells, decreased suppressive immune cells were observed in the tumor microenvironment and draining cervical lymph nodes (56). Multiple clinical trials are ongoing to evaluate PD-1/PD-L1 inhibitors as a monotherapy or in combination for treatment of recurrent GBM. Although in the Phase 3 CheckMate 143 study, single agent nivolumab did not improve OS in patients with recurrent GBM compared to bevacizumab

(9.8 versus 10 months), durable response was observed with nivolumab (DoR 11 versus

5.3 months) (30). CD38 protein expression was observed in glioblastoma biopsies, suggesting that addition of anti-CD38 therapy to anti-PD-1/PD-L1 may potentiate tumor-specific immune response (see Section 2.1).

2.2.2 Isatuximab

Isatuximab (SAR650984) is a mAb that binds selectively to a unique epitope on the human surface antigen CD38. Isatuximab kills tumor cells via multiple biological mechanisms; antibody-dependent cellular-mediated cytotoxicity, antibody-dependent cellular-mediated phagocytosis, complement-dependent cytotoxicity and direct induction of apoptosis

(pro-apoptosis) without crosslinking. Isatuximab treatment of CD38-expressing cells also results in inhibition of CD38 enzymatic activity.

At the cut-off date of 05 January 2018, a total of 675 patients were treated with isatuximab. All patients had hematological malignancy.

Refer to the isatuximab Investigator's Brochure for the most updated nonclinical and clinical

studies of isatuximab.

2.2.3 Atezolizumab

Atezolizumab is a humanized immunoglobulin G1 mAb that targets PD-L1 and inhibits the interaction between PD-L1 and its receptors, PD-1 and B7-1 (also known as CD80), both of which function as inhibitory receptors expressed on T cells. Therapeutic blockade of PD-L1 binding by atezolizumab has been shown to enhance the magnitude and quality of tumor-specific T cell responses, resulting in improved anti-tumor activity (57, 58). Atezolizumab has minimal binding to Fc receptors, thus eliminating detectable Fc-effector function and associated antibody-mediated clearance of activated effector T cells.

Atezolizumab shows anti-tumor activity in both nonclinical models and cancer patients and is being investigated as a potential therapy in a wide variety of malignancies. Atezolizumab is being studied as a single agent in the advanced cancer and adjuvant settings, as well as in combination with chemotherapy, targeted therapy, and cancer immunotherapy.

Atezolizumab is approved in multiple countries for the treatment of urothelial carcinoma (UC) and for the treatment of non-small cell lung cancer (NSCLC).

Refer to the atezolizumab Investigator's Brochure for details on nonclinical and clinical studies.

The current study (ACT15377) will evaluate the safety, tolerability, and PFS rate at 6 months (historic benchmark for GBM) of isatuximab in combination with atezolizumab as primary objective, in patients with recurrent GBM.

2.3 BENEFIT/RISK ASSESSMENT

Overall, scientific rationale (see Section 2.1) and the anticipated possible benefit/risk ratio of isatuximab in combination with atezolizumab support the conduct of study ACT15377 in participants with HCC, SCCHN, EOC, and GBM.

2.3.1 Benefits

Refer to Section 2.1.

2.3.2 Potential and identified risks

2.3.2.1 Isatuximab

Isatuximab has been investigated either as monotherapy or in combination in patients with hematological malignancies. The safety profile of isatuximab monotherapy has been best characterized in study TED10893 (Phase 1 and Phase 2, including 181 patients with MM), where the most common TEAEs, excluding the AEs corresponding to laboratory

abnormalities, include IARs, fatigue, nausea, upper respiratory infection, cough, back pain and diarrhea. Infusion-associated reactions occurred in 49.4% of the patients from TED10893 Phase 1 (concluded).

The IARs associated with isatuximab in patients who are administered appropriate primary prophylaxis (see also Section 2.3.4) are most common with the first administration of the drug, are not dose-dependent, are Grade 1 to 2 severity, are manageable with standardized precautions detailed in each study protocol, are resolved either spontaneously or with standard medication by the next day following the infusion, and the patients do not appear to sustain sequelae. The IARs generally do not cause treatment discontinuation, and do not tend to recur at subsequent administrations of isatuximab.

In addition to the occurrence of IARs, cytokine release syndrome, influenza-like illness, and fever have also been observed in patients treated with isatuximab; these reactions may involve immunogenicity mechanisms (human antihuman antigen) and hypersensitivity reactions, and are well-known to occur in association with other therapeutic mAb proteins. These adverse reactions, whether acute or delayed, may be serious and systemic (eg, anaphylactic reaction).

Please refer to the current version of the isatuximab Investigator's Brochure.

2.3.2.2 Atezolizumab

Atezolizumab has been investigated as monotherapy or in combination with other therapeutic regimens in multiple indications including HCC, SCCHN, EOC, and GBM. The safety profile of atezolizumab as a monotherapy has been best characterized in its approved indications including locally advanced or metastatic UC and metastatic NSCLC. The most common adverse reactions (≥20%) in these patients include fatigue, decreased appetite, nausea, and constipation, urinary tract infection (UC), diarrhea (UC), pyrexia (UC), dyspnea (NSCLC), cough (NSCLC), and musculoskeletal pain (NSCLC). Other important identified risks of atezolizumab consist of infusion-related reactions, and immune-related AEs (irAEs). Specifically, irAEs that were identified as risks for atezolizumab include immune-related pneumonitis, immune-related hepatitis, immune-related colitis, immune-related endocrinopathies, immune-related meningoencephalitis. Immune-related AEs are primarily manageable either by steroid treatments or withholding atezolizumab treatment. Recently, a new risk of SCARs has been identified, this risk is rare, potentially fatal, and mainly constituted by erythema multiforme, acute generalized exanthematous pustulosis, Stevens-Johnson syndrome (SJS), Toxic Epidermal Necrolysis (TEN), and drug rash with eosinophilia and systemic symptoms (DRESS).

Refer to the latest version of atezolizumab Investigator's Brochure for most updated details.

2.3.3 Potential risk related to the combination

Based on the available clinical data from each individual drug, the potentially overlapping adverse drug reactions (ADRs) anticipated with the isatuximab and atezolizumab combination consist mainly of IAR, pyrexia, and pneumonia, which are all manageable.

The irAEs specific to atezolizumab have not been identified as potential risks of isatuximab. The participants in the current study will be monitored according to the atezolizumab Investigator's Brochure, with additional preventative measures as described in detail below.

2.3.4 Preventative measures to minimize the risk from the combination

To minimize the risk of IARs, all the participants treated with isatuximab should routinely receive primary prophylactic treatment with diphenhydramine 25 to 50 mg IV (or equivalent), methylprednisolone 100 mg IV (or equivalent), ranitidine 50 mg IV, acetaminophen 650 to 1000 mg orally, and montelukast 10 mg orally, 30 to 60 minutes (and never longer than 60 minutes) prior to the isatuximab infusion to minimize the incidence and severity of IAR. To further mitigate the incidence and severity of IARs, it is recommended that the initial infusion rate of isatuximab should not exceed 175 mg of isatuximab per hour. In the absence of IARs after 1 hour of infusion, the infusion rate can be increased by 50 mg/hour increments every 30 minutes, to a maximum of 400 mg/hour. In the event of an IAR during study treatment infusion, action will be taken as per Section 10.21, Metamizole (dipyrone) is prohibited in treating atezolizumab associated infusion-associated reactions, due to its potential for causing agranulocytosis.

Guidelines for medical management of infusion-associated reactions are provided in Table 23.

Criteria for optional premedication for IARs:

- For a patient who has no IAR for the first 4 infusions: Premedication for the subsequent infusions is optional at the Investigator's discretion. However, if during the subsequent infusions without premedication the patient experiences an IAR (any grade), premedication must be restarted for all subsequent infusions.
- If a patient develops an IAR Grade ≤2 during their first infusion only and then experiences no further IARs during their next 3 infusions: The Investigator should discuss with the

Sponsor Medical Monitor when considering omitting premedication for the next infusion. If no IAR is observed for the next infusion without premedication, premedication is optional for the subsequent infusions at the Investigator's discretion. However, if during the next

infusion without premedication the patient experiences an IAR (any grade), premedication must be restarted for all subsequent infusions.

To minimize the risk of potential immune-related TEAEs related to atezolizumab, the exclusion criteria in the current study include:

- Treatment-related immune-mediated (or immune-related) AEs from immune-modulatory agents (including but not limited to anti-CTLA-4 mAbs) that caused permanent discontinuation of the agent, or that were Grade 3 or 4 in severity, or that have not resolved to baseline at least 3 months prior to initiation of IMP.
- Comorbidity requiring systemic corticosteroid therapy (>10 mg prednisone/day or equivalent for patients with HCC, SCCHN, and EOC). Physiologic replacement doses are allowed even if they are >10 mg of prednisone/day or equivalent, as long as they are not being administered for immunosuppressive intent.
- Active, known, or suspected autoimmune disease.
- History of or current interstitial lung disease or pneumonitis (radiation pneumonitis in the radiation field is permitted); history of thoracic radiation received thoracic radiation therapy of >30 Gy within 6 months of the first dose of trial treatment.
- History of moderate immune-mediated ADRs (eg, colitis, hepatitis, etc).

Additionally, careful monitoring of AEs and laboratory abnormalities, continuous direct communication between the Investigators and the monitoring team, and the adherence to the dose modification rules specified in the study protocol, are the continuous measures that will minimize the risks in study participants.

General guidelines for the management of irAEs, including some specific irAEs such as pneumonitis, hepatitis, colitis, myocarditis, meningoencephalitis, pancreatic AEs, endocrine AEs, ocular AEs, dermatologic AEs, neurologic AEs, are provided in Appendix 21: Section 10.21).

2.3.5 Conclusion

Overall, the anticipated benefit/risk ratio of isatuximab in combination with atezolizumab supports the conduct of study ACT15377 in patients with advanced HCC, SCCHN, EOC, and GBM.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of ACT15377 may be found in the Investigator's Brochure SAR650984 – Isatuximab and Investigator's Brochure-atezolizumab.

3 OBJECTIVES AND ENDPOINTS

Table 1 - Objectives and endpoints

• •	
• •	
• •	
• • Phase 2: To assess response rate (RR) of isatuximab in combination with atezolizumab in participants with HCC or SCCHN or EOC.	• • RR defined as the proportion of patients with complete response and partial response as best overall response (assessed by Investigators using RECIST 1.1 see Appendix 11: Section 10.11).
• • Phase 2: To assess the progression free survival rate at 6 months (PFS-6) of isatuximab in combination with atezolizumab, or as a single agent in participants with GBM	• PFS-6 defined as the PFS rate at 6 months (assessed by Investigators using Response Assessment for Neuro-Oncology [RANO] criteria).
Secondary	
• • To evaluate the safety (in Phase 2) profile of isatuximab monotherapy (GBM only), or in combination with atezolizumab	• • AEs/serious AEs and laboratory abnormalities (in Phase 2)
• • To evaluate the immunogenicity of isatuximab and atezolizumab	• • Incidence rate of anti-drug antibodies development (ADA: anti-isatuximab and anti-atezolizumab antibodies)
• • To characterize the pharmacokinetic (PK) profile of isatuximab single agent (GBM only) and atezolizumab in combination with isatuximab.	• PK assessed from concentrations of isatuximab (non-compartmental analysis and population PK approach) and atezolizumab (population PK approach).
• • To assess overall efficacy of isatuximab in combination with atezolizumab, or single agent (GBM only) and disease control rate (DCR) defined as the	• Best percent-change from baseline in Tumor burden change,

only) sum of the complete response, partial response and

stable disease rates, duration of response (DoR),

PFS (HCC, SCCHN, EOC per RECIST 1.1 and GBM per RANO), RR (GBM only, per RANO criteria)

Tertiary/exploratory • • To explore additional efficacy parameters of isatuximab in combination with atezolizumab, or single agent (GBM only).	• For participants with HCC, SCCHN, and EOC: - RR, DCR, DoR, and PFS by modified Response Evaluation Criteria in Solid Tumors for immune-based therapies (iRECIST (see Appendix 16 Section 10.16),

Objectives	Endpoints
	• Time to response (TTR), time to progression (TTP) based on RECIST 1.1 and iRECIST, and overall survival (OS).
• •	For participants with HCC: • Alpha-fetoprotein (AFP) reduction from baseline and relation with clinical response. For participants with EOC: - CA125 response by Gynaecologic Cancer
• •	Intergroup (GCIG) criteria (See Appendix 17: Section 10.17) and relation with clinical response. For participants with GBM: • RR, DCR, DoR, and PFS by Immunotherapy
• •	Response Assessment in Neuro-Oncology (iRANO) (See Section 10.18),

	• OS-6 defined as the overall survival rate at 6 months, • TTR, TTP (based on RANO and iRANO) and OS.
• To evaluate the relationships between clinical • response and tumor markers as potential predictive biomarkers of response.	The relationship between clinical response and CD38 expression (in infiltrating immune cells and tumor cells), PD-L1 expression (in tumor cells) and immune contexture in tumor at baseline.
• To explore immune genetic markers which are • important for effector functions of Isatuximab as potential predictive markers of response.	Immune genetic determinants (such as polymorphisms in FCγR receptors) in blood at baseline.
• To perform PK/ pharmacodynamics analysis if • possible with any relevant pharmacodynamics markers mentioned above, and correlation with safety/efficacy endpoints.	Pharmacodynamic biomarkers in response to IMP: immunophenotype in peripheral blood, immune contexture in tumor biopsies and cytokine levels in plasma or serum from peripheral blood.
• •	Tumor mutational profile will be analyzed at baseline and upon treatment in plasma cell free DNA from peripheral blood and correlated to response to IMP.
• •	If sufficient clinical response is observable in Phase 1 and Phase 2 Stage 1 patients, analysis of Isatuximab enzymatic activity might be performed at baseline and upon treatment by measuring metabolites in plasma or serum from peripheral blood and correlated to response to IMP.
• •	If sufficient clinical response is observable in Phase 1 and Phase 2

Stage 1 patients, further characterization of the immune response might be performed by analysing humoral and T cell adaptive immune response at baseline and upon treatment in peripheral blood and correlated to response to IMP.

- Determination of exposure-response relationships with efficacy, safety, and biomarkers, if possible.

3.1 APPROPRIATENESS OF MEASUREMENTS

Each of the efficacy and safety assessments chosen for use in this study is considered well established and relevant in a hemato-oncology setting. In addition, suitable steps have been built into each of these assessments to ensure their reliability and accuracy and to minimize any risks to patient safety.

4 STUDY DESIGN

4.1 OVERALL DESIGN

This is a Phase 1/2 open-label, non-randomized, multi-center, safety, preliminary efficacy, and PK study of isatuximab in combination with atezolizumab, or isatuximab alone in participants with advanced malignancies. The study will be conducted in 2 parts (see Section 1.2 for study design schema):

4.1.1 Phase 1 (safety run-in):

Participants with HCC, SCCHN, EOC, or GBM will be enrolled in Phase 1.

Starting dose and de-escalation design:

Starting dose is 1200 mg once every 3 weeks (Q3W) for atezolizumab with isatuximab given 10 mg/kg once weekly (QW) for 3 weeks followed by Q3W (atezolizumab given first). The table below (Table 2) details the dosing schedule modification for Phase 1. Based on safety, alternative dosing schedule may be considered. Overall safety monitoring will be performed throughout the conduct of the study.

Table 2 - Dosing schedule modification for Phase 1

Dose level (DL)	Isatuximab	Atezolizumab
Starting dose	10 mg/kg QW × 3 ->Q3W	1200 mg Q3W
Minus -1 (DL-1)	5 mg/kg QW × 3 ->Q3W	1200 mg Q3W

Abbreviations: DL: Dose level; QW: once weekly, Q3W: once every 3 weeks.

The DLT observation period is 1 cycle (21 days).

At starting dose, up to approximately 8 patients will be treated and decision will be based on the DLTs assessed in the first 6 DLT-evaluable participants (1 cycle, 21 days):

- If ≤1/6 participant has DLT, the starting dose will be the RP2D.
- If 2/6 participants have DLT, 6 additional participants will be enrolled at starting dose level:
  - If a total of 2/12 participants treated at starting dose have DLT, starting dose will be the RP2D,
  - If a total of ≥3/12 participants have DLT, dose will be de-escalated to dose level minus 1 (DL-1).

- If ≥3/6 participants have DLT, dose will be de-escalated to DL-1.

An additional 6 participants may be enrolled at DL-1:

- If ≤1/6 participant has DLT, DL-1 will be the RP2D.
- If 2/6 participants have DLT, 6 additional participants will be enrolled at DL-1:
  - If a total of 2/12 participants treated at starting dose have DLT, DL-1 will be the RP2D,
  - If a total of ≥3/6 or ≥3/12 participants have DLT, an alternative dose/schedule might be considered from a safety viewpoint by the Sponsor.

Investigational medical product initiation in each patient treated in Phase 1 is to be staggered by at least 3 days.

Dose limiting toxicity:

Any AEs specified below occurring during the first cycle of treatment, unless due to disease progression or an obviously unrelated cause will be considered a DLT, if confirmed by the Study Committee. The duration of the DLT observation period will be longer for participants who delay initiation of Cycle 2 due to treatment-related AE for which the duration must be assessed in order to determine if the event is a DLT. The NCI-CTCAE version 4.03 will be used to assess the severity of AEs.

Hematological abnormalities are defined as any of the following:

- Grade 4 neutropenia for 7 or more consecutive days.
- Grade 3 to 4 neutropenia complicated by fever (temperature ≥38.5°C on more than 1 occasion) or microbiologically or radiographically documented infection.
- Grade 3 thrombocytopenia associated with clinically significant bleeding requiring clinical intervention, or Grade 4 thrombocytopenia.

- Findings consistent with a Hy's law case, consisting of all the following 3 components:
  - Grade ≥2 AST or ALT elevation simultaneous with Grade ≥2 total bilirubin elevation without initial findings of cholestasis (such as elevated serum alkaline phosphatase [ALP]),
  - No other reason can be found to explain the combination of increased AST or ALT and bilirubin, such as viral hepatitis A, B, or C, pre-existing or acute liver disease (such as HCC or liver metastasis), or in absence of another drug capable of causing the observed injury.
- Grade 4 non-hematologic AE, except:

- Either Grade 4 AST, Grade 4 ALT, or bilirubin elevation Grade 4 that improve to Grade ≤2 within 3 weeks of onset for participants with SCCHN, EOC, or GBM without liver metastasis,
- Either Grade 4 AST, Grade 4 ALT, or bilirubin elevation Grade 4 that improve to Grade ≤3 within 3 weeks of onset for participants with liver metastasis or HCC with abnormal baseline value (ie, Grade 1 or 2),
- Grade 4 laboratory abnormality that is resolve within 3 days with or without therapeutic intervention.

- Grade 3 to 4 cytokine release syndrome.
- Grade 3 non-hematological AE lasting >3 days with optimal supportive care, except:
  - Grade 3 fatigue,
  - Allergic reaction/hypersensitivity attributed to isatuximab or atezolizumab,
  - Grade 3 laboratory abnormality that is asymptomatic,
  - Either Grade 3 AST, Grade 3 ALT, or bilirubin elevation Grade 3, for participants with liver metastasis or HCC with abnormal baseline value (ie, Grade 1 or 2),
  - Grade 3 nausea, vomiting, or diarrhea if well controlled by systemic medication within 7 days,
  - Grade 3 immune-related AE that improves to Grade ≤1 within 3 weeks of onset,
  - Grade 3 arthralgia that can be adequately managed with supportive care or that improves to Grade ≤2 within 7 days,
  - Grade 3 elevation of serum creatinine that is not accompanied by elevations in blood urea nitrogen (BUN) or other signs of renal injury or that can be attributed to other etiologies such as disease-related obstructions,
  - Grade 3 autoimmune thyroiditis or other endocrine abnormality that can be managed by endocrine therapy or hormone replacement,
  - Grade 3 infusion reaction,
  - Grade 3 skin rash that improves to Grade ≤1 within 7 days with appropriate supportive care.
- Delay in initiation of Cycle 2 more than 14 days due to treatment-related laboratory abnormalities/AE.
- In addition, any other AE that the Study Committee deems to be dose limiting, regardless of its grade, may also be considered as DLT.

Maximum tolerated dose and Recommended Phase 2 dose:

Any DLT observed during Cycle 1, and also overall safety including all the AEs occurring during treatment, unless due to disease progression or an obviously unrelated cause, will be taken into consideration by a Study Committee for the determination of the MTD and RP2D for the isatuximab and atezolizumab combination.

The MTD is defined as the highest dose level at which no more than 1 out of 6 participants

(starting dose or DL-1) or 2 out of 12 participants (starting dose) experience an IMP related DLT. The RP2D is defined as the dose selected for the Phase 2 portion.

Following the identification of the RP2D, Phase 2 will be initiated.

