Protocol number: GEM-2101

Phase II, Open-Label Study of preliminary efficacy of Sitravatinib in Combination with Tislelizumab in Patients with Metastatic Uveal Melanoma with liver metastases.

Acronym: SITISVEAL-M (Sitravatinib and Tislelizumab with Metastatic UVEAL Melanoma with Liver Metastases)

Sponsor: Spanish Multidisciplinary Melanoma Group (GEM)

GEM Secretaria:

[redacted]

Coordinating Investigator:

[redacted]

SPONSOR'S SIGNATURE PAGE

Study title: Phase II, Open-Label Study of preliminary efficacy of Sitravatinib in Combination with Tislelizumab in Patients with Metastatic Uveal Melanoma with liver metastases.

Acronym: SITISVEAL-M
Study code: GEM-2101
EudraCT: 2021-002474-99
Version number and date: 2.0 from 22/03/2023

[redacted]
GEM CHAIRMAN **Signature** **Signature date (DD-Mmm-YYYY)**

[redacted] **Signature** **Signature date (DD-Mmm-YYYY)**
Coordinating Investigator

Dr. , M.D., Ph.D. **Signature** **Signature date (DD-Mmm-YYYY)**
Principal Investigator
HOSPITAL

1. PROTOCOL SYNOPSIS

Study Title: Phase II, Open-Label Study of preliminary efficacy of Sitravatinib in Combination with Tislelizumab in Patients with Metastatic Uveal Melanoma with liver metastases. Acronym: SITISVEAL-M
Protocol Number: GEM-2101 EudraCT number: 2021-002474-99
Clinical Phase: Phase II single arm clinical trial
Study calendar (expected): ● Trial Initiation: 3Q 2022 ● First Patient In: 3Q 2022 ● Last Subject In: 2Q 2023 ● Last Patient Last Visit: 1Q 2024 ● Publication of results : 2Q 2024
Investigational Product(s) and Reference Therapy: Sitravatinib is an oral spectrum-selective tyrosine kinase inhibitor that targets the TAM (TYRO3/AXL/MERTK) and split (VEGFR2/KIT) family receptor tyrosine kinases (RTKs), as well as MET. Inhibition of TAM RTKs may promote the depletion of myeloid-derived suppressor cells (MDSCs) in the tumor microenvironment (TME) and repolarize tumor associated macrophages towards the pro-inflammatory M1 phenotype. Inhibition of the split RTKs may reduce immunosuppressive regulatory T cells in addition to MDSCs within the TME *(Percent et al 2020)*. Tislelizumab (BGB-A317): a humanized IgG4 anti–PD-1 monoclonal antibody specifically designed to minimize binding to FcγR on macrophages. In preclinical studies, binding to FcγR on macrophages has been shown to compromise the anti-tumor activity of PD-1 antibodies through activation of antibody-dependent macrophage-mediated killing of T effector cells. Tislelizumab is the first drug candidate produced from BeiGene's immuno-oncology biologic program, and we believe it could serve as a key element of our immuno-oncology combination platform. Tislelizumab is being developed as a monotherapy and in combination with other therapies for the treatment of a broad array of both solid tumor and hematologic cancers (www.beigene.com).
Research Hypothesis:

Treatment with Tislelizumab + Sitravatinib will increase the Objective Response Rate in patients with Metastatic Uveal Melanoma (mUM) with liver metastases, compared with the current standard of care.

Objectives:

Primary Objectives:

- The primary objective is to evaluate the efficacy of the combination of Sitravatinib and Tislelizumab in patients with mUM with liver metastases and biopsiable disease at first line or after failure to first line systemic therapy with Tebentafusp (only HLA-A02:01 positive patients) or liver directed therapy in terms of objective response rate according to RECIST 1.1 criteria.

Secondary Objective(s):

- The secondary objective is to evaluate the efficacy of the combination of Sitravatinib and Tislelizumab in patients with mUM with liver metastases and biopsiable disease at first line or after failure to first line systemic therapy with Tebentafusp (only HLA-A02:01 positive patients) or liver directed therapy in terms of:
    - PFS according to RECIST 1.1 criteria.
    - Overall Survival (OS).

Safety Objectives:

- Evaluate Safety of the combination of Sitravatinib plus Tislelizumab in terms of frequency and severity of Adverse Events (AEs) and treatment-related AEs coded using NCI-CTCAE version 5.0.

Translational Objectives:

- Study the efficacy of Sitravatinib and Tislelizumab in inducing inflammatory T-cell effector infiltrate in uveal melanoma liver metastases.
- Study the efficacy of Sitravatinib and Tislelizumab in changing macrophages, and other innate cells, phenotype from an immune-suppressed to an anti-tumoral state.
- Study molecular mechanisms behind inflammatory T-cell effector infiltrate induction in uveal melanoma with liver metastases.

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 and optional but strongly encouraged at the progression of the disease.

Subjects, either on treatment or 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 disease 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.

Number of Sites: 6 hospitals in Spain belonging to GEM (expected).

Number of Patients: 16 metastatic uveal melanoma patients with liver metastasis (expected)

It is possible that the total number of patients will increase up to 34 in case of ORR > 20%, additional information is available in the sample size justification section.

Study Population:

Metastatic uveal melanoma with liver metastasis.

Main Inclusion Criteria:

1. Patients must have histologically confirmed metastatic uveal melanoma with measurable disease not eligible for curative therapy.

2. Participants must have measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded for non-nodal lesions and short axis for nodal lesions) as ≥20 mm with conventional techniques or as ≥10 mm with spiral CT scan, MRI, or calipers by clinical exam. Patients must have at least 1 biopsiable liver metastasis.

3. Patients who are HLA-A02:01 positive can have received one prior therapy with Tebentafusp for metastatic disease.

4. Patients must be 18 years of age or older at time of study entry.

5. Eastern Cooperative Oncology Group (ECOG) Performance Status 0-1.

6. Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol. Written informed consent and any locally required authorization obtained from the patient/legal representative prior to performing any protocol-related procedures, including screening evaluations not performed according to normal practice. Patients must consent for liver metastasis biopsies donation at day 0 and day +42 since treatment initiation.

7. Adequate normal organ and marrow function as defined below:
    a. Haemoglobin ≥9.0 g/dL
    b. Absolute neutrophil count (ANC) $\geq$1.5 x 10^9/L ($\geq$ 1500 per mm^3)
    c. Platelet count ≥ 100 x 10^9/L ($\geq$75,000 per mm^3)
    d. Serum bilirubin ≤1.5 x institutional upper limit of normal (ULN). This will not apply to patients with confirmed Gilbert's syndrome (persistent or recurrent hyperbilirubinemia that is predominantly unconjugated in the absence of hemolysis or hepatic pathology), who will be allowed only in consultation with Coordinating Investigator
    e. Both AST and ALT must be < 5 x ULN.
    f. Creatinine clearance ⩾40 ml/min calculated by Cockcroft-Gault or another validated method
    g. Urine protein:creatinine ratio (UPC) ≤1 or ≤2+ proteinuria on 2 consecutive dipsticks taken no less than 1 week apart
    h. Subjects with 2+ proteinuria on dipstick must also have UPC < 0.5 on 2 consecutive samples.

8. Females of childbearing potential must be willing to use a highly effective method of birth control for the duration of the study, and for 4 months after the last dose of Tislelizumab and/or 6 months after the last dose of Sitravatinib, and have a negative urine or serum pregnancy test ≤ 7 days before first administration of Tislelizumab and Sitravatinib. Women will be considered post-menopausal if they have been amenorrheic for 12 months without an alternative medical cause. The following age-specific requirements apply:
    a. Amenorrheic for ≥1 year in the absence of chemotherapy and/or hormonal treatments
    b. Luteinizing hormone (LH) and/or follicle stimulating hormone and/or estradiol levels in the post-menopausal range
    c. Radiation induced oophorectomy with last menses >1 year ago
    d. Chemotherapy induced menopause with >1 year interval since last menses
    e. Surgical sterilization (bilateral oophorectomy or hysterectomy)
    f. Women <50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatments and if they have luteinizing hormone and follicle-stimulating hormone levels in the post-menopausal range for the institution or underwent surgical sterilization (bilateral oophorectomy or hysterectomy)

g. Women ≥50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of all exogenous hormonal treatments, had radiation-induced menopause with last menses >1 year ago, had chemotherapy-induced menopause with last menses >1 year ago, or underwent surgical sterilization (bilateral oophorectomy, bilateral salpingectomy or hysterectomy).

9. For both male and female patients/partners: Contraceptive use should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. Non-sterile males must be willing to use a highly effective method of birth control for the duration of the study and for ≥ 4 months after the last dose of Tislelizumab and/or 6 months after the last dose of Sitravatinib. A sterile male is defined as:
    a. One for whom azoospermia has been previously demonstrated in a semen sample examination as definitive evidence of infertility.
    b. Males with known "low sperm counts" (consistent with "sub-fertility") are not to be considered sterile for purposes of this study.

10. Patient is willing and able to comply with the protocol procedures for the duration of the study including undergoing treatment and scheduled visits and examinations including follow up.

11. Must have a life expectancy minimum of 4 months

12. Subjects must be able to swallow and retain oral medications and be without clinically significant gastrointestinal illnesses that would preclude absorption of Sitravatinib.

13. Adequately controlled blood pressure (BP):
    - Systolic BP ≤140 mmHg and diastolic BP ≤90 mmHg in the presence or absence of a stable regimen of antihypertensive therapy.

Exclusion Criteria:

1. Patients with concomitant malignancy other than non-melanoma skin cancer, or superficial bladder cancer controlled with local treatment.

2. Previous treatment with targeted therapies and/or anti-angiogenic agents such as VEGFR, MEK, BRAF, ERK inhibitors, with the exception of Tebentafusp.

3. Previous treatment with immune checkpoint inhibitors, either anti-PD1/PD-L1 (Including Tislelizumab), anti-CTLA-4, or other treatments.

4. Presence of brain or leptomeningeal involvement unless previously treated, off steroids at least 2 weeks, and considered stable. Patients with untreated central nervous system (CNS) metastases and/or carcinomatous meningitis identified either on the baseline brain imaging [RECIST]) obtained during the screening period or identified prior to signing the ICF. Patients whose brain metastases have been treated may participate provided they show radiographic stability (defined as 2 brain images, both of which are obtained after treatment to the brain metastases. These imaging scans should both be obtained at least four weeks apart and show no evidence of intracranial progression). In addition, any neurologic symptoms that developed either as a result of the brain

metastases or their treatment must have resolved or be stable either, without the use of steroids, or are stable on a steroid dose of ≤10mg/day of prednisone or its equivalent and anticonvulsants, for at least 14 days prior to the start of treatment. Brain metastases will not be recorded as RECIST Target Lesions at baseline.

5. Patients weighing <30kg will be excluded from enrollment.

6. Participation in another clinical study with an investigational product during the last 4 *weeks.*

7. Concurrent enrollment in another clinical study, unless it is an observational (non-interventional) clinical study or during the follow-up period of an interventional study.

8. Receipt of the last dose of anticancer therapy (chemotherapy, immunotherapy, endocrine therapy, targeted therapy, biologic therapy, tumor embolization, monoclonal antibodies) ≤28 days prior to the first dose of study drug. If sufficient wash-out time has not occurred due to the schedule or PK properties of an agent, a longer wash-out period will be required, as agreed by Sponsor designated Coordinating Investigator and Principal Investigator.

9. Any unresolved toxicity NCI CTCAE Grade ≥2 from previous anticancer therapy with the exception of alopecia, vitiligo, and the laboratory values defined in the inclusion criteria
    a. Patients with Grade ≥2 neuropathy will be evaluated on a case-by-case basis after consultation with the Coordinating Investigator.
    b. Patients with irreversible toxicity not reasonably expected to be exacerbated by treatment with Tislelizumab may be included only after consultation with the Coordinating Investigator.
    c. Known toxicity on prior checkpoint inhibitor treatment:
        i. Grade ≥ 3 immune-related AE related to checkpoint inhibitors.
        ii. Grade 2 immune-related AE associated with checkpoint inhibitor unless the AE resolved or was well controlled by withholding the checkpoint inhibitor and/or treatment with steroids, with the exception of prior colitis, myocarditis, and pneumonitis, which are exclusionary.
        iii. CNS or ocular AE of any grade related to checkpoint inhibitors.

    NOTE: Patients with a prior endocrine AE are permitted to enroll if they are stably maintained on appropriate replacement therapy and are asymptomatic.

10. Any concurrent chemotherapy, IMP, biologic, or hormonal therapy for cancer treatment different to Sitravatinib and/or Tislelizumab. Concurrent use of hormonal therapy for non-cancer-related conditions (e.g., hormone replacement therapy) is acceptable.

11. Radiotherapy treatment to more than 30% of the bone marrow or with a wide field of radiation prior to 4 weeks of the first dose of study drug.

12. Major surgery within a minimum of 4 weeks prior to inclusion; patients must have recovered from any effects of any major surgery prior to inclusion. Note: Local surgery of isolated lesions for palliative intent and minor surgeries performed to obtain biological material for the study (i.e. liver biopsy) are acceptable.

13. History of allogeneic organ transplantation.

14. Active or prior documented autoimmune or inflammatory disorders (including inflammatory bowel disease [e.g., colitis or Crohn's disease], diverticulitis [with the exception of diverticulosis], systemic lupus erythematosus, Sarcoidosis syndrome, or Wegener syndrome [granulomatosis with polyangiitis, Graves' disease, rheumatoid arthritis, hypophysitis, uveitis, etc]). The following are exceptions to this criterion:
    a. Patients with vitiligo or alopecia
    b. Patients with hypothyroidism (e.g., following Hashimoto syndrome) stable on hormone replacement
    c. Any chronic skin condition that does not require systemic therapy
    d. Patients without active disease in the last 5 years may be included but only after consultation with the Coordinating Investigator
    e. Patients with celiac disease controlled by diet alone

15. Uncontrolled intercurrent illness, including but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled/malignant hypertension, unstable angina pectoris, cardiac arrhythmia, interstitial lung disease, serious chronic gastrointestinal conditions associated with diarrhea, or psychiatric illness/social situations that would limit compliance with study requirement, compromise Sitravatinib absorption, substantially increase risk of incurring AEs or compromise the ability of the patient to give written informed consent.

16. History of another primary malignancy except for:
    a. Malignancy treated with curative intent and with no known active disease ≥5 years before the first dose of IMP and of low potential risk for recurrence
    b. Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease
    c. Adequately treated carcinoma in situ without evidence of disease

17. History of active primary immunodeficiency.

18. Active infection including tuberculosis (clinical evaluation that includes clinical history, physical examination and radiographic findings, and TB testing in line with local practice), hepatitis B (known positive HBV surface antigen (HBsAg) result), hepatitis C, or human immunodeficiency virus (positive HIV 1/2 antibodies). Patients with a past or resolved HBV infection (defined as the presence of hepatitis B core antibody [anti-HBc] and absence of HBsAg) are eligible. Patients positive for hepatitis C (HCV) antibodies are eligible only if polymerase chain reaction is negative for HCV RNA. Patients with HIV infection but with controlled and treated disease and undetectable viral load, would be eligible.

19. Current or prior use of immunosuppressive medication within 14 days before the first dose of Tislelizumab. The following are exceptions to this criterion:
    a. Intranasal, inhaled, topical steroids, or local steroid injections (e.g., intra articular injection)
    b. Systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or its equivalent
    c. Steroids as premedication for hypersensitivity reactions (e.g., CT scan premedication)

20. Receipt of live attenuated vaccine within 30 days prior to the first dose of IMP. Note: Patients, if enrolled, should not receive live vaccines whilst receiving IMP and up to 30 days after the last dose of IMP.

21. Female patients who are pregnant (confirmed with positive pregnancy test) or breastfeeding or male or female patients of reproductive potential who are not willing to employ effective birth control from screening to 4 months after the last dose of Tislelizumab and/or 6 months after the last dose of Sitravatinib therapy.

22. History of severe allergic reaction attributed to Sitravatinib or a similar VEGFR inhibitor or known hypersensitivity to any component of Sitravatinib dose composition

23. Known allergy or hypersensitivity to Tislelizumab or Sitravatinib or any of the excipients.

24. History of gastrointestinal perforation. Subjects with a history of abdominal fistula will be eligible if:
    a. the fistula has been surgically repaired,
    b. there is no evidence of fistula for at least 6 months prior to inclusion, and
    c. the subject is deemed to be at low risk of recurrent fistula in the opinion of the Investigator.

25. History of intra-abdominal abscess within 3 months prior to inclusion

26. Clinically significant signs and/or symptoms of bowel obstruction within 3 months prior to inclusion

27. Resting ECG with clinically significant abnormal findings. i.e. Mean QT interval corrected for heart rate using Fridericia's formula (QTcF) ≥470 ms calculated from 3 ECGs (within 15 minutes at 5 minutes apart).

28. Subjects with any one or more of the following:
    a. History of myocardial infarction within 6 months prior to inclusion; patients with a history of myocardial infarction within 6 to 12 months prior to inclusion may be allowed following assessment
    b. Unstable angina within 6 months prior to inclusion
    c. Known significant cardiac disease (New York Heart Association [NYHA] classification of III or IV).
    d. Concomitant medication known to cause prolonged QT which cannot be discontinued or changed to a different medication prior to enrollment

29. Left ventricular ejection fraction < lower limit of normal (LLN) per institutional guidelines, or <55%, if threshold for normal is not otherwise specified by institutional guidelines, for patients with the following risk factors:
    a. Prior or planned treatment with anthracyclines (ie, PLD)
    b. Prior treatment with trastuzumab
    c. Prior central thoracic radiation therapy (RT), including exposure of heart to therapeutic doses of ionizing RT
    d. History of myocardial infarction within 6 to 12 months prior to inclusion

e. Prior history of other significant impaired cardiac function.

30. History of stroke or transient ischemic attack within 6 months prior to inclusion

31. History of significant hemorrhage within 4 weeks prior of first dose date

32. Patients with:

    a. With uncontrolled diabetes or > Grade 1 laboratory test abnormalities in potassium, sodium, or corrected calcium despite standard medical management or ≥ Grade 3 hypoalbuminemia ≤ 14 days before

    b. Uncontrollable pleural effusion, pericardial effusion, or ascites requiring frequent drainage (recurrence ≤ 14 days after intervention)

    c. History of interstitial lung disease, non-infectious pneumonitis or uncontrolled lung diseases including pulmonary fibrosis, or acute lung diseases. Patients with significantly impaired pulmonary function, or who require supplemental oxygen at baseline must undergo an assessment of pulmonary function at screening

33. Evidence of any other disease, physical examination or laboratory finding giving reasonable suspicion of a disease or condition that puts the subject at high risk for treatment-related complication

34. Prior enrollment or treatment in a previous Tislelizumab and/or Sitravatinib clinical study regardless of treatment arm assignment.

35. Any serious medical condition or psychiatric illness that would interfere in understanding of the informed consent form.

Investigational Product(s), Dose and Mode of Administration:

Patients will receive Tislelizumab 200mg intravenous (IV), Q3W until confirmed disease progression unless there is unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met.

Patients will receive Sitravatinib 100 mg (malate formulation) capsules via oral daily until confirmed disease progression, unless there is unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met.

It is allowed to continue either Tislelizumab or Sitravatinib in case the other drug is required to be discontinued at the investigator discretion.

Study Assessments and Criteria for Evaluation:

Safety Assessments:

The safety objective of this trial is to characterize the safety and tolerability of Tislelizumab in combination with Sitravatinib in subjects with metastatic Uveal Melanoma with liver metastasis. The primary safety analysis will be based on subjects who experienced toxicities as defined by CTCAE, v5.0. The attribution to drug, time-of-onset from the first dose and last dose, duration of the event, severity /grade of the event, its outcomeand any concomitant medications administered will be recorded. AEs will be analyzed including but not limited to all AEs, SAEs, fatal AEs, all and related laboratory changes. Furthermore, specific immune-related adverse events (irAE) will be collected and designated as immune related events of clinical interest (AESIs).

Efficacy Assessments:

The primary efficacy objective of this study is to evaluate the anti-tumour activity of Tislelizumab in combination with Sitravatinib in subjects with mUM with liver metastasis measured by objective response rate (ORR). Subjects will undergo radiological evaluations of the tumor every 6 weeks during the first 12 months (48 weeks), and then every 12 weeks until the progression of disease.

Pharmacodynamic Assessments:

Our plan is to perform determinations on fresh tumor tissue from liver biopsies before starting combination therapy, and before 3rd Tislelizumab and Sitravatinib dose to compare stromal cell populations after combination treatment with Sitravatinib + Tislelizumab. To study spatial cell populations within the tumor we plan to perform Image Mass Cytometry.

Statistical Methods and Data Analysis:

Descriptive summary will be provided for all baseline variables, efficacy variables, and safety variables, as appropriate. Continuous variables will be summarized with mean, standard deviation, range, and median. Categorical variables will be summarized with frequency and percentage.

The primary efficacy analysis will be performed using descriptive statistics, frequency counts and percentage of subjects within each category will be provided. Ninety-five percent confidence intervals (95% CI) may be presented, as appropriate.

Survival analysis will be performed to analyze PFS and OS, Kaplan-Meier curves will be presented and possible comparisons among patient subgroups (i.e. stratification by prognostic factors) will be tested using the log-rank test or the Cox proportional hazard model for multivariate analysis, hazard ratios (HR) and their 95% CI will be provided.

