GEM 2101-SITISVEAL-M

Statistical Analysis Plan

PHASE II, OPEN-LABEL STUDY OF PRELIMINARY EFFICACY OF SITRAVATINIB IN COMBINATION WITH TISLELIZUMAB IN PATIENTS WITH METASTATIC UVEAL MELANOMA WITH LIVER METASTASES

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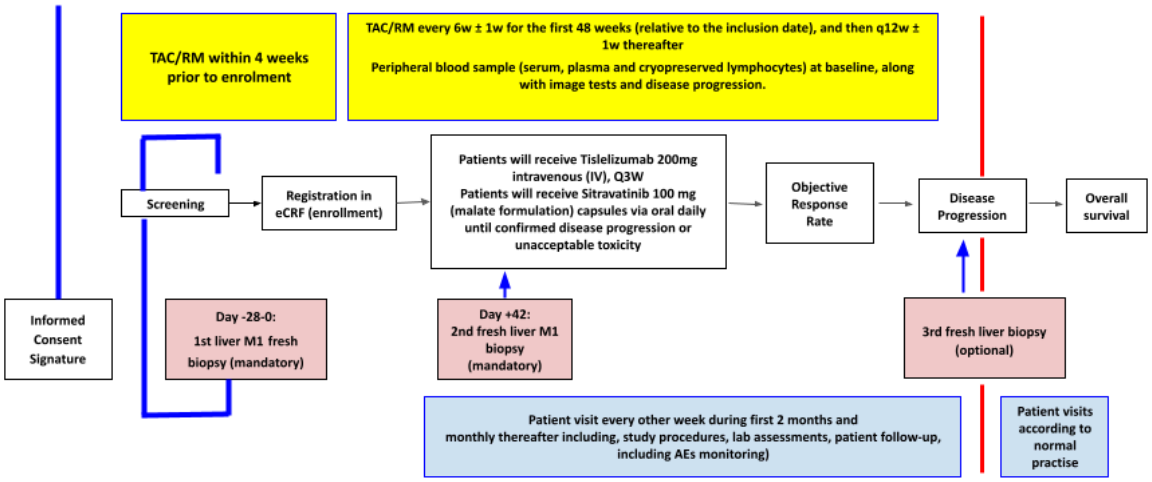
1. Table of Contents

This analysis was done with a database downloaded on XX/XX/20XX.

2. STUDY DESIGN

This is a non-randomized, single arm, multicenter, phase II study of Sitravatinib in combination with Tislelizumab in subjects with metastatic uveal melanoma and liver metastases. This study is divided into 3 phases: Screening, Treatment, and Follow-up. After informed consent is obtained, subjects will enter in the Screening phase to assess eligibility criteria and perform a mandatory tumor biopsy. Upon meeting criteria, eligible subjects will be entered into the Treatment phase. Patients will receive Sitravatinib 100 mg orally once daily in combination with tislelizumab 200 mg IV once every 3 weeks until progression of disease, unacceptable toxicity, death, or consent withdrawal, whichever occurs first. Treatment may be continued after progression according to physician criteria (with previous consultation with Coordinating investigator) until patients no longer receive clinical benefit.



Subjects will be seen by Investigators weekly during the first two cycles, to closely follow up diarrhea and hypertension that can be observed due to treatment with Sitravatinib. Patients should be visited at least every three weeks thereafter and every time that the Principal Investigator deemed necessary.

New tumor biopsy will be mandatory and performed before the 3rd dose of Tislelizumab.

Subjects, either on treatment of after they are no longer receiving Sitravatinib and Tislelizumab because of unacceptable toxicity or due to investigator judgment will undergo radiological evaluations of the tumor every 6 weeks during the first 12 months (48 weeks) after treatment initiation, and then every 12 weeks until the progression of disease (progression follow-up).

Subjects that are no longer receiving Sitravatinib and Tislelizumab because of progression will enter the long term OS follow-up until their death or until the end of the study (whatever happens before).

Subjects who have switched to an alternative treatment without disease progression will receive a formal follow-up with images tests until progression, and after progression long term follow up to record the date of death.