4.1.2 Phase 2 (efficacy signal search with a 2-stage design in each cohort):

Phase 2 may include up to 9 cohorts: Cohorts A, B, C, and D-1 will be initiated in parallel, while other cohorts of the same tumor type will be open depending on results observed at the end of Stage 2 of the corresponding initial tumor type cohort.

- Cohort A: HCC, isatuximab and atezolizumab combination.
- Cohort B: SCCHN, isatuximab and atezolizumab combination.
- Cohort C: EOC, isatuximab and atezolizumab combination.
- Cohort D-1: GBM, isatuximab and atezolizumab combination.
- Possibly Cohort D-2: GBM, isatuximab monotherapy.
- Possibly Cohort E: isatuximab and atezolizumab combination in participants with one tumor type (HCC, SCCHN, EOC, or GBM), or isatuximab monotherapy (GBM only), without initial isatuximab weekly dosing.

A 2-stage design will be used in each cohort. Enrollment in Cohort D-2 may start only if clinical benefit is observed in Cohort D-1 at the end of Phase 2 Stage 2 as determined by the Sponsor after consulting with Study Committee.

The participants treated at the RP2D of isatuximab and atezolizumab in combination during Phase 1 will be included in the efficacy analysis together with participants of the same tumor type in Phase 2 Stage 1. Based on the predefined number of objective responses in participants with SCCHN, HCC, EOC, or the predefined PFS-6 in participants with GBM, as well as any other relevant data observed within a treatment cohort in Phase 2 Stage 1, the study will proceed with Phase 2 Stage 2. After enrollment completion of Phase 2 Stage 1, if efficacy results do not warrant initiation of Stage 2, enrollment will be paused until sufficient results or analyses warrant initiation of Phase 2 Stage 2. In the case of inadequate efficacy for a cohort at interim analyses, the Sponsor will notify study sites regarding modification or termination of study procedures/scheduled activities for patients in that specific cohort.

For participants with GBM, if clinical benefit is observed in Cohort D-1 at the end of Phase 2

Stage 2 as determined in Section 9.2, an isatuximab monotherapy cohort may be initiated

(Cohort D-2). Participants with GBM will be enrolled into Cohort D-2, isatuximab monotherapy (Phase 2 Stage 1). The isatuximab single agent dose and schedule for Cohort D-2 will be determined based on results from Cohort D-1.

Based on the positive efficacy signal and the totality of data observed within a treatment cohort at end of Phase 2 Stage 2, the Sponsor may decide to further study in the same indication either isatuximab Q3W in combination with atezolizumab, or isatuximab Q3W as monotherapy in participants with GBM. This schedule without the initial weekly dosing may be more practical for participants and health care providers. Objectives and study design considerations for these cohorts are the same as those for other cohorts in the same tumor type, respectively.

4.2 DURATION OF STUDY PERIOD (PER PARTICIPANT)

The duration of the study for a participant will include a screening period (up to 28 days), a treatment period (up to 2 years), a safety follow-up period (90 days), and every 90 days follow-up visits or phone calls until death or study cut-off.

Treatment period: The cycle duration is 21 days. Participants will continue treatment until disease progression confirmed by imaging 4 weeks after initial evidence of progression, unacceptable AE, patient's decision to stop treatment, 2 years of uninterrupted delivery of IMP(s) without documented PD.

Safety follow-up period: After treatment discontinuation, participant will return to the study site

30 days (±7 days) after the last dose of IMP(s), or when the participant receives another anti-cancer therapy, whichever is earlier, for EOT assessments. In addition, there will be an extended safety follow-up period for 90 days after the last dose of IMP(s) for ADA assessment and for safety assessment.

Participants who discontinue the study treatment without PD will be followed at 90 days (±7 days) for disease assessment.

Survival follow-up period: The further follow-up schedule beyond 90 days after last dose of IMP(s) is according to the disease progression status:

- Participants who discontinue study treatment due to PD: phone call follow-up will be done every 90 days from the date of last IMP(s) administration until death or study cut-off date.
- Participants who discontinue the study treatment without PD: will be followed every 90 days for disease assessment until confirmation of PD or start treatment

with another anti-cancer therapy, or until study cut-off date whichever comes first. After PD, participant will be followed by phone call until death or study cut-off date.

- Participants who are still on study treatment after study cut-off date: will continue to receive study treatment if they benefit, and will undergo planned study procedures (except PK and ADA) until confirmation of PD, or start with another anti-cancer therapy, or treatment period ended, whichever comes first. All SAEs still ongoing at the end of the study treatment, and all AEs considered related to study treatment still ongoing or occurring after the end of study treatment, which will be followed until resolution/stabilization.

4.3 SCIENTIFIC RATIONALE FOR STUDY DESIGN

This is a Phase 1/2 open-label, non-randomized, multi-center, safety, preliminary efficacy, and PK study of isatuximab (SAR650984) in combination with atezolizumab or isatuximab alone in patients with advanced malignancies.

Treatment beyond the second or third line in those 4 indications remains challenging with a significant unmet need for patients with advanced malignancies. Combination strategies with immunotherapy agents have a potential to increasing their individual effectiveness in these patients.

Phase 1 is designed to characterize the safety and tolerability of isatuximab in combination with atezolizumab in patients with unresectable HCC, platinum-refractory recurrent/ metastatic SCCHN, platinum-refractory EOC, or recurrent GBM, and to confirm the RP2D.

Phase 2 is designed to assess RR of isatuximab in combination with atezolizumab in patients with HCC, or SCCHN, or EOC and to assess the PFS rate at 6 months (PFS-6) of isatuximab in combination with atezolizumab, or as a single agent in patients with GBM.

4.4 JUSTIFICATION FOR DOSE

Atezolizumab is administered as an IV infusion every 3 weeks at 1200 mg dose.

A flat IV atezolizumab dose of 1200 mg Q3W was selected as this is the standard dose used in the approved indications (UC and NSCLC).

In patients with MM, isatuximab exhibits non-linear PK due to the presence of target-mediated drug disposition. In addition, tumor burden impacts the PK of isatuximab.

Based on safety, efficacy, PK, and PK/pharmacodynamic analyses, the dose/schedule of isatuximab when used in combination with other therapies for the treatment of MM is 10 mg/kg QW × 4 followed by once every 2 weeks (Q2W). The half-life of isatuximab associated to the linear elimination is 18 days and we hypothesized that the immuno-

modulatory mechanisms of isatuximab will be mainly involved in the pharmacological activity of isatuximab; therefore, a less intensive schedule of administration for isatuximab is proposed compared to the schedule used in

patients with MMs: 10 mg/kg QW × 3 followed by Q3W. Of note, based on updated pharmacokinetic characterization of isatuximab in 2019, the plasma half-life has been re-estimated to 28 days.

Based on safety, efficacy, PK, and PK/pharmacodynamic data analyses, the dose/schedule of isatuximab when used as monotherapy for the treatment of MM is 20 mg/kg QW × 4 followed by Q2W. However, based on the reasons mentioned above and the hypothesis that tumor burden will be lower in patients with HCC, or SCCHN, or EOC, or GBM cancer compared to MM (ie, less target-mediated drug disposition), and because isatuximab monotherapy demonstrated activity at doses ≥10 mg/kg with no clear dose response between 10 mg/kg and 20 mg/kg, 10 mg/kg QW × 3 followed by Q3W is proposed to be tested in the monotherapy arm of this study.

Once the plan of care is established with isatuximab 10 mg/kg QW × 3/Q3W, Q3W may be tested as the loading period may not be necessary to ensure activity.

4.5 END OF STUDY DEFINITION

A participant is considered to have completed the study if he/she has completed all phases of the study including the last visit or the last scheduled procedure shown in the Schedule of Activities (SoA).

The end of study will occur at the study cut-off planned at 12 months after the last participant enters the study or when all participants have had the opportunity to complete the EOT visit 30 days after the last study treatment administration, whichever is the latest.

5 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 INCLUSION CRITERIA

Participants are eligible to be included in the study only if all of the following criteria apply:

Age

I 01. Participant must be at least 18 years of age, at the time of signing the informed consent.

I 02. For HCC, SCCHN, and EOC, disease location amenable to mandatory tumor biopsy at baseline (unless clinically unfeasible and after discussion with Sanofi Medical Monitor in Phase 1 and Phase 2 Stage 1, mandatory in Phase 2 Stage 2), and at Cycle 2 Day 1 if clinically feasible. Fine needle aspirates are not acceptable. Needle or excisional biopsies, or resected tissue are required. Provision of archival tumor tissue sample obtained at the time of or after progression of immediate previous line of anti-cancer treatment is allowed to replace mandatory baseline biopsy. For GBM, it is mandatory to provide archival tumor tissue sample. The biopsy taken at baseline and potentially Cycle 2 Day 1 should be from a lesion not previously irradiated (preferred), or the new growth area of a lesion that grows after irradiation.

I 03. At least one measurable lesion for HCC, SCCHN, EOC (per RECIST 1.1

[Appendix 11: Section 10.11]). Tumor lesions previously irradiated, or received other locoregional therapy, are usually not considered measurable unless there has been documented progression in the lesion.

I 04. Based on the Investigator's judgement, at this time, other anti-cancer therapy is not the best option for this specific patient.

For patients with HCC:

I 05. Histologically confirmed unresectable HCC (excluding fibrolamellar and mixed hepatocellular/cholangiocarcinoma). Radiology diagnosed HCC as per American Association for the Study of Liver Diseases criteria needs to be confirmed by histology before initiation of IMP.

I 06. Barcelona Clinic Liver Cancer (BCLC) Stage C disease, or BCLC Stage B disease not amenable to locoregional therapy or refractory to locoregional therapy, and not amenable to a curative treatment approach (see Appendix 12: Section 10.12).

I 07. Child Pugh Class A liver score within 14 days of initiation of IMP (see Appendix 13: Section 10.13).

I 08. Documentation of progressive disease (PD) during or after treatment with either sorafenib or lenvatinib, or intolerance to the therapy. Intolerance is defined as permanent discontinuation of sorafenib or lenvatinib due to occurrence of ≥CTCAE Grade 2 treatment-related adverse event (AE) which (1) persisted in spite of comprehensive supportive therapy according to institutional standards AND (2) persisted or recurred after sorafenib or lenvatinib treatment interruption of at least 7 days and dose reduction by one dose level.

For patients with SCCHN:

I 09. Histologically confirmed recurrent or metastatic SCCHN (oral cavity, pharynx, larynx),

not amenable to local therapy with curative intent (surgery or radiation therapy with or without chemotherapy).

I 10. Documentation of tumor recurrence or PD within 6 months of last platinum-based therapy in primary (ie, unresectable locally advanced disease with radiation), recurrent, or metastatic setting. Clinical progression after platinum-based therapy is defined as progression of a lesion at least 10 mm in size that is amenable to caliper measurement (eg, superficial skin lesion as per RECIST 1.1) or a lesion that has been visualized and photographically recorded with measurements and shown to have progression are eligible.

I 11. Received and failed up to 2 lines of prior systemic anti-cancer therapy. A line of systemic chemotherapy is defined as any chemotherapy that was administered as part of primary therapy for SCCHN (eg, induction or concurrent chemo-radiotherapy) or any single-agent or multiple-agent chemotherapy regimen that was administered after a diagnosis of recurrent and/or metastatic SCCHN.

I 12. Resting baseline O2 saturation by pulse oximetry of ≥92% at rest.

For patients with EOC:

I 13. Histologically confirmed advanced epithelial ovarian, fallopian tube, or peritoneal cancer, excluding mucinous histology but including malignant mixed Müllerian tumors with high grade serous component.

I 14. Platinum-resistant/refractory disease (specific to France only: see definition to I14 in Section 10.8.1):

- Received up to 3 lines of prior platinum-containing therapy when the disease was platinum-sensitive, and,
- The patients should not have received any systemic therapy for platinum-resistant/refractory disease. Platinum-resistant/refractory disease is defined as PD within 6 months following the last administered dose of platinum-containing therapy (resistant), or lack of response or disease progression while receiving the most recent platinum-containing therapy (refractory), respectively,
- Previous treatment with up to one line of PARP inhibitor therapy is allowed.

For patients with GBM:

I 15. Have histologically confirmed glioblastoma. Patients with the original histology as low grade glioma are NOT eligible.

I 16. Documentation of PD or first recurrence during (after at least 12 weeks from completion of irradiation) or after temozolomide maintenance therapy for newly diagnosed GBM treated with 1st line radiotherapy plus concurrent temozolomide. PD occurred within

12 weeks from completion of irradiation can only be defined by (1) new enhancement outside of the radiation field, or (2) unequivocal histological confirmation. Patients who received additional surgery after first recurrence ARE eligible.

Sex

I 17. Male or Female

I 18. Capable of giving signed informed consent as described in Appendix 1

(Section 10.1.2) which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

5.2 EXCLUSION CRITERIA

Participants are excluded from the study if any of the following criteria apply:

E 01. Eastern Cooperative Oncology Group (ECOG) performance status of ≥2 (for patients with HCC, SCCHN, and EOC), or Karnofsky performance score of ≤70 (for patients with GBM (see Appendix 14: Section 10.14).

E 02. Predicted life expectancy <3 months.

E 03. Active brain metastases or leptomeningeal metastases. Patients with asymptomatic central nervous system metastases which have been stable (defined as without evidence of progression by MRI for at least 28 days prior to initiation of IMP and any neurologic symptoms have returned to baseline) following treatment with surgery or radiation therapy are eligible.

E 04. Symptomatic or impending cord compression at study entry, unless appropriately treated beforehand and remained clinically stable and asymptomatic.

E 05. Comorbidity requiring systemic corticosteroid therapy (>10 mg prednisone/day or equivalent for patients with HCC, SCCHN, and EOC). Physiologic replacement doses are allowed even if they are >10 mg of prednisone/day or equivalent, as long as they are not being administered for immunosuppressive intent.

E 06. Significant cardiac dysfunction such as New York Heart Association classification for chronic heart failure III-IV, symptomatic coronary artery disease, major clinically significant electrocardiogram (ECG) abnormality, clinically significant ventricular arrhythmias; myocardial infarction within 6 months; unstable, poorly controlled angina pectoris despite treatment.

For patients with SCCHN:

E 07. Histologically confirmed recurrent or metastatic carcinoma of the nasopharynx, squamous cell carcinoma of unknown primary, and salivary gland or non-squamous histologies (eg, mucosal melanoma).

For patients with EOC:

E 08. Non-epithelial tumor or ovarian tumors with low malignant potential (ie, borderline tumors, eg, low grade serous).

For patients with GBM:

E 09. Have more than 1 prior recurrence.

E 10. Presence of diffuse leptomeningeal disease or extracranial metastases.

E 11. Tumors primarily localized or originated from the brainstem or spinal cord.

E 12. Requires treatment with dexamethasone >4 mg/day, or bioequivalent for at least 3 consecutive days, within 2 weeks before initiation of IMP.

E 13. Mental impairment that may compromise ability to give informed consent and comply with the requirements of the study.

E 14. Uncontrolled seizure by medication.

E 15. Prior treatment with an agent (approved or investigational) that blocks CD38 (patients who had previously participated in a study with an anti-CD38 but have written confirmation they were on control arm are allowed).

E 16. Prior treatment with an agent (approved or investigational) that blocks the PD-1/PD-L1 pathway (patients who had previously participated in a study with an anti-PD-1/PD-L1 but have written confirmation they were on control arm are allowed).

E 17. Prior intravenous (IV) cytotoxic chemotherapy, antineoplastic biological therapy within 21 days from initiation of IMP, major surgery with 28 days from initiation of IMP; and prior oral cytotoxic chemotherapy, hormonal therapy, tyrosine kinase inhibitor therapy, or completed palliative radiotherapy within 14 days from initiation of IMP.

For patients with GBM:

E 18. Received vascular endothelial growth factor (VEGF)/VEGF receptor directed therapy.

E 19. Locally directed therapies (except radiotherapy) including but not limited to stereotactic radiosurgery, re-irradiation, Gliadel, and therapeutics administered by direct injection or convection-enhanced delivery within 6 months before initiation of IMP.

Prior/concurrent clinical study experience

E 20. Last dose of prior investigational agent within 28 days from initiation of IMP.

E 21. Inadequate organ and bone marrow function at the Screening visit:

- White blood cell (WBC) <2000/mm3 (2.0 × 109/L),
- Absolute neutrophil count (ANC) <1500/mm3 (1.5 × 109/L),
- Platelets <100 × 109/L for patients with SCCHN, EOC and GBM; or <75 × 109 /L for patients with HCC. Platelet transfusion is not allowed within 7 days before the screening hematological test,
- Hemoglobin <9 g/dL or <5.6 mmol/L (without transfusion within 1 week),
- Total bilirubin >2 upper limit of normal (ULN),
- Aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) >3 × ULN

(or >5 × ULN for patients with liver metastases or HCC),

- For Phase 1, patients without pre-existing or acute liver disease (including viral hepatitis, HCC or liver metastasis), total bilirubin >1.5 × ULN, AST and/or ALT >2 × ULN, ALP >2.5 × ULN,
- International normalized ratio (INR) >1.7 or prothrombin time >4 seconds above control for patients with HCC,
- Albumin <2.8 g/dL for patients with HCC,
- Estimated glomerular filtration rate (eGFR) <30 mL/min/1.73m2 (Modification of Diet in Renal Disease [MDRD] Formula).

E 22. Prior solid organ or bone marrow transplantation.

E 23. Treatment-related immune-mediated (or immune-related) AEs from immune-modulatory agents (including but not limited to anti-CTLA4-mAbs) that caused permanent discontinuation of the agent, or that were Grade 3 or 4 in severity, or that have not resolved to baseline at least 3 months prior to initiation of IMP.

E 24. History of Grade 3 immune-mediated ADRs (eg, colitis, hepatitis, etc).

E 25. Ongoing AEs (excluding alopecia and fatigue) caused by any prior anti-cancer therapy >Grade 1 (NCI-CTCAE v4.03).

E 26. Active, known, or suspected autoimmune disease.

E 27. History of or current interstitial lung disease or pneumonitis (radiation pneumonitis in the radiation field is permitted); history of thoracic radiation received thoracic radiation therapy of >30 Gy within 6 months of the first dose of trial treatment.

E 28. Receipt of a live-virus vaccination within 28 days of planned treatment start. Seasonal flu vaccines that do not contain live virus are permitted.

E 29. Known additional malignancy either progressing or requiring active treatment within the last 3 years (except for basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or in situ cervical cancer that has undergone potentially curative therapy).

E 30. Women of childbearing potential (WOCBP) or male patients with female partners of childbearing potential not protected by highly effective method of birth control and/or who are unwilling or unable to be tested for pregnancy (see Appendix 4: Section 10.4).

E 31. Pregnant or breastfeeding women or women who intend to become pregnant during participation in the study.

E 32. Known intolerance or hypersensitivity to any component of isatuximab, atezolizumab, or pre-medication.

E 33. History or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the patient's participation for the full duration of the trial, or is not in the best interest of the patient to participate, in the opinion of the treating Investigator.

E 34. Known uncontrolled HIV infection, active tuberculosis, or severe infection requiring parenteral antibiotic treatment.

E 35. Known uncontrolled hepatitis B virus (HBV) infection:

- Anti-HBV therapy started before initiation of IMP and HBV viral load <2000 IU/mL (104 copies/mL) are eligible. The anti-HBV therapy should continue throughout the treatment period.
- Positive anti-HBc, anti-HBs, negative HBsAg, and HBV virus load without HBV therapy are eligible.

E 36. Known untreated current HCV infection.

- Anti-HCV therapy started before initiation of IMP are eligible. The anti-HCV therapy should continue throughout the treatment period until seroconversion.
- Positive HCV antibody and undetectable HCV RNA without anti-HCV therapy are eligible.

For patients with HCC:

E 37. Esophageal or gastric variceal bleeding within the past 12 weeks.

E 38. Clinically apparent ascites on physical examination. Ascites detectable on imaging

studies only ARE eligible.

E 39. Complete portal vein or inferior vena cava occlusion, or cardiac involvement of HCC based on imaging.

E 40. Clinically diagnosed hepatic encephalopathy within 3 months before initiation of IMP.

E 41. Prior systemic therapy for HCC in the advanced (incurable) setting other than sorafenib or lenvatinib.

E 42. Locoregional therapy to liver (transcatheter chemoembolization, transcatheter embolization, hepatic arterial infusion, radiation, radioembolization, or ablation) within 4 weeks before initiation of IMP.

5.3 LIFESTYLE CONSIDERATIONS

Not applicable.

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently treated. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Patient who does not meet protocol entry criteria may be rescreened once during the open screening period, providing he/she meets at that time all inclusion and exclusion criteria. A different patient identification will be issued, while the other identification for this patient should be recorded as Screen Failure. There is no requirement for a waiting period between a screen failure date and the rescreening date. Patients that are rescreened must sign a new consent form and all screening procedures must be repeated.