Patients who are lost to follow-up or who discontinued treatment will be included in the final analysis (Full Analysis Set).

Sample Size Determination:

Previous trials in mUM with TKIs have reported no responses to treatment (*Carvajal D. et al. 2018*)*(Buder et al. 2013, Daud et al. 2017, Scheulen et al. 2017),* whereas the largest retrospective study reported an ORR of 3% (*Algazi et al. 2016*). Recent prospective clinical trials with Nivolumab plus ipilimumab reported an ORR of up to 18% (*Piulats et al. 2020*)(*Pelster et al. 2021*). Finally, a phase II trial with adoptive cell therapy has shown an ORR of 35% (*Chandran et al. 2017*). Thus, we expect a response rate of 2% or less for the null hypothesis and a response rate equal or higher than 20% for the alternative hypothesis. Based in the Exact-proportion, difference from constant (binomial test, one sample case), assuming a constant proportion p0=0.02 in the population and an effect size g=0.18 (i.e. p1=0.02 + 0.18=0.2), a power of a one-sided test of 80% and alpha=0.05, a total sample size of N=14 will be required (G*Power Version 3.1.9.6. Franz Faul, Universität Kiel, Germany,Copyright © 1992-2020). Assuming a 10% attrition rate, the total required sample size is 16 patients to ensure the inclusion of at least 14 evaluable patients. We could reject the null hypothesis if in 2 out of the 14 possible cases the relevant event is observed.

After recruiting 16 patients, Mirati/BeiGene will be contacted to propose different alternatives to follow-up with the projects depending on different scenarios:

- Response rate ≥20%: Mirati/BeiGene will be approached to expand the cohort of patients to increase the number to 34 patients to demonstrate an increase in median PFS from 2.4 months to 5 months (one-sided; alpha error 0.05, and power 80%, accrual 9m, and follow up 12m)(https://stattools.crab.org/Calculators/oneNonParametricSurvival.htm). The null hypothesis was estimated in 2.4 months and the alternative hypothesis in 5 months based on the results from previous clinical trials that described a median PFS ranging from 2.1 (dabacarbacine)(*Carvajal D. et al. 2018*)(*Algazi et al. 2016*) to 5.5 months (*Piulats et al. 2020*)(*Pelster et al. 2021*).
- Response rate <20%: The patient enrollment will be considered closed.

SCHEDULE OF STUDY ASSESSMENTS

Table 1 Schedule of study assessments

	Screening	C1 D1	C1D8 and C1D15	C2D1	C2D8 and C2D15	C3	C4	C5 to PD	EOT	Safety FU1st	Safety FU2 nd	Long term FU	For details see Section
Week	-4 to 0	1	2/3	4	5/6	Q3W ±3 days unless dosing needs to be held for toxicity reasons			4 weeks after last dose	90 days after last dose of Sitravatinib	150 days after last dose of Tislelizumab	week X	
Day	-28 to 0	1[a]	8/15	22	29/36	Q21 days ±3 days unless dosing needs to be held for toxicity reasons			30 ±7 days			day X	
Informed Consent													
Informed consent: study procedures[b]	X												13.4 9.1
Consent: genetic sample and analysis (optional)	X												13.4 9.1.1
Study procedures													
Physical exam (full)	X												9.2.1
Targeted physical exam (based on symptoms)		X	X	X	X	X	X	X	X				9.2.1
Vital signs[c]	X	X	X	X	X	X	X	X	X				9.2.1
ECG[d]	X	As clinically indicated						X	X				9.2.1
ECHO/MUGA[d]	X					X	As clinically indicated		X				9.2.1

Concomitant medications	<----------												8.2
Demography, including baseline characteristics and tobacco use	X												9.1.1
Eligibility criteria	X												9.1.1
Laboratory Assessment													
Clinical chemistry[e]	X	X[f]	X	X	X	X	X	X	X				Table 1 0
Hematology[e]	X	X[f]	X	X	X	X	X	X	X				Table 9
TSH[g], (reflex free T3 or free T4[h])	X	X	X	X	X	X	X	X	X				9.2.2
Table 1 (Continued)	Screening	C1 D1	C1D8 and C1D15	C2D1	C2D8 and C2D15	C3	C4	C5 to PD	EOT	Safety FU1[u]	Safety FU2[u]	Long term FU	For details see Section
Week	-4 to 0	1	2	4	6	Q3W ±3 days unless dosing needs to be held for toxicity reasons			4 weeks after last dose	90 days after last dose of Sitravatinib	150 days after last dose of Tislelizumab	week X	
Day	-28 to 0	1[a]	8	22	29	Q21 days ±3 days unless dosing needs to be held for toxicity reasons			30 ±7 days			day X	
Hepatitis B and C and HIV	X												9.2.2
Pregnancy test[i]	X	X	X	X	X	X	X	X	X				9.2.2
Coagulation (PT, PTT, INR)	X	X	X	X	X	X	X	X	X				9.2.2
Urinalysis	X	X	X	X	X	X	X	X	X				Table 11

Creatinine Cleareance[l]	X	X	X	X	X	X		X	X				Table 9
CK, creatine kinase	X	X		X		X	X	X	X				
CK-MB, creatine kinase cardiac isoenzyme	in case CK is increased												
Monitoring													
ECOG performance status	X	X	X	X	X	X	X	X					9.1.1
AE/SAE assessment [j]	<----------											---------->	11
OS follow-up (patient status and subsequent treatment for MUM)[k]												X	9.1.5
IMP administration[l]													
Tislelizumab [m]		X		X		X	X	X					6.1
Sitravatinib[n]		100 mg orally daily until PD, unacceptable, consent or any other discontinuation criteria											6.2
Other assessments and assays													
Fresh tumor tissue from liver biopsies[o]	X			X				X					9.3
Newly acquired tumor biopsy formalin fixed and embedded in paraffin[p]	X			X				X					9.3
Table 1 (Continued)	Screening	C1 D1	C1D8 and C1D15	C2D1	C2D8 and C2D15	C3	C4	C5 to PD	EOT	Safety FU1[u]	Safety FU2[u]	Long term FU	For details see Section

Week	-4 to 0	1	2	4	6	Q3W ±3 days unless dosing needs to be held for toxicity reasons	4 weeks after last dose	90 days after last dose of Sitravatinib	150 days after last dose of Tislelizumab	week X	
Day	-28 to 0	1[a]	8	22	29	Q21 days ±3 days unless dosing needs to be held for toxicity reasons	30 ±7 days			day X	
Blood samples[r]	X	q6w ± 1w for the first 48 weeks (relative to the inclusion date), and then q12w ± 1w thereafter along with tumor evaluation by image, until confirmed objective disease progression/death (whichever comes first). The schedule of q6w ± 1 week for the first 48 weeks and then q12w ±1 w thereafter MUST be followed regardless of any delays in dosing.									9.3
Efficacy evaluations											
Tumor evaluation (CT or MRI) (RECIST 1.1)[s,t]	X	q6w ± 1w for the first 48 weeks (relative to the inclusion date), and then q12w ± 1w thereafter until confirmed objective disease progression/death (whichever comes first). The schedule of q6w ± 1 week for first 48 weeks and then q12w ±1 w thereafter MUST be followed regardless of any delays in dosing									10

a Every effort should be made to minimize the time between enrollment and starting treatment. (i.e. within 1 day of enrollment)

b Informed consent of study procedures and tumor biopsy samples should be obtained prior to the 28-day screening window, if necessary, in order to permit tumor biopsy sample acquisition and analysis prior to enrollment. The collection of tumor biopsies at the time of progression is optional but strongly encouraged. If laboratory or imaging procedures were performed for alternate reasons prior to signing consent, these can be used for screening purposes with consent of the patient. However, all screening laboratory and imaging results must have been obtained within 28 days of enrollment.

c Body weight is recorded at each visit along with vital signs.

d Any clinically significant abnormalities detected require triplicate ECG results. ECHO/MUGA at baseline, C3, then as clinically indicated, and at End of Treatment.

e Serum or plasma clinical chemistry (including LFT monitoring) and hematology may be performed more frequently if clinically indicated. Determination at screening will be performed within 7 days of cycle 1 day 1 for eligibility.

f If screening clinical chemistry and haematology assessments are performed within 3 days prior to Day 1 (first infusion day), they do not need to be repeated at Day 1.

g If TSH is measured within 7 days prior to Day 1 (first infusion day), it does not need to be repeated on day 1. Determination at screening will be performed within 7 days of cycle 1 day 1 for eligibility.

h Free T3 or free T4 will only be measured if TSH is abnormal or if there is clinical suspicion of an AE related to the endocrine system. Determination at screening will be performed within 7 days of cycle 1 day 1 for eligibility

i For women of childbearing potential only. A urine or serum pregnancy test is acceptable. Women of childbearing potential are required to have a pregnancy test within 7 days prior to the first dose of study drug and then every 4 weeks. Pregnancy test may occur on Day 1, but results must be available and reviewed by the treating physician or Investigator prior to commencing an infusion

j For AEs/SAEs reported during screening, additional information such as medical history and concomitant medications may be needed

k Patient alive, death or loss of follow-up. Subsequent treatment received by patients for MUM should be also recorded.

l Results for LFTs, full blood count, and creatinine must be available before commencing an infusion (within 3 days) or dispensing Sitravatinib, and reviewed by the treating physician or Investigator prior to dosing.

m During the combination portion of treatment, Tislelizumab will be administered independently of Sitravatinib. Patients with confirmed PD who continue to receive Tislelizumab + Sitravatinib combination therapy at the discretion of the Investigator (following consultation with Coordinating Investigator) can receive treatment until no longer having clinical benefit.

n Sitravatinib should be taken on an empty stomach, at least 1 hour before or 2 hours after a meal.

o Liver biopsies to be collected mandatory on baseline, before the 3rd dose of treatment and optionally but strongly encouraged at disease progression.

p A minimum of 2 core biopsies from liver lesions should be collected and processed to FFPE in a single block. Previously frozen tissue is not acceptable for processing to FFPE for PD-L1 testing. FFPE blocks should be stored at ambient temperature and protected from light until shipment by courier at ambient temperature.

r Peripheral blood sample (serum, plasma and cryopreserved lymphocytes) at baseline, along with image tests and disease progression. For translational research and ctDNA measurements.

s RECIST assessments will be performed on images from CT or MRI of, each preferably with IV contrast of the chest, abdomen (including liver and adrenal glands) and pelvis (when applicable). Additional anatomy should be imaged based on signs and symptoms of individual patients at baseline and follow-up. Baseline assessments should be performed no more than 28 days before the date of inclusion and, ideally, should be performed as close as possible to and prior to the start of IMP. Confirmation of CR and PR response is required, for that reason, criteria must be met again 4 weeks after initial documentation of response. Additionally, confirmatory scans for PD should be performed preferably at the next scheduled imaging visit and no less than 4 weeks after the prior assessment of PD (in the absence of clinically significant deterioration). If an unscheduled assessment was performed and the patient has not progressed, every attempt should be made to perform the subsequent assessments at their next scheduled visit.

t Patients will have scans done q6w for the first 48 weeks, and then q12w thereafter (relative to the date of enrollment) until confirmed objective disease progression.

u The FU visits can be done by phone calls.

Note: All assessments on treatment days are to be performed prior to infusion, unless otherwise indicated.

C : Cycle; ECG: Electrocardiogram; IM: Intramuscular; LFT: Liver function test; PGx: Pharmacogenetic research; qXw: Every X weeks; qXw: Every X weeks; SNP: Single nucleotide polymorphism; T_3: Triiodothyronine; T_4: Thyroxine; TSH: Thyroid-stimulating hormone.

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ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study Clinical Study Protocol.

Abbreviation or special term	Explanation
ADA	Anti-drug antibody
ADCC	Antibody-dependent cell-mediated cytotoxicity
AE	Adverse event
AESI	Adverse event of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute Neutrophil Count
anti-HBc	Hepatitis B core antibody
APC	Antigen-presenting cells
ASPS	Alveolar soft part sarcoma
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
BP	Blood Pressure
CDC	Complement-dependent cytotoxicity
CFR	Code of Federal Regulations
CI	Confidence interval
CL	Clearance

C_{max}	Peak concentration
$C_{max,ss}$	Peak concentration at steady state
C_{min}	Trough concentration
$C_{min,ss}$	Trough concentration at steady state
CNS	Central nervous system
CR	Complete response
CRA	Clinical Research Associate
CRO	Contract Research Organization
CT	Computed tomography
CTC	Common Toxicity Criteria
CTLA-4	Cytotoxic T-lymphocyte-associated antigen-4
DB	Database
DC	Disease control
DCR	Disease control rate
DFS	Disease Free Survival
DLT	Dose-limiting toxicity
DMP	Data Management Plan
DNA	Deoxyribonucleic acid
DoR	Duration of response
EC	Ethic Committee

ECG	Electrocardiogram
ECIs	Events of Clinical Interest
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EDTA	Disodium edetate dihydrate
EEA	European Economic Area
EOT	End of treatment
ESR	Externally Sponsored Research
FAS	Full Analysis Set
Fc	Fragment crystallizable
FDA	Food and Drug Administration
FFPE	Formalin fixed paraffin embedded
GBM	Glioblastoma
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GEM	Grupo Español Multidisciplinar de Melanoma
GMP	Good Manufacturing Practice
GLP	Good Laboratory Practice
HBsAg	Surface Antigen of the Hepatitis B Virus
HCl	Hydrochloride

HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HCC	Hepatocellular carcinoma
HDPE	High Density Polyethylene
HNSCC	Head and neck squamous cell carcinoma
HPD	Highest Probability Density
HR	Hazard Ratio
HRCT	high-resolution computed tomography
HUVEC	Human Umbilical Vein Endothelial Cells
ICF	Informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IFN	Interferon
IGF	Insulin-like growth factor
IgG1	Immunoglobulin G1
IgG2	Immunoglobulin G2
IGSF	Immunoglobulin superfamily
IHC	Immunohistochemistry
IL	Interleukin
ILD	Interstitial lung disease
imAE	Immune-mediated adverse event

IMP	Investigational medicinal product
IRB	Institutional Review Board
ISF	Investigator Site File
IV	Intravenous(ly)
IWRS	Interactive Web Response System
LFT	Liver function test
MAb	Monoclonal antibody
MDS	Myelodysplastic syndrome
MDSC	Myeloid-derived suppressor cells
MedDRA	Medical Dictionary for Regulatory Activities
miRNA	Micro ribonucleic acid
MRI	Magnetic resonance imaging
mRNA	Messenger ribonucleic acid
MTD	Maximum tolerated dose
mUM	Metastatic Uveal Melanoma
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NK	Natural killer
NOAEL	No-observed-adverse-effect level
NSCLC	Non-small cell lung cancer
OCT	Optimal cutting temperature

OR	Objective response
ORR	Objective response rate
OS	Overall survival
OTEL	Open To Enrollment Letter
PBMC	Peripheral blood mononuclear cell
PD	Progressive disease
PD-1	Programmed cell death 1
PD-L1	Programmed cell death ligand 1
PD-L2	Programmed cell death ligand 2
PFS	Progression-free survival
PI	Principal Investigator
PK	Pharmacokinetic(s)
PR	Partial response
PRES	Reversible Posterior Encephalopathy Syndrome
PRO	Patient-reported outcome
PUMMA	Past 25 years in Uveal Melanoma; a Meta-Analysis
PVC	Polyvinyl chloride
PVDC	Polyvinylidene chloride
Q2W	Every 2 weeks
Q3M	Every 3 months
Q3W	Every 3 weeks

Q4W	Every 4 weeks
Q12W	Every 12 weeks
QTc	Time between the start of the Q wave and the end of the T wave corrected for heart rate
QTcF	QT interval on ECG corrected using the Frederica's formula
RCC	Renal cell carcinoma
RD	Royal Decree
RECIST	Response Evaluation Criteria in Solid Tumors
REEC	Spanish Registry of Clinical Studies
RNA	Ribonucleic acid
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Stable disease
SID	Subject identification
SNP	Single nucleotide polymorphism
sPD-L1	Soluble programmed cell death ligand 1
SoC	Standard of Care
SOCS3	Suppressor of cytokine signaling 3
SOPs	Standard Operating Procedures
SUSAR	Suspected unexpected serious adverse reaction
$t_{½}$	Half life

TB	Tuberculosis
TCGA	The Cancer Genome Atlas
TEAE	Treatment-emergent adverse event
TIL	Tumor infiltrating lymphocyte
T_{max}	Time to peak concentration
$T_{max,ss}$	Time to peak concentration at steady state
TMG	Toxicity Management Guidelines
TNF-α	Tumor necrosis factor alpha
TSH	Thyroid stimulating hormone
UM	Uveal Melanoma
ULN	Upper limit of normal
USA	United States of America
WFI	Water for injection
WHO	World Health Organization
WT	Body Weight
XQ	“X” Quarter

2. INTRODUCTION

Uveal melanoma (UM) is a rare type of melanoma, with an incidence of 4.4 cases per million in Europe each year *(Mallone et al. 2012)*. During recent years, different treatment approaches have been tested in patients with metastatic UM. Responses have been reported mainly with localized treatment in patients with a limited number of metastases in the liver *(Hugues et al. 2016, Stinauer et al. 2011, Shashank et al. 2014, Huppert et al. 2010, Pawlik et al. 2006)*. When diffuse liver involvement and/or extrahepatic disease have developed, systemic therapies are warranted. So far, systemic therapies such as targeted therapy with selumetinib *(Carvajal et al. 2014)* or classic chemotherapy *(Kivelä et al. 2003)* have failed in metastasized UM.

As of December 2018, there are available few finished clinical trials with novel immunotherapy for metastatic UM using ipilimumab *(Zimmer et al. 2015, Piulats et al. 2014, Piulats et al. 2017, Piulats et al. 2018, Piulats et al. 2020)*. In our experience using ipilimumab 10 mg/kg or the combination of nivolumab 1 mg/kg plus ipilimumab 3 mg/kg we observed 10% response rate and 48%-52% of patients alive at 1 year. With longer follow up 25% of patients alive at 2 and 3 years. In the longest retrospective series published so far we demonstrated a 3% ORR and less than 10 months OS *(Algazi et al. 2016)*. A clinical trial with anti-PD1/PDL1 Pembrolizumab in monotherapy reported an ORR of 25% in a small sample of 5 mUM patients, pointing out that more often in patients without bulky liver metastases *(Johnson et al. 2019)*.

Vascular abnormalities are a hallmark of most solid tumors and facilitate immune evasion *(Fukumura et al. 2018)*. And angiogenic signatures are frequently enriched in tumors with resistance to checkpoint inhibitors *(Hugo et al. 2016)*. Compelling evidence support the combination of both approaches indicating that through modulation of both the tumor vasculature and the tumor immune microenvironment could increase patient survival beyond the currently conferred by each approach individually *(Fukumura et al. 2018)*. Moreover, vascular endothelial growth factor (VEGF) and other angiogenic factor play an important role modulating the immune system directly by suppressing dendritic cell maturation *(Yu-Ling et al. 2016)*, inhibition of T-cell effector response *(Ohm et al. 2003)*, and recruitment of myeloid derived suppressor cells *(Horikawa et al. 2016)*.
Based on previous assumptions exposed in this introduction, we consider that there is enough rationale to explore the combination of an antiangiogenic drug such as Sitravatinib and an anti-PDL1 blockade with Tislelizumab in patients with metastatic UM.

2.1. DISEASE BACKGROUND

Uveal melanoma (UM) is the most frequent primary malignant tumor in the eye in adults. The 5-year relative survival is 78% *(Caminal et al. 2012)*, lower than cutaneous melanoma. Patients with big tumors (COMS3) relapse rate is as high as 50% (***Figure 1***), and once metastatic disease appears OS is as short as 6-8 months *(Pons et al. 2011)*.

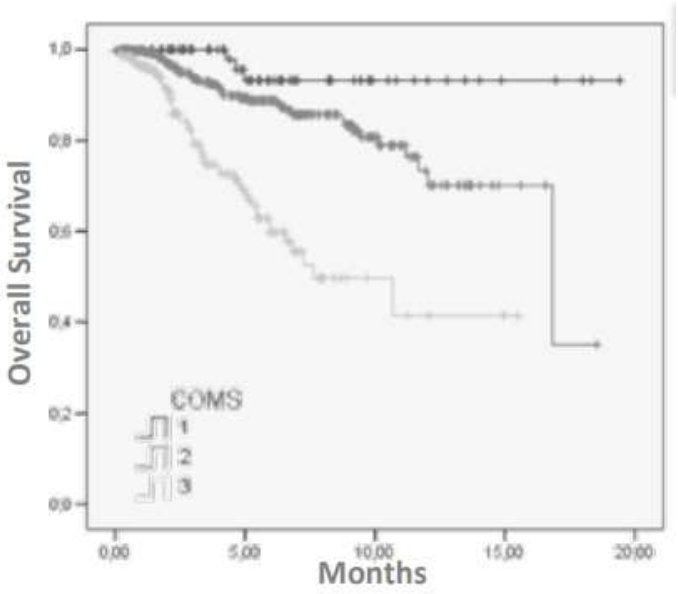

Figure 1. Overall survival data from our institution showing low survival rate for patients with big tumors treated with surgery

UM has pure hematogenous spread, and liver is involved in 80% of patients being in half of metastatic patients the only organ affected *(Pons et al. 2011)*. No treatment has ever demonstrated to be effective in the metastatic setting. Overall survival is low in clinical trials and ORR never has reached 10% in any clinical trial *(Buder et al. 2013)*. Additionally, UM patients have been systematically excluded from clinical trials for melanoma because it is considered refractory to chemotherapy and immunotherapy, and has poor prognosis *(Bishop et al. 2014)*.