3. Screening Failures

Table 1: Screening failures

Overall	Overall (N=)
Screening failures	
No	
Yes	

Table 2: List of patients with screening failure

Patient Number	Hospital	Screening failures	Screening Failure Specify

4. Baseline characteristics

Table 3: Summary of Baseline characteristics

Overall	Overall (N=)
Hospital	
INSTITUT CATALÀ D'ONCOLOGIA L'HOSPITALET (ICO)	
HOSPITAL VIRGEN MACARENA	
HOSPITAL UNIVERSITARIO LA PAZ	
Patient Age	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
Weight	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
Sex	
Female	
Male	
Systolic Blood Pressure	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
Race	
Caucasian	
Diastolic Blood Pressure	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
Temperature	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
Respiration rate	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
Height	
N	
Mean (95%CI)	
SD	
Median (95%CI)	

Overall	Overall (N=)
Range	
Pulse rate	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
ECOG	
0	
1	
Physical exam	
Normal	
Tobacco Smoking History	
Never smoker	
Former smoker	
Smoker	
Unknown	
Baseline LDH	
LDH > ULN	
LDH ≤ ULN	
Baseline GGT	
Missing data	
GGT > ULN	
GGT ≤ ULN	
Baseline Alcaline P.	
Alcaline P. > ULN	
Alcaline P. ≤ ULN	

4.1. Cancer history: Primary cancer and treatments

Table 4: Patients without previous oncologic treatments or with the first previous oncologic treatment earlier than metastatic date

Patient Number	Hospital	Date of first previous oncologic treatment	Metastatic date	Time from first previous oncologic treatment to metastatic date less or greater than 2 years

Table 5: Summary of Cancer history: Primary cancer and treatments variables

Overall	Overall (N=)
T Stage	
T3	
T3a	
T3b	
T4a	
Tx	
N Stage	
N0	
Nx	
M Stage	

Overall	Overall (N=)
M0	
M1a	
M1b	
M1c	
Cancer Histological Grade	
Missing data	
G1	
G3	
Gx	
UK	
Cancer Stage	
IIB	
IIIA	
IV	
UK	
Conservative Surgery	
Yes	
No	
Enucleation	
Yes	
No	
Brachytherapy	
Yes	
No	
Beam Therapy	
No	
UK	
Proton Beam Therapy	
Yes	
No	
UK	
Photon Beam Therapy	
Yes	
No	
UK	
Radioembolization	
No	
UK	
Stereotactic Radiosurgery (SRS)	
No	
UK	
External Radiotherapy	
Yes	
No	
UK	
Other previous treatments in the metastatic setting	
Yes	
No	
Previous Treatments Schemes	
Previous Tebentafusp treatment	
Yes	

Overall	Overall (N=)
No	
Previous Treatment Best Response	
Missing data	
SD	
PD	
Previous Treatment progresion	
Other cancer history	
Yes	
No	
UK	
Other Cancer Type	
Other Cancer Treatment	
Time from first previous oncologic treatment to metastatic date	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
Time from first previous oncologic treatment to metastatic date less or greater than 2 years	
Missing data	
> 2 years	
≤ 2 years	

4.2. CURRENT STATUS

Table 6: Summary of Current status variables

Overall	Overall (N=)
T Stage	
T0	
T3	
T3a	
T3b	
T3c	
T4a	
Tx	
N Stage	
N0	
N1	
N1a	
Nx	
M Stage	
M1	
M1a	

Overall	Overall (N=)
M1b	
M1c	
Cancer Stage	
IV	
Current Metastasis Liver	
Yes	
Current Metastasis Peritoneum	
No	
Yes	
Current Metastasis Lung	
No	
Yes	
Current Metastasis Bone	
No	
Yes	
Current Metastasis Skin	
No	
Yes	
Current Metastasis Lymph nodes	
No	
Yes	
Current Metastasis Other	
No	
Yes	
Current Metastasis Other specify	
Missing data	
Current Metastasis in other Location than Liver	
No	
Yes	
Current Metastasis Number of liver metastasis	
1	
2	
3	
4	
8	
>10	
UK	
Liver Metastasis Affectation	
Unilobular disease	
Multilobular disease	
UK	
Liver Metastasis Larger size	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
Liver metastasis size	
< 3 cm	
3 - 8 cm	
> 8 cm	

4.3. Comorbidities and Concomitant Medications

It has to be taken into account that patients can have several comorbidities or concomitant medications.

Table 7: Number of patients with some comorbidity / concomitant medication

Overall	Overall (N=)
Any Comorbidity	
No	
Yes	
Any Concomitant Medication	
No	
Yes	

Table 8: Frequency of comorbidities

	Overall
Comorbidities (CTC-AE)	**N (%)**
Comorbidity 1	
Comorbidity 2	

Table 9: Frequency of concomitant medications

		Overall
Concomitant medications (ACTC5)	**Other Concomitant medications**	**N (%)**
- Other		

5. TREATMENT COMPLIANCE

The start of study treatment is established as the first date between Sitravatinib start date and Tislelizumab administration dates for each patient.