6 STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

6.1 STUDY INTERVENTION(S) ADMINISTERED

INVESTIGATIONAL MEDICINAL PRODUCTS:

Table 3 - Overview of study interventions administered

Study intervention name	Isatuximab	Atezolizumab
Dosage formulation	Concentrated solution for infusion	Concentrated solution for infusion
Unit dose strength(s)/Dosage level(s)	20 mg/mL (500 mg/25 mL) isatuximab in 20 mM histidine, 10% (w/v) sucrose, 0.02% (w/v) polysorbate 80, pH 6.0	1200 mg/20 mL (60 mg/mL)
Route of administration and duration	Intravenous infusion as described in the pharmacy manual	Intravenous infusion over 60 (±15) minutes per administration. If the first infusion is tolerated, all subsequent infusions may be delivered over 30 (±10) minutes.
Dosing instructions	Phase 1 Starting dose: Isatuximab: 10 mg/kg weekly for 3 weeks (QW × 3; ie. on D1, D8, and D15 of Cycle 1), then every 3 weeks (Q3W) (ie, on Day 1 of each 21-day cycle) Atezolizumab (administrated before isatuximab): 1200 mg Q3W, (ie, on Day 1 of each 21-day cycle) Dose Level -1 (may be implemented if ≥3/12 with DLT or if ≥3/6 participants with DLT at starting dose): Isatuximab: 5 mg/kg QW × 3, then Q3W Atezolizumab (administrated before isatuximab): 1200 mg Q3W Phase 2:	

	For the combination Cohorts A, B, C, and D-1, atezolizumab will be administered first followed by isatuximab on Day 1 of each cycle. Isatuximab will be administered at the RP2D determined based on safety data from Phase 1. Monotherapy dose for GBM in Cohort D-2 will be determined based on results from Cohort D-1 and schedule of administration will be weekly for first cycle, followed by one dose every 3 weeks. For the possible Cohort E, implemented if positive results are observed in the Phase 2 Stage 2 one tumor type (same as A, B, C, or D-1/D-2), atezolizumab will be administered first followed by isatuximab on Day 1 of each cycle (for combination regimen), and isatuximab will be administered at the RP2D determined based on safety data from Phase 1RP2D without initial isatuximab weekly dosing.	
Amended Clinical Trial Protocol 05 ACT15377 – isatuximab	23-Nov-2020 Version number: 1	
Study intervention name	Isatuximab	Atezolizumab
Packaging and labeling	In single dose vials 30 mL (C1P2F2) glass vials fitted with elastomeric closure. The label contents will be in accordance with the local regulatory specifications and requirements. ISATUXIMAB will be presented as a concentrate for solution for infusion in vials containing 20 mg/mL (500 mg/25 mL) isatuximab in 20 mM histidine, 10% (w/v) sucrose, and 0.02% (w/v) polysorbate 80 at pH 6.0 buffer. This product will be supplied	In single dose vials Glass vial fitted with elastomeric closure. The label contents will be in accordance with the local regulatory specifications and requirements ATEZOLIZUMAB will be presented as a concentrate for solution for infusion in vials containing 60 mg/

	for parenteral administration as a sterile, nonpyrogenic, injectable, 20 mg/mL concentrate for solution for infusion, essentially free of visible particulates. Each vial will contain a nominal content of 500 mg isatuximab C1P2F2. The fill volume will be established to ensure removal of 25 mL.	mL. Each 20 mL vial of concentrate contains 1200 mg atezolizumab. After dilution, 1 mL of solution contains approximately 4.4 mg of atezolizumab.
	For participant administration, the appropriate volume of isatuximab will be diluted in an infusion bag of 0.9% sodium chloride solution. The final infusion volume corresponding to the dose of isatuximab will be administered for a period of time that will depend on the dose administered and will be based on protein amount given per hour.	Preferred diluents are: sodium chloride 9 mg/mL (0.9%) solution No incompatibilities have been observed between Tecentriq and intravenous bags with productcontacting surfaces of PVC, PE or polyolefin. In addition, no incompatibilities have been observed with in-line filter membranes composed of polyethersulfone or polysulfone, and infusion sets and other infusion aids composed of PVC, PE, polybutadiene, or polyetherurethane. The use of in-line filter membranes is optional.
	Preferred diluents are: 0.9% Sodium chloride for injection 100 mL, 250 mL or 500 mL bags in polyolefins (so covers also polyethylene (PE) or polypropylene (PP)) or polyvinyl chloride (PVC) (with DEHP) Or Dextrose 5% for injection 100 mL, 250 mL or 500 mL bags in polyolefins (so covers also PE or PP) or PVC (with DEHP).	
	Detailed instructions for dilution of the isatuximab concentrate are provided in the Pharmacy Manual.	Detailed instructions for dilution of the atezolizumab concentrate are provided in the Pharmacy Manual.
Manufacturer	Bulk Drug Product SANOFI AVENTIS DEUTSCHLAND GmbH FRANKFURT GERMANY Industriepark Höchst 65926 FRANKFURT GERMANY	Manufacturer of the biological active substance F. Hoffmann-La Roche AG Grenzacherstrasse 124 4070 Basel SWITZERLAND

Manufacturer responsible for batch release

Roche Pharma AG Emil-Barell-Strasse 1 79639 Grenzach-Whylen GERMANY

Rate and duration of infusion:

The duration of infusion for atezolizumab is 1200 mg over 60 minutes per administration. If the first infusion is tolerated, all subsequent infusions may be delivered over 30 minutes.

For isatuximab, the rate of infusion should be initiated at 175 mg/hour:

- First infusion: initiate infusion at 175 mg/hour. In the absence of IARs after 1 hour of infusion, increase infusion rate by 50 mg/hour increments every 30 minutes, to a maximum of 400 mg/hour.
- Subsequent infusions: initiate infusion at 175 mg/hour. In the absence of IAR after 1 hour of infusion, increase rate by 100 mg/hour increments every 30 minutes, to a maximum of 400 mg/hour.

NON INVESTIGATIONAL MEDICINAL PRODUCTS:

Non investigational medicinal products will be locally sourced and formulation may vary.

All participants will receive the following premedications to prevent or reduce incidence or severity of IARs, 30 to 60 minutes prior to the isatuximab infusion (no longer than 60 minutes). The premedication agents will consist of:

- Acetaminophen 650 to 1000 mg oral route (PO) (or equivalent).
- Ranitidine 50 mg IV (or equivalent).
- Diphenhydramine 25 to 50 mg IV (or equivalent).
- Methylprednisolone 100 mg IV (or equivalent).
- Montelukast 10 mg oral route (PO) (or equivalent).

Criteria for optional premedication for IARs:

- For a patient who has no IAR for the first 4 infusions: Premedication for the subsequent infusions is optional at the Investigator’s discretion. However, if during the subsequent infusions without premedication the patient experiences an IAR (any grade), premedication must be restarted for all subsequent infusions.
- If a patient develops an IAR Grade ≤2 during their first infusion only and then experiences no further IARs during their next 3 infusions: The Investigator

should discuss with the

Sponsor Medical Monitor when considering omitting premedication for the next infusion. If no IAR is observed for the next infusion without premedication, premedication is optional for the subsequent infusions at the Investigator's discretion. However, if during the next infusion without premedication the patient experiences an IAR (any grade), premedication must be restarted for all subsequent infusions.

When isatuximab and atezolizumab are to be administrated on the same day, the administration sequence is: atezolizumab, followed by premedications, followed by isatuximab.

When only isatuximab is to be administrated on a day, the administration sequence is: premedications, followed by isatuximab.

METHOD OF ASSIGNING PATIENTS TO THE STUDY:

All patients who signed the study ICF will be assigned a patient number. Each patient will receive an incremental identification number per site corresponding to their order of enrollment in the study. Those patients, who meet all the inclusion criteria and none of the exclusion criteria, will be eligible for registration in the study.

All eligible patients will be enrolled into the Phase 1 (safety run-in) of the study. Any proportion of patients with each tumor type can be enrolled.

Once RP2D has been determined, eligible patients will then enter in parallel the Phase 2 part of

Cohorts A, B, C, and D-1 depending on the type of tumor. If positive benefits observed from GBM Cohort D-1 Phase 2 Stage 2, an isatuximab monotherapy cohort (Cohort D-2) will be initiated for patient with GBM.

6.2 PREPARATION/HANDLING/STORAGE/ ACCOUNTABILITY

- The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
- Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.

- The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
- Further guidance and information for the final disposition of unused study interventions are provided in the pharmacy manual and/or monitoring plan.

Any quality issue noticed with the receipt or use of an IMP (deficiency in condition, appearance, pertaining documentation, labeling, expiration date, etc) must be promptly notified to the Sponsor. Some deficiencies may be recorded through a complaint procedure.

A potential defect in the quality of IMP may be subject to initiation of a recall procedure by the Sponsor. In this case, the Investigator will be responsible for promptly addressing any request made by the Sponsor, in order to recall the IMP and eliminate potential hazards.

Under no circumstances will the Investigator supply IMPs to a third party (except for DTP shipment, for which a courier company has been approved by the Sponsor), allow the IMPs to be used other than as directed by this clinical trial protocol, or dispose of IMPs in any other manner.

Storage conditions:

Isatuximab: Control of isatuximab storage conditions, especially control of temperature (eg, refrigerated storage), and information on in-use stability and instructions for handling the Sanofi compound should be managed according to the rules provided by the Sponsor.

Isatuximab is to be stored at +2°C to +8°C (36°F to 46°F), protected from light. All vials must be kept in their box until use. No protection from light is required for storage in the infusion bags.

Details of the storage conditions for the diluted solution are provided in the Pharmacy Manual.

Atezolizumab: Control of atezolizumab storage conditions, especially control of temperature (eg, refrigerated storage), and information on in-use stability and instructions for handling the compound should be managed according to the rules provided by the Sponsor.

Atezolizumab is to be stored at +2°C to +8°C (36°F to 46°F), protected from light. All vials must be kept in their box until use. No protection from light is required for storage in the infusion bags.

Details of the storage conditions for the diluted solution are provided in the Pharmacy

Manual.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

This is an open-label, non-randomized study; therefore, blinding is not applicable.

6.4 STUDY INTERVENTION COMPLIANCE

Administration of the IMP will be supervised by the Investigator or Sub-investigator.

The person responsible for drug dispensing is required to maintain adequate records of the IMPs.

These records (eg, drug movement form) include the date the IMPs are received from the Sponsor, dispensed to the participant and destroyed or returned to the Sponsor. The packaging batch number (IP number) and the treatment number on the vial must be recorded on the drug accountability form. The person responsible for drug administration to the participant will record precisely the date and the time of the drug administration to the participant.

6.4.1 Return and/or destruction of treatments

Partially-used and used study treatments will be destroyed at the study site according to the standard practices of the site after an accurate accountability has been performed and signed by the Investigator (or the pharmacist). A detailed treatment log form of the destroyed study treatment will be established with the Investigator (or the pharmacist) and countersigned by the Investigator and the Monitoring Team.

The Investigator must not destroy the unused IMP unless Sanofi provides written authorization.

6.5 CONCOMITANT THERAPY

Participants must abstain from taking prescription or nonprescription drugs (including vitamins and dietary or herbal supplements) within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) before the start of study intervention until completion of the follow-up visit, unless, in the opinion of the Investigator and Sponsor, the medication will not interfere with the study.

- • Concomitant medications forbidden for use are described below:
- Concurrent treatment with any other anti-neoplasm therapy not specified in the protocol, including chemotherapy, immunotherapy, hormonal therapy, targeted therapy, biological therapy, or other investigational drug or curative radiotherapy. However, palliative radiotherapy or procedures may be given to

control symptoms. The irradiated area should be as small as possible. In all such cases, the possibility of tumor progression should be ruled out by physical, biochemical, and radiological assessments of the tumor. The irradiated area cannot be used as a parameter for response assessment,

- Investigational therapy (other than protocol-mandated study treatment) is prohibited within 28 days prior to initiation of study treatment and during study treatment, - Concomitant systemic corticosteroids are prohibited, except for:
- The participants with GBM or central nervous system lesions as an urgent treatment,
- Use in the premedication defined in the study protocol,
- Treatment of an irAE,
- Treatment of any life-threatening emergency,
- Physiologic replacement, as long as they are not being administered for immunosuppressive intent, and
- A brief course (≤7 days) of systemic corticosteroid for prophylaxis (eg, contrast dye allergy) or for the treatment of non-autoimmune conditions (eg, delayed-type hypersensitivity reactions caused by contact allergen).
- Live attenuated vaccines (eg, FluMist®) are prohibited within 4 weeks prior to initiation of study treatment, and for 5 months after the last dose of atezolizumab.

Prophylactic vaccination that does not contain live virus is recommended for influenza A and B virus, pneumococci, and haemophilus influenza,

- Prophylactic use of hematopoietic growth factors (eg, granulocyte colony-stimulating factor, granulocyte macrophage colony-stimulating factor, erythropoietin) during the DLT observation period. Curative treatment is allowed,
- Systemic immunostimulatory agents (including, but not limited to, interferons and interleukin-2) are prohibited within 4 weeks or 5 half-lives of the drug, whichever is longer, prior to initiation of study treatment and during study treatment because these agents could potentially increase the risk for autoimmune conditions when given in combination with atezolizumab,
- Systemic immunosuppressive medications (including, but not limited to, cyclophosphamide, azathioprine, methotrexate, and thalidomide) are prohibited during study treatment because these agents could potentially alter the efficacy and safety of atezolizumab.

Other concomitant medication may be considered on a case-by-case basis by the Investigator in consultation with the Medical Monitor if required.

6.6 DOSE MODIFICATION

6.6.1 General rules

Cycle delay (ie, delay of both IMPs for Cycle ≥2), dose delay of isatuximab within Cycle 1 or dose omission (ie, omission of either isatuximab or atezolizumab within a cycle for combination cohorts) are permitted in case of toxicity.

Administration of the study treatment will be discontinued in the event of a TEAE that persists despite appropriate dose modifications or any other AE that, in the opinion of the Investigator, warrants discontinuation.

There will be no dose adjustment for atezolizumab or isatuximab.

If 1 of the 2 drugs (atezolizumab or isatuximab) is prematurely permanently discontinued, the other drug can be continued until disease progression confirmed by imaging no less than 4 weeks after initial evidence of progression, unacceptable AE, participant's decision to stop the treatment, 2 years of uninterrupted delivery of IMP without documented PD. The end of treatment (EOT) assessment in this case will be 30 days after the date of the last IMP administration.

6.6.2 Dose delay and dose omission

Within a cycle, the treatment window is ±1 day for each of the weekly isatuximab administrations and ±2 days for each of the Q3W administrations. Within a cycle, a dose is deemed to have been delayed if the treatment is ≥2 days beyond the theoretical day of treatment for weekly isatuximab dose, and ≥3 days beyond the theoretical day of treatment for Q3W cycle. The participant will receive the next infusion/cycle after recovery from the AE.

Participants may have dose delay, cycle delay, or dose omission if an AE occurs and he/she does not recover according to the following rules:

- In Cycle 1 (for weekly administration of isatuximab) if an AE occurs and the participant does not recover on the day of planned infusion or within the following 3 days, infusion of isatuximab (in D8 or D15) may be omitted.
- In Cycle 2 and beyond, if an AE occurs and the participant does not recover on the day of planned infusion, the cycle will be delayed up to a maximum of 2 weeks.
- If the AE is not recovered within 14 days:
  - Study treatment may resume with one IMP and omission of the other. (Either isatuximab or atezolizumab) providing the participant's benefit from the study treatment as per Investigator's

judgment,
- Study treatment may be delayed up to 84 days,
- After a cycle delay of >14 days and ≤84 days, or 2 to 4 consecutive dose omissions of one IMP, it is per Investigator's decision to restart the study treatment or the IMP that is omitted, if a clear benefit from therapy is observed and after consultation with the Sponsor,
- The study treatment must be definitely permanently discontinued if the cycle delay is longer than 84 days, or if more than 4 consecutive dose omissions of one IMP, the IMP will be prematurely discontinued.

6.6.3 General Guidelines for Immune-Related Adverse Events (irAEs)

Investigators must be extremely vigilant and be ready to intervene early in the management of immune-mediated AEs (irAEs) because the onset of symptoms of irAEs (eg, pneumonitis) may be subtle.

Detailed guidance for the management of specific irAEs (colitis, endocrine AE, pneumonitis, dermatologic AE, hepatitis, ophthalmologic AE [uveitis], myocarditis, IARs, pancreatitis, neurologic, and meningoencephalitis), is provided in Appendix 21 (Section 10.21).

- General guidance is provided in Table 4.
- If a participant experiences several irAEs which involve different recommendations, the most conservative recommendation should be followed.

The recommendations provided in Appendix 21 (Section 10.21) and Table 4 should be seen as guidelines, and the treating physician should exercise clinical judgment based on the symptoms and condition of the individual participant.

Table 4 - General Guidelines for Immune-Related Adverse Events

Severity	Next administration Isatuximab and/or Atezolizumab	Supportive care
Grade 1	No action	Provide symptomatic treatment
Grade 2	May delay cycle	Consider systematic corticosteroids (prednisone 0.5 to 1 mg/Kg/day or equivalent) in addition to appropriate symptomatic treatment.

	Delay the cycle until the toxicity improves to Grade≤1 or baseline.	For any (Grade 3-4) irAE, if symptoms worsen or do not improve on adequate corticosteroids
Grade 3	Discontinue prematurely Atezolizumab if unable to reduce corticosteroid dose to <10 mg per day prednisone equivalent within 12 weeks of toxicity.	(prednisone 1 to 2 mg/kg/day or equivalent) within 48 to 72 hours, consider adding additional immunosuppressive agents (to be selected from agents such as: infliximab, cyclophosphamide, cyclosporine, and mycophenolate mofetil). Referral of the participant to a specialized unit for assessment and treatment should be considered.
Grade 4		

6.6.4 General guidelines for the management of infusion-associated reactions

Participants should routinely receive premedications prior to isatuximab infusion as detailed in Section 6.1 to reduce the risk and severity of IARs commonly observed with mAbs.

Infusion-associated reactions typically occur within 24 hours from the start of the infusion.

If an IAR is observed, participants must also be informed of the potential risk of recurrent similar reactions at subsequent infusions. The guidelines for management of IARs, cytokine release syndrome, and anaphylactic reactions are summarized in Table 5.

Participants who experience Grade 2 IARs may resume isatuximab/atezolizumab infusion after temporary interruption, under close monitoring and with therapy as needed.

Participants may receive additional medication per the judgment of the Investigator. Additional

recommended medications are: diphenhydramine 25 mg IV (or equivalent) and methylprednisolone 100 mg IV (or equivalent).

Once a Grade 2 IAR has improved or resolved according to Table 5 and Metamizole (dipyrone) is prohibited in treating atezolizumab associated infusion-associated reactions, due to its potential for causing agranulocytosis.

Guidelines for medical management of infusion-associated reactions are provided in Table 23.

Table 23, the infusion may be restarted:

- For atezolizumab, the infusion should be restarted at half the rate being given at the time of event onset.

- For isatuximab, the infusion should be restarted at half (87.5 mg/h) the initial infusion rate. If symptoms do not recur after 30 minutes, the infusion rate may be increased in 50 mg/hour increments every 30 minutes, to a maximum of 400 mg/hour.

Participants with Grade 3 or 4 IAR must have atezolizumab and/or isatuximab prematurely permanently discontinued and appropriate therapy should be administered:

- If a Grade 3 or higher IAR occurs during atezolizumab infusion, it should be prematurely permanently discontinued. The participant can continue treatment with isatuximab.
- If a Grade 3 or higher IAR occurs after the start of isatuximab infusion, the participant should prematurely permanently discontinue treatment with both atezolizumab and isatuximab.

Grade 2 or higher IARs for isatuximab and any grade IARs for atezolizumab must be reported as AESIs (see Section 8.3). Study personnel should consult the Medical Monitor for further guidance regarding re-treatment of participants with infusion reactions and regarding issues of premedication management (eg, alternative medications for participants allergic or intolerant to premedication agents), or to determine if locally used equivalent medications are acceptable.

Table 5 - Management Guidelines for Infusion-Associated Reactions

Event	Management Atezolizumab	Management Isatuximab
IAR, Grade 1	Reduce infusion rate to half the rate being given at the time of event onset. After the event has resolved, the investigator should wait for 30 minutes while delivering the infusion at the reduced rate. If the infusion is tolerated at the reduced rate for 30 minutes after symptoms have resolved, the infusion rate may be increased to the original rate.	Continue isatuximab infusion per the judgment of the Investigator following close direct monitoring of the participant's clinical status. Isatuximab infusion may be stopped at any time if deemed necessary. If stopped, IAR will be classified as Grade 2 as per NCI-CTCAE
IAR, Grade	Interrupt atezolizumab/isatuximab infusion.	