UM develops in one of the most capillary-rich tissues of the body and is disseminated hematogenously. Most UM cell lines, but not normal melanocytes, strongly synthesize and secrete VEGF, and bFGF during cell culture *(Notting et al. 2006)*. Additionally, in orthotopic UM mouse models bevacizumab suppresses primary tumor growth and the formation of hepatic micrometastasis *(Yang et al. 2010)*. We have applied a well-established molecular signature for angiogenesis to the expression data available from the UM TCGA. Tumors from the TCGA that relapse systemically show a much higher angiogenesis enrichment score than non-relapsed patients (***Figure 2***). Differences in disease free survival comparing high vs low angiogenesis enrichment score (***Figure 3A***) were statistically significant. OS were not significant although 60% of patients with high enrichment score died of disease compared to less than 20% in the group with low score (***Figure 3B***).

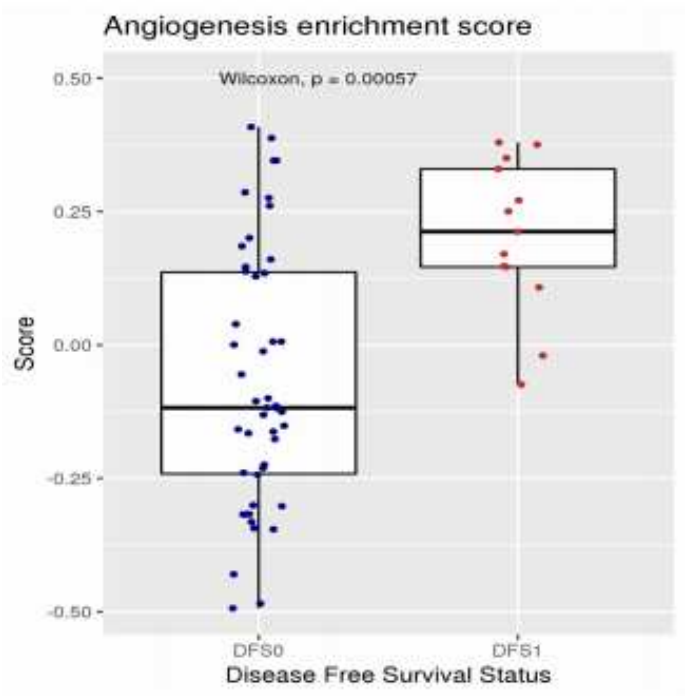

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Figure 2. ***Angiogenesis enrichment score from patients included in the UM TCGA that relapsed (DFS1) vs non-relapsed (DFS2).***

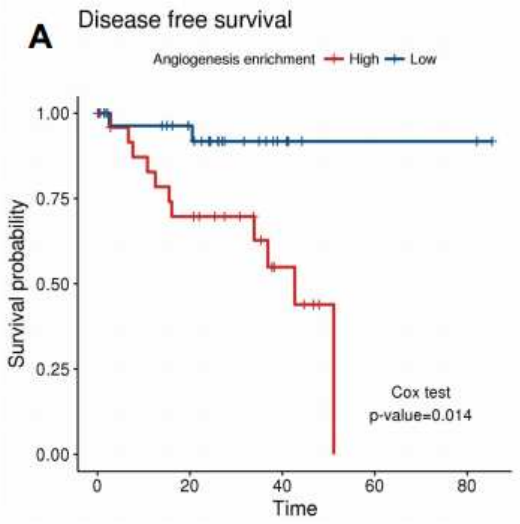


Figure 3. ***Disease free survival (A) and OS (B) from patients included in the UM TCGA comparing 50% with higher angiogenesis enrichment score with 50% with the lowest score.***

Several antiangiogenic drugs have been used in monotherapy or combination in metastatic UM *(Buder et al. 2013, Daud et al. 2017, Scheulen et al. 2017)*. It is difficult to arrive to a full conclusion because most of the trials are small and lack a comparator arm, but from the results we can resume that although no objective responses are seen, clinical trials with antiangiogenic drugs usually show higher OS than

clinical trials with conventional chemotherapy. We are going to do special mention to three clinical trials involving 2 different drugs. First, cabozantinib showed reduction in target lesions from baseline in 59% of patients with metastatic UM *(Daud et al. 2017)*. PFS and OS were 4.8 and 12.6 months respectively. Interestingly the trial included patients with uveal and cutaneous melanoma, and metastatic UM patients were much higher than in cutaneous melanoma. Unfortunately end-points for the study including both populations in a whole were not met. With these promising results a second randomized clinical trial was launched. The Alliance A091201 randomized patients 2:1 to receive either cabozantinib versus temozolomide or dacarbazine. There was no improvement in PFS at 4 months (primary endpoint), median PFS, or median OS. The OS for both arms was very short and compatible with patients treated in 3rd line (median lines of prior treatment were 2). In the second study sorafenib was administered for a 56 days run-in period to 149 patients *(Scheulen et al. 2017)*. After the run-in period patients with stable disease were randomly assigned to blinded sorafenib or placebo. Up to 66.1% of patients achieved SD and were randomized to sorafenib or placebo. Median PFS from randomization was significantly longer with sorafenib (5.5 months) than placebo (1.9 months). OS was not different between arms but both arms showed a surprising 15 months OS. In *(Castet et al. 2019)* we performed a literature review of preclinical and clinical published data to expand on the idea of using antiangiogenics in combinations to treat mUM.

Immune system in UM. UM is very different to its cutaneous counterpart when comparing the inflammatory tumor microenvironment *(Ock et al. 2016)*. UM shows less CD8 infiltration ***(figure 4A)***, and lymphocytes are less activated as UM shows low levels of PD-L1 expression ***(figure 4A***) and perforin ***(figure 4B)***. This might be mainly because UM has a very low mutation rate compared to cutaneous melanoma ***(figure 4C)***.

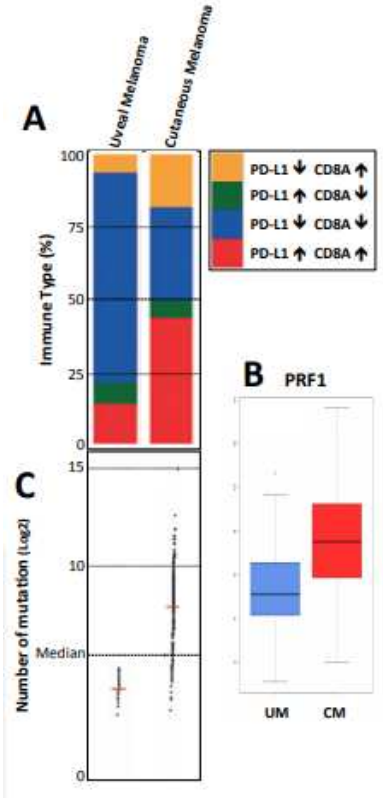


Figure 4. - ***Data extracted from TCGA database***

Figure 4.- Data extracted from TCGA database. (A) UM shows less than 20% tumors expressing high CD8A and PD-L1, whereas cutaneous melanoma has close to 50% tumors expressing high levels of both genes. (B) PRF1 codifies for perforin, a molecule expressed in activated effector T-cells. Levels of PRF1 are much high in cutaneous melanoma than UM. (C) Mutation load of UM is in the lowest among all TCGAs, compared to cutaneous melanoma that is the highest. Median line has been calculated for all tumors included in the TCGA database. UM Uveal melanoma; CM Cutaneous Melanoma

Recent research has focused on the role of immune checkpoint inhibitors (ICIs), which reactivate immune responses that are silenced by immune checkpoints. Immunotherapy has achieved outstanding results for different types of tumors and has changed the paradigm of treatment for CM. However, survival rates for those with mUM have not changed for decades. The largest retrospective series of anti PD-1 and anti PD-L1 published so far reported a 3% ORR and a median OS of less than 10 months *(Algazi et al. 2016)*. By December 2018, only 2 studies have reported final results on immunotherapy with ipilimumab: 3 mg/kg treatment associated with a 6.8 months OS *(Zimmer et al. 2015)*, and the GEM experience in a first phase II trial where ipilimumab 10 mg/kg was evaluated as a single-agent for the first-line treatment of patients with mUM with preliminary data on OS of 9.8 months *(Piulats et al. 2014)*. There are two retrospective experiences with nivolumab/ipilimumab combination in pre-treated patients with mUM. Their respective median OS of 14·2 and 16·1 months *(Karidevu et al. 2019 and Heppt et al. 2019)*, are superior to the 9.3 months (95% CI 8.4-10.1) estimated from the PUMMA meta-analysis for systemic therapy *(Khoja et al. 2019)*. Also, the interim analysis of the other phase II trial with the same combination performed by the MD Anderson group showed a 1-year OS of 62% *(Patel et al. 2017)*. Our experience from the GEM1402 trial is the largest prospective set of patients treated with nivolumab/ipilimumab combination, and it is the only one performed exclusively in the first line setting *(Piulats et al. 2020)*. Median OS was 12.7 (95% CI, 7.1–18.3) months, with OS rates of 51.9% and 26·4% at 12 and 24 months, respectively. Interestingly, OS in patients with exclusive liver metastasis was shorter (9.2 months vs. 23.5 months for patients with other locations beyond the liver). This seems to differ from the PUMMA findings, where patients with extrahepatic disease had a similar or even shorter survival when compared with patients exclusively affected by liver metastasis. More recently, we have performed a meta-analysis involving patients with mUM recruited in the 2 trials testing nivolumab + ipilimumab combination reported by the Spanish Melanoma Group and MD Anderson *(Piulats et al. 2021)*. The study used inverse probability of treatment propensity-score matching (PSM) using individualized patient data collected in the PUMMA meta-analysis. After applying PSM 85(Nivolumab/Ipilimumab):170(PUMMA) patients were matched by age, sex, ECOG, LDH, and largest metastasis size. For patients with only extrahepatic metastases, expected survival was > 3.2 times higher in nivolumab + ipilimumab treated patients (HR 0.28; 95%CI 0.11- 0.69)***(figure 5)***. In patients with liver only (HR 1.02; 95%CI 0.59-1.56) or liver+extrahepatic (HR 1.05; 95%CI 0.54-2.03) no differences were observed in expected survival between treatments. This is the first time that a treatment strategy shows impact in OS in mUM. Unfortunately, less than^{o} 20% of patients with mUM show only extrahepatic disease. Finally, a phase II trial with adoptive cell therapy has shown promising results with 35% ORR but no data about PFS or OS have been reported so far *(Chandran et al. 2017)*. Because of these extraordinary results, adoptive cell therapy is being explored in several clinical trials (NCT03068624) (NCT03467516) in the US, but there are no clinical trials actively exploring this strategy in Europe.

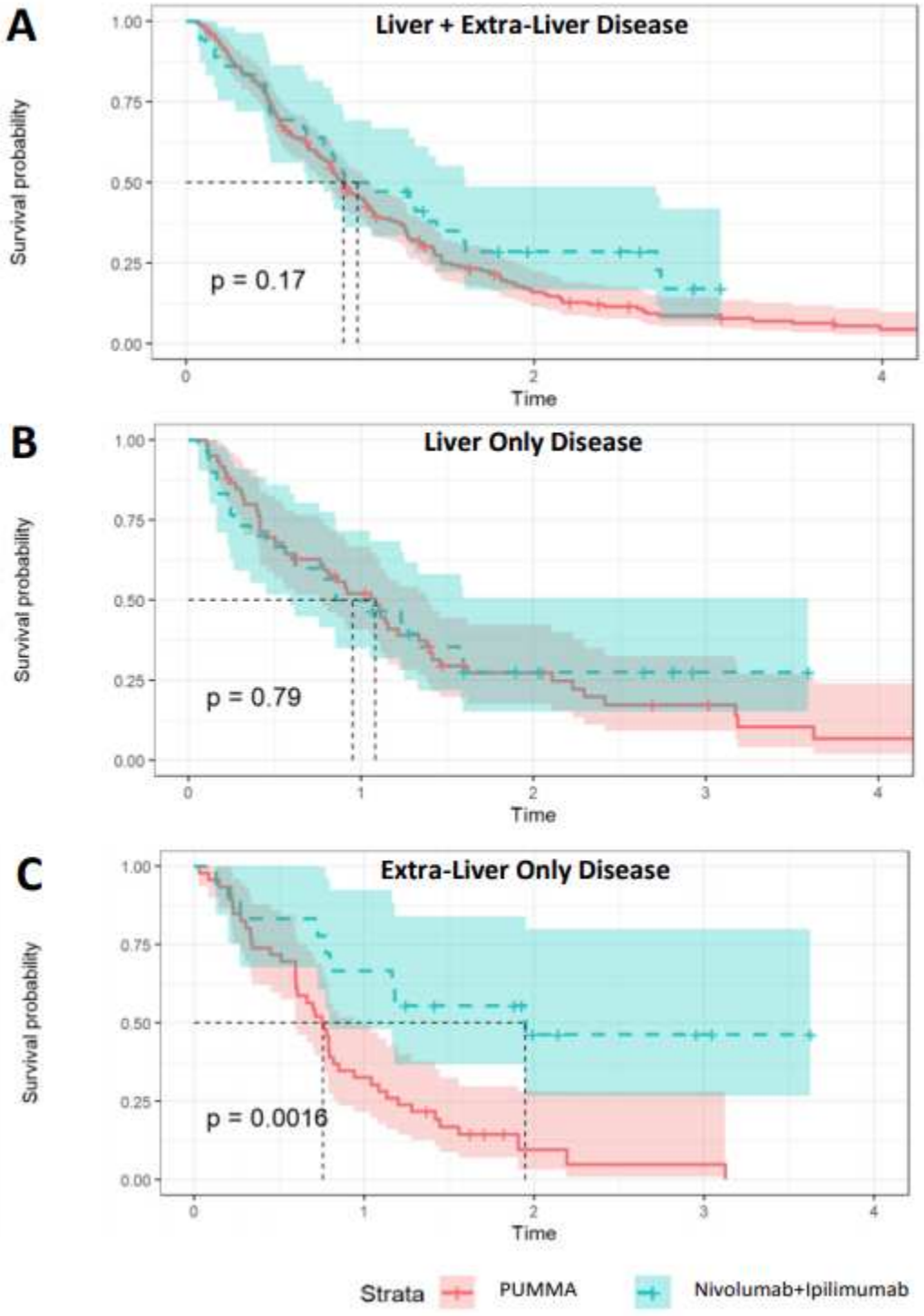


Figure 5.- Kaplan-Mayer (K-M) curves for OS from the GEM1402 trial testing nivolumab + ipilimumab in mUM. This is a propensity-score matching using individualized patient data collected in the PUMMA meta-analysis for patients with liver and extra-liver disease (A), liver only disease (B) and extra-liver only disease (C).

Liver Metastases Show Worst Response to Immunotherapy. The liver-immunotherapy issue has been reported elsewhere for other cancers such as CM, and lung cancer. In a recent paper analyzing long-term OS among patients receiving nivolumab found that the presence of liver (OR, 0.31; P = .02) or bone metastases (OR, 0.31; P = .04) were independently associated with reduced likelihood of survival at 5 years *(Topalian et al. 2014, Topalian et al. 2019)*. Another recent paper found that CM patients treated with nivolumab + ipilimumab with metastases in different anatomical locations display distinct response patterns, and different ORR and OS *(Pires da Silva et al. 2020)*. Soft-tissue and lung metastases had the highest ORR (79% and 77%, respectively), whereas liver metastases had the lowest (46%). In the multivariate analysis, patients with lung metastases had superior ORR (OR, 2.75; P = .02), whereas those with liver metastases had inferior ORR (OR, 0.33; P = .02), and OS (HR, 3.17; P = .01). We have used gene expression data of metastatic samples from different tumor primaries (n=374) from four secondary sites (brain, bone, liver, and lung) to characterize samples on the basis of their immune and stromal infiltration using gene signatures and cell quantification tools *(Garcia-Mulero, et al. 2020)*. A clustering analysis was done that separated metastatic samples into three different immune categories: High, Intermediate and Low Immune. Significant differences were found between the immune profiles of samples metastasizing in distinct organs, for example metastases in the lung showed a higher immunogenic score, but liver metastases showed the lowest ***(figure 6)***. From these data we can conclude that the liver tumor microenvironment might be different than in other organs and might contribute to the lower response rate to ICIs in different diseases.

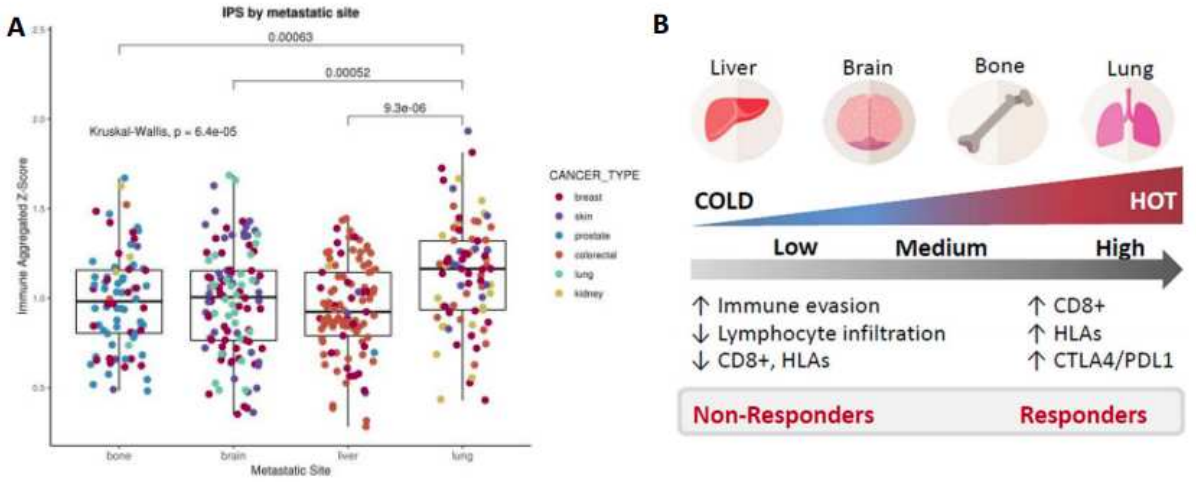


Figure 6.- (A) Immune aggregated z-score estimated by Immunophenoscore. Metastases in the lung show a higher immunogenic score than metastasis in the brain, lung or liver (Anova test, p<0.01), being the liver the coldest, suggesting a different immune micro-environment modulation. (B) Figure representing our hypothesis for the paper.

Interestingly, another highly angiogenic disease with liver involvement, hepatocellular carcinoma, has demonstrated to respond to ICIs combined with antiangiogenic treatment. The IMbrave150 study randomized patients 2:1 to receive Atezolizumab 1200 mg IV combined with Bevacizumab 15 mg/kg IV every 3 weeks vs Sorafenib 400 mg twice daily *(Cheng, et al. 2019)*. With median follow-up of 8.6 months, median OS with the atezolizumab combination was not estimable compared to 13.2 months (95%

CI, 10.4, NE) with sorafenib (HR 0.58; 95% CI, 0.42-0.79;p = 0.0006). Median PFS with the combination was 6.8 months (95% CI, 5.7-8.3) versus 4.5 (95% CI, 4.0-5.6) with sorafenib (HR 0.59 (95% CI, 0.47-0.76; p < 0.0001). The ORR for combination arm vs sorafenib was 27% versus 12% respectively (p < 0.0001) per IRF RECIST v1.1. According to IRF HCC mRECIST criteria, the response was nearly 3-fold higher with atezolizumab plus bevacizumab compared to sorafenib; the ORR was 33% versus 13% (p < 0.0001), respectively. According to the investigators, the results were generally consistent across the clinical subgroups evaluated. They also reported that atezolizumab/bevacizumab delayed deterioration of quality of life compared to sorafenib. The median duration of treatment was 7.4 months with the combination and 2.8 months for sorafenib. Sitravatinib is a potent, spectrum-selective RTK inhibitor. It inhibits several closely related RTKs, including the TAM family (TYRO3, AXL, and MER), VEGFR2, and KIT. This inhibition weakens the cancer's defenses in the tumor microenvironment. Specially blocking TAM family of kinases enhances immune responses through activation of key innate immune cell types including macrophages, dendritic cells, and NK cells. Interestingly macrophages are abundant in the liver, the organ where uveal melanoma relapse in the majority of patients. In addition we have checked TAM kinases expression levels among TCGA datasets and we have found that TYRO3 and MER-TK are highly expressed in uveal melanoma ***(figure 7)***. We next tested whether expression levels of different Sitravatinib targets were prognostic in uveal melanoma ***(figure 8)***. TYRO3, MERTK, KIT, and KDR are more expressed in primary tumors that relapse systemically than in primary tumors that do not relapse. Also, all 5 genes show statistical significance or a strong trend for relapse free survival. The TCGA for this disease do not have enough follow up to show overall survival, but we have to remember that uveal melanoma relapse mainly in the liver and OS once patient relapse is less than 12 months.