Additionally, it has to be taken into account that some patients remain in treatment despite progression, as they can receive treatment until no longer having clinical benefit according to the protocol. For the time being, the treatment compliance is reported including treatment after progression in patients who have it.

5.1. NUMBER OF CYCLES OF TISLELIZUMAB

Table 10: Summary of the number Tislelizumab cycles.

Overall	Overall (N=)
Number of cycles of Tislelizumab	
1	
2	
3	
4	
…	

5.2. DELAY DOSES OF TISLELIZUMAB

Table 11: Number of patients with some delay doses of Tislelizumab.

Overall	Overall (N=)
Some delay doses of Tislelizumab	
No	
Yes	

Table 12: Tislelizumab delay reasons.

Overall	Overall (N=)
Delay reason	

Table 13: Tislelizumab delay reasons specify.

Overall	Overall (N=)
Treatment delay reason specify	

5.3. Omitted doses of Tislelizumab

In the following table, omission is considered when there is no administration of Tislelizumab on a visit posterior than the end of Tislelizumab treatment.

Table 14: Number of patients with some omissions of Tislelizumab dose.

Overall	Overall (N=)
Some omission of Tislelizumab dose	
No	
Yes	

Table 15: Tislelizumab omission reasons.

Overall	Overall (N=)
Omission reason	
AE not related to the treatment study	
Other	
Unacceptable toxicity	

Table 16: Tislelizumab omission reasons specify.

Overall	Overall (N=)
Omission reason specify	

5.4. Sitravatinib incidences

Table 17: Number of patients with each incidence associated with Sitravatinib treatment.

Overall	Overall (N=)
Some dose reduction	
No	
Yes	
Some dose escalation	
No	
Some temporary interruption	
No	
Yes	
Some other incidence	
No	
Yes	

Table 18: Incidence reasons associated with Sitravatinib treatment.

Overall	Overall (N=)
Incidence reason	
AE	
Investigator's decision	
Toxicity	

5.5. End of treatments

Table 19: Reasons for end of treatments.

Overall	Overall (N=)
Sitravatinib End of Treatment Reason	
Missing data	
Study treatment completion	
Progression according RECIST 1.1	
Unacceptable toxicity	
AE not related to the treatment study	
Investigator decision	
Withdraw consent	
Symptomatic deterioration	
Lost of follow up	
Protocol violation	
Pregnancy	
Death	
Other	
Tislelizumab End of Treatment Reason	
Missing data	
Study treatment completion	
Progression according RECIST 1.1	
Unacceptable toxicity	
AE not related to the treatment study	
Investigator decision	
Withdraw consent	
Symptomatic deterioration	
Lost of follow up	
Protocol violation	
Pregnancy	
Death	
Other	

Table 20: Sitravatinib reason for end specify of patients who end treatment due to Unacceptable toxicity, AE not related to the treatment study, Investigator decision, Protocol violation or Other causes.

Patient Number	Hospital	Sitravatinib End of Treatment Reason	Sitravatinib Reason Specify

Table 21: Tislelizumab reason for end specify of patients who end treatment due to Unnacceptable toxicity, AE not related to the treatment study, Investigator decision, Protocol violation or Other causes.

Patient Number	Hospital	Tislelizumab End of Treatment Reason	Tislelizumab Reason Specify

5.6. Duration of treatments

The duration of treatments includes the periods of delay and missed doses.

Table 22: Patients with date of Sitravatinib permanent interruption distinct from End of Sitravatinib treatment date

Patient Number	Hospital	Last date of Sitravatinib administration	Sitravatinib last dose date

Table 23: Patients with last Tislelizumab administration date distinct from End of Tislelizumab treatment date

Patient Number	Hospital	Last date of Tislelizumab administration	Tislelizumab last dose date

The duration of each treatment is calculated with the end of treatment date (Treatments last dose date) and, when it is missing, with the last date of treatment administration. In relation to Sitravatinib, the last date of treatment administration is the last visit date associated with Sitravatinib pills received for the next cycle in Treatment Phase - Visit Data form.