	Administer aggressive symptomatic treatment (eg, oral or IV antihistamine, anti-pyretic medication, glucocorticoids, epinephrine, bronchodilators, oxygen). After symptoms have resolved to Grade ≤1 (for isatuximab) or baseline (for atezolizumab), resume infusion at half the initial infusion rate for isatuximab and at half the rate being given at the time of event onset for atezolizumab. For subsequent infusions, consider administration of oral premedication with antihistamines, anti-pyretics, and/or analgesics and monitor closely for IARs. -Blood samples for additional safety labs will be collected for isatuximab Stop infusion.
2	
IAR*, Grade 3 or 4	Administer aggressive symptomatic treatment (eg, oral or IV antihistamine, anti-pyretic, glucocorticoids, epinephrine, bronchodilators, oxygen). Prematurely permanently discontinue atezolizumab or Isatuximab or permanently discontinue both atezolizumab and isatuximab and contact Medical Monitor.

IAR = infusion-associated reaction; NCI-CTCAE = National Cancer Institute-common terminology criteria for adverse events * Applicable to Grade 3 or 4 cytokine release syndrome and anaphylactic reactions

6.6.5 Retreatment of participants

The participants must have recovered to NCI-CTC AE Grade ≤1 or to his/her baseline status before initiation of the next cycle at the same dose level. In those cases of clear clinical benefit, a participant will continue treatment until disease progression confirmed by imaging 4 weeks after initial evidence of progression as detailed in Section 4.2, unacceptable AE, participant's decision to stop the treatment, 2 years of uninterrupted delivery of IMP without documented PD.

A cycle is 21 days, and deemed to have been delayed if the treatment is >3 days beyond the theoretical day of treatment. The reason for dose delay will be provided. In the event of an AE causing a delay, including a DLT, in order for participants to be retreated, see Section 6.6 and Appendix 21 (Section 10.21) for retreatment recommendations.

6.7 INTERVENTION AFTER THE END OF THE STUDY

The IMPs will not be provided after the end of the treatment period.

The participant's treatment after discontinuation of last IMP will be at the discretion of the treating physician.

7 DISCONTINUATION OF STUDY INTERVENTION AND

7.1 DISCONTINUATION OF STUDY INTERVENTION

The IMPs should be continued whenever possible.

In case the IMP is stopped, it should be determined whether the stop can be made temporarily; permanent IMP discontinuation before disease progression should be a last resort. Any IMP discontinuation must be fully documented in the electronic case report form (eCRF). In any case, the patient should remain in the study until the documentation of progressive disease.

Pregnancy will lead to definitive treatment discontinuation in all cases.

Treatment with the IMPs or the last IMP should be discontinued in any of the following cases:

- • At the participant's request, at any time and irrespective of the reason (participant's decision), or at the request of their legally authorized representative without any effect on their care.

"Legally authorized representative" is considered to be an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective patient to the patient's participation in the procedure(s) involved in the research.

Participant's decision for treatment should be distinguished from participant's decision for follow-up visits and from participant's decision for non-participant contact follow-up, eg, medical records check. The value of all their study data collected during their continued involvement will be emphasized as important to the public health value of the study.

Participants who withdraw should be explicitly asked about the contribution of possible AEs to their decision to withdraw consent, and any AE information elicited should be documented.

Preferably the participant should withdraw consent in writing and, if the participant or the participant's representative refuses or is physically unavailable, the site should document any case of participant's decision.

- If, in the Investigator's opinion, continuation of the study treatment would be detrimental to the participant's well-being, such as:
- ◦ Confirmation of disease progression,
  ◦ Unacceptable AE,
  ◦ Poor compliance to the study protocol,
  ◦ Any other reason such as intercurrent illness that prevents further

administration of study treatment (will be specified).

- Participant is lost to follow-up.
- Completion of the 2 year treatment period.

See the SoA for data to be collected at the time of intervention discontinuation and follow-up and for any further evaluations that need to be completed.

All permanent treatment discontinuation must be recorded by the Investigator in the appropriate screen of eCRF when considered as confirmed. After study treatment is discontinued, participants should complete a visit 30 days after the last administration of the IMP or before administration of further anti-cancer therapy, whichever is earlier as described in the Study reference manual.

Participants who have been withdrawn from the study treatment cannot be re-entered into the study. Participants will be followed-up according to the study procedures specified in this protocol up to the scheduled date of study completion, or up to recovery or stabilization of any AE to be followed-up as specified in this protocol, whichever comes last.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons.

If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.

See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

If participants no longer wish to take the IMP(s), they will be encouraged to remain in the study.

The Investigators should discuss with them key visits to attend. The value of all their study data collected during their continued involvement will be emphasized as important to the public health value of the study.

Participants who withdraw from the study intervention should be explicitly asked about the contribution of possible AEs to their decision, and any AE information elicited must be documented.

All study withdrawals should be recorded by the Investigator in the appropriate screens of the eCRF and in the participant's medical records. In the medical record, at least the date of the withdrawal and the reason should be documented.

In addition, a participant may withdraw his/her consent to stop participating in the study. Withdrawal of consent for intervention should be distinguished from withdrawal of consent for follow-up visits and from withdrawal of consent for non-participant contact follow-up, eg, medical record checks. The site should document any case of withdrawal of consent.

Participants who have withdrawn from the study cannot be treated in the study. Their inclusion and intervention numbers must not be reused.

7.3 LOST TO FOLLOW UP

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

7.4 REPLACEMENT OF PARTICIPANTS

During the Phase 1 part of the study, a participant may be considered not evaluable for DLT and may be replaced at the same dose level as described in Section 4.1.1.

Participants treated in the Phase 2 part of the study who are withdrawn from study treatment will not be replaced.

8 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.

- Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

8.1 EFFICACY ASSESSMENTS

The primary and secondary efficacy endpoint will be assessed by RECIST 1.1 (Appendix 11: Section 10.11) criteria for participants with HCC, SCCHN and EOC. All participants treated must have at least one measurable intact lesion for inclusion (see Section 5.1, inclusion criterion I 04).

For participants with GBM, efficacy will be assessed by RANO criteria (Appendix 15: Section 10.15).

Tumor assessment will be performed at fixed intervals as described in SoA, and the assessment window is not impacted by dose delay or dose omission.

All tumor assessment data should be recorded to related eCRF pages based on RECIST 1.1 criteria (Appendix 11;Section 10.11). As a requirement of RECIST 1.1 criteria, a partial or complete response must be confirmed on a second examination done at least 4 weeks apart, in order to be documented as a confirmed response to therapy. Based on RECIST for immunotherapies (iRECIST [Appendix 16: Appendix 16: Section 10.16]), progressive disease should also be confirmed on a second examination done at least 4 weeks apart to exclude pseudo progression.

Exploratory efficacy endpoints will be assessed by iRECIST (Appendix 16: Section 10.16), for participants with HCC, SCCHN or EOC or iRANO (Appendix 18: Section 10.18), for participants with GBM and some biomarkers.

Imaging should be available for a central review upon Sponsor’s request.

8.2 SAFETY ASSESSMENTS

Planned time points for all safety assessments are provided in the SoA.

8.2.1 Physical examinations

- A complete physical examination will include, at a minimum, assessments of the major body systems. Height only at baseline and weight will also be measured and recorded.
- Performance status as measured by the ECOG (for HCC, SCCHN, and EOC) or Karnofsky scale (for GBM).
- Investigators should pay special attention to clinical signs related to previous illnesses.
- Any new finding or worsening of previous finding during treatment period should be reported as a new AE.

8.2.2 Vital signs

During treatment phase, vital signs are to be monitored just before starting infusion of the IMPs, every hour during the infusion, and at the end of infusion. Also to be performed as clinically indicated.

- Temperature, pulse rate, respiratory rate, and blood pressure will be assessed.
- Blood pressure and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (eg, television, cell phones).
- Oxygen saturation (SCCHN only).

8.2.3 Electrocardiograms

- • 12-lead ECG will be obtained as outlined in the SoA (see Section 1.3).

Single 12-lead ECG will be obtained as outlined in the SoA (see Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. Clinically significant abnormalities should be reported as AE, except for at the screening assessment if the detected finding is linked to a preexisting condition. In that case, the diagnosis should be recorded in the patient’s medical history.

8.2.4 Clinical safety laboratory assessments

See Appendix 2 (Section 10.3) for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.

- The Investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents. Clinically significant

abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition and that either lead to IMP(s) discontinuation or dose modification or fulfill a serious or AESI definition (note: remaining laboratory tests are reported in eCRF pages for Hematology, Biochemistry).

- All laboratory tests with values considered clinically significantly abnormal during participation in the study or after the last dose of study intervention should be repeated until the values return to normal or baseline or are no

longer considered clinically significant by the Investigator or Medical Monitor.

- If such values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified and the Sponsor notified.
- All protocol-required laboratory assessments, as defined in Appendix 2 (Section 10.2), must be conducted in accordance with the laboratory manual and the SoA.
- If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the Investigator (eg, SAE or AE or dose modification), then the results must be recorded in the eCRF.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

The safety of the participants in this clinical trial is primarily dependent on the clinical Investigator's monitoring and assessment of their participants.

After the occurrence of two patients with Grade ≥3 or one patient with Grade ≥4 reports of cytokine release syndrome or anaphylactic reactions, unless they result from an obviously unrelated cause, further enrollment will be halted until a thorough safety review is conducted and submitted to FDA for review.

An AESI is an AE (serious or non-serious) of scientific and medical concern specific to the isatuximab or atezolizumab programs, for which ongoing monitoring and immediate notification by the Investigator to the Sponsor is required. Such AEs may require further investigation in order to characterize and understand them. Adverse events of special interest may be added, modified or removed during a study by protocol amendment.

Dose limiting toxicities (as defined in Section 4.1) are considered as AESIs in the Phase 1 of this study, and as such, the Investigators will be required to report them to the Sponsor within 24 hours of the Investigator becoming aware of the AE. The Investigator will attach the DLT-specific eCRF page to the DLT/AESI form.

The following conditions are also considered AESIs and as such, the Investigators will be required to report them to the Sponsor within 24 hours of the Investigator becoming aware of the AE:

- Grade ≥2 acute IARs with isatuximab.
- Any grade IARs with atezolizumab.
- Grade ≥3 immune-related TEAEs.
- Any grade of the following TEAEs with atezolizumab: pneumonitis, colitis, endocrinopathies (diabetes mellitus, pancreatitis, adrenal insufficiency,

hyperthyroidism, and hypophysitis), systemic lupus erythematosus, neurologic disorders (Guillain-Barré syndrome, myasthenic syndrome, myasthenia gravis, and meningoencephalitis), nephritis, ocular toxicities, myositis, myopathies, vasculitis, and autoimmune hemolytic anemia.
- Grade ≥2 cardiac disorders with atezolizumab.
- Pregnancy of a female subject entered in a study as well as pregnancy occurring in a female partner of a male subject entered in a study with IMP/ noninvestigational medicinal product (NIMP).

Pregnancy occurring in a female participant entered in the clinical trial or in a female partner of a male participant entered in the clinical trial. It will be qualified as an SAE only if it fulfills one of the seriousness criteria (see Appendix 3 [Section 10.3]).

- ◦ In the event of pregnancy in a female participant, IMP should be discontinued.
- ◦ Follow-up of the pregnancy in a female participant or in a female partner of a male participant is mandatory until the outcome has been determined

(See Appendix 4 [Section 10.4])

- Symptomatic overdose (serious or non-serious) with isatuximab/NIMP:
- ◦ An overdose (accidental or intentional) with isatuximab is defined as an increase of at least 30% of the intended administered dose at each infusion (expressed in unit per body weight) to be administered in the specified duration or if the dose is administered in less than half the recommended duration of administration.
- ◦ An overdose (accidental or intentional) with the NIMP is defined as increase of at least 30% of the intended administered dose at each administration expressed in unit per body weight.
- ◦ In case of accidental or intentional overdose with the IMP/NIMP, even not fulfilling a seriousness criterion, is to be reported to the Sponsor immediately (within 24 hours) using the AE form together with the SAE complementary form to be entered in the eCRF.
- Of note, asymptomatic overdose has to be reported as a standard AE.

The definitions of an AE or SAE can be found in Appendix 3 (Section 10.3).

An AE will be reported by the patient (or, when appropriate, by a caregiver, surrogate, or the patient's legally authorized representative).

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for

following up AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study treatments (see Section 7).

8.3.1 Time period and frequency for collecting AE and SAE information

All the SAEs and AEs will be collected from the signing of the ICF until the last follow-up visit at the time points specified in the SoA (Section 1.3).

All the SAEs and AESIs will be recorded and reported to the Sponsor or designee within 24 hours, as indicated in Appendix 3 (Section 10.2). The Investigator will submit any updated SAE data to the Sponsor within 24 hours of them being available.

Investigators are not obligated to actively seek AE or SAE after conclusion of the study participation. However, if the Investigator learns of any SAE, or of a death, that occurs after the last dose of the IMP administration, and he/she considers the AE or outcome to be reasonably related to the study intervention or study participation, the Investigator must promptly notify the Sponsor.

The method of recording, evaluating, and assessing the causal relationship of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3 (Section 10.2).

8.3.2 Method of detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each participant at subsequent visits. All SAEs and AESIs and related as defined in Section 8.3, will be followed until resolution, stabilization, or up to when the participant is lost to follow-up (as defined in

Section 7.3). Further information on follow-up procedures is given in Appendix 3 (Section 10.2).

8.3.4 Regulatory reporting requirements for SAEs

- Prompt notification by the Investigator to the Sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of

participants and the safety of a study intervention under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs), and Investigators.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary. The respective IBs of isatuximab and atezolizumab contain the Reference Safety Information (RSI) to be used in the determination of whether an ADR is to be considered expected.
- An Investigator who receives an Investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5 Pregnancy

- Details of all pregnancies in female participants and, if indicated, female partners of male participants will be collected after the start of study intervention and until 5 months after the last dose of isatuximab (male and female participants) or atezolizumab (female participants only), whichever comes last.
- If a pregnancy is reported, the Investigator should inform the Sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4 (Section 10.4).

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, and ectopic pregnancy) are considered SAEs.

8.3.6 Disease related events and/ or disease related outcomes not qualifying as AEs or SAEs

The following disease related events (DREs) are common in patients with cancer and can be serious/life threatening:

- Progression of underlying disease, as it is the study endpoint.
- Death due to progression of underlying disease, if it occurs after 30 days of the last IMP administration. All other deaths that occur within the 30 days of last

study intervention should be reported as a SAE.

Because these events are typically associated with the disease under study, they will not be reported according to the standard process for expedited reporting of SAEs even though the event may meet the definition of a SAE. These events will be recorded on the corresponding page in the patient's eCRF within the appropriate time frame.

8.3.7 Guidelines for reporting product complaints incidents (including malfunctions)

Any defect in the IMP(s) must be reported as soon as possible by the Investigator to the monitoring team that will complete a product complaint form within required timelines.

Appropriate information (eg, samples, labels or documents like pictures or photocopies) related to product identification and to the potential deficiencies may need to be gathered. The Investigator will assess whether or not the quality issue has to be reported together with an AE or SAE.

8.4 TREATMENT OF OVERDOSE

There is no information on specific recommendations regarding overdose with isatuximab or atezolizumab. In case of overdose, patients should be closely monitored for signs or symptoms of adverse reactions, and appropriate symptomatic treatment should be instituted.

In the event of an overdose, the Investigator should:

- Contact the Medical Monitor immediately.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities.
- Document the quantity of the excess dose as well as the duration of the overdose in the eCRF.

Decisions regarding dose interruptions or modifications will be made by the Investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

8.5 PHARMACOKINETICS

8.5.1 Sampling time

The sampling times for blood collection can be found in the PK and immunogenicity flow chart (Section 1.3).

It is of utmost importance to collect all blood samples at the specified times and according to the specifications for collection, storage, and shipment as defined in a separate laboratory manual.

Samples missed or lost, for any reason, should be recorded. Actual dates and times of blood collection should be recorded in the eCRF. The dates and times of drug administration should also be precisely recorded.

8.5.2 Pharmacokinetic sample handling procedure

Detailed instructions for sample preparation and shipping for atezolizumab and isatuximab PK will be provided to the study sites in a separate Laboratory Manual.

8.5.3 Bioanalytical Methods

Isatuximab in plasma and atezolizumab in serum will be analyzed by immunoassay. Details will be provided in a separate Laboratory Manual.

8.5.4 Pharmacokinetic parameters

8.5.4.1 Non-compartmental analysis - isatuximab

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

Table 6 - List of pharmacokinetic parameters and definitions for isatuximab

Parameters	Definition
Ceoi	Concentration observed at the end of intravenous infusion
Cmax	Maximum concentration observed after the first infusion
tmax	Time to reach Cmax
Clast	Last concentration observed above the lower limit of quantification after the first infusion
tlast	Time of Clast
Ctrough	Concentration observed just before treatment administration during repeated dosing
AUC0-T	Area under the plasma concentration versus time curve calculated using the trapezoidal method over the dosing interval (T; ie, 7 days for isatuximab) after the first infusion

8.5.4.2 Population approach – isatuximab and atezolizumab

In addition to atezolizumab, population PK approaches may be used for isatuximab. If done,

the data generated will be reported in a separate stand-alone report(s).

8.6 PHARMACODYNAMICS

Tumor biopsies* will be collected at baseline** and during treatment**, for the following pharmacodynamic biomarker analyses:

- CD38 positive cells, PD-L1 positive cells and immune-contexture (such as T cells, B cells, activating or inhibitory receptors) by immunohistochemistry (IHC) or Fluorescent Multiplex IHC in formalin-fixed paraffin-embedded (FFPE) tumors.
- Transcriptomic immune profiling by techniques such as NGS (RNAseq) on RNAlater preserved tumor if enough tumor material is available or by Nanostring on available FFPE tumor sample.

*Fine needle aspirates are not acceptable. Needle or excisional biopsies, or resected tissue are required. Provision of adequate archival tumor tissue sample obtained at the time of or after progression of immediate previous line of anti-cancer treatment is allowed to replace mandatory baseline biopsy. For GBM, it is mandatory to provide archival tumor tissue sample. The biopsy taken at baseline and potentially Cycle 2 Day 1 should be from a lesion not previously irradiated (preferred), or the new growth area of a lesion that grows after irradiation.

** Tumor biopsy at baseline is mandatory (unless clinically unfeasible and after discussion with Sanofi Medical Monitor in Phase 1 and Phase 2 Stage 1, mandatory in Phase 2 Stage 2). During treatment, tumor biopsies will be taken at Cycle 2 Day 1, unless clinically unfeasible and after discussion with Sanofi Medical Monitor. Peripheral blood samples will be collected at baseline and during treatment, for the following pharmacodynamics biomarker analyses:

Immunophenotyping to assess the immunomodulatory effects of isatuximab and atezolizumab. More particularly, immune cell subsets (such as B cells, T cells, NK cells, neutrophils, and regulatory cells), as well as immune regulatory markers (such as activating and inhibitory receptors) will be characterized by techniques such as flow cytometry at baseline, during, and after treatment only on Phase 2 Stage 2 patients.

Peripheral blood cytokine concentration (such as interferon-γ, tumor necrosis factor-α, interleukin (IL)-2, IL-6, IL-12, IL-4, IL-10, transforming growth factor-ß) will be evaluated at baseline, during, and after treatment by enzyme-linked immunosorbent assay-based techniques.

Tumor mutational profile (ie, somatic mutations in genes) will be analyzed at baseline, during and after treatment in plasma cell free DNA and followed as a potential marker of response to IMP or of acquired resistance to treatment. Subtractive mutation analysis will be performed with germline DNA data to identify tumoral specific variations.

If sufficient clinical response is observable in Phase 1 and Phase 2 Stage 1 patients, further characterization of the immune response might be performed on Phase 2 Stage 2 patients by analyzing humoral and T cell adaptive immune response at baseline, during and after treatment in peripheral blood.

If sufficient clinical response is observable in Phase 1 and Phase 2 Stage 1 patients, analysis of Isatuximab enzymatic activity might be performed at baseline, during, and after treatment by measuring metabolites in plasma or serum from peripheral blood.

8.7 GENETICS

Blood sample for DNA isolation will be collected from participants during the clinical study.

Plasma cell free DNA will be isolated from peripheral blood at baseline, during and after treatment to analyze tumor mutational profile (ie, somatic mutations), as described in Section 8.6.

Peripheral blood samples will be collected for DNA isolation at baseline for the following biomarker analyses:

- Immune genetic determinants (including FcγRIII polymorphisms) will be analyzed.
- Peripheral blood samples will also be used as a control for tumor mutational profile analysis as described in Section 8.6. Subtractive mutation analysis will be performed with germline DNA from this peripheral blood sample data to identify tumoral specific variations.

Blood DNA for immune genetic determinants and for control of tumor mutational profile analysis will not be used to determine the likelihood of the participant or his/her family members developing a disease.

See Appendix 5 (Section 10.5) for Information regarding genetic research. Details on processes for collection and shipment and destruction of these samples can be found in laboratory manual.

8.8 BIOMARKERS

During the study additional analyses, not specified in the protocol but related to the drug action and/or effect of isatuximab/atezolizumab, may be conducted on samples pending evolving literature.