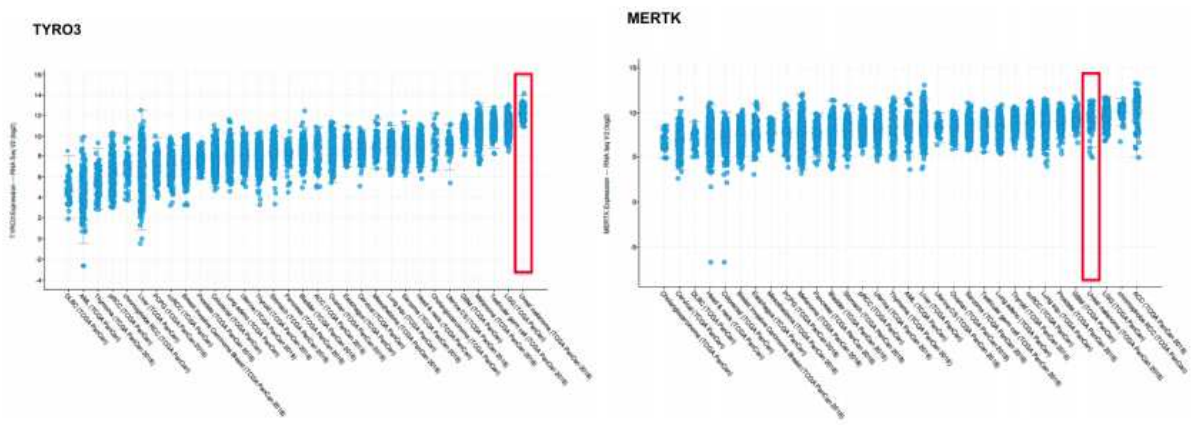


Figure 7.- TYRO3 and MER-TK expression levels comparing all datasets included in the TCGA. Uveal melanoma shows the highest expression levels among solid tumors.

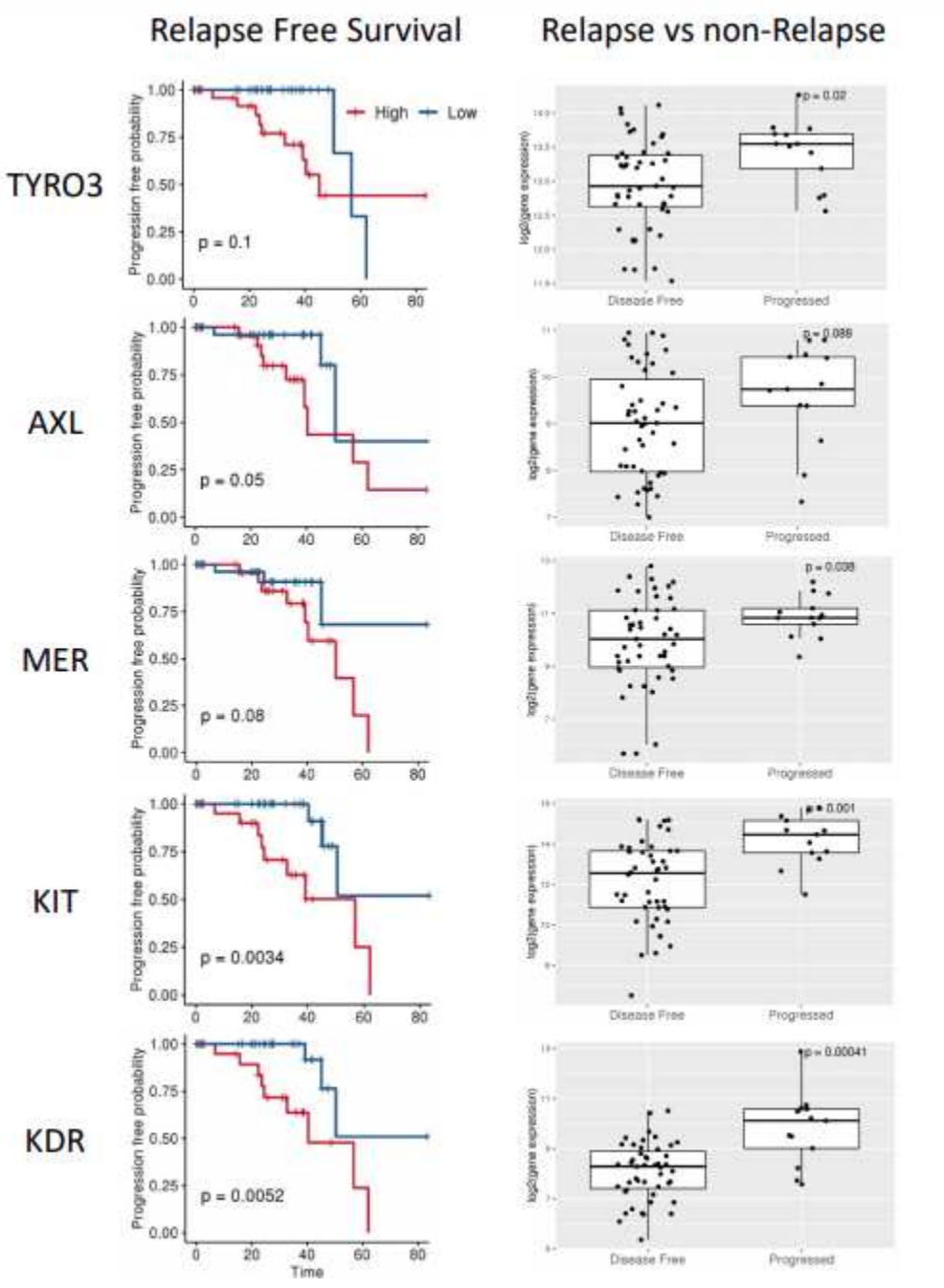


Figure 8.- First column shows relapse free survival difference between 50% tumors with higher expression vs 50% with lower expression of the primary tumors included in the uveal melanoma TCGA. Second column shows differences in expression levels between non-relapsed tumors vs primary tumors that relapsed with time.

Vascular abnormalities are a hallmark of most solid tumors and facilitate immune evasion *(Fukumura et al. 2018)* and angiogenic signatures are frequently enriched in tumors with resistance to checkpoint inhibitors *(Hugo et al. 2016)*. Compelling evidence supports the combination of both approaches indicating that through modulation of both the tumor vasculature and the tumor immune

microenvironment could increase patient survival beyond the currently conferred by each approach individually. Moreover, VEGF and other angiogenic factors play an important role modulating the immune system directly by suppressing dendritic cell maturation *(Voron et al. 2014)*, inhibition of T-cell effector response *(Hugo et al. 2016)*, and recruitment of myeloid derived suppressor cells *(Hugo et al. 2016)*. Based on previous assumptions exposed in this introduction, we consider that there is enough rationale to explore the combination of antiangiogenic drugs such as Sitravatinib and anti-PD1 blockade with Tislelizumab in patients with metastatic UM.

2.1.1. Immunotherapies

It is increasingly understood that cancers are recognized by the immune system, and, under some circumstances, the immune system may control or even eliminate tumors *(Dunn et al. 2004)*.

PD-L1 is part of a complex system of receptors and ligands that are involved in controlling T-cell activation. The PD-1 receptor (CD279) is expressed on the surface of activated T cells *(Keir et al. 2008)*. It has 2 known ligands: PD-L1 (B7-H1; CD274) and PD-L2 (B7-DC; CD273) (*Okazaki and Honjo 2007*). The PD-1 and PD-L1/PD-L2 belong to the family of immune checkpoint proteins that act as co-inhibitory factors, which can halt or limit the development of T cell response. When PD-L1 binds to PD-1, an inhibitory signal is transmitted into the T cell, which reduces cytokine production and suppresses T-cell proliferation. Tumor cells exploit this immune checkpoint pathway as a mechanism to evade detection and inhibit immune response.

PD-L1 is constitutively expressed by B-cells, dendritic cells, and macrophages *(Qin et al. 2016)*. Importantly, PD-L1 is commonly over-expressed on tumor cells or on non-transformed cells in the tumor microenvironment *(Pardoll 2012)*. PD-L1 expressed on the tumor cells binds to PD-1 receptors on the activated T-cells leading to the inhibition of cytotoxic T cells. These deactivated T cells remain inhibited in the tumor microenvironment. The PD-1/PD-L1 pathway represents an adaptive immune resistance mechanism that is exerted by tumor cells in response to endogenous anti-tumor activity.

The inhibitory mechanism described above is co-opted by tumors that express PD-L1 as a way of evading immune detection and elimination. The binding of an anti–PD-L1 agent to the PD-L1 receptor inhibits the interaction of PD-L1 with the PD-1 and CD80 receptors expressed on immune cells. This activity overcomes PD-L1–mediated inhibition of antitumor immunity. While functional blockade of PD-L1 results in T-cell reactivation, this mechanism of action is different from direct agonism of a stimulatory receptor such as CD28.

PD-L1 is expressed in a broad range of cancers. Based on these findings, an anti–PD-L1 antibody could be used therapeutically to enhance antitumor immune responses in patients with cancer. Results of non-clinical and clinical studies of monoclonal antibodies (mAbs) targeting the PD-L1/PD-1 pathway have shown evidence of clinical activity and a manageable safety profile, supporting the hypothesis that an anti–PD-L1 antibody could be used to therapeutically enhance antitumor immune response in cancer patients *(Brahmer et al. 2012; Hirano et al. 2005; Iwai et al. 2002; Okudaira et al. 2009; Topalian et al. 2012; Zhang et al. 2008*) with responses that tend to be more pronounced in patients with tumors that express PD-L1 (*Powles et al. 2014; Rizvi et al. 2015; Segal et al. 2015)*. In addition, high mutational

burden (e.g., in bladder carcinoma *(Alexandrov et al. 2013)* may contribute to the responses seen with immunotherapy.

In contrast, cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) is constitutively expressed by regulatory T cells and upregulated on activated T cells. CTLA-4 delivers a negative regulatory signal to T cells upon binding of CD80 (B7.1) or CD86 (B7.2) ligands on antigen-presenting cells *(Fife and Bluestone, 2008)*. Blockade of CTLA-4 binding to CD80/86 by anti–CTLA-4 antibodies results in markedly enhanced T-cell activation and antitumor activity in animal models, including killing of established murine solid tumors and induction of protective antitumor immunity. Therefore, it is expected that treatment with an anti–CTLA-4 antibody will lead to increased activation of the human immune system, increasing antitumor activity in patients with solid tumors.

Pre-clinical data have now been added to with a wealth of clinical data showing that blockade of negative regulatory signals to T-cells such as cytotoxic T-lymphocyte antigen 4 (CTLA-4) and programmed death ligand 1 (PD-L1) has promising clinical activity. Ipilimumab was granted United States (US) Food and Drug Administration (FDA) approval for the treatment of metastatic melanoma and is currently under investigation for several other malignancies, whilst nivolumab and pembrolizumab, two anti–PD-1 agents, and atezolizumab, an anti–PD-L1, agent have been granted approvals by agencies such as the US FDA and the European Medicines Agency approval for the treatment of a number of malignancies including metastatic melanoma, squamous and non-squamous cell non-small-cell lung cancer and urothelial carcinoma. In addition, there are data from agents in the anti–PD-1/PD-L1 class showing clinical activity in a wide range of tumor types.

Tebentafusp is a bispecific protein consisting of an affinity-enhanced T-cell receptor fused to an anti-CD3 effector that can redirect T cells to target glycoprotein 100–positive cells. Treatment with tebentafusp resulted in longer overall survival than the control therapy among previously untreated patients with metastatic uveal melanoma. The phase III trial reported an OS rate at 1 year of 73% in the tebentafusp group and 59% in the control group (hazard ratio for death, 0.51; 95% CI: 0.37 - 0.71; P<0.001)(*Nathan et al. 2021*). Based on this promising results, the FDA granted a Breakthrough Therapy Designation (BTD) to tebentafusp (IMCgp100) for the treatment of HLA-A*02:01-positive adult patients with unresectable or metastatic uveal melanoma (mUM). For this reason tebentafusp will be allowed as previous treatment in this trial.

2.2. TISLELIZUMAB BACKGROUND / NON-CLINICAL AND CLINICAL EXPERIENCE

Pharmacology

Tislelizumab is a humanized IgG4 variant mAb against PD-1, binding to the ECD of human PD1 with high specificity and affinity (KD = 0.15 nM). Tislelizumab competitively blocks the binding of both PD-L1 and PD-L2, inhibiting PD-1-mediated negative signaling and enhancing the functional activity in T cells in in vitro cell-based assays. In addition, tislelizumab demonstrated antitumor activity in several human cancer allogeneic xenograft models and a human PD-1 transgenic mouse model.

The IgG4 variant antibody has very low binding affinity to Fc RIIIA and C1q by in vitro assays, suggesting a low or no ADCC and CDC effect in humans. Unlike natural IgG4 antibody, tislelizumab has no observable Fab-arm exchange activity by the in vitro assay, predicting the antibody would be stable in vivo, unlikely forming bispecific antibodies.

Pharmacokinetics

The PK of tislelizumab was best characterized using a 3-compartmental linear population PK model with linear clearance mechanisms. No time-varying clearance was observed in tislelizumab PK. The Cmax and AUC increased in a nearly dose-proportional manner from 0.5 mg/kg to 10 mg /kg. The terminal t1/2 was estimated to be approximately 25.5 days, and the steady state is expected to be reached in 76 days. Population PK analysis showed that patient body weight is not a significant covariate on the CL of tislelizumab, which supports a fixed dose of 200 mg Q3W. Tislelizumab PK was generally similar between Chinese patients and other ethnic groups and across tumor types.

Pharmacodynamics/Efficacy

Studies with other PD-1 antibodies have demonstrated that maximal receptor occupancy on circulating CD3+ T cells occurs at concentrations that are much lower (0.1 mg/kg [nivolumab] to 1 mg/kg [pembrolizumab]) than the clinical dose *(Topalian et al. 2012; Patnaik et al. 2015)*. A FACS-based pharmacodynamics receptor occupancy assay has been implemented in the clinical setting for tislelizumab, and patient samples are being evaluated, but data are not yet available.

Preliminary antitumor activity has been observed across multiple tumor subtypes.

The non-clinical and clinical experience is fully described in the most current version of the Tislelizumab Investigator's Brochure.

2.3. SITRAVATINIB BACKGROUND/NON-CLINICAL AND CLINICAL EXPERIENCE

Nonclinical pharmacokinetic (PK) and toxicology studies support clinical evaluation of sitravatinib. Sitravatinib was systemically absorbed, and mean C max and AUC increased with increasing dose. Metabolic clearance was the major route of elimination of circulating sitravatinib in rats and dogs. Following oral administration of 14 C-labelled sitravatinib to Sprague-Dawley rats, fecal excretion of radiocarbon was the predominant route of elimination, with MGCD516, the active pharmaceutical ingredient of sitravatinib, as the major component.

Urinary excretion was a minor contributor (<1%) to the elimination of sitravatinib. Numerous cytochrome P450 (CYP) oxidative enzymes were implicated in metabolism of sitravatinib, no single CYP enzyme contributing to more than 25% of the total metabolism of sitravatinib in human hepatocytes. In vitro, sitravatinib is a substrate of P-glycoprotein (P-gp) but is not a substrate of Breast Cancer Resistance Protein (BCRP), Organic Anion Transporter (OAT) 1 and 3, Organic Cation Transporter (OCT) 2, Organic Transporting Polypeptide (OATP) 1B1 and 1B3, Multi-Antimicrobial Extrusion Protein (MATE) 1 or 2K. Sitravatinib demonstrated direct inhibition of CYP2C8, CYP2C9, CYP2C19, CYP2D6, and

CYP3A4/5, with IC50 values of 2.9, 11, 10, 1.9, 11, and 0.81 μM, respectively. Sitravatinib inhibited the efflux transporters P-gp and BCRP, and Bile Salt Export Pump (BSEP) mediated transport with IC50 values of 0.838, 1.51, and 5.06 μM, respectively.

Repeat-dose toxicology studies in rats and dogs were conducted up to 13-weeks in duration. In rats, VEGF-related target organs included the adrenal gland, Brunner's glands in the duodenum, lymphoid tissues, ovary, kidney (increased basophilic tubules), liver, pancreas, tongue, bone and teeth. All effects in rats, except those in the kidney, bile duct, and pancreas, either recovered or showed partial recovery. During the 13-week dog study VEGF-related target organs were identified at the high dose (2 mg/kg/day) including the female reproductive system, and large intestine/ileum. Only the inflammation-related findings in the female reproductive system were noted as adverse and these findings were absent in recovery animals indicating full recovery.

The non-clinical and clinical experience is fully described in the most current version of the Sitravatinib Investigator's Brochure.

2.4. RESEARCH HYPOTHESIS

Treatment with Tislelizumab combined with Sitravatinib will improve ORR in subjects with metastatic uveal melanoma, compared to published results of phase II trials.

2.5. RATIONALE FOR CONDUCTING THIS STUDY

Vascular abnormalities are a hallmark of most solid tumors and facilitate immune evasion *(Fukumura et al. 2018)*. And angiogenic signatures are frequently enriched in tumors with resistance to checkpoint inhibitors *(Hugo et al. 2016)*. Compelling evidence supports the combination of both approaches indicating that through modulation of both the tumor vasculature and the tumor immune microenvironment could increase patient survival beyond the currently conferred by each approach individually. Moreover, VEGF and other angiogenic factors play an important role modulating the immune system directly by suppressing dendritic cell maturation *(Voron et al. 2014)*, inhibition of T-cell effector response *(Hugo et al. 2016)*, and recruitment of myeloid derived suppressor cells *(Hugo et al. 2016)*. Based on previous assumptions exposed in this introduction, we consider that there is enough rationale to explore the combination of antiangiogenic drugs such as Sitravatinib and anti-PD1 blockade with Tislelizumab in patients with metastatic UM.

Objective Response Rate (ORR) is the primary end-point for this trial because it is widely accepted by oncologists in guiding cancer treatment and it is directly attributable to drug effect. Single-arm trials conducted in patients where no available therapy exists, provide an accurate assessment of ORR as a subrogate efficacy endpoint. Finally, the poor prognosis of patients with mUM makes it necessary to closely follow-up patients adjusting treatment approaches.

As secondary efficacy objectives PFS and OS will be studied, although the sample is powered to detect differences in ORR. PFS, OS, 1y-OS and 2y-OS will be analysed in order to detect trends and compare with other series already published.

Regarding safety, this trial will evaluate the safety of the combination Sitravatinib and Tislelizumab according to NCI-CTCAE version 5.0, as limited information regarding the combination is available, it is extremely needed to determine the safety profile of the combination.

Also, translational research will be performed, to study cell populations (stromal and spatial cells) in tumors before and after treatment initiation.

2.5.1. Rationale for dosing of Tislelizumab

The PK of Tislelizumab was best characterized using a 3-compartmental linear population PK model with linear clearance mechanisms. No time-varying clearance was observed in Tislelizumab PK. The Cmax and AUC increased in a nearly dose-proportional manner from 0.5 mg/kg to 10 mg /kg. The terminal t1/2 was estimated to be approximately 25.5 days, and the steady state is expected to be reached in 76 days. Population PK analysis showed that patient body weight is not a significant covariate on the clearance (CL) of Tislelizumab, which supports a fixed dose of 200 mg Q3W. Tislelizumab PK was generally similar between Chinese patients and other ethnic groups and across tumor types.

2.5.2. Rationale for dosing of Sitravatinib

Available nonclinical, safety, and PK data from ongoing studies were analyzed to determine the recommended dose of Sitravatinib. Nonclinical toxicology studies as well as clinical safety data from the Phase 1/1b and Phase 2 studies suggest that AEs associated with Sitravatinib are similar to those observed with other small-molecule inhibitors of the VEGFR pathway.

In Study 516-001, 150 mg once daily was originally recommended as the RP2D for monotherapy. Based on a recent evaluation of the Sitravatinib clinical program, it is recommended that the starting dose be lowered to 120 mg orally once daily, using the Sitravatinib free base capsule formulation.

In Study MRTX-500, patients with NSCLC received Sitravatinib 120 mg once daily in combination with nivolumab. As of June 2021, 206 patients have been enrolled in this ongoing study. The 120-mg dose of Sitravatinib free base capsule formulation is expected to achieve plasma exposure required for inhibition of VEGFR and TAM receptors necessary to achieve antitumor efficacy in the combination setting.

In studies BGB-900-103 and BGB-900-104, the RP2D of Sitravatinib in combination with Tislelizumab was further evaluated in patients with advanced or metastatic malignancies, including squamous and nonsquamous NSCLC, renal cell carcinoma, platinum-resistant ovarian cancer, hepatocellular carcinoma, or gastric or gastroesophageal junction cancer. As of 26 June 2021, a total of 317 patients were enrolled and the tolerability data for these patients further supports the RP2D of Sitravatinib free base at 120 mg across tumor types, either as monotherapy or in combination with Tislelizumab. Based on the preliminary PK analysis in 77 patients, race and tumor type were not significant covariants of the PK profile of Sitravatinib. The available efficacy and safety data in patients with NSCLC, treated with Sitravatinib free base 120 mg once daily in combination with Tislelizumab, is promising. The recommended dose for Sitravatinib free base capsule of 120 mg once daily was considered to be safe in patients with NSCLC.

With the purpose of optimizing product characteristics and manufacturing efficiency, Sitravatinib malate capsule formulation was developed and compared with the free base formulation. In Study 516-006, the inferential statistical analysis showed that the ratio and 90% confidence interval of the geometric least squares means of AUC0-∞, AUC0-t and Cmax were within the regulatory acceptance range of 80% to 125%, demonstrating that the 120 mg Sitravatinib free base and 100 mg malate capsule formulations are bioequivalent.