Table 24: Summary of the duration of treatments

Overall	Overall (N=)
Duration of Sitravatinib + Tislelizumab treatment in months	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
Duration of Tislelizumab treatment in months	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
Duration of Sitravatinib treatment in months	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	

6. Primary objective: Efficacy analysis in terms of Objective Response Rate (ORR)

The ORR is defined as the proportion of patients with at least one visit response of CR or PR according to RECIST 1.1 criteria that is confirmed at least 4 weeks later. The best OR and confirmed best OR according to RECIST 1.1 criteria are calculated using global responses.

Table 25: Patients with best OR different from best OR confirmed response.

Patient Number	Hospital	Best OR (Recist 1.1)	Best confirmed OR (Recist 1.1)

Table 26: Table of frequencies of confirmed Best OR.

Overall	Overall (N=)
Best confirmed OR (Recist 1.1)	
CR	
PR	
SD	
PD	
NE	
UK	
Best Overall Response (Recist 1.1)	
CR	
PR	
No confirmed response	
NE	
UK	

The following table shows the duration of response, which is defined as the time from the first occurrence of PR or CR as best OR until PD or death, whichever occurs first, in patients with CR or PR as best OR.

Patient Number	Hospital	Best confirmed OR (Recist 1.1)	Duration of response (weeks)

6.1. Univariate logistic regression

The event of interest for the logistic regression of the possible prognostic factors of ORR was reaching response (CR/PR). Sex, LDH, GGT, Alcaline P. and Liver metastasis size variables are omitted from the analysis because there are not patients in all groups.

In relation to p-values, both the Cox regression table and the Forest plot show p-values from Wald test.

Table 27: Univariate Logistic Regression Models: ORR (EVENT: CR/PR) vs FACTORS.

Variables	Total N available	N (per category)	OR[1]	95% CI[1]	p-value

[1]OR = Odds Ratio, CI = Confidence Interval

Figure 1: Forest plot: Univariate logistic model

7. SECONDARY OBJECTIVES

7.1. PROGRESSION FREE SURVIVAL (PFS) FROM THE FIRST DOSE OF STUDY TREATMENT

In this analysis, patients are censored on the following dates:

- In general, patients who have a PD or die are censored on the date of the corresponding event, and alive patients without PD are censored on their last tumor imaging evaluation with non-missing OR.

The progression dates and the exitus dates considered are from PROG and End Of Study forms, respectively.

Now, there are applied the following conditions.

- Patients that start a new anti-cancer treatment are censored on last adequate tumor assessment date, which is the last tumor assessment date before new treatment.

- Patients who are lost to follow-up or who discontinued treatment will be included in the final analysis (Full Analysis Set) if they have at least baseline and two subsequent tumor evaluations.

Table 28: Patients who start study treatment and do not have baseline tumor assessment.

Patient Number	Hospital	Patient Inclusion date	First date of Sitravatinib or Tislelizumab administration	Tumor assessment date

Table 29: Patients who start study treatment and do not have two or more tumor assessments after baseline.

Patient Number	Hospital	Patient Inclusion date	First date of Sitravatinib or Tislelizumab administration	Tumor assessment date	Global response

Table 30: Patients who start study treatment and do not have two or more tumor assessments after baseline before PFS date.

Patient Number	Hospital	Patient Inclusion date	First date of Sitravatinib or Tislelizumab administration	Tumor assessment date	Global response

7.1.1. KAPLAN-MEIER

Table 31: Summary of the PFS time

Overall	Overall (N=)
Time from 1st administration of study treatment to PFS date	
N	