After study completion, for patients who have consented to it, remaining samples will be kept for other possible exploratory analyses. Results of these analyses will not be included in the clinical study report (CSR) but in a stand-alone report, if applicable.

These other research analyses will help to understand either disease subtypes or drug response, or to develop and/or validate a bioassay method, or to identify new drug targets or biomarkers.

These samples will remain labelled with the same identifiers used during the study (ie, participant ID).

They will be transferred to a Sanofi site (or a subcontractor site) which can be located outside of the country where the study is conducted. The Sponsor has included safeguards for protecting patient confidentiality and personal data (see Section 10.1.3).These samples maybe stored for a period of up to 5 years after completion of the final study report. After that period, any samples remaining will be destroyed.

8.8.1 Immunogenicity assessments

The atezolizumab and isatuximab ADA sampling times for blood collection can be found in the PK/PD Flow Chart (Section 1.3).

It is of the utmost importance to collect all the blood samples at the specified times and according to specifications for collection, storage, and shipment as defined in a separate laboratory manual.

Samples missed or lost, for any reason should be recorded. Actual dates and times of blood collection should be recorded in the eCRF. The dates and times of drug administration should also be precisely recorded.

ADA against isatuximab in plasma and ADA against atezolizumab in serum will be analyzed by immunoassay. Details will be provided in a separate Laboratory Manual.

8.8.2 RNA transcriptome research

Transcriptome studies will be conducted using NGS (RNAseq) on RNAlater preserved tumor if enough tumor material is available or by Nanostring on available FFPE tumor sample and/ or alternative equivalent technologies, which facilitates the simultaneous measurement of the relative abundances of thousands of ribonucleic acid (RNA) species resulting in a transcriptome profile for each and tumor biopsy sample. This will enable the evaluation of changes in transcriptome profiles that may correlate with biological response relating to disease or the action of study intervention.

The same samples may also be used to confirm findings by application of alternative technologies.

8.9 HEALTH ECONOMICS OR MEDICAL RESOURCE UTILIZATION AND HEALTH ECONOMICS

Not applicable.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

Phase 1

There is no formal statistical hypothesis in Phase 1 safety run-in.

For HCC and SCCHN, the null hypothesis is that the true RR is ≤15%, and the alternative hypothesis is that the true RR is ≥30%. For EOC, the null hypothesis is that the true RR is ≤20% and the alternative hypothesis is that the true RR is ≥40%.

For GBM, the null hypothesis is that the true PFS-6 is ≤20% and the alternative hypothesis is that the true PFS-6 is ≥35%.

9.2 SAMPLE SIZE DETERMINATION

Approximately 6 (assuming 6 participants for the starting dose) to 24 (assuming 12 participants for the starting dose, and 12 participants for DL-1) DLT evaluable participants are expected to be enrolled. The actual sample size will vary depending on DLTs observed and the number of dose levels explored. Participants who are not evaluable for DLT assessment in Phase 1 may be replaced.

Phase 2 of the study is to evaluate initial anti-tumor activity based on tumor response using RECIST 1.1 criteria for HCC, SCCHN and EOC, and RANO criteria for GBM. The efficacy evaluation is based on 2-stage design with 85% power at 5% one-sided alpha level for each of the participant cohorts, respectively.

The assumption of RR, the required sample sizes, and the number of responders at each stage are provided below for HCC, SCCHN and EOC:

EOC 20% 40% 17 37 ≥4 (23.5%) ≥12 (32.4%)

Abbreviations: H0=null hypothesis; H1=alternative hypothesis; HCC=hepatocellular carcinoma; SCCHN=squamous cell carcinoma of the head and neck; EOC=epithelial ovarian cancer.

Note: Based on the number of objective responses and the totality of data observed within a treatment cohort in Phase 2 Stage 1, the Sponsor may decide to advance such a treatment cohort to Phase 2 Stage 2 after consulting with Study Committee.

The assumption of PFS-6, the required sample sizes, and PFS-6 at each stage are provided below for GBM:

Indication	H0	H1	Sample size		Number (%) of responses to reject H0	
	Stage 1	Final	Stage 1	Final		
GBM	20%	35%	31	65	>19.4%	>27.7%

Abbreviations: H0=null hypothesis; H1=alternative hypothesis; GBM=glioblastoma multiforme.

Note: Based on the PFS-6 and the totality of data observed within a treatment cohort in Phase 2 Stage 1, the Sponsor may decide to advance such a treatment cohort to Phase 2 Stage 2 after consulting with Study Committee.

Participants who received the recommended dose regimen in Phase 1 will be also included in Phase 2 Stage 1 (eg, if 6 HCC participants were enrolled in Phase 1, only 20 HCC participants will be needed to complete the Phase 2 Stage 1 HCC cohort).

In Phase 2, approximately 285 participants are expected to be enrolled (assuming Cohort A, B, C, D-1, and D-2 complete 2 stages), including approximately 131 in Phase 2 Stage 1 and approximately 154 participants in Phase 2 Stage 2. The participants who are treated with RP2D in Phase 1 will be counted as Phase 2 participants.

If isatuximab Q3W in combination with atezolizumab or as monotherapy (GBM only) without the isatuximab QW for 3 weeks is to be tested in HCC, SCCHN, EOC, or GBM 65 additional participants are expected to be enrolled. As a consequence, a total to up to 350 participants may be enrolled.

9.3 POPULATIONS FOR ANALYSES

For purposes of analysis, the following populations are defined (Table 7):

Table 7 - Populations for analyses

Population	Description
All treated	For both Phase 1 and Phase 2 of the study, the all-treated population will include all participants who have given their informed consent and received at least 1 dose (even incomplete) of either isatuximab or atezolizumab. This population is the primary population for the analyses of efficacy and safety parameters, unless otherwise noted. All analyses using this population will be based on the dose level actually received in the first cycle.
DLT evaluable (Phase 1)	The DLT evaluable population is defined as participants in Phase 1 who received the planned doses of isatuximab and atezolizumab during Cycle 1, and complete the DLT observation period after the first IMP administration, unless they discontinue the study treatment(s) due to DLT. The dose recommended for Phase 2 will be determined on the DLT evaluable population.
Response evaluable population	The response evaluable population will include all patients who fulfill eligibility criteria in the all-treated population with an evaluable baseline assessment and at least one evaluable post-baseline response assessment during the treatment period. This population is the secondary analysis population for efficacy.

Population	Description
PK	The PK population will include all participants from the all-treated population with at least 1 drug concentration after drug administration (whatever the cycle and even if the dose is uncomplete).
ADA evaluable	The ADA evaluable population includes all participants from the all-treated population with at least 1 non-missing ADA result after the drug administration.
PDy	The pharmacodynamic population will include all participants from the all-treated population with at least 1 pharmacodynamic marker result after the first dose of study treatment.

Abbreviations: ADA=Anti-drug antibody; DLT=Dose limiting toxicities; PDy=Pharmacodynamics; PK=Pharmacokinetics.

9.4 STATISTICAL ANALYSES

The statistical analysis plan will be developed and finalized before database lock and will describe the participant populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

General statistical approach:

Data from HCC, SCCHN, EOC, and GBM cohorts (Cohorts A, B, C, D-1, and D-2) in Phase 2 will be analyzed and reported separately by cohort.

Planned date for analysis cut-off:

For each cohort, the analysis cut-off date for the primary analysis (RR for HCC, SCCHN and EOC, PFS-6 for GBM) is planned at 6 months after the last participant's first treatment in the cohort.

The analysis cut-off date for secondary efficacy endpoints including DoR and PFS will be 12 months after the last participant's first treatment in the cohort. The primary analysis of RR in the cohort for HCC, SCCHN, and EOC, and of PFS-6 in the cohort for GMB will be updated.

9.4.1 Efficacy analyses

All-treated population will be the primary analysis population for efficacy endpoints. In addition, similar analysis will be performed using the response evaluable population as a secondary analysis.

9.4.1.1 Analysis of primary efficacy endpoints

For HCC, SCCHN and EOC, RR will be summarized with descriptive statistics. A 90% 2-sided confidence interval will be computed using Clopper-Pearson method. The statistical inference will be based on the hypothesis and alpha level defined in the sample size calculation section.

For GBM, PFS-6 will be summarized using Kaplan-Meier method.

9.4.1.2 Analysis of secondary efficacy endpoints:

The following secondary endpoints will be analyzed:

- Tumor burden change: the best percent-change from baseline in tumor burden will be summarized and presented graphically. In addition, a summary of the area under the curve (AUC) and the time adjusted AUC of percent-change from baseline in tumor burden will also be provided as an exploratory analysis.

- DOR and PFS will be summarized using Kaplan-Meier method.
- RR for GBM and DCR (complete response + partial response + stable disease) will be summarized with descriptive statistics.

Table 8 - Efficacy analyses

Endpoint	Statistical Analysis Methods
Primary	
RR for HCC, SCCHN and EOC	Descriptive statistics and Clopper-Pearson method
PFS-6 for GBM	Kaplan-Meier method
Secondary Tumor burden change	Descriptive statistics
DOR and PFS	Kaplan-Meier method
RR for GBM and DCR	Descriptive statistics
Exploratory	Will be described in the statistical analysis plan finalized before database lock

Abbreviations: DCR=Disease control rate; DOR=Duration of response; EOC=Epithelial ovarian cancer; GBM=Glioblastoma multiforme; HCC=Hepatocellular carcinoma; PFS=Progression free survival rate; PFS-6=Progression free survival rate at 6 months; RR=Response rate; SCCHN=Sqamous cell carcinoma of the head and neck.

9.4.2 Safety analyses

All safety analyses will be performed on the all-treated population.

Table 9 - Safety analyses

Endpoint	Statistical Analysis Methods
Primary	
DLTs, AEs/Serious AEs, and laboratory abnormalities in Phase 1	Descriptive statistics
Secondary	
AEs/SAEs and laboratory abnormalities in	Descriptive statistics

Phase 2	
ADA against isatuximab and against atezolizumab	Descriptive analysis
Exploratory	Will be described in the statistical analysis plan finalized before database lock

Abbreviations: AE=Adverse event; ADA=Anti-drug antibody; DLT=Dose limiting toxicity; SAE=Serious adverse event.

9.4.2.1 Dose limiting toxicities

In Phase 1, the DLTs will be listed by participant using the DLT evaluable population.

9.4.2.2 Analyses of adverse events

The observation period will be divided into 3 segments: screening, TEAE and post-treatment:

- The screening period is defined as the time informed consent is signed until the first dose of study treatment administration.
- The TEAE period is defined as the time from the first dose of study treatments up to 30 days after last dose of study treatments.
- The post-treatment period is defined as the time starting 31 days after the last dose of study treatments to study closure or death, whichever occurs first.

Pre-treatment AEs are defined as any AE during the screening period. Treatment-emergent AEs are defined as AEs that develop, worsen (according to the Investigator's opinion) or become serious during the TEAE period. Post-treatment AEs are defined as AEs that are reported during the post-treatment period. The primary focus of AE reporting will be on TEAEs. Pre-treatment and post-treatment AEs will be described separately.

The TEAEs will be coded according to MedDRA. AEs will be graded according to the

NCI-CTCAE version 4.03. The grade will be taken into account in the summary. For participants with multiple occurrences of the same PT, the maximum grade will be used.

An overall summary of TEAEs will be provided. The number and percentage of participants who experience any of the following will be provided:

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

- Serious TEAEs.
- Serious treatment-related TEAEs.
- TEAE leading to permanent (full study treatment) discontinuation/premature (partial study treatment) discontinuation.
- AESIs, and IARs in particular.
- Treatment-related TEAEs.

Treatment-related TEAEs of ≥Grade 3.

The number and percentage of participants experiencing TEAEs by primary system organ class (SOC) and PT will be summarized by NCI-CTCAE grade (all grades and ≥Grade 3). Similar tables will be prepared for treatment-related TEAEs, AESIs, TEAEs leading to permanent or premature discontinuation, TEAEs leading to dose modification, serious TEAEs, TEAEs with fatal outcome and AEs/SAEs occurring during the post-treatment dosing period.

Sorting within tables should ensure the same presentation for the set of all AEs within the observation period (screening, on-treatment, and post-treatment). For that purpose, the table of all TEAEs will be presented by SOC and PT sorted by internationally agreed order unless otherwise specified.

9.4.2.3 Clinical laboratory evaluations

All the laboratory abnormalities will be graded according to NCI-CTCAE version 4.03, when applicable. Number (%) of participants with laboratory abnormalities (ie, all grades and Grade ≥3) using the worst grade during the TEAE period will be provided for the all-treated population.

When the NCI-CTCAE version 4.03 scale is not applicable, the number of participants with laboratory abnormality out-of-normal laboratory range value will be displayed.

9.4.2.4 Immunogenicity

The findings from the analyses of immunogenicity for isatuximab and atezolizumab will be summarized.

9.4.3 Other analyses

Pharmacokinetics, pharmacodynamic, and biomarker exploratory analyses will be described in the statistical analysis plan finalized before database lock. The population PK analysis and pharmacodynamic analyses will be presented separately from the CSR.

9.4.3.1 Analysis of PK endpoints

Individual concentrations and non-compartmental PK parameters of isatuximab will be

summarized by descriptive statistics (such as mean, geometric mean, median, standard deviation, standard error of the mean, coefficient of variation, and minimum and maximum) under the responsibility of Sanofi, Pharmacokinetic, Dynamic, and Metabolism department.). Individual and mean profiles will be presented graphically.

9.4.3.2 Analysis of pharmacodynamic endpoints

Findings from pharmacodynamics markers will be descriptively summarized and tabulated.

9.5 INTERIM ANALYSES

The Statistical Analysis Plan will describe the planned interim analyses in greater detail.

An interim analysis for each cohort will be performed for HCC, SCCHN, EOC, and GBM cohorts after the last participants remaining in the treatment period among the first 26, 26, 17 and 31 participants, respectively, in Phase 2 have completed approximately 6 months of study treatment or permanently discontinued both atezolizumab and isatuximab, whichever comes first. The interim analysis may be conducted earlier if the required number of responses for proceeding to Phase 2 Stage 2 is achieved for HCC, SCCHN, and EOC cohorts.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 APPENDIX 1: REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
- ◦ Consensus ethical principles derived from international guidelines including the

Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines,

- ◦ Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines,
  ◦ Applicable laws and regulations.
- The protocol, protocol amendments, ICF, Investigator's Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The Investigator will be responsible for the following:
- ◦ Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC,
  ◦ Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures,
  ◦ Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

10.1.2 Informed Consent Process

- The Investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations,

ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.

- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.
- Participants who are rescreened are required to sign a new ICF.
- The ICF will contain a separate section that addresses the participation in the post-dose PK assessment sub-study. The Investigator or authorized designee will explain to each participant the objectives of the exploratory research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a participant's agreement to allow any remaining specimens to be used for exploratory research. Participants who decline to participate in this optional research will not provide this separate signature

10.1.3 Data Protection

- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the

Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.4 Committees Structure

Data Monitoring Committee: An independent Data Monitoring Committee (DMC) will periodically evaluate ongoing safety data at intervals planned to be no longer than 3 months (starting from the confirmation of recommended Phase 2 dose) and make appropriate recommendations regarding the conduct of Phase 2 of this study.

Study committee: Composition of the Study Committee will vary based on the matter discussed, but it will generally include Sponsor representatives and at least 2 Investigators responsible for the indication in matter. Sponsor representatives and Investigators who have enrolled at least 1 patient will review clinical data approximately every 2 weeks during the course of the Phase 1 part. Then Study Committee will convene regularly or ad hoc when required, to review data and provide strategic recommendations on study medical decisions such as at the end of the Stage 1 of each cohorts and Stage 2 of Cohort A to D-2.

10.1.5 Dissemination of Clinical Study Data

Sanofi shares information about clinical trials and results on publicly accessible websites, based on company commitments, international and local legal and regulatory requirements, and other clinical trial disclosure commitments established by pharmaceutical industry associations. These websites include clinicaltrials.gov, EU clinical trial register (eu.ctr), and sanofi.com, as well as some national registries.

In addition, results from clinical trials in patients are required to be submitted to peer-reviewed journals following internal company review for accuracy, fair balance and intellectual property. For those journals that request sharing of the analyzable data sets that are reported in the publication, interested researchers are directed to submit their request to clinicalstudydatarequest.com.

Individual participant data and supporting clinical documents are available for request at clinicalstudydatarequest.com. While making information available we continue to protect the privacy of participants in our clinical trials. Details on data sharing criteria and process for requesting access can be found at this web address: clinicalstudydatarequest.com.

10.1.6 Data Quality Assurance

- All participant data relating to the study will be recorded on eCRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete,

and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 25 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.7 Source documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.
- Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- The informed consent form will include a statement by which the patient allowing the Sponsor's duly authorized personnel, the ethics committee (IRB/IEC), and the regulatory authorities to have direct access to original medical records which support the data in the eCRF (eg, patient's medical file, appointment books, and original laboratory records). These personnel, bound by professional secrecy, must maintain the confidentiality of all personal identity or personal medical information (according to confidentiality rules).

10.1.8 Study and Site Closure

The Sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.

The Investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the

IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines.
- Inadequate recruitment of participants by the Investigator.
- Discontinuation of further study intervention development.

10.1.9 Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.
- The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2 APPENDIX 2: ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

DEFINITION OF AE

- An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) impacting study intervention (leading to discontinuation or dose modification.
- Other safety assessments (eg, ECG, radiological scans, and vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (ie, not related to progression of underlying disease).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.

- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.
- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as an AE or SAE if they fulfill the definition of an AE or SAE.

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

A SAE is defined as any untoward medical occurrence that, at any dose:

- Results in death.
- Is life-threatening:

The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

- Requires inpatient hospitalization or prolongation of existing hospitalization:

In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

- Results in persistent disability/incapacity:
- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
- Is a congenital anomaly/birth defect.
- Other situations:
- • Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

RECORDING AND FOLLOW-UP OF AE AND/OR SAE

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information in the eCRF.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/ SAE.

- The Investigator is obligated to assess the causal relationship between study intervention and each occurrence of each AE/SAE; the causal relationship must be reported as YES or NO.
- A "reasonable possibility" of a causal relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a causal relationship cannot be ruled out.
- The Investigator will use clinical judgment to determine the causal relationship.
- Alternative etiologies, such as underlying disease(s), concomitant therapy, and

other risk factors, as well as the temporal relationship of the AE to study intervention administration will be investigated and considered.

- The Investigator will also consult the Investigator's Brochure (IB), and/or Labeling Information for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causal relationship.
- There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report to Monitoring team. However, it is necessary that the Investigator always make an assessment of causal relationship for every AE before the initial transmission of the SAE data to Monitoring team.
- The Investigator may change his/her opinion regarding causal relationship in light of follow-up information, and send an SAE follow-up report with the updated causal relationship assessment.
- The causal relationship assessment is one of the criteria used when determining regulatory reporting requirements.

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by monitoring team to elucidate the nature and/or causal relationship of AEs as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- New or updated information will be recorded in the originally completed eCRF.
- The Investigator will submit any updated SAE or AESI data to the monitoring team within 24 hours of receipt of the information.

REPORTING OF SAEs

- The primary mechanism for reporting an SAE or AESI to Monitoring team will be the electronic data collection tool.
- If the electronic system is unavailable for more than 24 hours, then the site will use the paper SAE/AESI data collection tool (see next section).
- The site will subsequently enter the SAE/AESI data into the electronic system as soon as it becomes available again.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE/AESI from a study participant or receives updated data on a previously reported SAE / AESI after the electronic data

collection tool has been taken off-line, then the site can report this information on a paper SAE / AESI form or to the monitoring team by fax or email.
- Contact information for SAE/AESI reporting can be found in study reference manual.

10.3 APPENDIX 3: CLINICAL LABORATORY TESTS

The tests detailed in Table 10 will be performed by the local laboratory.

- The results must be entered into the eCRF.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.

Hematology	Platelet count Red blood cell (RBC) count Hemoglobin Hematocrit		White blood cell (WBC) count with differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Clinical chemistry	Urea or Blood urea nitrogen (BUN) Uric acid Creatinine eGFR (MDRD)	Potassium Chloride Bicarbonate/ carbon dioxide Sodium Magnesium Phosphate	Aspartate aminotransferase (AST)/ Serum glutamic-oxaloacetic transaminase (SGOT) Alanine aminotransferase (ALT)/ Serum glutamicpyruvic transaminase	Total and direct bilirubin LDH Total protein Albumin Thyroid-stimulating hormone (TSH), free T4, free T3/total T3 (screening, C1D1, every 4th cycle

			(SGPT)	thereafter)
	Glucose fasting	Calcium	Alkaline phosphatase	
Routine urinalysis	PH, glucose, protein, blood, leukocyte esterase, and microscopic examination (if blood or protein is abnormal) at baseline and if required. Quantitative or semi-quantitative (according to site practice and if such method can provide absolute numeric value of the parameters) analysis is only required at baseline. Subsequent urinalysis may be performed; in case of positive dipstick results, quantitative or semi-quantitative analysis would be required.			
Other screening tests	Serum (at baseline) or urine human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential).(urine pregnancy test on Day 1 of each cycle, EOT visit, and every 30±7 days until 5 months after last dose of study treatment) • Coagulation: prothrombin time or INR and activated PTT. • Blood typing interference test. Serology hepatitis B surface antigen [HBsAg], and hepatitis C virus antibody for HCC only.			