Based on the available data described above, 100 mg once daily of Sitravatinib malate capsule formulation is considered safe and is the recommended dose in NSCLC patients.

2.5.3. Rationale for dosing of treatment under study

As of 26 June 2021, safety data are available for a total of 1,106 subjects with advanced solid malignancies treated with sitravatinib, either as a single-agent (n = 220), in combination with the PD-1 inhibitor nivolumab (estimated; n = 565), in combination with nivolumab and ipilimumab (n = 10), in combination with tislelizumab (n = 300), or in combination with pembrolizumab and the antibody-drug conjugate (ADC) enfortumab vedotin-ejfv (pembro/EV) (n = 13)

The overall safety experience with tislelizumab, as a monotherapy or in combination with other therapeutics, is based on experience in 1917 patients treated as of the cutoff date 20 May 2020. For monotherapy, the safety profile is similar across tumor types. There is no pattern in the incidence, severity, or causality of adverse events (AEs) to tislelizumab dose level. The safety profile for single-agent tislelizumab is similar to those observed with other PD-1 inhibitors. The initial data collected in these studies suggest that tislelizumab can result in antitumor activity across a variety of tumor types. Antitumor activity has been observed across the dose ranges evaluated in patients. For combination studies, the safety profile of tislelizumab is generally consistent with use as a single agent and appears to be safe and well tolerated when used in combination with other agents and in multiple different chemotherapy backbones. Preliminary antitumor activities of tislelizumab in combination with chemotherapy and other agents have been observed in multiple tumor types.

Study BGB-900-103 is an open-label, multi-center, Phase 1b study sponsored by BeiGene, Ltd. (BeiGene). The study is designed to evaluate sitravatinib in combination with tislelizumab (an anti-PD-1 monoclonal antibody) in subjects with advanced or metastatic malignancies, including squamous and non-squamous NSCLC, RCC, or epithelial ovarian cancer (OC). The primary objective is to evaluate the safety of sitravatinib in combination with tislelizumab. Secondary objectives include assessment of the preliminary antitumor activity of the combination in selected tumor types, and PK. Subjects receive sitravatinib 120 mg PO QD in combination with tislelizumab 200 mg IV Q3W. As of 26 June 2021, a total of 216 subjects have been enrolled and treated.

Treatment-related SAEs were reported in 70 subjects (32%), and included diarrhea in 8 subjects (4%), hepatic function abnormality in 5 subjects (2%), and pneumonia and transaminases increased in 4 subjects (2%) each. All other treatment-related SAEs occurred in 2 or fewer subjects (<2%) overall.

Treatment Discontinuation and Deaths: Of the 216 subjects receiving study treatment, 179 (83%) have discontinued sitravatinib and 176 (82%) have discontinued tislelizumab treatment. The most common

reasons for discontinuation from sitravatinib were progressive disease (116 subjects [54%]), AE (42 [19%]), and withdrawal by subject (15 [7%]). The most common reasons for discontinuation from tislelizumab were progressive disease (128 subjects [59%]), AE (26 [12%]), and withdrawal by subject (18 [8%]). A total of 103 deaths have been reported, and the primary cause of death was progressive disease, (83 of 103 subjects [81%]).

Study BGB-900-104 is an open-label, multicenter, Phase 1/2 study sponsored by BeiGene. The study is designed to evaluate single-agent sitravatinib and sitravatinib in combination with tislelizumab in subjects with advanced or metastatic HCC or gastric/gastroesophageal junction (G/GEJ) cancer. The primary objective is to evaluate the safety of sitravatinib as monotherapy and in combination with tislelizumab, and to determine the RP2D of sitravatinib as monotherapy and when administered in combination with tislelizumab, 200 mg IV Q3W, in Phase 1 dose escalation starting with a dose of 80 mg QD. Secondary objectives include assessment of the preliminary antitumor activity of sitravatinib administered either as a single agent or in combination with tislelizumab, and PK. As of 26 June 2021, a total of 111 subjects with advanced HCC or G/GEJ cancer have received study treatment, including 27 subjects receiving sitravatinib monotherapy, and 84 receiving sitravatinib in combination with tislelizumab. All subjects treated in the study were Asian (Chinese) and not of Hispanic or Latino ethnicity.

Treatment-related SAEs were reported for 22 subjects (20%) overall. Sitravatinib-related SAEs in 2 or more subjects included death (4 subjects [4.8%]), haemoptysis, hepatic encephalopathy, and pneumonia (2 each [2.4%]) in the combination group. Tislelizumab-related SAEs in 2 or more subjects included death (3 [3.6%]) and pneumonia (2 [2.4%]).

Treatment Discontinuation and Deaths: Among the 111 subjects treated with sitravatinib, 89 (80%) have discontinued sitravatinib treatment, in most cases due to progressive disease (50 subjects [45%]), withdrawal by subject (19 [17%]), or AE (9 [8%]). Among the 84 subjects treated with tislelizumab, 66 (79%) have discontinued tislelizumab treatment, in most cases due to progressive disease (36 subjects [43%]), withdrawal by subject (14 [17%]), or AE (7 [8%]). A total of 32 deaths were reported for this study, 20 of 32 deaths (63%) were due to progressive disease.

For an overview of the clinical studies for the combination, please refer to Tislelizumab/Sitravatinib IBs.

Considering the information previously described, the dose selected for this study is Tislelizumab 200mg intravenous (IV), Q3W and Sitravatinib 100 mg capsules via oral daily until confirmed disease progression unless there is unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met.

2.6. BENEFIT/RISK AND ETHICAL ASSESSMENT

2.6.1. Potential benefits

Immune checkpoint inhibitors targeting the PD-1/PD-L1 pathway have demonstrated clinical activity across various cancer types, including non-small cell lung cancer *(Brahmer et al. 2015, Borghaei et al. 2015, Rizvi et al. 2015)*. While this therapy leads to durable clinical responses in a subset of patients, strategies to improve its clinical efficacy and overcome innate or acquired resistance to checkpoint

inhibitor monotherapy are needed. Combination therapy with agents that target the molecular and cellular mechanisms of resistance to checkpoint inhibitor therapy (CIT) is a rational approach to improving outcomes in patients.

2.6.1.1. Tislelizumab

Preliminary data from the ongoing Phase 1 and Phase 2 studies show that tislelizumab has been well tolerated in patients with advanced tumors in multiple solid and hematological malignancies. The safety profile for single-agent tislelizumab is similar to those observed in other PD-1 inhibitors. Two pivotal Phase 2 trials demonstrated clinical meaningful benefit. The initial data collected in other studies suggest that tislelizumab can result in antitumor activity across a variety of tumor types. Antitumor activity has been observed across the dose ranges evaluated in patients. Therefore, the benefit-risk profile for tislelizumab monotherapy appears to be favorable in the oncology population based on preliminary efficacy and safety data.

Combination therapy with Sitravatinib, BGB-A425, and BGB-A333 Preliminary data from the ongoing Phase 1/2 studies show that tislelizumab in combination with sitravatinib/BGB-A425/BGB-A333 appears to be well tolerated. Preliminary antitumor activity of the combination(s) has not been evaluated. The risk-benefit of this combination is acceptable in an oncology population based on preliminary safety data.

Additional information can be found in Tislelizumab IB.

2.6.1.2. Sitravatinib

Sitravatinib (MGCD516) is an orally administered, multitargeted receptor tyrosine kinase (RTK) inhibitor under development for the treatment of advanced solid malignancies. Sitravatinib inhibits several closely related RTKs, including MET, TAM (Tyro3, AXL, MERTK) family, VEGFR family, PDGFR family, KIT, FLT3, TRK family, RET, DDR2, and selected EPH family members. This subset of tyrosine kinases is involved in a number of processes implicated in human cancers including regulation of immune response, tumor growth and cell survival pathways, tumor invasion and metastatic progression, as well as tumor angiogenesis. Antitumor activity of sitravatinib has been observed in several human tumor xenograft models exhibiting genetic alterations in RTK targets, providing rationale for evaluating sitravatinib monotherapy in tumors driven by these pathways in the clinical setting.

Additionally, based on its tyrosine kinase target profile, sitravatinib may modulate effects on the tumor microenvironment to overcome resistance to checkpoint inhibitors by effects on relevant immune cell populations. Inhibition of the TAM RTKs, MERTK and AXL, expressed by macrophages and dendritic cells may enhance the innate, M1 macrophage pro-inflammatory cytokine response and suppress M2 macrophage anti-inflammatory cytokine production, while inhibition of AXL and MERTK on natural killer (NK) cells may abrogate negative regulation of anti-tumor NK cell activity. Inhibition of the split kinase receptors may enhance anti-tumor immunoreactivity by depletion of regulatory T cells (Treg) through VEGFR2 and myeloid- derived suppressor cells (MDSCs) via KIT and VEGFR family members, resulting in the expansion and migration of anti-tumor cytotoxic T cells, and their infiltration into tumor tissue.

Inhibition of MET may inhibit expansion of MDSCs and restore antigen-presenting cell function. Together, these effects are predicted to complement and augment the activity observed with checkpoint inhibitor therapy (CIT).

Collectively, the dysregulation of sitravatinib RTK targets in a variety of cancers provides a number of clinical opportunities including targeting genetically altered oncogenic drivers in selected cancers as well as targeting mechanisms of resistance to targeted therapies such as EGFR, BRAF, or VEGF pathway inhibitors.

Additional information can be found in Sitravatinib IB.

2.7.1. Overall risks

Based on review of the AEs reported with sitravatinib in context of the mechanism of action, nonclinical data, frequency, and Investigator assessment of causality, the following AEs have been assessed as expected serious adverse reactions (SARs) for sitravatinib, or SAEs with at least a reasonable possibility of a causal relationship to sitravatinib administered as monotherapy or in combination with other agents: diarrhea, ejection fraction decreased, fatigue, increased transaminases, thrombotic events (embolism, and pulmonary embolism), hypertension, nausea/vomiting, PPES, and pneumonitis.

2.7.1.1. Tislelizumab

The safety profile of tislelizumab is consistent with the therapeutic class of the drug with a relatively low rate of treatment-related Grade 3 or above toxicity.

Across the monotherapy studies, the safety profile was consistent in the Phase 1 and Phase 2 studies. While approximately 96% of patients experienced a TEAE of any causality in the monotherapy setting, the frequency of treatment-related events of any grade in the solid tumor studies (N = 1992) and hematologic malignancy studies (N = 181) was 70.2% and 80.1%, respectively. For treatment-related ≥ Grade 3 events, the frequency was 13.5% in the solid tumor studies and 19.3% in the hematologic malignancy studies. Immune-mediated AEs of any grade were reported in 16.3% of patients in the solid tumor studies and 28.6% of patients in the hematologic malignancy studies, while ≥ Grade 3 imAEs were reported in 4.3.% and 76.1% of patients in those settings, respectively. These imAEs, however, have well-established algorithms for treatment and are therefore considered manageable.

In studies with tislelizumab combined with chemotherapy, the AE profile is consistent with the now well-established profile of an immune checkpoint inhibitor in combination with the standard chemotherapy agent. Of the patients (N = 1047) in these pooled studies, 77.7% experienced a tislelizumab-related TEAE, though the frequency of ≥ Grade 3 tislelizumab-related events was lower (32.1%)

A detailed summary of Tislelizumab monotherapy or in combination AE data can be found in the current version of the tislelizumab IB.

2.7.1.2. Sitravatinib

The sitravatinib clinical development program includes Phase 1 and 2 studies investigating sitravatinib as a single-agent and in combination with other anticancer therapies in non-small cell lung cancer (NSCLC), urothelial cancer (UC), renal cell carcinoma (RCC), and hepatocellular carcinoma (HCC), among other malignancies. In addition, sitravatinib is being evaluated in a Phase 3 study in combination with nivolumab and in a Phase 3 study in combination with tislelizumab, both for the treatment of NSCLC.

The safety analysis of sitravatinib includes 18 sitravatinib clinical studies, 14 sponsored by Mirati (including 6 studies in adult subjects with advanced solid malignancies, 7 pharmacokinetic studies, and an open-label extension study), and 4 sponsored by BeiGene, Ltd. (BeiGene), Mirati's Asia-Pacific region partner company (3 studies in adult subjects with advanced solid malignancies and a PK study in healthy volunteers).

As of 26 June 2022, an estimated 1546 subjects have received sitravatinib across the 18 clinical studies. Overall, an estimated total of 1,1331 subjects with solid malignancies have received with sitravatinib alone, in combination with the PD-1 inhibitor nivolumab, in combination with nivolumab and ipilimumab, in combination with tislelizumab, or in combination with pembrolizumab and the antibody-drug conjugate (ADC) enfortumab vedotin-ejfv (pembro/EV). Subject numbers are estimated for ongoing studies where the study treatment s masked After single oral administration of 10 to 200 mg sitravatinib (free-base formulation) under fasting conditions, the median time to reach sitravatinib peak concentration (Tmax) was approximately 3.02 to 8.87 hours (Study 516-001). The arithmetic mean terminal half-life (t½) ranged from 42.1 to 51.5 hours. After multiple oral administrations, steady state appeared to have been reached by Day 8 and Cmax and AUCτ, accumulation ratios at steady-state ranged from 1.82- to 6.89 and 2.13 to 8.34, respectively. Sitravatinib exposure (Cmax and AUCs) appeared to increase in a dose-proportional manner following single- and multiple-dose once daily administration of sitravatinib over the dose range of 10 mg to 200 mg. There was no drug interaction between sitravatinib and a proton-pump inhibitor. A low-fat/low-calorie meal had no effect on sitravatinib malate bioavailability while a high-fat, high-calorie meal increased sitravatinib malate bioavailability by approximately 20% to 28%.

Sitravatinib-related adverse events (AEs) reported in ≥20% of the 1279 subjects with solid malignancies that were included in the analysis of safety were diarrhea (48%), fatigue (32%), hypertension (31%), decreased appetite (28%), nausea (27%), alanine aminotransferase (ALT) increased (25%), aspartate aminotransferase (AST) increased (24%), and palmar-plantar erythrodysaesthesia syndrome (PPES) (22%). Among the subjects with solid malignancies, sitravatinib- related SAEs in ≥0.5% of subjects included diarrhea (3%), pulmonary embolism (1.0%), vomiting (0.9%), nausea and fatigue (0.7% each), hypertension (0.6%), pneumonitis and cardiac failure (0.5% each), and pancreatitis, hemoptysis, deep vein thrombosis, embolism and hyponatremia (0.4% each). In PK studies of sitravatinib, 2 subjects (1%) experienced an SAE in Study 516-010, Part 1. Of these, an SAE of hepatic failure was considered related to treatment with sitravatinib. In Study 516-010, Part 2, 5 subjects experienced an SAE. Of these, events of diarrhea and hepatic failure were considered related to treatment with sitravatinib. In Study 516-012, 1 subjected experienced an SAE which was not considered related to treatment with sitravatinib.

Based on review of the AEs reported with sitravatinib in the context of the mechanism of action, nonclinical data, frequency, and Investigator assessment of causality, the following AEs have been assessed as expected serious adverse reactions (SARs) for sitravatinib: diarrhea, left ventricular dysfunction, ejection fraction decreased, fatigue, hepatic function abnormal, increased transaminases, venous thromboembolic events (embolism and pulmonary embolism), hypertension, nausea/vomiting, arterial thromboembolic events (myocardial infarction, transient ischemic attack, cerebrovascular accident, cerebral infarction), PPES, pneumonitis, and hypothyroidism.

A detailed summary of Sitravatinib monotherapy or in combination AE data can be found in the current version of the Sitravatinib IB.

2.7.1.3. Overall benefit-risk

Considering the disease under study, the design of the study and the safety profile, the overall benefit-risk of the combination of Tislelizumab and Sitravatinib is acceptable in an oncology population based on preliminary safety data.

3. STUDY OBJECTIVES

3.1. PRIMARY OBJECTIVE

The primary objective of this trial is to evaluate the efficacy of the combination of Sitravatinib and Tislelizumab in terms of response rate in patients with mUM with liver metastasis and biopsiable disease at the first line or after failure to systemic first line therapy with Tebentafusp (only HLA-A02:01 positive patients) or liver directed therapy.

Primary efficacy endpoint: Objective Response rate (ORR) according to RECIST 1.1 criteria.

Objective Response Rate (ORR) is defined as the proportion of patients with at least one response of CR or PR that is confirmed at least 4 weeks later. Where PR is at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters as long as criteria for PD are not met, and CR is the disappearance of all target lesions. Any pathological lymph nodes selected as target lesions must have a reduction in short axis to <10mm

Following RECIST 1.1 criteria, for non-randomised trials where response is the primary endpoint, confirmation of PR and CR is required to ensure responses identified are not the result of measurement error. ORR defined in this manner is a direct measure of drug antitumor activity, which can be evaluated in a single-arm study, providing an accurate assessment of a surrogate efficacy endpoint.

3.2. SECONDARY OBJECTIVES

The secondary objective of this trial is to evaluate the efficacy of the combination of Sitravatinib and Tislelizumab in terms of PFS and OS.

Secondary efficacy endpoints:

1. *Progression Free Survival (PFS) according to RECIST 1.1 criteria.*

For this protocol, PFS is defined as the time from the first dose of study treatment until objective tumor progression or death according to section 12.1.2.

2. *Overall Survival (OS).*

Overall Survival is defined as the time from the first dose of study treatment until death from any cause.

3.3. SAFETY OBJECTIVE

Evaluate Safety of the combination with Sitravatinib and Tislelizumab using NCI-CTCAE version 5.0

The safety objective of this trial is to characterize the safety and tolerability of Tislelizumab in combination with Sitravatinib in subjects with mUM and liver metastasis. The safety analysis will be based on subjects who experienced toxicities as defined by CTCAE, v5.0, the attribution to drug, time-of-onset, from the first dose and last dose, duration of the event, its severity / grade, its outcome, and any concomitant medications administered will be recorded. AEs will be analysed including but not limited to all AEs, SAEs, fatal AEs, all and related laboratory changes. Furthermore, specific

immune-related adverse events (irAEs) will be collected and designated as immune related events of clinical interest (AESIs).

3.4. TRANSLATIONAL OBJECTIVES

1. *Study the efficacy of Sitravatinib combined with Tislelizumab in inducing inflammatory T-cell effector infiltrate in uveal melanoma liver metastases.*
2. *Study the efficacy of Sitravatinib and Tislelizumab in changing macrophages, and other innate cells, phenotype from an immune-suppressed to an anti-tumoral state.*
3. *Study molecular mechanisms behind inflammatory T-cell effector infiltrate induction in uveal melanoma liver metastases.*

Molecular determinations will be performed to fresh tumor tissue from liver biopsies before starting combination therapy, and before 3rd dose, and at PD to compare stromal cell populations after combination treatment with Sitravatinib + Tislelizumab. To study spatial cell populations within the tumor we plan to perform Image Mass Cytometry.

4. STUDY DESIGN

4.1. OVERVIEW OF STUDY DESIGN

This is a single arm, multi-center, phase II study of Sitravatinib in combination with Tislelizumab in subjects with metastatic uveal melanoma with liver metastasis. This study is divided into 3 phases: Screening, Treatment, and Follow-up. After informed consent is obtained, subjects will enter 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 Tislelizumab 200mg intravenously (IV), Q3W and Sitravatinib 100 mg capsules via orally daily until confirmed disease progression or death unless there is unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met.

Subjects will be visited 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.

Patients with confirmed PD who continue to receive Tislelizumab + Sitravatinib combination therapy at the discretion of the Investigator (following consultation with Coordinating Investigator) can receive treatment until no longer having clinical benefit.

Subjects, either those on study treatment or those that 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), 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 radiological evaluations of the tumor every 6 weeks during the first 12 months after inclusion (48 weeks), and then every 12 weeks until progression, and after progression long term follow up to record the date of death.

Screening phase
Screening will occur between Day -28 and Day 0 that is before the first treatment administration. The purpose of the screening period is to establish protocol eligibility, as specified in the inclusion/exclusion criteria. Protocol waivers or exemptions to eligibility criteria are not allowed.

Informed consent of study procedures and tumor biopsy samples should be obtained prior to the 28-day screening window after the study has been fully explained to each subject, in order to permit tumor biopsy sample acquisition and analysis prior to enrollment.

If laboratory or imaging procedures were performed for alternate reasons prior to signing consent, these can be used for screening purposes with consent of the patient. However, all screening laboratory tests

(within 7 days of cycle 1 day 1 for eligibility) and imaging results must have been obtained within 28 days of enrollment.

A mandatory fresh tumor tissue from liver biopsies before starting combination therapy, to compare stromal cell populations after combination treatment with Sitravatinib + Tislelizumab should be collected during screening visit **(after informed consent is signed by the patient)** and managed according to what is detailed in the laboratory manual. The collection of baseline tumor biopsies and prior C3 (around day +42) is mandated, the Investigator must consult with the Coordinating Investigator if such sampling is not feasible. The collection of tumor biopsies at the time of progression is optional but strongly encouraged.

Results from screening assessments must be obtained prior to the first dose of study drug (Cycle 1/Day 1). Assessments may be performed on Day -1 or on Cycle 1/Day 1 prior to dosing. Clinical laboratory tests including pregnancy tests (where applicable) can be performed within 72 hours prior to the first dose of study drug. Subjects who complete the baseline visit and continue meeting the inclusion/exclusion criteria will begin the treatment phase of this study.