Overall	Overall (N=)
Mean (95%CI)	
SD	
Median (95%CI)	
Range	

Table 32: Events type PFS

PFS status	N	%	95%CI
Alive free of event			
PD			
Total			

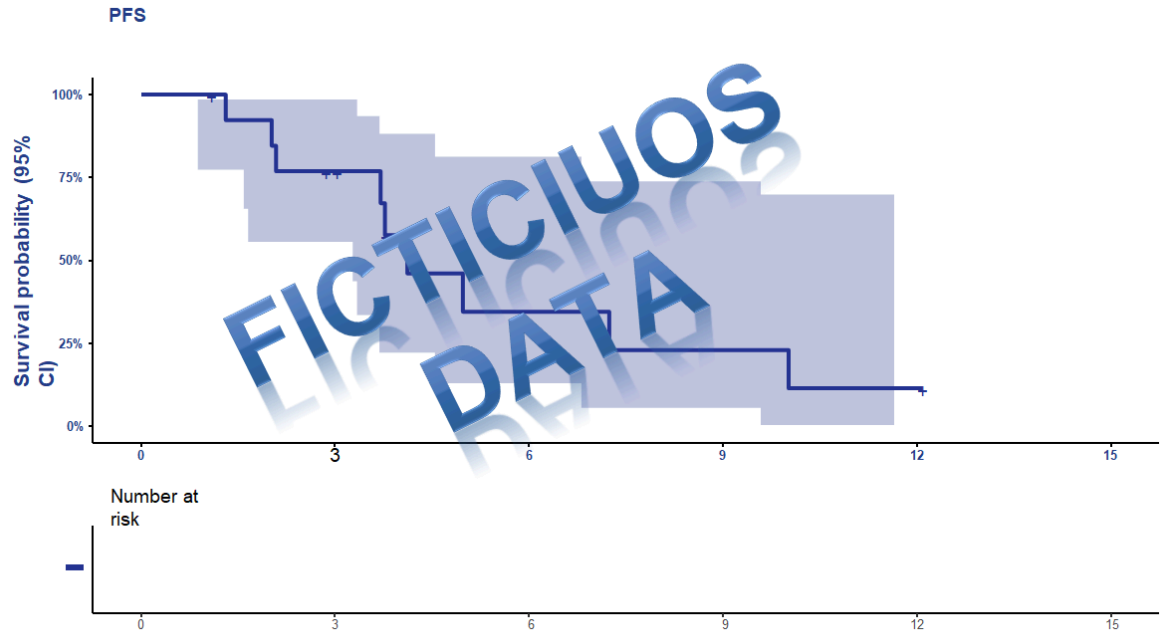
Table 33: Median/mean PFS (estimated by Kaplan-Meier)

	Median (months)	CI 95%	Mean	CI 95%
PFS from 1st administration of the combination of Sitravatinib and Tislelizumab				

Table 34: PFS estimated survival ratio

PFS	Events (%, total N)	Patients at risk	% estimated cumulative survival ratio	CI 95%
At 3 months				
At 6 months				
At 12 months				

Figure 2: PFS from 1st administration of the combination of Sitravatinib and Tislelizumab



7.1.2. Univariate Cox regression

In relation to p-values, both the table and the Forest plot show the p-values of Wald test.

Table 35: PFS analysis: Univariate Cox Model

Characteristic	N	Event N	HR[1]	95% CI[1]	p-value

[1]HR = Hazard Ratio, CI = Confidence Interval

Figure 3: Forest plot: Univariate Cox Model

7.2. Overall survival (OS) from the first dose of study treatment

OS is defined as the time from first dosing date to the date of death. Those patients that do not present a death event or are lost to follow up will be censored at the date of the last contact. Concretely, OS date associated with alive patients is the last date of all dates registered in the following forms: Treatment phase, End Treatment, Safety Visit, PFS Follow up, Tumor Assessment, Progression, Survival Follow up, Subsequent Treatments and End of Trial.

Table 36: OS Status

Overall	Overall (N=)
OS status	
Alive	
Death	

Table 37: OS exitus reasons

Overall	Overall (N=)
Exitus Reason	
Progression disease	
Toxicity due to study treatment	
Other	

7.2.1. Kaplan-Meier

Table 38: Follow up time (naive estimation)

Overall	Overall (N=)
Time from 1st administration of study treatment to death or censorship	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	

Table 39: Time to lost follow-up (estimated by Kaplan-Meier)