NOTES :

Blood chemistry, hematology: assessments are not required to be repeated prior to Cycle 1 Day 1 if the screening laboratory assessments were performed within 7 days prior to first IMP administration and met entry criteria.

The window for blood chemistry, hematology, and urinalysis is within 1 working day prior to IMP administration.

Investigators must document their review of each laboratory safety report.

10.4 APPENDIX 4: CONTRACEPTIVE GUIDANCE AND COLLECTION OF PREGNANCY INFORMATION

DEFINITIONS:

1. Premenopausal female with 1 of the following:

- Documented hysterectomy.
- Documented bilateral salpingectomy.
- Documented bilateral oophorectomy.

2. Postmenopausal female

- • A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

- Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

A woman is considered of reproductive potential (WOCBP), ie, fertile, following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Females of childbearing potential or male subjects with female partners of childbearing potential are required to use effective contraceptive methods starting 2 weeks before study treatment administration, during treatment period, until 5 months after the last dose of isatuximab (male and female participants) or atezolizumab (female participants only), whichever comes last.

- • Male subjects with heterosexual partners of reproductive potential (WOCBP) are eligible to participate if they agree to use the following during the protocol defined timeline:

- Refrain from donating sperm.

- At least 1 of the following conditions applies:
- Are and agree to remain abstinent from penile-vaginal intercourse on a long-term and persistent basis, when this is their preferred and usual lifestyle.

- Agree to use a male condom plus an additional contraceptive method with a failure rate of <1% per year (see table for female subjects).

- • Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom for the time defined in the protocol.

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in Table 11.

Table 11 - Highly effective contraceptive methods

Highly effective contraceptive methods that are user dependenta Failure rate of <1% per year when used consistently and correctly.

Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulationb

- Oral.
- Intravaginal.
- Transdermal.

Progestogen only hormonal contraception associated with inhibition of ovulation

- Oral.
- Injectable.

Implantable progestogen only hormonal contraception associated with inhibition of ovulationb

- Intrauterine device (IUD).
- Intrauterine hormone-releasing system (IUS).
- Bilateral tubal occlusion.

A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.

Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

NOTES:

- Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies.
- Hormonal contraception may be susceptible to interaction with the study intervention, which may reduce the efficacy of the contraceptive method. In this case, two highly effective methods of contraception should be utilized during the intervention period and for at least 5 months after the last dose of study intervention

PREGNANCY TESTING:

- ◦ WOCBP should only be included after a confirmed menstrual period and a negative highly sensitive serum pregnancy test.
  ◦ Additional pregnancy testing is required during the intervention period and up to 5 months after the last dose of study intervention.
  ◦ Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected.

COLLECTION OF PREGNANCY INFORMATION:

- The Investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive study intervention.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, the follow-up will be 1 year following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

- The Investigator will collect pregnancy information on any female participant who becomes pregnant 2 weeks before the first dose of isatuximab treatment, during the study, and within 5 months after the last dose of study treatment. Information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a participant's pregnancy. The participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the Sponsor. Generally, follow-up will be required for 1 year beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- Any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such. Any post-study pregnancy related SAE considered reasonably related to the study intervention by the Investigator will be reported to the Sponsor as described in Section 8.3.4. While the Investigator is not obligated to actively seek this information in former study participants, he

or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study intervention.

10.5 APPENDIX 5: GENETICS

- Genetic variation may impact a participant's response to study intervention, susceptibility to, and severity and progression of disease. Variable response to study intervention may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated.
- DNA samples will be used for research related to IMP and related diseases. They may also be used to develop tests/assays including diagnostic tests related to IMP administration. Genetic research may consist of the analysis of one or more candidate genes or analysis of the entire genome (as appropriate).
- DNA samples will be analyzed for immune genetic markers (such as FcgRIII polymorphism) and a panel of tumor somatic mutations. Additional analyses may be conducted if it is hypothesized that this may help further understand the clinical data.
- The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to IMP or study interventions of this class to understand study disease or related conditions.
- The results of genetic analyses may be reported in the CSR or in a separate study summary.
- The Sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on IMP continues but no longer than 5 years (or other period as per local requirements) after completion of the final study report.

- ◦ APPENDIX 6: LIVER AND OTHER SAFETY: SUGGESTED ACTIONS AND FOLLOW-UP ASSESSMENTS

Not applicable.

- ◦ APPENDIX 7: MEDICAL DEVICE INCIDENTS: DEFINITION AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

Not applicable.

10.8 APPENDIX 8: COUNTRY-SPECIFIC REQUIREMENTS

10.8.1 Amendment for France

I14. Platinum-resistant/refractory disease:

- Received up to 3 lines of prior platinum-containing therapy when the disease was platinum-sensitive, and,
- Documentation of PD on or after 1 line of anti-cancer therapy for platinum-resistant/refractory disease (unless patients are ineligible or intolerant to standard of care for platinum-resistant/refractory disease). Platinum-resistant/ refractory disease is defined as PD within 6 months following the last administered dose of platinumcontaining therapy (resistant), or lack of response or disease progression while receiving the most recent platinum-containing therapy (refractory), respectively.
- Previous treatment with up to one line of PARP inhibitor therapy is allowed.

10.9 APPENDIX 9: ABBREVIATIONS

ADA:	anti-drug antibody
ADR:	adverse drug reaction
AE:	adverse event
AESI:	adverse event of special interest
AFP:	alpha-fetoprotein
ALP:	alkaline phosphatase
ALT:	alanine aminotransferase
AP:	antibody-plasma
AS:	antibody-serum
AST:	aspartate aminotransferase
AUC:	area under the curve
BBB:	blood brain barrier

BCLC: Barcelona Clinic Liver Cancer

BRCA1: breast cancer type 1 susceptibility protein

BRCA2: breast cancer type 2 susceptibility protein

BUN: Blood urea nitrogen

CD38: cluster of differentiation 38

CSR: clinical study report

CTCAE: common terminology criteria for adverse events

CTLA-4: cytotoxic T-lymphocyte-associated protein 4

DCR: disease control rate

DIL: Dear Investigator Letter

DL: dose level

DL-1: dose level minus -1

DLT: dose limiting toxicity

DoR: duration of response

DRE: disease related event

DRESS: drug rash with eosinophilia and systemic symptoms

ECG: electrocardiogram

ECOG: Eastern Cooperative Oncology Group

eCRF: electronic case report form

eGFR: estimated glomerular filtration rate

EOC: epithelial ovarian cancer

EOI: end of infusion

EOT: end of treatment

FDA: Food and Drug Administration

FFPE:	formalin-fixed paraffin-embedded
FUp:	follow-up period
GBM:	glioblastoma multiforme
GCIG:	Gynaecologic Cancer Intergroup
HBV:	hepatitis B virus
HCC:	hepatocellular carcinoma
HCV:	hepatitis C virus
IAR:	infusion associated reaction, infusion associated reaction
ICH:	International Council for Harmonisation
IHC:	immunohistochemistry
IMP:	investigational medicinal product
INR:	international normalized ratio
irAE:	immune-related adverse event
iRANO:	Immunotherapy Response Assessment in Neuro-Oncology
iRECIST:	Response Evaluation Criteria in Solid Tumors for immune-based therapies , RECIST for immunotherapies
ITSM:	immunoreceptor tyrosine-based switch motif
IV:	intravenous
mAb:	monoclonal antibody, monoclonal antibody
MDRD:	modification of diet in renal disease
MedDRA:	Medical Dictionary for Regulatory Activities
MM:	multiple myeloma
MRI:	magnetic resonance imaging
MTD:	maximum tolerated dose

NCI: national cancer institute, National Cancer Institute

NIMP: noninvestigational medicinal product

NK: natural killer

NSCLC: non-small cell lung cancer

OS: overall survival

P: plasma

PARP: poly (ADP ribose) polymerase

PD: progressive disease

PD-1: programmed cell death-1

PD-L1: programmed cell death-ligand 1

PD-L1: programmed cell death-ligand 1

PD-L2: programmed cell death-ligand 2

PFS: progression free survival

PFS-6: progression free survival rate at 6 months

PK: pharmacokinetic

PLD: pegylated liposomal doxorubicin

PO: oral route

PP: Polypropylene

PT: preferred term

Q2W: once every 2 weeks

Q3W: once every 3 weeks

QW: once weekly

RANO: response assessment for neuro-oncology

RECIST: Response Evaluation Criteria in Solid Tumors

RNT: relative nominal time

RP2D: recommended phase 2 dose

RR: response rate

S: serum

SAE: serious adverse event

SAE: serious adverse event

SCARs: severe cutaneous adverse reactions

SCCHN: squamous cell carcinoma of the head and neck

SJS: Stevens-Johnson Syndrome

SoA: Schedule of Activities

SOC: system organ class

SOI: start of infusion

TEAE: treatment-emergent adverse event

TEN: Toxic Epidermal Necrolysis

TTP: Time to progression

TTR: Time to response

UC: urothelial carcinoma

ULN: upper limit of the normal range

VEGF: vascular endothelial growth factor

WOCBP: woman of child-bearing potential

10.10 APPENDIX 10: PROTOCOL AMENDMENT HISTORY

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

10.10.1 Amendment 01 (06-April-2018)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of

Directive 2001/20/EC of the European Parliament and the Council of the European Union

Revised DLT definition and incorporated stopping rules into the protocol to mitigate patient risk for cytokine release syndrome and anaphylactic reactions. In addition, possible cohorts F-H were removed and Q3W isatuximab regimen wil be studied in one separate cohort only. General provision of testing an isatuximab dose of 20 mg/kg in combination with atezolizumab was also removed from the protocol.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis, 4.1.2 Phase 2 (efficacy signal search with a 2-stage design in each cohort), 9.1 Statistical hypotheses	Updating Phase 2 may include up to 6 cohorts, with cohort E remaining to evaluate Q3W isatuximab regimen (without initial weekly loading dose for 3 weeks) in one disease subgroup. Consequently, total number of participants for the study is now reduced to 350.	Q3W isatuximab regimen will be studied in one separate cohort only, if initiated.
4.1.1 Phase 1 (safety run-in)	DLT definition is revised.	DLT definition is revised to address Grade 4 thrombocytopenia (regardless of evidence of bleeding) and Grade 3 cytokine release syndrome are to be considered as DLT, as well as clarify time to resolution to baseline for a Grade 4 AST, ALT or bilirubin elevation in patients with liver metastases or HCC to be excluded from DLT definition.
4.1.2 Phase 2 (efficacy signal search with a 2-stage design in each cohort)	Remove general provision of testing an isatuximab dose of 20 mg/kg in combination with atezolizumab.	A protocol amendment along with supporting rationale will be submitted if a 20 mg/kg dose is to be evaluated.

6.6.4 General guidelines for management of infusionassociated reactions, 10.21 Appendix 21	Indicate using the same stopping rules for infusion associated reactions are applied also for cytokine release syndrome and for anaphylactic reactions. Corrected inconsistencies between Table 5 and Table 25, as well as clarify that for G2 IAR, symptoms have to resolve to ≤G1 for isatuximab or baseline for atezolizumab before resuming infusion.	Incorporate stopping rules to mitigate patient risk for cytokine release syndrome and anaphylaxis. Correction of inconsistencies among these tables and in accordance with IB.
8.3 Adverse events and serious adverse events	Added trial stopping rule where enrollment will be halted for safety review after two patients with Grade ≥3 or one patient with Grade ≥4 cytokine release syndrome or anaphylaxis events, unless resulting from an obviously unrelated cause.	Incorporate trial stopping rules for cytokine release syndrome and anaphylaxis.
Table 5	Correction of typographical error in title.	Typographical error
10.11 Appendix 11	Correction of typographical error in description of non-target lesion consideration for pathological lymph nodes.	Typographical error

10.10.2 Amendment 02 (09-August-2018)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

An independent Data Monitoring Committee (DMC) is implemented to review ongoing safety data. Inclusion and exclusion criteria are updated to reflect mandatory tumor biopsy requirement and clarify exclusion of participants with active infections. Other modifications or editorial changes were included to correct inconsistencies and improve operational feasibility.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis and 10.1.4 Committees Structure	An independent Data Monitoring Committee (DMC) is implemented to review ongoing safety data (starting from confirmation of recommended Phase 2 dose).	DMC is implemented to monitor safety of the isatuximab + atezolizumab combination for Phase 2 in addition to biweekly Study Committee which will monitor safety data of Phase 1.
	Treatment time window of C1D1 is updated from ±2 days to ±1 day.	Corrected typographical error and in accordance with Section 6.6.2.
1.3 Schedule of Activities (SOA)	Merged columns “Cycle 2-8”, “Cycle 9”, “ Cycle 10 and Beyond” into one column “Cycle 2 and Beyond” for clarify; study procedures have not been changed.	Disease assessment schedule was ambiguous with the previous table format that it was unclear that frequency change should follow calendar days and not cycles.
1.3 Pharmacokinetics and Immunogenicity Flow Chart, 8.5.1 Sampling Time, 8.8.1 Immunogenicity assessments	Clarified sample collection details and updated sample collection time windows within flow chart to be consistent with footnote descriptions. No further isatuximab ADA sample will be collected after FUP even if status is positive or inconclusive. Defined abbreviation ID and ADA, removed AFP. Updated Table 8.	Clarification and minor corrections are implemented in PK/ADA flow chart to improve clarify and operation. Table 8 was updated to reflect details regarding bioanalytical methods for anti-atezolizumab antibody.
1.3 Exploratory Biomarker Flow	Updated Biomarker Flow Chart and I02 to mandate tumor biopsy (for HCC, SCCHN, and	To enable translational research in understanding the mechanism of isatuximab +

Chart 5.1 Inclusion Criteria	EOC) in Phase 1 and Phase 2 Stage 1 unless clinically unfeasible, or provision of archival tissue (for GBM).	atezolizumab in the 4 disease types, and identify potentially predictive biomarker.
2.2.2 Isatuximab	Under background of Isatuximab, updated number of patients treated with isatuximab.	Updated per IB Edition 9.
5.2 Exclusion Criteria	Updated E34 to exclude participants with active tuberculosis, or severe infection requiring parenteral antibiotic treatment.	This is added to avoid any potential complications that may be brought upon by the immune modulating activity of atezolizumab (anti-PD-L1).
6.1 Study Intervention(s) Administered	Added time windows for atezolizumab infusion as over 60 ± 15 mins for first infusion, and 30 ± 10 mins for subsequent infusions.	Time windows were omitted by mistake in the original protocol.
6.6.4 General guidelines for the management of infusion-associated reactions and 10.21 Appendix 21	In Table 5 and Table 25, for G2 IAR, infusion may be resumed at half the original infusion rate for isatuximab and at half the rate at time of event onset for atezolizumab (instead of at the time of event onset for both IMPs).	This is corrected to be in accordance with IBs.
8.3 Adverse Events and Serious Adverse Events	Remove atezolizumab from symptomatic overdose definition.	Current definition of symptomatic overdose only applies to isatuximab and not atezolizumab; overdose with atezolizumab is also not an AESI per IB.
8.5.3 Bioanalytical Methods	Lower limit of quantification is updated from 0.500 ng/mL to 0.500 µg/	Table 6 was updated as new bioanalytical method will be used for isatuximab and the bioanalysis site for atezolizumab assay will be ICON.

	mL. Analytical technique is updated to Immunoassay. Site of bioanalysis for atezolizumab was updated to ICON (NY, USA).	
8.5.4.1 Noncompartmental analysis – isatuximab	Specified PK parameters will be calculated from isatuximab plasma concentrations. AUClast is removed from the parameters and added "after the first infusion" at the end of definition for AUC0-T.	Previously "plasma" was omitted by mistake. Clarified definition of AUC0-T. AUClast was deleted from Table 7 as this is not relevant for isatuximab.
8.5.4.2 Population approach – isatuximab and atezolizumab	Removed "and more precisely to analyze the isatuximab plasma concentration-time profiles".	Plasma concentration-time profile is not relevant in this context as population PK approach will be used.
8.8.1 Immunogenicity assessments	Table 8 was updated	Table 8 was updated by adding the bioanalytical method and location for anti-atezolizumab antibody.
9.4.3.1 Analysis of PK endpoints	"Standard error of means" was added as part of descriptive statistics. Additional details were also provided on endpoints.	These changes were omitted by mistake in the previous version of the protocol.
10.2 Appendix 2: Clinical laboratory tests	Added time window for blood chemistry, hematology, and urinalysis is within 1 working day prior to IMP	This is added in accordance with time window stated in Study Reference Manual.

	administration.	
10.2 Appendix 2: Clinical laboratory tests	To allow semi-quantitative urinalysis (according to site practice and if such method can provide absolute numeric value of the parameters).	Standard practice of some study sites utilize semiquantitative urinalysis.
Throughout	Grammatical corrections and formatting edits.	To correct grammatical errors and improve readability.

10.10.3 Amendment 03 (07 DECEMBER 2018)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union

The main reason for this amendment was to include management guidelines for renal events relating to a new identified risk of atezolizumab (previously communicated to study sites in a study memo). Management guideline for systemic immune activation recently provided by F. Hoffmann-La Roche Ltd. was also included in this amendment. Premedication requirements were modified to allow patients with no or mild infusion associated reactions to omit premedications at Investigators' discretion. Other modifications or editorial changes were included to correct inconsistencies and improve operational feasibility.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis 2.3.4 Preventive measures to minimize the risk from the combination 6.1 Study intervention(s)	Premedication requirements were modified. In Section 2.3.4, premedication administration timing was corrected from "15 to 30 minutes" to "30 to 60 minutes" prior to isatuximab infusion for consistency with the rest of the protocol.	Change based on data from completed and ongoing studies to allow patients with no or Grade ≤2 infusion associated reactions (IARs) to omit premedications at Investigators' discretion. Montelukast 10 mg orally or equivalent was added as a premedication based on recent references (i, ii, iii) that this addition may decrease incidence and

		respiratory symptoms of IAR. Correction was made in Section 2.3.4 for consistency. References: • Chari A, Mark TM, Krishnan A, Stockerl-Goldstein K, Usmani SZ, Londhe A, et al. Use of Montelukast to Reduce Infusion Reactions in an Early Access Program (EAP) of Daratumumab in United States Patients with Relapsed or Refractory Multiple Myeloma [abstract]. Blood. 2016;128:2142. • Nooka AK, Gleason C, Sargeant MO, Walker M, Watson M, Panjic EH, Lonial S. Managing Infusion Reactions to New Monoclonal Antibodies in Multiple Myeloma: Daratumumab and Elotuzumab. J Oncol Pract. 2018;14(7):414-22. • Reece DE and Phillips MJ. Infusion Reactions With Monoclonal Antibody Therapy in Myeloma: Learning From Experience. J Oncol Pract. 2018; 14(7): 425-6.
administered		
1.3 Pharmacokinetics and Immunogenicity	Specified that PK/ADA sample collection may be reduced upon notification from the Sponsor based on updated knowledge of isatuximab on PK/ADA.	To allow flexibility and quick implementation in reducing PK/ADA sampling if updated knowledge becomes available,

Flow Chart

2.2.1.3 Epithelial ovarian cancer	Corrected EOC patients should receive no more than 3 lines (instead of 2 lines) of systemic therapy for platinum-sensitive disease for consistency with I14.	Correction of typographical error.

Section # and Name	Description of Change	Brief Rationale
2.3.4 Preventive measures to minimize the risk from the combination 5.2 Exclusion Criteria	"Inhaled or topical steroids are permitted, provided that they are not for treatment of an autoimmune disorder" was removed from Section 2.3.4 and E05. Specified that the exclusion of patients with comorbidity requiring corticosteroid therapy refers to systemic corticosteroid therapy only.	Clarification - as participants with active, known or suspected autoimmune disorder are ineligible per E26.
4.1.2 Phase 2 (efficacy signal search with a 2stage design in each cohort)	Removed duplicated text regarding timing of observed responses before proceeding to Stage 2.	Original wording created confusion. The deletion also removes unnecessary duplication, as this is covered in Section 9.5.
5.1 Inclusion Criteria	Corrected "radiatherapy" to "radiotherapy" in I11. Also, corrected "after a diagnosis of recurrent SCCHN" to "after a diagnosis of recurrent and/or metastatic SCCHN" for consistency with other eligibility criteria.	Correction of typographical error, and the incorrect omission of "and/or metastatic" SCCHN.
5.1 Inclusion Criteria	The phrase in I16 "unless the recurrence is outside the radiation field or there is unequivocal histologic confirmation of tumor progression" is replaced with "PD occurred within 12 weeks from completion	Original wording in I16 created confusion. This eligibility criterion is clarified to improve study sites' understanding without changing the patient population.

	of irradiation can only be defined by (1) new enhancement outside of the radiation field, or (2) unequivocal histological confirmation.”.	
5.1 Inclusion Criteria Section 10.8	I14 was clarified that only patients with resistant-refractory disease are eligible for EOC cohort, for consistency with the rest of the protocol. France only Amendment: I14 was modified to enroll EOC patients who have received or failed 1 line of anti-cancer therapy for platinum-resistant/refractory disease (unless patients are ineligible or intolerant to standard of care for platinum resistant/ refractory disease).	Clarification. While the EOC Treatment Guidelines recommend clinical trials, chemotherapy, or targeted therapy for patients with platinumresistant/refractory disease, patients in France will receive (unless ineligible or intolerant to) one other available therapy before joining this study.
5.2 Exclusion Criteria Section 10.22	Added a new criterion (E36) to exclude patients with known untreated current hepatitis C (HCV) virus (subsequent criteria renumbered accordingly). Added guidelines of patients with HCV infection.	Specific guidelines are put in place on how to manage patients with positive HCV results at screening.
6.5 Concomitant Therapy	Clarified that any palliative procedures (including radiotherapy) may be given to control symptom.	Clarification and alignment within program.