Treatment phase

The treatment phase will begin at the time of enrolment of the first patient and will consist of the study treatment cycles of 3 weeks (21 days). The treatment phase will end when the last patient discontinued both study drugs.

Once registered and having received the confirmation of enrolment form from eCRF, subjects will receive Tislelizumab 200mg intravenously (IV), Q3W and Sitravatinib 100 mg capsules orally daily until confirmed disease progression, unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met. Every effort should be made to minimize the time between enrollment and starting treatment. (i.e. within 1 day of enrollment).

Patients with confirmed PD who continue to receive Tislelizumab + Sitravatinib combination therapy at the discretion of the Investigator (following consultation with Coordinating Investigator) can receive treatment until no longer having clinical benefit.

Sitravatinib malate capsules can may be taken on an empty stomach or with a low-fat meal, sitravatinib freebase capsules should be taken on an empty stomach, at least 2 hours after the previous meal and preferably in 1 hour before the morning next meal. Sitravatinib capsules should be taken with at least 200 mL of water preferably in the morning. The capsules are to be swallowed whole and should not be chewed, crushed, or opened. If vomiting occurs after dosing, the Sitravatinib dose should not be replaced.

Tislelizumab 200 mg will be administered on Day 1 of each 21-day cycle (once every 3 weeks).

Tislelizumab will be administered by intravenous infusion through an intravenous line containing a sterile, nonpyrogenic, low-protein-binding 0.2- or 0.22-micron in-line or add-on filter. Specific instructions for product preparation, storage, and administration are provided in the Pharmacy Manual.

The delivery period of the initial infusion (Day 1 of Cycle 1) will be ≥ 60 minutes; if this is well tolerated, then the delivery period of subsequent infusions may be shortened to ≥ 30 minutes, which is the shortest

time period permissible for infusion. Tislelizumab must not be concurrently administered with any other drug (refer to Section 8.2).

As a routine precaution, after infusion of Tislelizumab on Day 1 of Cycle 1, patients must be monitored for ≥ 60 minutes afterward in an area with resuscitation equipment and emergency agents. From Cycle 2 onward, a monitoring period of ≥ 30 minutes is required.

Guidelines for dosage modification and treatment interruption or discontinuation are provided in Section 7.2.

An additional mandatory fresh tumor tissue from liver biopsies on day +42 +/- 3 days should be collected to compare stromal cell populations after combination treatment with Sitravatinib + Tislelizumab. Management of samples is detailed in the laboratory manual.

Results for LFTs, full blood count, and creatinine must be available before commencing an infusion of Tislelizumab (within 3 days) or dispensing Sitravatinib, and reviewed by the treating physician or Investigator prior to dosing/dispensing.

Subjects will be visited 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.

Subjects will undergo radiological evaluations of the tumor every 6 weeks during the first 48 weeks and then, every 12 weeks until disease progression. This schedule MUST be followed regardless of any delays in dosing or end of treatment due to other reasons than disease progression.

Safety assessments will be performed at each visit and include patient interview and reviewing of additional source documentation such as investigations, medical history and concomitant medications, as needed.

End of treatment visit

An end-of-treatment visit should be scheduled for 30 +/-7 days after the end of treatment for any reason. For this trial, up to two end of treatment visits may be done, considering that patients can end one treatment of the combination and continue with the other as monotherapy if PI considers that is the best option for the patient. Reasons for the end of treatment visit should be clearly specified in the eCRF.

Patients who discontinue treatment for any reason will be asked to return to the clinic for the EOT Visit (to occur 30 days [± 7 days] after the last dose of study drug(s), or before the initiation of a new anticancer treatment, whichever occurs first). In addition, telephone contacts (safety follow-up phone call) with patients should be conducted to assess irAEs and concomitant medications (if appropriate, i.e., associated with an irAE or is a new anticancer therapy) at 90 days (± 14 days) after the last dose of sitravatinib and 150 days (+-14 days) after the last dose of tislelizumab, regardless of whether or not the patient starts a new anticancer therapy. If patients report a suspected irAE at a telephone follow-up contact, the investigator should arrange an unscheduled visit if further assessment is indicated.

Safety follow up:
All patients after ending study treatment should be followed for AEs and concomitant medications according to *Section 11* up to 90 days after the last dose of Sitravatinib or Tislelizumab.

PFS follow up:
Patients that end treatment due to any reason other than disease progression according to RECIST 1.1 (including patients who have switched to an alternative treatment without documented progression), will follow tumor evaluations every 8 weeks (up to week 48 after inclusion) and every 12 weeks or clinically indicated thereafter, until disease progression.

Long term follow-up phase
All patients after disease progression should be followed until death or study closure, as per *Section 5.3*. Date and reason of death should be documented consistently in patient records and in the eCRF.

4.2. STUDY SCHEMA

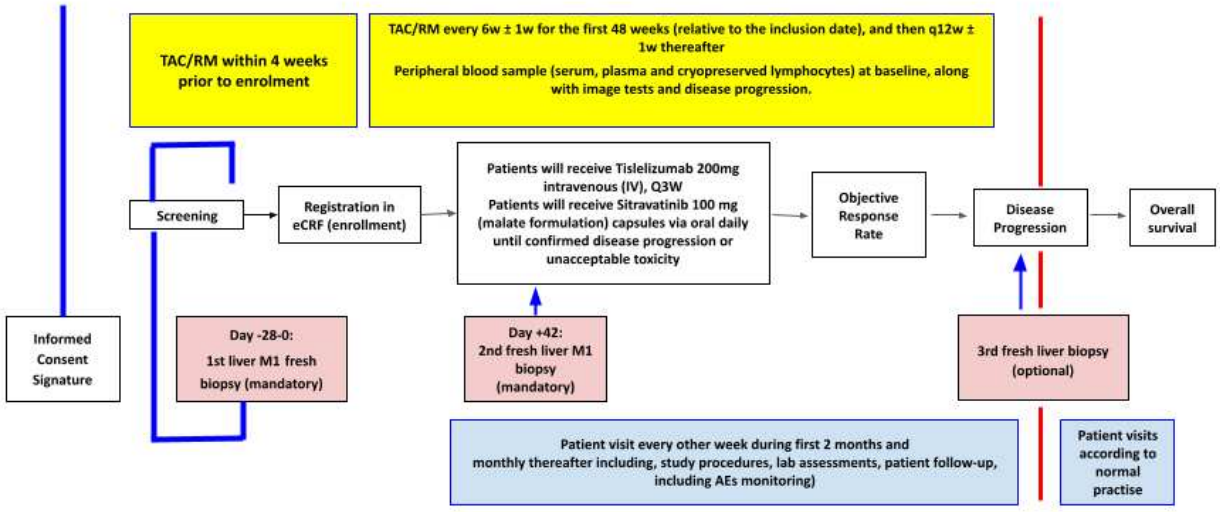


Figure 9. Study flow chart

4.3. STUDY OVERSIGHT FOR SAFETY EVALUATION

A subject may elect to discontinue study drugs at any time for safety, medical, or personal reasons. Patients who choose to discontinue study drug prior to disease progression will be followed in the PFS follow up period and continue to undergo regularly scheduled disease assessment until documentation of disease progression. It is allowed to continue either Tislelizumab or Sitravatinib alone in case the other drug is required to be discontinued at the investigator discretion.

All subjects who discontinue study drugs will be followed for overall survival and all post progression cancer treatments administered will be recorded. Subjects may at any time withdraw consent for further study participation. The investigator will promptly explain to the subject involved that the study drug will be discontinued for that subject and provide appropriate medical treatment and other necessary measures. A subject who has ceased to return for visits will be followed up by mail, phone, or other means as much as possible to gather information such as the reason for failure to return and the status of treatment compliance, presence or absence of adverse events, and clinical courses of signs and symptoms, and the information will be recorded in the eCRF.

Subjects who early withdrew from the study or treatment will be discontinued for 1 of these primary reasons: adverse event(s), loss to follow-up, subject choice, progressive disease, or administrative/other. In addition to the primary reason, the subject may have indicated 1 or more of these reasons as secondary reasons for discontinuation. Study disposition information will be collected on the appropriate eCRF. A subject removed from the study for any reason may not be replaced.

Safety will be assessed by monitoring and recording all AEs including all CTCAE grades (for both increasing and decreasing severity) and serious adverse events (SAEs); regular monitoring of hematology and clinical chemistry; physical examinations; and regular measurement of vital signs, and electrocardiograms (ECGs) as detailed in the schedule of visits and procedures.

Safety evaluation will be performed by PI in each visit, all findings will be collected in the eCRF and, when applicable, will be expeditiously informed to Sponsor according to what is detailed in section 11 of this protocol. Coordinating Investigator will be the principal contact in GEM for pharmacovigilance surveillance and will be informed by the CRO of each new SAE received and will participate in the management of study emergent toxicities. Furthermore, a monthly report with all new SAE reported by sites will be distributed both, to sites and Sponsor. Annual Safety Reports (DSUR) will be elaborated with the cumulative safety information of the trial and submitted to Coordinating Investigator, Sponsor and Industry Partner, before sending to Competent Authorities as required by current regulation for clinical trials.

Additionally, the GEM Executive Board at least once a year, during Annual Cooperative Group Assembly, or when needed, will oversee the safety profile of the Study.

If at any time the safety profile of the study is not acceptable, corrective measures will be implemented by the Sponsor, otherwise the study would be halted.

5. PATIENT SELECTION

5.1. INCLUSION CRITERIA

For inclusion in the study patients must fulfill all of the following criteria:

1. Patients must have histologically confirmed metastatic uveal melanoma with measurable disease not eligible for curative therapy.

2. Participants must have measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded for non-nodal lesions and short axis for nodal lesions) as ≥20 mm with conventional techniques or as ≥10 mm with spiral CT scan, MRI, or calipers by clinical exam. Patients must have at least 1 biopsiable liver metastasis.

3. Patients who are HLA-A02:01 positive can have received one prior therapy with Tebentafusp for metastatic disease.

4. Patients must be 18 years of age or older at time of study entry.

5. Eastern Cooperative Oncology Group (ECOG) Performance Status 0-1.

6. Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol. Written informed consent and any locally required authorization obtained from the patient/legal representative prior to performing any protocol-related procedures, including screening evaluations not performed according to normal practice. Patients must consent for liver metastasis biopsies donation at day 0 and day +42 since treatment initiation.

7. Adequate normal organ and marrow function as defined below:
   a. Haemoglobin ≥9.0 g/dL
   b. Absolute neutrophil count (ANC) $\geq$ 1.5 x 10^9/L ($\geq$ 1500 per mm^3)
   c. Platelet count ≥ *100* x 10^9/L ($\geq$100,000 per mm^3)
   d. Serum bilirubin ≤1.5 x institutional upper limit of normal (ULN). This will not apply to patients with confirmed Gilbert's syndrome (persistent or recurrent hyperbilirubinemia that is predominantly unconjugated in the absence of hemolysis or hepatic pathology), who will be allowed only in consultation with the Coordinating Investigator.
   e. Both AST and ALT must be < 5 x ULN.
   f. Creatinine clearance ≥ 40 ml/min calculated by Cockcroft-Gault or another validated method
   g. Urine protein:creatinine ratio (UPC) ≤1 or ≤2+ proteinuria on 2 consecutive dipsticks taken no less than 1 week apart.
   h. Subjects with 2+ proteinuria on dipstick must also have UPC < 0.5 on 2 consecutive samples.

8. Females of childbearing potential must be willing to use a highly effective method of birth control for the duration of the study, and for 4 months after the last dose of Tislelizumab and/or 6 months after the last dose of Sitravatinib, and have a negative urine or serum pregnancy test ≤ 7 days before first administration of Tislelizumab and Sitravatinib. Women will be considered post-menopausal if they have been amenorrheic for 12 months without an alternative medical cause. The following age-specific requirements apply:
    a. Amenorrheic for ≥1 year in the absence of chemotherapy and/or hormonal treatments
    b. Luteinizing hormone (LH) and/or follicle stimulating hormone and/or estradiol levels in the post-menopausal range
    c. Radiation induced oophorectomy with last menses >1 year ago
    d. Chemotherapy induced menopause with >1 year interval since last menses
    e. Surgical sterilization (bilateral oophorectomy or hysterectomy)
    f. Women <50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatments and if they have luteinizing hormone and follicle-stimulating hormone levels in the post-menopausal range for the institution or underwent surgical sterilization (bilateral oophorectomy or hysterectomy).
    g. Women ≥50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of all exogenous hormonal treatments, had radiation-induced menopause with last menses >1 year ago, had chemotherapy-induced menopause with last menses >1 year ago, or underwent surgical sterilization (bilateral oophorectomy, bilateral salpingectomy or hysterectomy).

9. For both male and females patients/partners: Contraceptive use should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. Non-sterile males must be willing to use a highly effective method of birth control for the duration of the study and for ≥ 4 months after the last dose of Tislelizumab and/or 6 months after the last dose of Sitravatinib. A sterile male is defined as:
    a. One for whom azoospermia has been previously demonstrated in a semen sample examination as definitive evidence of infertility.
    b. Males with known “low sperm counts” (consistent with “sub-fertility”) are not to be considered sterile for purposes of this study

10. Patient is willing and able to comply with the protocol for the duration of the study including undergoing treatment and scheduled visits and examinations including follow up.

11. Must have a life expectancy of minimum of 4 months.

12. Subjects must be able to swallow and retain oral medications and be without clinically significant gastrointestinal illnesses that would preclude absorption of Sitravatinib.

13. Adequately controlled BP:
    - Systolic BP ≤140 mmHg and diastolic BP ≤90 mmHg in the presence or absence of a stable regimen of antihypertensive therapy.

5.2. EXCLUSION CRITERIA

Patients should not enter the study if any of the following exclusion criteria are fulfilled:

1. Patients with concomitant malignancy other than non-melanoma skin cancer, or superficial bladder cancer controlled with local treatment.

2. Previous treatment with targeted therapies and/or anti-angiogenic agents such as VEGFR, MEK, BRAF, ERK inhibitors, with the exception of Tebentafusp.

3. Previous treatment with immune checkpoint inhibitors, either anti-PD1/PDL1 (including Tislelizumab), anti-CTLA-4, or other treatments.

4. Presence of brain or leptomeningeal involvement unless previously treated, off steroids at least 2 weeks, and considered stable. Patients with untreated central nervous system (CNS) metastases and/or carcinomatous meningitis identified either on the baseline brain imaging [RECIST]) obtained during the screening period or identified prior to signing the ICF. Patients whose brain metastases have been treated may participate provided they show radiographic stability (defined as 2 brain images, both of which are obtained after treatment to the brain metastases. These imaging scans should both be obtained at least four weeks apart and show no evidence of intracranial progression). In addition, any neurologic symptoms that developed either as a result of the brain metastases or their treatment must have resolved or be stable either, without the use of steroids, or are stable on a steroid dose of ≤10mg/day of prednisone or its equivalent and anticonvulsants, for at least 14 days prior to the start of treatment. Brain metastases will not be recorded as RECIST Target Lesions at baseline.

5. Patients weighing <30kg will be excluded from enrollment.

6. Participation in another clinical study with an investigational product during the last 4 *weeks.*

7. Concurrent enrolment in another clinical study, unless it is an observational (non-interventional) clinical study or during the follow-up period of an interventional study

8. Receipt of the last dose of anticancer therapy (chemotherapy, immunotherapy, endocrine therapy, targeted therapy, biologic therapy, tumor embolization, monoclonal antibodies) ≤28 days prior to the first dose of study drug If sufficient wash-out time has not occurred due to the schedule or PK properties of an agent, a longer wash-out period will be required, as agreed by Sponsor designated Coordinating Investigator and Principal Investigator.

9. Any unresolved toxicity NCI CTCAE Grade ≥2 from previous anticancer therapy with the exception of alopecia, vitiligo, and the laboratory values defined in the inclusion criteria
    a. Patients with Grade ≥2 neuropathy will be evaluated on a case-by-case basis after consultation with the Coordinating Investigator.

b. Patients with irreversible toxicity not reasonably expected to be exacerbated by treatment with Tislelizumab may be included only after consultation with the Coordinating Investigator.
c. Known toxicity on prior checkpoint inhibitor treatment:
    i. Grade ≥ 3 immune-related AE related to checkpoint inhibitors.
    ii. Grade 2 immune-related AE associated with checkpoint inhibitor unless the AE resolved or was well controlled by withholding the checkpoint inhibitor and/or treatment with steroids, with the exception of prior colitis, myocarditis, and pneumonitis, which are exclusionary.
    iii. CNS or ocular AE of any grade related to checkpoint inhibitors.

NOTE: Patients with a prior endocrine AE are permitted to enroll if they are stably maintained on appropriate replacement therapy and are asymptomatic.

10. Any concurrent chemotherapy, IMP, biologic, or hormonal therapy for cancer treatment different to Sitravatinib and/or Tislelizumab. Concurrent use of hormonal therapy for non-cancer-related conditions (e.g., hormone replacement therapy) is acceptable.

11. Radiotherapy treatment to more than 30% of the bone marrow or with a wide field of radiation prior to 4 weeks of the first dose of study drug.

12. Major surgery within a minimum of 4 weeks prior to inclusion; patients must have recovered from any effects of any major surgery prior to inclusion. Note: Local surgery of isolated lesions for palliative intent and minor surgeries performed to obtain biological material for the study (i.e. liver biopsy) are acceptable.

13. History of allogeneic organ transplantation.

14. Active or prior documented autoimmune or inflammatory disorders (including inflammatory bowel disease [e.g., colitis or Crohn's disease], diverticulitis [with the exception of diverticulosis], systemic lupus erythematosus, Sarcoidosis syndrome, or Wegener syndrome [granulomatosis with polyangiitis, Graves' disease, rheumatoid arthritis, hypophysitis, uveitis, etc]). The following are exceptions to this criterion:
    a. Patients with vitiligo or alopecia
    b. Patients with hypothyroidism (e.g., following Hashimoto syndrome) stable on hormone replacement
    c. Any chronic skin condition that does not require systemic therapy
    d. Patients without active disease in the last 5 years may be included but only after consultation with the Coordinating Investigator
    e. Patients with celiac disease, controlled by diet alone.

15. Uncontrolled intercurrent illness, including but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled/malignant hypertension, unstable angina pectoris, cardiac arrhythmia, interstitial lung disease, serious chronic gastrointestinal conditions associated with diarrhea, or psychiatric illness/social situations that would limit compliance

with study requirement, compromise Sitravatinib absorption, substantially increase risk of incurring AEs or compromise the ability of the patient to give written informed consent.

16. History of another primary malignancy, except for:
    a. Malignancy treated with curative intent and with no known active disease ≥5 years before the first dose of IMP and of low potential risk for recurrence
    b. Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease
    c. Adequately treated carcinoma in situ without evidence of disease

17. History of active primary immunodeficiency

18. Active infection including **tuberculosis** (clinical evaluation that includes clinical history, physical examination and radiographic findings, and TB testing in line with local practice), **hepatitis B** (known positive HBV surface antigen (HBsAg) result), **hepatitis C**, or **human immunodeficiency virus** (positive HIV 1/2 antibodies). Patients with a past or resolved HBV infection (defined as the presence of hepatitis B core antibody [anti-HBc] and absence of HBsAg) are eligible. Patients positive for hepatitis C (HCV) antibodies are eligible only if polymerase chain reaction is negative for HCV RNA.Patients with HIV infection but with controlled and treated disease and undetectable viral load, would be eligible.

19. Current or prior use of immunosuppressive medication within 14 days before the first dose of Tislelizumab. The following are exceptions to this criterion:
    a. Intranasal, inhaled, topical steroids, or local steroid injections (e.g., intra articular injection)
    b. Systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or its equivalent
    c. Steroids as premedication for hypersensitivity reactions (e.g., CT scan premedication)

20. Receipt of live attenuated vaccine within 30 days prior to the first dose of IMP. Note: Patients, if enrolled, should not receive live vaccines whilst receiving IMP and up to 30 days after the last dose of IMP.

21. Female patients who are pregnant (confirmed with positive pregnancy test) or breastfeeding or male or female patients of reproductive potential who are not willing to employ effective birth control from screening to 4 months after the last dose of Tislelizumab and or 6 months after the last dose of Sitravatinib therapy.

22. History of severe allergic reaction attributed to Sitravatinib or a similar VEGFR inhibitor or known hypersensitivity to any component of Sitravatinib dose composition.

23. Known allergy or hypersensitivity to Tislelizumab or any of the Tislelizumab excipients.

24. History of gastrointestinal perforation. Subjects with a history of abdominal fistula will be eligible if:
    a. the fistula has been surgically repaired,
    b. there is no evidence of fistula for at least 6 months prior to inclusion, and
    c. the subject is deemed to be at low risk of recurrent fistula in the opinion of the Investigator.

25. History of intra-abdominal abscess within 3 months prior to inclusion.

26. Clinically significant signs and/or symptoms of bowel obstruction within 3 months prior to inclusion.

27. Resting ECG with clinically significant abnormal findings. i.e. Mean QT interval corrected for heart rate using Fridericia's formula (QTcF) ≥470 ms calculated from 3 ECGs (within 15 minutes at 5 minutes apart).

28. Subjects with any one or more of the following:
    a. History of myocardial infarction within 6 months prior to inclusion; patients with a history of myocardial infarction within 6 to 12 months prior to inclusion may be allowed following assessment
    b. Unstable angina within 6 months prior to inclusion
    c. Known significant cardiac disease (New York Heart Association [NYHA] classification of III or IV).
    d. Concomitant medication known to cause prolonged QT which cannot be discontinued or changed to a different medication prior to enrollment.