	Median (months)	CI 95%	Mean	CI 95%
Time to lost follow-up				

Table 40: Events type Overall survival

OS status	N	%	95%CI
Alive			
Death			
Total			

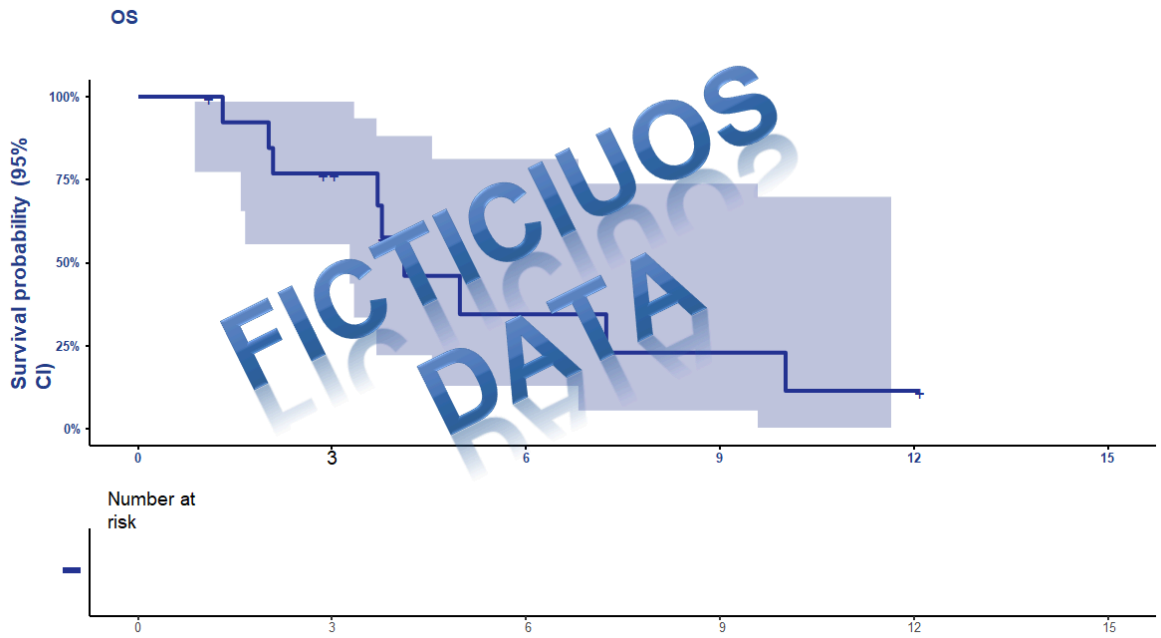
Table 41: Median/mean Overall survival (estimated by Kaplan-Meier)

	Median (months)	CI 95%	Mean	CI 95%
OS from 1st administration of the combination of Sitravatinib and Tislelizumab				

Table 42: Overall survival estimated survival ratio

Overall survival	Events (%, total N)	Patients at risk	% estimated cumulative survival ratio	CI 95%
At 3 months				
At 6 months				
At 12 months				

Figure 4: OS from 1st administration of the combination of Sitravatinib and Tislelizumab



7.2.2. Univariate Cox regression

In relation to p-values, both the table and the Forest plot show the p-values of Wald test.

Table 43: PFS analysis: Univariate Cox Model

Characteristic	N	Event N	HR[1]	95% CI[1]	p-value

[1]HR = Hazard Ratio, CI = Confidence Interval

Figure 5: Forest plot: Univariate Cox Model

8. SAFETY

According to protocol, patients will be followed at 90 days after the last dose of Sitravatinib and at 150 days after the last dose of Tislelizumab treatment administration.

8.1. ADVERSE EVENTS

In the following tables, the adverse event which are not completely ruled out as toxicities or serious are considered toxicities and SAEs respectively.

Table 44: Overall safety

Overall	Overall (N=)
Adverse Events	
Yes	
No	
Unknown	
AE Grade >=3	
No	
Yes	
Toxicity: AE related to Sitravatinib	
No	
Yes	
Toxicity: AE related to Tislelizumab	
No	
Yes	
Toxicity: AE related to all treatments	
No	
Yes	
Toxicity: AE related to any treatment	
No	
Yes	
Toxicity grade >=3	
No	
Yes	
Toxicity related to Sitravatinib grade >=3	
No	
Yes	
Toxicity related to Tislelizumab grade >=3	
No	
Yes	
Toxicity related to all treatments grade >=3	
No	
Yes	
SAE	
No	
Yes	

Table 45: Most frequent toxicities with 5% threshold

Toxicity	Frequency	Percentage (%)

Toxicity	Frequency	Percentage (%)

Table 46: Grade of most frequent toxicities with 5% threshold overall

Toxicity	No	G-UK	G-1	G-2	G-3	G-4	G-5

Table 47: List of toxicities grade >=3 in all patients

Patient Number	AE CTCAE	AE Grade	AE Related	AE Related to

Table 48: Most frequent AEs with 5% threshold

AE	Frequency	Percentage (%)

Table 49: Grade of most frequent AEs with 5% threshold overall

AE	No	G-UK	G-1	G-2	G-3	G-4	G-5

Table 50: List of all SAEs

Patient Number	AE CTCAE	AE Grade	AE Start Date	AE Stop Date	AE Related	AE Related to	AE SAE	AE Intensity

8.2. ANNEX 1

Table 51: List of all toxicities

Patient Number	AE CTCAE	AE Grade	AE Start Date	AE Stop Date	AE Related	AE Related to	AE SAE	AE Intensity