Section # and Name	Description of Change	Brief Rationale
6.5 Concomitant Therapy	Clarified exceptions for use of systemic corticosteroids (including management of irAEs).	Previous guidance on prohibited use of corticosteroids was inconsistent with management guidelines.
6.6.2 Dose delay and dose omission	Treatment window of "±1 day" and "±2 days" corresponds to delay of beyond "≥2 days" and "≥3 days" (corrected from ">2	To correct inconsistency in treatment windows. Within Cycle 1, dose delay was not

	days" and ">3 days").	
	In Cycle 1, if an AE occurs and the participant does not recover within 3 days, infusion of isatuximab (D8 or D15) may be omitted only; therefore the words “or delayed” have been removed.	intended to be allowed as Cycle 1 consists of weekly dosing of isatuximab (delay of infusion for more than 3 days should result in dose omission instead).
6.6.4 General guidelines for management of infusionassociated reactions	Following Grade 2 IAR, infusion may be restarted for atezolizumab at half the rate being given at the time of event onset, and not “half the original infusion rate”.	This correction was missed in the previous amendment where the same change was applied in Tables 5 and 25.
8.5.3 Bioanalytical Methods	Removed Table 6 (Bioanalytical methods for isatuximab and atezolizumab pharmacokinetic analysis).	Details on bioanalytical methods will be provided in Laboratory Manual instead.
8.8.1 Immunogenicity assessments	Removed Table 8 (Bioanalytical methods for immunogenicity assessment) and removed duplicated information presented in Section 1.3.	Clarification; details on bioanalytical methods for immunogenicity assessment will be provided in Laboratory Manual instead.
9.3 Populations for Analyses	Response evaluable population: Added that patients must fulfill all eligibility criteria.	Clarification.
9.5 Interim Analyses	To clarify the timing of interim analysis and that interim analysis is performed on a per-cohort basis. Interim analyses for HCC, SCCHN, and EOC cohorts are changed to be performed when the last participants remaining in the	Original wording on interim analyses created confusion. Interim analyses for HCC, SCCHN, and EOC cohorts are changed to coincide with previously defined primary analysis cut-off date to alleviate operational burden.

	treatment period of Phase 2 Stage 1 have completed approximately “6 months” of study treatment instead of “6 cycles”.	
10.21 Management of AtezolizumabSpecific Adverse Events	Included management guidelines for renal events and systemic immune activation.	F. Hoffmann-La Roche Ltd. reported a new identified risk of immune-related nephritis associated with the use of atezolizumab. The company has also provided additional management guideline on systemic immune activation to be included in study protocol.
Section # and Name	Description of Change	Brief Rationale
Section 10.21	Other changes include: Inconsistencies correction. Introductory paragraphs were included for each type of atezolizumab-specific AE.	Inconsistencies include, for example: correction of “delay cycle” to “delay or omit dose” for consistency with Section 6.6.2 where dose omission is allowed; ensuring descriptions for isatuximab management are in the correct column of the tables. To provide additional relevant information for management of atezolizumab-specific AEs in alignment with the atezolizumab program (adapted from atezolizumab IB).
Throughout	Grammatical corrections and formatting edits.	To correct grammatical errors and improve readability.

10.10.4 Amendment 04 (11 June 2019)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union

Based on updated pharmacokinetic characterization of isatuximab, the plasma half-life has been re-estimated to 28 days. As duration of contraceptive measures is required to last for

5 half-lives, a revised duration of contraceptive measures of 5 months after the last isatuximab dose is required. In addition, management guidelines for immune-related myositis are also included in the Appendix (information that has previously been communicated in February 2019 to study Investigators).

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of activities; 8.3.5 Pregnancy; 10.3 Clinical laboratory tests; 10.4 Contraceptive guidance and collection of pregnancy information	Pregnancy test is extended to monthly until 5 months after last dose of study treatment.	Monthly pregnancy test is implemented until end of the extended contraception period.
4.4 Justification for Dose	Re-estimation of isatuximab half-life of 28 days is included.	Based on updated pharmacokinetic characterization of isatuximab.
10.4 Contraceptive guidance and collection of pregnancy information	Updated effective contraceptive methods are required until 5 months after last dose of study treatment.	5 months of contraception period after last dose of isatuximab is required based on updated pharmacokinetic analysis.
10.21 Management of AtezolizumabSpecific	Management guideline for immune-related myositis is included.	Immune-related myositis was identified as a risk for atezolizumab. Management guideline for immunerelated myositis was previously communicated and was not included in the

Adverse Events

protocol amendment.

10.11 APPENDIX 11: RESPONSE EVALUATION CRITERIA IN SOLID TUMORS VERSION 1.1

Details provided in bibliographic reference (59).

At baseline, tumor lesions/lymph nodes will be categorized measurable or non-measurable as follows.

Measurable lesions must be accurately measured in at least 1 dimension (longest diameter in the plane of the measurement to be recorded) with a minimum size of:

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm).
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable).
- 20 mm by chest X-ray.

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable lesions are all other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis), as well as non-measurable lesions. Lesions considered non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, and abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

Special considerations regarding lesion measurability:

- Bone lesions:
  - Bone scan, positron emission tomography scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions,
  - Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above, - Blastic bone lesions

are non-measurable.

- Cystic lesions:
  - Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts,
  - 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.
- Lesions with prior local treatment:
  - Tumor lesions situated in a previously irradiated area, or in an area subjected to other locoregional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion.

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging based evaluation should always be performed rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical examination.

- Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and ≥10 mm diameter as assessed using calipers. For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may be reviewed at the end of the study.
- Chest X-ray: Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.
- CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. Measurability of lesions on CT scan is based on the assumption that CT slice thickness is 5 mm or less. When CT scans

have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness.

- Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised.
- Endoscopy, laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised.
- Tumor markers: Tumor markers alone cannot be used to assess objective tumor response.
- Cytology, histology: These techniques can be used to differentiate between PR and CR in rare cases if required by protocol.

When more than 1 measurable lesion is present at baseline all lesions up to a maximum of 5 lesions total (and a maximum of 2 lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline.

Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, and should lend themselves to reproducible repeated measurements.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. All other pathological nodes (those with short axis ≥10 mm but <15 mm) should be considered non-target lesions. Nodes that have a short axis <10 mm are considered non-pathological and should not be recorded or followed.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as ‘present’, ‘absent’, or ‘unequivocal progression’. In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case (eg, ‘multiple enlarged pelvic lymph nodes’ or ‘multiple liver metastases’).

Response criteria are described in Table 12.

Table 12 - Response criteria

Response criteria	Evaluation of target lesions
CR	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
PR	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
PD	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of 1 or more new lesions is also considered progression).
SD	Neither sufficient shrinkage from the baseline study to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Abbreviations: CR=complete response; PD=progressive disease; PR=partial response; SD=stable disease.

Lymph nodes identified as target lesions should always have the actual short axis measurement recorded and should be measured in the same anatomical plane as the baseline examination, even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if CR criteria are met, since a normal lymph node is defined as having a short axis of <10 mm. For PR, SD and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

Target lesions that become 'too small to measure': All lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (eg, 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being 'too small to measure'. When this occurs it is important that a value be recorded on the eCRF. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned.

When non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter

measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the ‘coalesced lesion’.

While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

- CR: Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).
- Non-CR/Non-PD: Persistence of 1 or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.
- Progressive Disease: Unequivocal progression of existing non-target lesions. (Note: the appearance of 1 or more new lesions is also considered progression).

The concept of progression of non-target disease requires additional explanation as follows:

When the patient also has measurable disease; in this setting, to achieve ‘unequivocal progression’ on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest ‘increase’ in the size of 1 or more non-target lesions is usually not sufficient to qualify for unequivocal progression status.

When the patient has only non-measurable disease; to achieve ‘unequivocal progression’ on the basis of the non-target disease, there must be an overall level of substantial worsening such that the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest ‘increase’ in the size of 1 or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: ie, an increase in tumor burden representing an additional 73% increase in ‘volume’ (which is equivalent to a

20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from ‘trace’ to ‘large’, an increase in lymphangitic disease from localized to widespread, or may be described in protocols as ‘sufficient to require a change in therapy’. If ‘unequivocal progression’ is seen, the patient should be considered to have had overall PD at that point.

The appearance of new malignant lesions denotes disease progression. The finding of a new lesion should be unequivocal: ie, not attributable to differences in scanning technique,

change in imaging modality or findings thought to represent something other than tumor (for example, some ‘new’ bone lesions may be simply healing or flare of preexisting lesions). This is particularly important when the patient’s baseline lesions show PR or CR. For example, necrosis of a liver lesion may be reported on a CT scan report as a ‘new’ cystic lesion, which it is not.

A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the patient who has visceral disease at baseline and while on study has a CT or MRI brain ordered which reveals metastases. The patient’s brain metastases are considered to constitute PD even if he/she did not have brain imaging at baseline.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents new disease. If repeat scans confirm that there is a new lesion, then progression should be declared using the date of the initial scan.

While fluorodeoxyglucose-positron emission tomography (FDG-PET) response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible ‘new’ disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

- Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
- No FDG-PET at baseline and a positive FDG-PET at follow-up:
  - If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD,
  - If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG PET scan). If the positive FDG PET at follow-up corresponds to a preexisting site of disease on CT that is not progressing on the basis of anatomic images, this is not PD.

Time point response: At each protocol-specified time point, a response assessment should occur. Table 13 provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline.

Table 13 - Response in patients with target disease

Target lesions	Non-target lesions	New lesions	Overall response

CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	Inevaluable
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Abbreviations: CR=complete response; PD=progressive disease; PR=partial response; SD=stable disease.

When patients have non-measurable (therefore non-target) disease only, Table 14 is to be used.

Table 14 - Response in patients with non-target disease only

Non-target lesions	New lesions	Overall response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD
Not all evaluated	No	Inevaluable
Unequivocal PD	Yes or No	PD
Any	Yes	PD

Abbreviations: CR=complete response; PD=progressive disease; PR=partial response; SD=stable disease.

Missing assessments and inevaluable designation: When no imaging/measurement is done at all at a particular time point, the patient is not evaluable (NE) at that time point.

If only a subset of lesion measurements are made at an assessment, usually the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point

response. This would be most likely to happen in the case of PD. When no imaging/ measurement is done at all at a particular time point, the patient is NE at that time point.

If only a subset of lesion measurements are made at an assessment, usually the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of PD.

When nodal disease is included in the sum of target lesions and the nodes decrease to 'normal' size (<10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of 'zero' on the eCRF.

In trials where confirmation of response is required, repeated 'NE' time point assessments may complicate best response determination. The analysis plan for the trial must address how missing data/assessments will be addressed in determination of response and progression. For example, in most trials it is reasonable to consider a patient with time point responses of PR, -NE, and -PR as a confirmed response.

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as 'symptomatic deterioration'. Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy.

The objective response status of such patients is to be determined by evaluation of target and non target disease. For equivocal findings of progression (eg, very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

The duration of overall response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or PD is objectively documented (taking as reference for PD the smallest measurements recorded on study).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, this is the reference for calculation of PD).

Reproduced from: Eisenhauer EA, Therasse P, Bogaerts J et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45:228 47.

10.12 APPENDIX 12: BARCELONA CLINIC LIVER CANCER (BCLC) STAGING

Stage (60)	PST	Tumor Stage	Okuda Stage	Liver function studies
		Stage A: early HCC		
A1	0	Single	I	No portal hypertension and normal bilirubin
A2	0	Single	I	Portal hypertension and normal bilirubin
A3	0	Single	I	Portal hypertension and abnormal bilirubin
A4	0	3 tumors <3 cm	I-II	Child-Pugh A-B
Stage B: intermediate HCC	0	Large multinodular	I-II	Child-Pugh A-B
Stage C: advanced HCC	1-2*	Vascular invasion or extrahepatic spread	I-II	Child-Pugh A-B
Stage D: end-stage HCC	3-4†	Any	III	Child-Pugh C

PST, Performance Status Test

Stage A and B, All criteria should be fulfilled

* Stage C, at least one criteria: PST 1-2 or vascular invasion/extrahepatic spread

†Stage D, at least one criteria: PST 3-4 or Okuda Stage III/Child-Pugh C

10.13 APPENDIX 13: CHILD PUGH SCORE

Score	Points

Child-Pugh A	5-6
Child-Pugh B	7-9
Child-Pugh C	>9

Scoring

		Score	
Measure	1 Point	2 Points	3 Points
Ascites	Absent	Slight	Moderate
Serum bilirubin (mg/dL)	<2.0	2.0 – 3.0	>3.0
Serum albumin (g/dL)	>3.5	2.8 – 3.5	<2.8
PT prolongation or INR	<4 sec	4 – 6 sec	>6 sec
	<1.7	1.7 – 2.3	>2.3
Encephalopathy grade	None	1 – 2	3 – 4

Encephalopathy Grade	Clinical Definition
Grade 0	Normal consciousness, personality, and neurological examination
Grade 1	Restless, sleep disturbed, irritable/agitated, tremor, and impaired handwriting
Grade 2	Lethargic, time-disoriented, inappropriate, asterixis, and ataxia
Grade 3	Somnolent, stuporous, place-disoriented, hyperactive reflexes, and rigidity
Grade 4	Unrousable coma, no personality/behavior, decerebrate

10.14 APPENDIX 14: PERFORMANCE STATUS

Karnofsky Performance Scale (62)

Grade	Descriptions	Percentage	Description
0	Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
1	Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work).	90	Able to carry on normal activity; minor signs or symptoms of disease.
		80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death no imminent.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

10.15 APPENDIX 15: RESPONSE ASSESSMENT IN NEURO-ONCOLOGY (RANO) CRITERIA

Details provided in bibliographic reference (63).

Criterion	CR	PR	SD	PD
T1 gadolinium enhancing disease	None	≥50% ↓	<50% ↓ but <25% ↑	≥25% ↑ *
T2/FLAIR	Stable or ↓	Stable or ↓	Stable or ↓	↑ *
New lesion	None	None	None	Present *
Corticosteroids	None	Stable or ↓	Stable or ↓	NA †
Clinical status	Stable or ↓	Stable or ↑	Stable or ↑	↓ *
Requirement for response	All	All	All	Any *

Abbreviations: CR = complete response; PR = partial response; SD = stable disease, PD = progressive disease; FLAIR = fluid-attenuated inversion recovery; NA = not applicable.

* Progression occurs when this criterion is present.

† Increase in corticosteroids alone will not be taken into account in determining progression in the absence of persistent clinical deterioration.

10.16 APPENDIX 16: MODIFIED RESPONSE EVALUATION CRITERIA IN SOLID TUMORS

Details provided in bibliographic reference (56).

Response Evaluation Criteria in Solid Tumors for immune based therapies (iRECIST)

	RECIST 1.1	iRECIST
Definitions of measurable and non-measurable disease; numbers, and site of target disease	Measurable lesions are ≥10 mm in diameter (≥15 mm for nodal lesions); maximum of 5 lesions (2 per organ); all other disease is considered non-target (must be ≥10 mm in short axis for nodal disease)	No change from RECIST 1.1; however, new lesions are assessed as per RECIST 1.1 but are recorded separately on the case report form (but not included in the sum of lesions for

		target lesions identified at baseline)
Complete response, partial response, or stable disease	Cannot have met criteria for progression before complete response, partial response, or stable disease	Can have had iUPD (one or more instances), but not iCPD, before iCR, iPR, or iSD
Confirmation of complete response or partial response	Only required for non-randomized trials	As per RECIST 1.1
Confirmation of stable disease	Not required	As per RECIST 1.1

	RECIST 1.1	iRECIST
New lesions	Result in progression; recorded but not measured	Results in iUPD but iCPD is only assigned on the basis of this category if at next assessment additional new lesions appear or an increase in size of new lesions is seen (≥5 mm for sum of new lesion target or any increase in new lesion non-target); the appearance of new lesions when none have previously been recorded, can also confirm iCPD
Independent	Recommended in some circumstances	Collection of scans (but not

blinded review and central collection of scans	eg, in some trials with progression-based endpoints planned for marketing approval	independent review) recommended for all trials
Confirmation of progression	Not required (unless equivocal)	Required
Consideration of clinical status	Not included in assessment	Clinical stability is considered when deciding whether treatment is continued after iUPD

"i" indicated immune responses assigned using iRECIST.

Abbreviations: iCPD=confirmed progression; iCR=complete response; iPR=partial response; iSD=stable disease; iUPD=unconfirmed progression; RECIST=Response Evaluation Criteria in Solid Tumors

Tumors for immune based therapies (iRECIST)

Target lesions	Non-target lesions	New lesions	Timepoint response with no previous iUPD in any category	Timepoint response with previous iUPD in any categorya
iCR	iCR	No	iCR	iCR
iCR	Non-iCR/ non-iUPD	No	iPR	iPR
iPR	Non-iCR/ non-iUPD	No	iPR	iPR
iSD	Non-iCR/ non-iUPD	No	iSD	iSD
iUPD with no change,	iUPD with no	Yes	Not applicable	New lesions confirm iCPD if new lesions were previously identified and they have increased in

				size (≥5 mm in sum
or with a decrease from last timepoint	change, or decrease from last timepoint			of measures for new lesion target or any increase for new lesion non-target) or number; if no change is seen in new lesions (size or number) from last timepoint, assignment
iSD, iPR, iCR	iUPD	No	iUPD	remains iUPD Remains iUPD unless iCPD is confirmed on the basis of a further increase in the size of non-target disease (does not need to meet RECIST 1.1 criteria for unequivocal progression)
iUPD	Non-iCR/ non-iUPD, or iCR	No	iUPD	Remains iUPD unless iCPD is confirmed on the basis of a further increase in sum of measures ≥5 mm; otherwise, assignment remains iUPD
Target lesions	Non-target lesions	New lesions	Timepoint response with no previous iUPD in any category	Timepoint response with previous iUPD in any categorya
iUPD	iUPD	No	iUPD	Remains iUPD unless iCPD is confirmed based on a further increase in previously identified target lesion iUPD in sum of measures ≥5 mm or non-target lesion iUPD (previous assessment need not have shown unequivocal progression)
iUPD	iUPD	Yes	iUPD	Remains iUPD unless iCPD is confirmed on the basis of a further increase in previously identified

				target lesion iUPD
				sum of measures ≥5 mm, previously identified non-target lesion iUPD (does not need to be unequivocal), or an increase in the size or number of new lesions previously
				identified
Non-iUPD or progression	Non-iUPD or progression	Yes	iUPD	Remains iUPD unless iCPD is confirmed on the basis of an increase in the size or number of new lesions previously identified

a Previously identified in assessment immediately before this timepoint.

"i" indicates immune responses assigned using iRECIST Target lesions, non-target lesions, and new lesions defined according to RECIST 1.1 principles; if no pseudoprogression occurs, RECIST 1.1 and iRECIST categories for complete response, partial response, and stable disease would be the same.

Abbreviations: iCPD=confirmed progression; iCR=complete response; iPR=partial response; iSD=stable disease; iUPD=unconfirmed progression; non-iCR/non-iUPD=criteria for neither CR nor PD have been met; RECIST=Response Evaluation Criteria in Solid Tumors.

10.17 APPENDIX 17: CA125 RESPONSE BY GYNAECOLOGIC CANCER INTERGROUP

Guidelines for using CA-125 response have been developed. Please refer to http://www.gcig.igcs.org/CA-125.html. Patients should have a pre-treatment CA-125 of at least twice the ULN in order to be considered for CA-125 response. Patients are not evaluable by CA-125 if they have received mouse antibodies or if there has been medical and/or surgical interference with their peritoneum or pleura during the previous 28 days. In those patients, a CA-125 response would be obtained the moment the CA-125 is reduced by 50% and this should be confirmed with a consecutive CA-125 assessment not earlier than 28 days after the previous one, with however the date of the first 50% reduction to be the reference date for the CA-125 response.