29. Left ventricular ejection fraction < lower limit of normal (LLN) per institutional guidelines, or <55%, if threshold for normal is not otherwise specified by institutional guidelines, for patients with the following risk factors:
    a. Prior or planned treatment with anthracyclines (ie, PLD)
    b. Prior treatment with trastuzumab
    c. Prior central thoracic radiation therapy (RT), including exposure of heart to therapeutic doses of ionizing RT
    d. History of myocardial infarction within 6 to 12 months prior to inclusion
    e. Prior history of other significant impaired cardiac function.

30. History of stroke or transient ischemic attack within 6 months prior to inclusion.

31. History of significant hemorrhage within 4 weeks prior of first dose date.

32. Patients with:
    a. With uncontrolled diabetes or > Grade 1 laboratory test abnormalities in potassium, sodium, or corrected calcium despite standard medical management or ≥ Grade 3 hypoalbuminemia ≤ 14 days before

b. Uncontrollable pleural effusion, pericardial effusion, or ascites requiring frequent drainage (recurrence ≤ 14 days after intervention)

c. History of interstitial lung disease, non-infectious pneumonitis or uncontrolled lung diseases including pulmonary fibrosis, or acute lung diseases. Patients with significantly impaired pulmonary function, or who require supplemental oxygen at baseline must undergo an assessment of pulmonary function at screening

33. Evidence of any other disease, physical examination or laboratory finding gives reasonable suspicion of a disease or condition that puts the subject at high risk for treatment-related complication.

34. Prior enrollment or treatment in a previous Tislelizumab and/or Sitravatinib clinical study regardless of treatment arm assignment.

35. Any serious medical condition or psychiatric illness that would interfere in understanding of the informed consent form.

Procedures for withdrawal of incorrectly enrolled patients are presented in Section 7.1.2

5.3. WITHDRAWAL OF PATIENTS FROM STUDY TREATMENT AND/OR STUDY

5.3.1. Permanent discontinuation of study treatment

An individual patient will not receive any further investigational product if any of the following occur in the patient in question:

1. Withdrawal of consent or lost to follow-up
2. Adverse event that, in the opinion of the investigator or the sponsor, contraindicates further dosing
3. Patient is determined to have met one or more of the exclusion criteria for study participation at study entry and continuing investigational therapy might constitute a safety risk
4. Pregnancy or intent to become pregnant
5. Any AE that meets criteria for discontinuation
6. Grade ≥3 infusion reaction
7. Patient noncompliance that, in the opinion of the investigator or sponsor, warrants withdrawal; e.g., refusal to adhere to scheduled visits
8. Initiation of alternative anticancer therapy including another investigational agent

9. Confirmation of PD and investigator determination that the patient is no longer benefiting from study treatment. Patients who are permanently discontinued from further receipt of investigational product, regardless of the reason (withdrawal of consent, due to an AE, other), will be identified as having permanently discontinued treatment

Patients who are permanently discontinued from receiving investigational products will be followed for safety per Section 11.3.1, unless consent is withdrawn or the patient is lost to follow-up or enrolled in another clinical study. All patients will be followed for survival. Patients who decline to return to the site for evaluations will be offered follow-up by phone every 3 months as an alternative.

5.3.2. Withdrawal of consent

Patients are free to withdraw from the study at any time (IMP and assessments) without prejudice to further treatment.

Patients who withdraw consent for further participation in the study will not receive any further IMP or further study observation, with the exception of follow-up for survival, which will continue until the end of the study unless the patient has expressly withdrawn their consent to survival follow-up. Note that the patient may be offered additional tests or tapering of treatment to withdraw safely.

A patient who withdraws consent will always be asked about the reason(s) for withdrawal and the presence of any AE. The Investigator will follow up AEs outside of the clinical study.

If a patient withdraws consent, they will be specifically asked if they are withdrawing consent to:

- all further participation in the study including any further follow up (e.g., survival contact telephone calls)
- withdrawal of consent to the use of their study generated data
- withdrawal to the use of any samples

5.3.3. Management of patient's request to withdraw from the study

If a patient does not return for a scheduled visit, every effort should be made to contact the patient. All attempts to contact the patient and information received during contact attempts must be documented in the patient's medical record. In any circumstances, every effort should be made to document patient outcomes, if possible. The investigator should inquire about the reason for withdrawal, request the patient to return all unused investigational product(s), request that the patient return for a final visit, if applicable, and follow up with the patient regarding any unresolved AEs.

If the patient withdraws from the study, and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

Date of withdrawal from the study, with reason for withdrawal, will be recorded on the eCRF and in the patient record. In the case of death, a death certificate should be obtained if possible, with the cause of death evaluated and documented.

Each instance of a subject's withdrawal as follows:

- Document the request to revoke authorization and/or withdraw consent. Specifically, identify who received the revocation request & effective date of revocation when protected health information (PHI) will no longer be collected or disclosed.
- A member of the study team should update the participant's research record, and eCRF. When required, the ECs should be informed.

  NOTE: If the withdrawal is related to an unanticipated problem involving risks to the subject, prompt reporting would be required.

5.4. REPLACEMENT OF PATIENTS

Subjects who do not receive at least one dose of study treatment or who are screening failure will be replaced. If a patient withdraws from participation in the study, then his or her study code cannot be reused. Withdrawn patients after receiving at least one dose of study treatment will not be replaced.

6. INVESTIGATIONAL PRODUCT(S)

6.1. TISLELIZUMAB

The anti-PD-1 monoclonal antibody (mAb), tislelizumab, is manufactured in compliance with Good Manufacturing Practice. The clinical study drug product is formulated in an aqueous buffer with pH 6.5 and isotonic osmolality and presented as a sterile, injectable solution. The administration route is intravenous (IV) infusion after the appropriate dilution in 0.9% sodium chloride solution.

6.1.1. Formulation/packaging/storage

Tislelizumab is presented as a sterile, nonpyrogenic, and isotonic injectable solution for IV administration in buffered formulation at pH 6.5, consisting of citrate, histidine, trehalose, polysorbate-20, and Water for Injection.
The drug product is fill-finished in a single-use glass vial with a rubber stopper and capped by an aluminum flip-off seal cap. Each vial contains a total of 100 mg of tislelizumab mAb in 10 mL of buffered isotonic solution with a concentration of 10 mg/mL.

The investigational drug product should be stored in the carton box it came in at the specified conditions on the label until time to use.

6.1.2. Tislelizumab doses and treatment regimens

Patients will receive Tislelizumab 200mg intravenous (IV), Q3W until confirmed disease progression unless there is unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met.

6.1.3. Preparation of Tislelizumab doses for IV administration

Tislelizumab 200 mg will be administered on Day 1 of each 21-day cycle (once every 3 weeks).

Tislelizumab will be administered by intravenous infusion through an intravenous line containing a sterile, nonpyrogenic, low-protein-binding 0.2- or 0.22-micron in-line or add-on filter. Specific instructions for product preparation, storage, and administration are provided in the Pharmacy Manual.

The delivery period of the initial infusion (Day 1 of Cycle 1) will be ≥ 60 minutes; if this is well tolerated, then the delivery period of subsequent infusions may be shortened to ≥ 30 minutes, which is the shortest time period permissible for infusion.

Tislelizumab must not be concurrently administered with any other drug (refer to Section 8.2).

6.1.4. Monitoring of dose administration for Tislelizumab

As a routine precaution, after infusion of Tislelizumab on Day 1 of Cycle 1, patients must be monitored for ≥ 60 minutes afterward in an area with resuscitation equipment and emergency agents. From Cycle 2 onward, a monitoring period of ≥ 30 minutes is required. Patients will be monitored before, during and after the infusion of Tislelizumab patients vital signs are to be monitored (pulse rate, blood pressure)

every 30 minutes during the infusion period (including times where infusion rate is slowed or temporarily stopped).

In the event of a ≤Grade 2 infusion-related reaction, the infusion rate of study drug may be decreased by 50% or interrupted until resolution of the event (up to 4 hours) and re-initiated at 50% of the initial rate until completion of the infusion. For patients with a ≤Grade 2 infusion-related reaction, subsequent infusions may be administered at 50% of the initial rate. Acetaminophen and/or an antihistamine (e.g., diphenhydramine) or equivalent medications per institutional standard may be administered at the discretion of the investigator. If the infusion-related reaction is Grade 3 or higher in severity, study drugs will be discontinued. The standard infusion time is one hour, however if there are interruptions during infusion, the total allowed time from infusion start to completion of infusion should not exceed 4 hours at room temperature, with maximum total time at room temperature not exceeding 4 hours (otherwise requires new infusion preparation).

As with any antibody, allergic reactions to dose administration are possible. Appropriate drugs and medical equipment to treat acute anaphylactic reactions must be immediately available, and study personnel must be trained to recognize and treat anaphylaxis. The study site must have immediate access to emergency resuscitation teams and equipment in addition to the ability to admit patients to an intensive care unit if necessary.

6.2 SITRAVATINIB

Sitravatinib capsules used in clinical studies to date have contained either Sitravatinib (MGCD516) free base drug substance or Sitravatinib (MGCD516) malate drug substance plus excipients. Sitravatinib capsules will be provided by the Sponsor as the malate drug product packaged in 30-count, high-density polyethylene, white opaque, round 60cc bottles. Formulation and dosage strengths are specified in the section 6.2.1 of this protocol. A tamper resistant heat induction seal and a child-resistant closure are used for all dose strengths.

The storage area should be secure with limited access. Only qualified personnel who are familiar with procedures that minimize undue exposure to them and to the environment should undertake the preparation, handling, and safe disposal of small molecule therapeutic agents It is the sponsor’s responsibility to provide the sites with the study drug, for this trial Sitravatinib will be directly shipped from Mirati Depot to sites.

Each IMP pack will have an investigational product label permanently affixed to the outside, stating that the material is for clinical trial/investigational use only and should be kept out of reach and sight of children. The label will include dosing instructions and a space for entering the enrolment code (patient inclusion number); the code will be added at the time of dispensing treatment. Labels will fulfill the GMP Annex 13 requirements for labelling. Label text will be translated into the appropriate local language.

6.2.1. Formulation/packaging/storage

The sitravatinib capsule formulations currently used in this clinical study is as follows:

- The malate capsule product consists of a blend of MGCD516 malate drug substance, microcrystalline cellulose, mannitol, croscarmellose sodium, colloidal silicon dioxide, and magnesium stearate. The blend is filled into hard gelatin capsules. The malate formulation is provided in dose strengths from 10 to 60 mg.

The storage area should be secure with limited access. Only qualified personnel who are familiar with procedures that minimize undue exposure to them and to the environment should undertake the preparation, handling, and safe disposal of small molecule therapeutic agents It is the sponsor's responsibility to provide the sites with the study drug.

Each IMP pack will have an investigational product label permanently affixed to the outside, stating that the material is for clinical trial/investigational use only and should be kept out of reach and sight of children. The label will include dosing instructions and a space for entering the enrolment code (patient inclusion number); the code will be added at the time of dispensing treatment. Labels will fulfill the GMP Annex 13 requirements for labelling. Label text will be translated into the appropriate local language.

6.2.2. Sitravatinib doses and treatment regimens

Patients will receive Sitravatinib 100 mg (malate formulation) capsules via oral daily until confirmed disease progression, unless there is unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met.

Sitravatinib malate capsules may be taken on an empty stomach or with a low-fat meal; sitravatinib freebase capsules should be taken on an empty stomach, at least 2 hours after the previous meal and 1 hour before the next meal, and preferably in the morning. Sitravatinib capsules should be taken with at least 200 mL of water, preferably in the morning. The capsules are to be swallowed whole and should not be chewed, crushed, or opened. If vomiting occurs after dosing, the sitravatinib dose should not be replaced.

Missed doses may be taken if within 12 hours of the scheduled time and the next dose should be taken at its scheduled time.

On the day of Tislelizumab infusion, patients will follow the instructions of the treating physician regarding when to take Sitravatinib, taking into account that the interaction potential is very low, local practice should be followed in regards to the recommendations.

6.2.3. Preparation of Sitravatinib

Not applicable, Sitravatinib will be provided as capsules for use in clinical trials. Patients will self-administer Sitravatinib according to the instructions provided in this protocol and follow the recommendation of treating Physicians.

6.2.4. Monitoring of dose administration for Sitravatinib

Treatment with Sitravatinib should be initiated and supervised by a physician experienced in the use of anticancer medicinal products.

Sitravatinib tablets are formulated to be administered orally with water. Sitravatinib should be taken on an empty stomach, at least 1 hour before or 2 hours after a meal. In the case of vomiting after taking a tablet, the patient should not take an additional Sitravatinib dose until the next scheduled dose.

Missed doses may be taken if within 12 hours of the scheduled time and the next dose should be taken at its scheduled time.

A patient medication diary will be provided for each patient. Patients or caregivers should complete this diary during the entire study.

6.3. ACCOUNTABILITY AND DISPENSATION

The trial medication will be sent to the investigator's site pharmacy preceded by the Regulatory Green Light. The medication is to be used exclusively in the clinical trial according to the instructions of this trial protocol.

When a drug shipment is received, the Investigator or designee will check the amount and condition of the delivery, drug expiration date, and sign the Receipt of Shipment Form provided. The Receipt of Shipment Form should be faxed or emailed to the CRO. The original form will preliminarily be retained at the site and will be collected at the next monitoring visit by the monitor and stored in the Trial Master File at CRO. A copy remains in the Investigator File at the site. In case of shipment problems the Investigator or designee shall contact the CRA as soon as possible.

For this trial a IWRS system will be used for IMP stock management, Pharmacy or PI designee properly identified in the personnel list and tasks delegation log, will get access to the web based platform to update receptions, destructions and dispensing of IMPs. The record must be continuously updated and contain the dates, quantities and compounds of drugs received, medication identification number(s), the patient identification number to whom the trial medication was dispensed, date and quantity of medication dispensed. The system includes an audit trail that allows unequivocal identification of the staff member and the field modification at any time.

The Investigator (or a specified designee) will be responsible for ensuring IMP accountability, including reconciliation of drugs and maintenance of records.

- Upon receipt of the IMP, the responsible person will check for accurate delivery, acknowledge receipt by signing/initialing and dating the appropriate documentation, and return it to the specified location. A copy will be archived in the Investigator Site File.
- The IMP dispensing will be recorded on the appropriate drug accountability forms so that accurate records will be available for verification at each monitoring visit. All used packs (or the corresponding labeling) will be available for monitoring.
- Trial site IMP accountability records will include the following:
    - Confirmation of receipt of IMP in good condition and in the defined temperature range.
    - The inventory of IMP provided for the clinical trial and of that prepared at the site.
    - The use of each dose by each subject.
    - The disposal (including return, if applicable) of any unused IMP.
    - Dates, quantities, batch numbers, packs numbers, expiry dates, and the individual subject trial numbers.
    - The Investigator of the site will maintain records that adequately document that subjects were provided the doses specified in this protocol, and all IMPs provided were fully reconciled.
- No IMP that is dispensed to a subject may be re-dispensed to a different subject.
- A Trial Monitor will periodically collect the IMP accountability forms.
- A record of the number of Tislelizumab/Sitravatinib dispensed to and returned by each subject must be maintained and reconciled with the patient record.
- Copies of all forms documenting receipt of study drug by the study site dispensing and return of study drug (if applicable), together with drug accountability records, will be retained according to the local regulations governing record retention.

6.4. DISPOSITION OF UNUSED INVESTIGATIONAL STUDY DRUG

Trial medication will be monitored by the CRA at the respective hospital pharmacy prior to destruction after having completed a final inventory, when applicable. Local or institutional regulations may require immediate destruction of the study drug used for safety reasons, e.g., cytotoxicity or to maintain the storage capacity and functionality of the storage at the site. In these cases, it may be acceptable to destroy it by the research staff, including partially used and empty vials, dispensed before a monitoring inspection, if the verification of original documents of empty boxes that indicate the information of batch number and dispensing date to the patient on the label. This documentation will be verified against the quantity shipped, dispensed, returned and destroyed. Drug supplies will be destroyed according to the legal requirements in Spain. All trial medication inventory forms must be made available for inspection by a Sponsor authorized representative or designee and regulatory agency inspectors. The Investigator is responsible for the accountability of all used and unused study supplies at the site.

Site Pharmacy will provide the corresponding unused IMP destruction certification to properly document the destruction procedure.

7. TREATMENT PLAN

7.1. PATIENT ENROLLMENT

7.1.1. Procedures for enrollment

Once completed all regulatory and Sponsor requirements and after receiving the "**O**pen **T**o **E**nrollment **Communication**" (OTEC), confirming that study is fully active in the corresponding site, the trial (informed consent) can be offered to potential patients.

Informed consent will be obtained prior to the start of the specified screening window. Procedures conducted as part of the subject's routine clinical management (e.g. blood count determinations and imaging studies such as bone scans) prior to signing of informed consent may be used for screening or for defining baseline data, provided these procedures are conducted as specified in the protocol. Once an informed consent form (ICFs) is signed, a trial screening number will be assigned to each patient after registering at the Electronic Data Capture (EDC) platform. Each site will receive access to the EDC platform in order to register each screened case, since as per GCP guidelines it is mandatory to register every patient who signs a consent form.
Furthermore, within the Investigator Site File (ISF), a Patient Identification List will be included in order to identify patients according to local normal practice. This document will allow for immediate and unequivocal identification of patients participating in this clinical trial. This document will always be stored under Investigator staff custody at the site. The screening number will identify patients throughout the screening period while procedures needed to confirm the subjects' suitability for the trial protocol, such as clinical laboratory tests, imaging, and others are performed.

Screening determinations include obtaining informed consent, signature and registration, patient record review, clinical consultation, imaging procedures, and laboratory analyses including haematology, biochemistry, and urine tests. The screening period weeks prior to cycle 1 day 1 (28 days). Determination at screening will be performed within 7 days of cycle 1 day 1 for eligibility unless otherwise specified. Additional information about screening procedures can be found in section 9.1.1 of this protocol.

After confirming that a patient fulfills all eligibility criteria of the study (inclusion/exclusion criteria), site staff will initiate the eCRF registration procedure. Once procedure is fulfilled the site staff will receive the "Inclusion confirmation communication", and then protocol-specific treatment can be initiated.

7.1.2. Procedures for handling patients incorrectly enrolled

Patients incorrectly enrolled in the trial will be considered as protocol deviations. If the investigator considered that the patient is obtaining benefit of the investigational treatment, patients could continue therapy. They will not be considered for the primary endpoint of the trial, neither for efficacy nor biomarker secondary and exploratory analyses. Patients incorrectly enrolled that continue on treatment can be assessed for safety profile endpoint.

Subjects who are permanently discontinued from further receipt of investigational products, regardless of the reason (withdrawal of consent, due to an AE, other), will be identified as having permanently discontinued treatment.

Subjects who are permanently discontinued from receiving investigational products will attend the end of treatment visit and will be followed for safety and efficacy, including the collection of any protocol-specified blood specimens, unless consent is withdrawn or the subject is lost to follow-up or enrolled in another clinical study. Patients that end treatment due to any reason other than disease progression according to RECIST 1.1 (including patients who have switched to an alternative treatment without documented progression), will follow tumor evaluations every 8 weeks (up to week 48 after inclusion) and every 12 weeks or clinically indicated thereafter, until disease progression. Subjects who decline to return to the site for evaluations will be offered follow-up by phone every 3 months as an alternative.

7.2. TOXICITY MANAGEMENT GUIDELINES

7.2.1. Tislelizumab

The safety profile of tislelizumab is consistent with the therapeutic class of the drug with a relatively low rate of treatment-related Grade 3 or above toxicity.

Across the monotherapy studies, the safety profile was generally consistent between studies. While about approximately 96% of patients experienced a TEAE of any causality in the monotherapy setting, the frequency of treatment-related events of any grade in the solid tumor studies (N = 1992) and hematologic malignancy studies (N = 181) and 70.2% and 80.1% respectively. For treatment-related ≥ Grade 3 events, the frequency was 13.5% in the solid tumor studies and 19.3% in the hematologic malignancy studies. Immune-mediated AEs of any grade were reported in 16.3% of patients in the solid tumor studies and 28.6% of patients in the hematologic malignancy studies, while ≥ Grade 3 imAEs were reported in 4.3% and 6.1% of patients in those settings, respectively. These imAEs, however, have well-established algorithms for treatment and are therefore considered manageable.

In studies with tislelizumab combined with chemotherapy, the AE profile is consistent with the now well-established profile of an immune checkpoint inhibitor in combination with a standard chemotherapy agent. Over 77.7% of patients in these studies experienced a treatment-related TEAE, though ≥ Grade 3 events were lower (32.1%).

Generally, the safety profile is well tolerated and as expected with the safety profile of the same class agent combination. In these studies, over 60% of patients experienced a treatment-related TEAE, though ≥ Grade 3 events were lower (3.8% to 38.7%). These data should be interpreted with some caution as the sample sizes are relatively small for these ongoing studies.

7.2.1.1 Management of Identified Risks of Tislelizumab

Every effort should be made to administer the study drug(s) according to the planned dose and schedule. In the event of significant toxicities, dosing may be delayed and/or reduced based on the guidelines

below. Reasons for dose reductions or delays, the supportive measures taken, and the outcome will be documented in the patient's chart and recorded in the eCRF.