10.18 APPENDIX 18: IMMUNOTHERAPY RESPONSE ASSESSMENT IN NEURO-ONCOLOGY (IRANO)

Details provided in bibliographic reference (64).

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10.20 APPENDIX 20: MODIFICATION OF DIET IN RENAL DISEASE (MDRD) EQUATION

Glomerular filtration rate (mL/min/1.73 m2) = 175 × (Serum Creatinine)-1.154 × (Age)-0.203 × (0.742 if Female) × (1.212 if African American).

10.21 APPENDIX 21: MANAGEMENT OF ATEZOLIZUMAB-SPECIFIC ADVERSE EVENTS

All pulmonary events should be thoroughly evaluated for other commonly reported etiologies such as pneumonia or other infection, lymphangitic carcinomatosis, pulmonary embolism, heart failure, chronic obstructive pulmonary disease, or pulmonary hypertension. Management guidelines for pulmonary events are provided in Table 17.

Event	Isatuximab management	Atezolizumab management	Action and guidance
Pulmonary event, Grade 1	No change in dose	No change in dose	Monitor closely Re-evaluate on serial imaging. Consider patient referral to pulmonary specialist.
Pulmonary event, Grade 2	Delay or omit dose until resolves to Grade ≤1 for a maximum of 2 weeks (see Section 6.6.2)	Delay cycle until Grade ≤1a If event resolves to Grade 1 or better, resume atezolizumaba And isatuximab If event does not resolve to Grade 1 or better, permanently	Refer patient to pulmonary and infectious disease specialists and consider bronchoscopy or BAL. Initiate treatment with 1−2 mg/kg/day oral prednisone or equivalent. Contact Medical Monitorb For recurrent events, treat as a Grade 3 or 4 event.

		discontinue atezolizumab and resume isatuximabb	
			Contact Medical Monitorc
Pulmonary event, Grade 3 or 4	Grade 3: Delay or omit isatuximab until resolves to Grade ≤1 for a maximum of 2 weeks (see Section 6.6.2) Grade 4: discontinue isatuximab	Discontinue atezolizumab	Bronchoscopy or BAL is recommended. Initiate treatment with 1−2 mg/kg/day oral prednisone or equivalent If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month

a Atezolizumab may be withheld for a longer period of time (ie, > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor. b If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

c Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor. Abbreviation: BAL = bronchoscopic alveolar lavage

Eligible patients must have adequate liver function, as manifested by measurements of total bilirubin and hepatic transaminases, and liver function will be monitored throughout study treatment. Management guidelines for hepatic events are provided in Table 18.

For patients with elevated LFTs, concurrent medication, viral hepatitis, and toxic or neoplastic etiologies should be considered and addressed, as appropriate.

Event	Isatuximab management	Atezolizumab management	Action and guidance

Hepatic event, Grade 1	No change in dose	No change in dose	Monitor LFTs until values resolve to within normal limits
Hepatic event, Grade 2	No change in dose	Withhold or omit dose until Grade ≤1a If event resolves to Grade 1 or better, resume atezolizumabb If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumabc	All events: Monitor LFTs more frequently until return to baseline values Events of >5 days' duration: Initiate treatment with 1−2 mg/kg/day oral prednisone or equivalent Contact Medical Monitorc
Hepatic event, Grade 3 or 4	Delay or omit isatuximab until Grade ≤2 for a maximum of 2 weeks (see Section 6.6.2)	Discontinue atezolizumab	Contact Medical Monitorc Consider patient referral to gastrointestinal specialist for evaluation and liver biopsy to establish etiology of hepatic injury Initiate treatment with 1−2 mg/kg/day oral prednisone or equivalent If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month

a Atezolizumab may be withheld for a longer period of time (ie, > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor. b If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

c Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the Investigator (or an appropriate delegate) and the Medical Monitor. Abbreviation: LFT = liver function tests.

Management guidelines for diarrhea or colitis are provided in Table 19.

All events of diarrhea or colitis should be thoroughly evaluated for other more common etiologies.

Table 19 - Management Guidelines for Gastrointestinal Events (Diarrhea or Colitis)

Event	Isatuximab management	Atezolizumab management	Action and guidance
Diarrhea or colitis, Grade 1	No change in dose	No change in dose	Initiate symptomatic treatment Endoscopy is recommended if symptoms persist for >7 days Monitor closely
Diarrhea or colitis, Grade 2	Delay or omit dose until ≤Grade1 for a maximum of 2 weeks (see Section 6.6.2)	Delay cycle until Grade ≤1a If event resolves to Grade 1 or better, resume atezolizumab and isatuximabb If event does not resolve to Grade 1 or better, permanently discontinue atezolizumab and resume isatuximabc	Initiate symptomatic treatment. Patient referral to GI specialist is recommended For recurrent events or events that persist 5 days, initiate treatment with 1−2 mg/kg/day oral prednisone or equivalent Contact Medical Monitorc

Diarrhea or colitis, Grade 3	Delay or omit dose until ≤Grade 1 for a maximum of 2 weeks (see Section 6.6.2)	Delay dose until Grade ≤1a If event resolves to Grade 1 or better, resume atezolizumab and isatuximabb If event does not resolve to Grade 1 or better, permanently discontinue atezolizumab and resume isatuximabc	Refer patient to GI specialist for evaluation and confirmatory biopsy. Initiate treatment with 1−2 mg/kg/day IV methylprednisolone or equivalent and convert to 1−2 mg/kg/day oral prednisone or equivalent upon improvement. Contact Medical Monitorc
Diarrhea or colitis, Grade 4	Discontinue treatment	Discontinue treatment	Contact Medical Monitorc Refer patient to GI specialist for evaluation and confirmation biopsy Initiate treatment with 1−2 mg/kg/day IV methylprednisolone or equivalent and convert to 1−2 mg/kg/day oral prednisone or equivalent upon improvement If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

- Atezolizumab may be withheld for a longer period of time (ie, > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the Investigator and the Medical Monitor.
- If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.
- Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

Abbreviation: GI = gastrointestinal.

Management guidelines for endocrine events are provided in Table 20.

The patient should be referred to an endocrinologist if an endocrinopathy is suspected.

Event	Isatuximab management	Atezolizumab management	Action and guidance
Asymptomatic hypothyroidism	No change in dose	No change in dose	Initiate treatment with thyroid replacement hormone. Monitor TSH weekly.
Symptomatic hypothyroidism	Delay or omit dose until resolve to ≤Grade 2 for a maximum of 2 weeks (see Section 6.6.2)	Delay cycle. Resume atezolizumab and isatuximab when symptoms are controlled and thyroid function is improving.	Initiate treatment with thyroid replacement hormone. Monitor TSH weekly. Consider patient referral to endocrinologist.
Asymptomatic hyperthyroidism	No change in dose	No change in dose	TSH ≥0.1 mU/L and <0.5 mU/L: Monitor TSH every 4 weeks. TSH <0.1 mU/L: Follow guidelines for symptomatic hyperthyroidism.
Symptomatic hyperthyroidism	Delay or omit dose until resolve to ≤Grade 2 for	Delay cycle. Discontinue treatment and contact Medical Monitor for life-threatening immune-related hyperthyroidismc	Initiate treatment with anti-thyroid drug such as methimazole or carbimazole as needed. Consider patient referral to

	a maximum of 2 weeks (see Section 6.6.2)	Resume atezolizumab and isatuximab when symptoms are controlled and thyroid function is improving.	endocrinologist.
Symptomatic adrenal insufficiency, Grade 2–4	Grade 2: no change in dose. Grade 3, 4: delay or omit dose until resolves to ≤Grade 2 for a maximum of 2 weeks (see Section 6.6.2)	Omit/withhold atezolizumab until ≤Grade 1a If event resolves to Grade 1 or better and patient is stable on replacement therapy, resume atezolizumabb If event does not resolve to Grade 1 or better or patient is not stable on replacement therapy while withholding atezolizumab, permanently discontinue atezolizumab and continue/resume isatuximabc	Refer patient to endocrinologist. Perform appropriate imaging. Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. Contact Medical Monitorc

Event	Isatuximab management	Atezolizumab management	Action and guidance
Hyperglycemia, Grade 1 or 2	No change in dose.	No change in dose	Initiate treatment with insulin if needed. Monitor for glucose control.
Hyperglycemia, Grade 3 or 4	Delay or omit dose for a maximum of 2 weeks (see Section 6.6.2) Resume isatuximab when symptoms resolve and glucose levels are stable.	Delay cycle. Resume atezolizumab when symptoms resolve and glucose levels are	Initiate treatment with insulin. Monitor for glucose control.

		stable.	
		Omit/withhold atezolizumaba	Refer patient to endocrinologist. Perform brain MRI (pituitary protocol).
Hypophysitis (pan-hypopituitarism), Grade 2 or 3	Grade 2: No change in dose Grade 3: delay or omit dose until resolves to ≤Grade 2 for a maximum of 2 weeks (see Section 6.6.2)	If event resolves to Grade 1 or better, resume atezolizumabb If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumabc	Initiate treatment with 1−2 mg/kg/day IV methylprednisolone or equivalent and convert to 1−2 mg/kg/day oral prednisone or equivalent upon improvement. Initiate hormone replacement as clinically needed. Contact Medical Monitorc For recurrent hypophysitis, treat as a Grade 4 event.
Hypophysitis (pan-hypopituitarism), Grade 4	Delay or omit isatuximab until resolves to ≤Grade 2 for a maximum of 2 weeks (see Section 6.6.2)	Discontinue atezolizumab	Contact Medical Monitorc Refer patient to endocrinologist. Perform brain MRI (pituitary protocol). Initiate treatment with 1−2 mg/kg/day IV methylprednisolone or equivalent and convert to 1−2 mg/kg/day oral prednisone or equivalent upon improvement. Initiate hormone replacement as clinically needed.

a Atezolizumab may be withheld for a longer period of time (ie, >12 weeks after event

onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor. b If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

c Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the Investigator (or an appropriate delegate) and the Medical Monitor.

Abbreviation: MRI: magnetic resonance imaging; TSH: thyroid-stimulating hormone.

An ophthalmologist should evaluate visual complaints (eg, uveitis, retinal events).

Management guidelines for ocular events are provided in Table 21.

Table 21 - Management Guidelines for Ocular Events

Event	Isatuximab management	Atezolizumab management	Action and guidance
Ocular event, Grade 1	No change in dose	No change in dose	Patient referral to ophthalmologist is strongly recommended. Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy. If symptoms persist, treat as a Grade 2 event.
Ocular event, Grade 2	No change in dose	Omit/withhold dose until Grade ≤1a If event resolves to Grade 1 or better, resume atezolizumabb If event does not resolve to Grade 1 or better while withholding atezolizumab,	Patient referral to ophthalmologist is strongly recommended. Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy. Contact Medical Monitorc

		permanently	
		discontinue atezolizumab and continue/ resume isatuximabc	
Ocular event, Grade 3 or 4	Delay or omit isatuximab until resolves to ≤Grade 2 for a maximum of 2 weeks (see Section 6.6.2)	Discontinue atezolizumab	Contact Medical Monitorc Refer patient to ophthalmologist. Initiate treatment with 1−2 mg/kg/day oral prednisone or equivalent. If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

- Atezolizumab may be withheld for a longer period of time (ie, > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.
- If corticosteroids have been initiated, they must be tapered over ≥1 month to ≤10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.
- Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

Immune-related myocarditis needs to be distinguished from myocarditis resulting from infection (commonly viral, eg, in a patient who reports a recent history of gastrointestinal illness), ischemic events, underlying arrhythmias, exacerbation of pre-existing cardiac conditions, or progression of malignancy. A cardiologist should be consulted.

Patients with signs and symptoms of myocarditis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 22.

Table 22 - Management Guidelines for Immune-Related Myocarditis

Event	isatuximab management	Atezolizumab management	Action and guidance

Immune-related myocarditis, Grade 1	No change in dose	No change in dose	Refer patient to cardiologist. Initiate treatment as per institutional guidelines.
Immune-related myocarditis, Grade 2	No change in dose	Omit/withhold dose until Grade ≤1a If event resolves to Grade 1 or better, resume atezolizumabb If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and resume/continue isatuximabc	Contact Medical Monitor. Refer patient to cardiologist. Initiate treatment as per institutional guidelines and consider antiarrhythmic drugs, temporary pacemaker, ECMO, or VAD as appropriate. Consider treatment with 1−2 mg/kg/day IV methylprednisolone or equivalent and convert to 1−2 mg/kg/day oral prednisone or equivalent upon improvementa Contact Medical Monitorc
Immune-related myocarditis, Grade 3−4	Delay or omit isatuximab until resolves to ≤Grade 2 for a maximum of 2 weeks (see Section 6.6.2)	Discontinue atezolizumab	Contact Medical Monitorc Refer patient to cardiologist. Initiate treatment as per institutional guidelines and consider antiarrhythmic drugs, temporary pacemaker, ECMO, or VAD as appropriate. Initiate treatment with 1−2 mg/kg/day IV methylprednisolone or equivalent and convert to 1−2 mg/kg/day oral prednisone or equivalent upon improvement a, b

If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.

If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

- Atezolizumab may be withheld for a longer period of time (ie, >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.
- If corticosteroids have been initiated, they must be tapered over ≥1 month to ≤10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.
- Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

Abbreviation: ECMO = extracorporeal membrane oxygenation; VAD = ventricular assist device.

Metamizole (dipyrone) is prohibited in treating atezolizumab associated infusion-associated reactions, due to its potential for causing agranulocytosis.

Guidelines for medical management of infusion-associated reactions are provided in Table 23.

Table 23 - Management Guidelines for Infusion-Associated Reactions

Event	Management isatuximab	Management atezolizumab	Action and guidance
IAR, Grade 1	Continue isatuximab infusion per the judgment of the Investigator following close direct monitoring of the patient's clinical status. Isatuximab infusion may be	Reduce infusion rate to half the rate being given at the time of event onset.	For atezolizumab, after the event has resolved, the investigator should wait for 30 minutes while delivering the infusion at the reduced rate. If the infusion is tolerated at the reduced rate for 30 minutes after

	stopped at any time if deemed necessary. If stopped, IAR will be classified as Grade 2		symptoms have resolved, the infusion rate may be increased to the original rate. Administer aggressive symptomatic treatment (eg, oral or IV antihistamine, anti-pyretic medication, glucocorticoids, epinephrine, bronchodilators, oxygen). After symptoms have resolved to Grade ≤1
IAR, Grade 2	Interrupt isatuximab infusion	Interrupt atezolizumab infusion.	(for isatuximab) or baseline (for atezolizumab), resume infusion at half the initial rate for isatuximab and at half the rate being given at the time of event onset for atezolizumab. For subsequent infusions, consider administration of oral premedication with antihistamines, anti-pyretics, and/or analgesics and monitor closely for IARs.
IAR*, Grade 3 or 4	Stop infusion. If occurred during atezolizumab infusion, permanently discontinue atezolizumab and continue with isatuximab. If occurred during	Stop infusion. Permanently discontinue atezolizumab	Administer aggressive symptomatic treatment (eg, oral or IV antihistamine, anti-pyretic, glucocorticoids, epinephrine, bronchodilators, oxygen). Contact Medical Monitora

isatuximab infusion, permanently discontinue both.

a Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

Abbreviation: IAR = infusion-associated reaction.

* Applicable to Grade 3 or 4 cytokine release syndrome and anaphylactic reactions.

The differential diagnosis of acute abdominal pain should include pancreatitis. Management guidelines for pancreatic events, including pancreatitis, are provided in Table 24.

Event	Isatuximab management	Atezolizumab management	Action and guidance
Amylase and/or lipase elevation, Grade 1	No change in dose	No change in dose	Monitor amylase and lipase prior to dosing.
Amylase and/or lipase elevation, Grade 2	No change in dose	No change in dose	Monitor amylase and lipase weekly. For prolonged elevation (eg >3 weeks), consider treatment with 10 mg/day oral prednisone or equivalent. Refer patient to GI specialist.
Amylase and/or lipase elevation, Grade 3 or 4	Delay or omit dose until ≤Grade 2 for a maximum of 2 weeks (see Section 6.6.2) and resume isatuximab	Delay cycle and then Withhold/omit atezolizumab for up to 12 weeks after event onseta	Monitor amylase and lipase every other day. If no improvement, consider treatment with 1−2 mg/kg/day oral prednisone or equivalent.

		If event resolves to Grade 1 or better, resume atezolizumabb	
		If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab	Contact Medical Monitorc For recurrent events, permanently discontinue atezolizumab and contact Medical Monitorc
Immune-related pancreatitis, Grade 2 or 3	Grade 2: no change in dose Grade 3: delay or omit dose until ≤Grade 2 for a maximum of 2 weeks (see Section 6.6.2)	Grade 2: omit/ withhold atezolizumab Grade 3: Delay cycle and then Withhold/omit atezolizumaba If event resolves to Grade 1 or better, resume atezolizumabb	Refer patient to GI specialist. Initiate treatment with 1−2 mg/ kg/day IV methylprednisolone or equivalent and convert to 1−2 mg/kg/day oral prednisone or equivalent upon improvement. Contact Medical Monitorc
		If event does not resolve to Grade 1 or better while withholding atezolizumab,	For recurrent events, permanently discontinue atezolizumab and contact Medical Monitorc

Event	Isatuximab management	Atezolizumab management	Action and guidance
		permanently discontinue atezolizumabc	
Immune-related pancreatitis, Grade 4	Discontinue isatuximab	Discontinue atezolizumab	Contact Medical Monitorc Refer patient to GI specialist. Initiate treatment with 1−2 mg/kg/day IV methylprednisolone or equivalent and convert to 1−2 mg/kg/day oral prednisone or equivalent upon improvement. If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

a Atezolizumab may be withheld for a longer period of time (ie, > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor. b If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

c Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor. Abbreviation: GI = gastrointestinal.

Severe Cutaneous Adverse Reactions (SCARs) are a heterogeneous group of immunologically mediated drug eruptions.

Although rare, these events are potentially fatal, and mainly constituted by erythema multiforme, acute generalized exanthematous pustulosis, SJS, TEN, and DRESS.

The recommendations for SCARs are:

- For suspected SCARs the patients should be referred to a dermatologist for further diagnosis and management
- Atezolizumab should be withheld for patients with suspected SJS or TEN
- Atezolizumab should be permanently withdrawn for any grade confirmed SJS or TEN
- Caution should be used when considering the use of atezolizumab in a patient who has previously experienced a severe or life-threatening skin adverse reaction on prior treatment with other immune-stimulatory anticancer agents.

Regarding other dermatological events, a dermatologist should evaluate persistent and/or severe rash or pruritus. Management guidelines for other dermatologic events are provided in Table 25.

Table 25 - Management Guidelines for Dermatologic Events

Event	Isatuximab management	Atezolizumab management	Action and guidance
Dermatologic event, Grade 1	No change in dose	No change in dose	Consider treatment with topical corticosteroids and/or other symptomatic therapy (eg, antihistamines). Consider patient referral to dermatologist.
Dermatologic event, Grade 2	No change in dose	No change in dose	Initiate treatment with topical corticosteroids. Consider treatment with higher-potency topical corticosteroids if event does not improve.
		Omit/withold atezolizumaba	Refer patient to dermatologist.
Dermatologic event, Grade 3	No change in dose	If event resolves to Grade 1 or better, resume atezolizumabb	Initiate treatment with 10 mg/day oral prednisone or equivalent, increasing dose to 1–2 mg/kg/day if event does not improve within 48–72 hours.
		If event does not	Contact Medical Monitorc

		resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab
Dermatologic event, Grade 4	Delay or comit isatuximab until ≤Grade 3 fo	

10.22 APPENDIX 22: MANAGEMENT OF PATIENTS WITH HCV INFECTION

Recommended management for recurrent HCV infection or an HCV flare are described below.

- Recurrent HCV infection: If the patient entered the study with an HCV RNA test of "Target not Detected" and has confirmed detectable HCV RNA (2 specimens, 1 week apart), then the patient has experienced a late HCV relapse or a recurrent infection.
  - Question the patient about use of injection or inhalation drugs,
  - At the time of first detection of HCV RNA, send a specimen for HCV genotyping,
  - Measure AST, ALT, ALP, total bilirubin, direct bilirubin, and INR weekly,
  - Measure HCV RNA levels every 2 weeks,
  - Therapy with HCV antiviral treatments should be strongly considered.
- HCV Flare:
  - At the time of first detection of HCV RNA, send a specimen for HCV genotyping,
  - Measure AST, ALT, ALP, total bilirubin, direct bilirubin, and INR weekly,
  - Measure HCV RNA levels every 2 weeks,
  - Therapy with HCV antiviral treatments should be strongly considered.

- For both recurrent infection and HCV flare: If ALT returns to normal or Grade 1 (if normal at baseline), or to baseline grade (if Grade 2 at baseline) within 12 weeks, and the patient is clinically stable, the patient may restart study treatment. If these conditions are not met, then study treatment should be permanently discontinued.

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