The dose modification guidelines in this section are not intended to be a substitute for clinical judgment. Investigators may delay or reduce doses for other reasons (eg, AEs or laboratory findings) as appropriate.

There will be no dose reduction for tislelizumab in this study.

Tislelizumab treatment may be temporarily suspended if the patient experiences a toxicity that is suspected to be related to tislelizumab or comparator and requires a dose to be withheld. Tislelizumab treatment should resume as soon as possible after the AEs recover to baseline or Grade 1 (whichever is more severe) as long as resolution occurs ≤ 12 weeks after the last dose of tislelizumab. If the administration of tislelizumab can resume ≤ 10 days after the originally planned administration date, it should be administered in the current cycle. If the tislelizumab dose needs to be withheld for > 10 days, it should be omitted from the current cycle and administration should continue at the start of the next cycle. If the patient is unable to resume tislelizumab ≤ 12 weeks after the last dose of tislelizumab, then the patient should be discontinued from treatment. If the patient is not able to resume tislelizumab ≤ 12 weeks after the last dose for unforeseen non-drug-related reasons, continued treatment may be allowed if approved by the medical monitor.

Tislelizumab administration may continue if Sitravatinib is delayed or discontinued.

By disrupting PD-1-mediated signaling, tislelizumab acts to restore antitumor immunity and halt progression of tumor growth. This restoration of immune system activity may result in immune-mediated adverse reactions involving 1 or more body systems, which can be life threatening or fatal in rare cases. While these events usually become manifest during treatment with tislelizumab, they can also occur after discontinuation of tislelizumab therapy.

Tislelizumab treatment should be withheld in patients with severe symptoms, and oral or intravenous corticosteroids should be administered as appropriate. Prolonged or high-dose corticosteroid therapy should be tapered. Consultation with the appropriate clinical specialists is recommended as indicated.

Specific information and treatment modifications to manage tislelizumab-related toxicities, such as imAEs and infusion-related reactions, are described in this section and APPENDIX 1.

7.2.1.2 Immune-Mediated Hepatitis

Tislelizumab can cause immune-mediated hepatic events, defined as requiring use of corticosteroids and with no clear alternative etiology. Fatal cases have been reported. Monitor patients for signs and symptoms of hepatic events, including liver enzyme monitoring; For further information please refer to APPENDIX 1.

7.2.1.3. Immune-Mediated Nephritis

Tislelizumab can cause immune-mediated nephritis events, defined as requiring use of corticosteroids and with no clear alternative etiology. Patients should be carefully monitored periodically for changes in renal

function. In the event of immune-mediated nephritis, the frequency of renal function tests should be increased.

For further information please refer to APPENDIX 1.

7.2.1.4. Immune-Mediated Pneumonitis

Tislelizumab can cause immune-mediated pneumonitis, defined as requiring the use of corticosteroids and withoutclear alternative etiology. Fatal cases have been reported. Monitor patients for signs and symptoms of pneumonitis, including diagnostic imaging as appropriate.

Table 2: Pneumonitis/ Interstitial Lung Disease (ILD) toxicity management

Pneumonitis/ Interstitial Lung Disease (ILD)	Any Grade	General Guidance	For Any Grade: – Monitor patients for signs and symptoms of pneumonitis or ILD (new onset or worsening shortness of breath or cough). Patients should be evaluated with imaging and pulmonary function tests, including other diagnostic procedures as described below. – Initial work-up may include clinical evaluation, monitoring of oxygenation via pulse oximetry (resting and exertion), laboratory work-up, and high- resolution CT scan.
	Grade 1 (asymptomatic, clinical or diagnostic observations only; intervention not indicated)	No dose modifications required. However, consider holding study drug/study regimen dose as clinically appropriate and during diagnostic work-up for other etiologies.	For Grade 1 (radiographic changes only): – Monitor and closely follow up in 2 to 4 days for clinical symptoms, pulse oximetry (resting and exertion), and laboratory work-up and then as clinically indicated. – Consider Pulmonary and Infectious Disease consults.
	Grade 2 (symptomatic; medical intervention indicated; limiting instrumental ADL)	Hold study drug/study regimen dose until Grade 2 resolution to Grade ≤1. ● If toxicity worsens, then treat it as Grade 3 or Grade 4. ● If toxicity improves to Grade ≤1, then the decision to reinitiate study drug/study regimen will be based upon treating physician's clinical judgment and after completion of steroid taper.	For Grade 2 (mild to moderate new symptoms): – Monitor symptoms daily and consider hospitalization. – Promptly start systemic steroids (e.g., prednisone 1 to 2 mg/kg/day PO or IV equivalent). – Reimage as clinically indicated. – If no improvement within 3 to 5 days, additional workup should be considered and prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day started – If still no improvement within 3 to 5 days despite IV methylprednisolone at 2 to 4 mg/kg/day, promptly start immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg every 2 weeks). Caution: It is important to rule out sepsis and refer to the infliximab label for general guidance before using infliximab. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections)[a] – Consider Pulmonary and Infectious Disease consults.

			– Consider, as necessary, discussing with the Coordinating Investigator.
	Grade 3 or 4 (Grade 3: severe symptoms; limiting self-care ADL; oxygen indicated) (Grade 4: life-threatening respiratory compromise; urgent intervention indicated [e.g., tracheostomy or intubation])	Permanently discontinue study drug/study regimen.	For Grade 3 or 4 (severe or new symptoms, new/worsening hypoxia, life-threatening): – Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent. – Obtain Pulmonary and Infectious Disease consults; consider, as necessary, discussing with the Coordinating Investigator. – Hospitalize the patient. – Supportive care (e.g., oxygen). – If no improvement within 3 to 5 days, additional workup should be considered and prompt treatment with additional immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg every 2 weeks' dose) started. Caution: rule out sepsis and refer to the infliximab label for general guidance before using infliximab. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and, in particular, anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a]

7.2.1.5. Immune-Mediated Colitis and Diarrhea

Tislelizumab can cause immune-mediated colitis and diarrhea, defined as requiring corticosteroids and with no clear alternative etiology. Monitor patients for signs and symptoms of colitis, or severe diarrhea.

Monitor patients for signs and symptoms of colitis or severe diarrhea.

For further information please refer to APPENDIX 1.

7.2.1.6. Immune-Mediated Endocrinopathies

Tislelizumab can cause immune-mediated endocrinopathies, including thyroid disorders, diabetes mellitus, adrenal insufficiency, pancreatitis and hypophysitis, which may require supportive treatment depending on the specific endocrine disorder.

Hypophysitis: Monitor patients for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency). Diabetes Mellitus: Monitor patients for hyperglycemia or other signs and symptoms of diabetes. Thyroid Disorders: Monitor patients for thyroid disorders and changes in thyroid function.

Other Immune-Mediated Endocrine Disorders: Monitor patients for the potential occurrence for other immune-mediated endocrine disorders.

For further information please refer to APPENDIX 1.

7.2.1.7. Immune-Mediated Skin Reactions

Tislelizumab can cause immune-mediated skin adverse reactions. Cases of Stevens-Johnson syndrome and toxic epidermal necrolysis have occurred in patients treated with anti-PD-1/PD-L1 antibodies. Patients should be monitored for cutaneous toxicity, including severe skin reactions (Stevens-Johnson syndrome and toxic epidermal necrolysis). Exclude alternative causes for skin lesions.

For further information please refer to APPENDIX 1.

7.2.1.8. Other Immune-Mediated Adverse Reactions

The following immune-mediated adverse reactions occurred in less than 1% of patients treated with tislelizumab: arthritis, encephalitis, Guillain-Barré syndrome, myocarditis, myositis, neuropathy, pericarditis, polymyalgia rheumatica, and rhabdomyolysis.In addition, pancreatitis and uveitis have been identified as adverse eventsAEs possibly related to tislelizumab and these may be immune-mediated.

Solid organ transplant rejection has been reported in the postmarketing setting in patients treated with PD-1 inhibitors. Treatment with tislelizumab may increase the risk of rejection in solid organ transplant recipients. The benefit of treatment with tislelizumab versus the risk of possible organ rejection should be considered in these patients.

For further information please refer to APPENDIX 1.

7.2.1.9. Infusion-Related Reactions

The symptoms of IRRs that may be observed with tislelizumab include fever, chills/rigor, nausea, pruritus, angioedema, hypotension, headache, bronchospasm, urticaria, rash, vomiting, myalgia, dizziness, or hypertension. Rarely, life-threatening reactions may occur. Therefore, patients should be closely monitored for these signs and symptoms during the infusion.

For further information please refer to APPENDIX 1.

7.2.1.10 Management of Potential Risks of Tislelizumab

7.2.1.10.1. Immune-Mediated Disorders Not Reported to Date

Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue in patients receiving tislelizumab. Immune-mediated AEs can escalate quickly; study treatment interruption, close monitoring, timely diagnostic work-up and treatment intervention, as appropriate, with patients is required.

7.2.1.11. Reproductive and Developmental Toxicity

There are no available data on the use of tislelizumab in pregnant women. Based on its mechanism of action, tislelizumab may cause fetal harm when administered to a pregnant woman. Tislelizumab has the potential to be passed from the mother to the developing fetus. Tislelizumab is a humanized IgG4-variant mAb, and IgG4 is known to cross the placental barrier. Animal reproduction studies have not been conducted with tislelizumab to evaluate its effect on reproduction and fetal development. Blockade of PD-L1 signaling has been shown in murine models of pregnancy to disrupt tolerance to the fetus and to result in an increase in fetal loss. Therefore, potential risks of administering tislelizumab during pregnancy include increased rates of abortion or stillbirth. Tislelizumab should not be used during pregnancy or in women of childbearing potential unless a highly effective method of birth control is used or the clinical condition of the woman requires treatment with tislelizumab.

Advise women of the potential risk to a fetus. Women of childbearing potential should use a highly effective method of birth control during treatment with tislelizumab and for at least 4 months after the last dose of tislelizumab.

Because of the potential for adverse reactions in breastfed children, advise women not to breastfeed during treatment with tislelizumab and for at least 4 months after the last dose.

7.2.1.12. Immunogenicity

As expected with any recombinant antibody, tislelizumab may elicit an immune response and patients may develop antibodies against tislelizumab. Appropriate validated screening and confirmatory assays were employed to detect ADAs at multiple timepoints before, during, and after treatment with tislelizumab. The immunogenicity results were evaluated with a 3-tiered approach, consisting of a screening assay, followed by a more stringent confirmatory assay, and finally various ADA characterization (titer determination and neutralizing antibodies were evaluated for confirmed positive ADA samples). The summary of immunogenicity is provided in Section 5.2.1.10 of the tislelizumab IB.

7.2.1.13. Drug Interactions

Information about clinical drug interactions with tislelizumab is not available. No dedicated drug-drug interaction studies are planned.

The potential for drug-drug interaction between the study drugs (tislelizumab), standard chemotherapy, and small-molecule drug products is very low, given that tislelizumab is a therapeutic monoclonal antibody. Tislelizumab is unlikely to affect drug-metabolizing enzymes or transporters because it is expected to be degraded into amino acids and recycled into other proteins.

Additional information is provided in section 8.2.

7.2.1.14. Treatment of Overdose

There is no specific antidote for tislelizumab. Patients who experience an overdose should be closely monitored and provided with appropriate supportive treatment.

7.2.2. Sitravatinib

Non-hematological toxicities Grade ≥3 assessed as related to sitravatinib treatment should be managed with sitravatinib interruption until resolution of toxicity severity to Grade ≤1 or baseline. In general, treatment may then be resumed at 1 or more levels below the dose level where toxicity was observed. Dose interruption and/or dose reduction for asymptomatic Grade 2 sitravatinib-related AEs is at the discretion of the investigator. However, dose reduction is recommended for symptomatic Grade 2 sitravatinib-related AEs. Similar dose interruptions and reductions should be considered for Grade ≥3 sitravatinib-related hematological toxicities that cannot be adequately managed with supportive care. The recommended dose modifications for Sitravatinib are listed on Table 3.

Table 3. Sitravatinib dose reductions.

Dose Level 1	100 mg once daily
Dose Level -1	70 mg once daily
Dose Level -2	50 mg once daily

Sitravatinib administration may continue if Tislelizumab is delayed or discontinued.

Based on reported experience with sitravatinib and similar agents, and nonclinical data with sitravatinib, guidance to the Investigator is provided for selected AEs.

7.2.2.1. Hypertension

Hypertension is reported regularly in cancer patients, with estimates approaching 40% in cancer populations *(Fraeman et al. 2013)*. Hypertension is also among the most common AEs observed in patients being administered drugs with systemic inhibition of VEGF signaling *(Kamba et al. 2007)*. Given that hypertension has been reported as a ‘suspected’ SAR more than once, several subjects who were normotensive at baseline experienced hypertension shortly after the first administration of sitravatinib, and there is corroboration with preclinical data and other VEGFR inhibitors, hypertension has been assessed as an expected SAR of sitravatinib.

Sitravatinib dose modifications for increased blood pressure are outlined in Table 4 Hypertension, including a Grade 4 event, has been reported with sitravatinib. Dihydropyridine calcium channel blockers such as nifedipine, amlodipine, and nicardipine may be considered if anti-hypertensive therapy is required and should be considered for subjects with Grade 3 hypertension without clinically significant increases in blood pressure.

In cases of Grade 3 hypertension with clinically significant increases in blood pressure, suspension of sitravatinib dosing is recommended until blood pressure is controlled (Grade ≤2 or return to baseline).

Treatment with sitravatinib may resume at the same or a lower dose at the discretion of the Investigator. If clinically significant hypertension recurs, options include change in medical management of the subject, reduction of sitravatinib dose, or discontinuation of study treatment, at the discretion of the Investigator. In the event of Grade 4 hypertension, sitravatinib should be permanently discontinued.

Table 4. Sitravatinib Dose Modification for Increased Blood Pressure

Toxicity	Treatment Interruption	Dose Reduction
Grade 1 or 2 hypertension	Investigator discretion.	
Grade 3 hypertension without clinically significant increases in BP as defined below	Investigator discretion. Consider anti-hypertensives.	
Grade 3 hypertension with clinically significant increases in BP defined as EITHER an increase of ≥30 mmHg in systolic BP to ≥180 mmHg OR increase of ≥20 mmHg in diastolic BP to ≥110 mmHg, confirmed with repeated testing after at least 5 minutes	Hold until Grade ≤2 or return to baseline	Investigator discretion.
Grade 4 hypertension	Discontinue sitravatinib.	

Abbreviations: BP = blood pressure.

7.2.2.2. Palmar-Plantar Erythrodysesthesia Syndrome

Palmar-plantar erythrodysesthesia syndrome (PPES) has been reported with sitravatinib. Signs and symptoms of PPES include redness, swelling, pain, and less commonly blisters on the palms of the hands and/or the soles of the feet. Subjects who develop PPES should be counseled on measures to mitigate the effects of PPES. Such measures include avoidance of exposure of hands and feet to hot water when washing dishes or bathing, or to other sources of heat, avoidance of activities that cause unnecessary force or friction (rubbing) on the hands or feet, avoiding contact with harsh chemicals such as cleaning products, use of tools or household items that result in pressure on the hands, such as garden tools, knives, and screwdrivers, and wearing of loose fitting, well-ventilated shoes and clothes. Treatment may include use of topical moisturizing agents, topical anesthetics, or topical anti-inflammatory medications such as corticosteroid creams. In more severe cases, dose interruption and reduction may be warranted.

7.2.2.3. Diarrhea

Diarrhea has been reported with sitravatinib treatment as with other small molecule RTK inhibitors, though the mechanism remains unclear. Subjects should be counseled that diarrhea is a possible side effect and advised to take loperamide or a similar medication as needed if diarrhea develops. Dose reduction is recommended for Grade 2 sitravatinib-related diarrhea. Diarrhea due to sitravatinib typically improves within several days if sitravatinib treatment is interrupted or dose reduced; any subjects developing dehydration or clinically significant electrolyte abnormalities should interrupt treatment, but treatment may be restarted once diarrhea is controlled.

When sitravatinib is used in combination with checkpoint inhibitors, investigators should evaluate whether diarrhea may be attributable to immune-related colitis. The presence of abdominal pain, mucus or blood in the stool or peritoneal signs should raise the index of suspicion for immune-mediated colitis, as

these features are generally not observed with diarrhea occurring with sitravatinib monotherapy. If any features of the clinical presentation, including timing of presentation, failure to improve with dose interruption, and/or laboratory or radiologic tests suggesting the presence of immune-mediated colitis, then all study medications should be withheld and treatment with immuno-suppressive therapy initiated.

7.2.2.4. Increased Transaminases

Sitravatinib dose modifications for increased transaminases are outlined in Table 5. Increased transaminases have been observed in subjects treated with sitravatinib. Most cases were asymptomatic elevations in ALT or AST, while some were associated with liver metastases or cholestasis. No cases of drug-induced liver injury meeting Hy's Law have been identified. In the setting of sitravatinib monotherapy, Grade 2 transaminase increases related to treatment should generally be managed with dose reduction in sitravatinib. For Grade ≥3 increases, dose interruption until return to baseline followed by dose reduction may be warranted. In cases of prolonged interruptions, sitravatinib should be discontinued.

Special consideration should be given to the potential for immune-mediated hepatitis in cases of combination treatment with checkpoint inhibitors. Where immune-mediated hepatitis is suspected, management should be consistent with standard treatment for immune-mediated hepatitis in consideration of the severity, and treatment with sitravatinib should also be interrupted.

Table 5: Sitravatinib Dose Modification for Increased Hepatic Transaminases

Toxicity	Treatment interruption	Dose reduction
Grade 1	May be implemented based on Investigator and subject discretion	
Grade 2	May be implemented based on Investigator and subject discretion	Decrease by 1 dose level
Grade ¾	Hold until Grade ≤1 or return to baseline	If resolution occurs within 29 days, decrease by 1 dose level. If no resolution within 29 days, discontinue sitravatinib.

7.2.2.5. Increased Amylase and Lipase

Increased amylase and lipase have been observed in subjects treated with sitravatinib. Although the mechanism has not been fully elucidated, inhibition of VEGF may lead to acinar cell apoptosis resulting in the release of autodigestive enzymes *(Sevin et al. 2012)*. Accordingly, increases in amylase and lipase, and pancreatitis have been reported with other inhibitors of the VEGF pathway. Most sitravatinib-related treatment-emergent events of increased amylase and lipase were asymptomatic while some were associated with signs and/or symptoms of pancreatitis. Treatment with sitravatinib may continue without dose modification (eg, interruption or reduction) in cases of asymptomatic amylase and/or lipase increases in the absence of other clinical evidence of pancreatitis (eg, symptoms, electrolyte abnormalities,

radiographic changes) at the investigator's discretion. Sitravatinib should be interrupted for any grade of pancreatitis and the subject managed according to standard-of-care. After resolution of pancreatitis, sitravatinib resumption is at the discretion of the investigator; if pancreatitis is assessed as sitravatinib treatment-related and treatment is resumed, a dose reduction is recommended.

Increased lipase is a serious adverse reaction (SAR) found associated with the combination of Tislelizumab and Sitravatinib.

7.2.2.6. Decreased Left Ventricular Ejection Fraction (LVEF)

Decreased left ventricular ejection fraction (LVEF) has been observed with sitravatinib. In cases where LVEF decreases by ≥20% to an LVEF <50%, the dose of sitravatinib should be interrupted and/or reduced. Permanent discontinuation should be considered for subjects requiring acute hospitalization for treatment of congestive heart failure (CHF).

7.2.2.7. Hypothyroidism

Hypothyroidism and blood thyroid stimulating hormone (TSH) increased have been observed with sitravatinib, consistent with literature reports of thyroid dysfunction with RTK inhibitors, which are typically reported as hypothyroidism that is sometimes preceded by a brief period of hyperthyroidism. Thyroid stimulating hormone should be monitored during treatment with sitravatinib. Subjects diagnosed with hypothyroidism should be treated with thyroid replacement and may continue treatment with sitravatinib. When sitravatinib is used in combination with checkpoint inhibitors, thyroid dysfunction, including thyroiditis and hypothyroidism, may be immune-mediated.

7.2.2.8. Proteinuria

Proteinuria has been observed with sitravatinib and described with other inhibitors of the VEGFR pathway. Urinalysis for urine protein should be performed prior to treatment and as clinically warranted during treatment with sitravatinib. Subjects who develop ≥2+ proteinuria should undergo 24-hour urine collection for assessment of urine protein; treatment with sitravatinib should be discontinued in the presence of ≥2 grams of proteinuria/24 hours and may be restarted when protein levels decrease to less than 2 grams/24 hours. Subjects who develop nephrotic syndrome should be withdrawn from treatment with sitravatinib.

7.2.2.9. Thrombotic Events

Arterial and venous thrombotic events have been observed with sitravatinib and described with other inhibitors of the VEGFR pathway. The majority of thrombotic events observed with sitravatinib have been venous thrombotic events. The occurrence of thrombotic events with sitravatinib is being monitored for further characterization. Precautions should be taken in subjects with recent, clinically significant thrombotic events, and treatment should be permanently discontinued in subjects who develop clinically significant thromboembolic complications.

7.2.2.10. Hemorrhagic Events

The risk of hemorrhagic events with sitravatinib has not been fully characterized; however, such events have been reported with inhibitors of VEGFR. Subjects with active hemoptysis or gastrointestinal bleeding should not take sitravatinib, and interruption of treatment is recommended for subjects developing clinically significant bleeding.

7.2.2.11 Gastrointestinal Perforation

Gastrointestinal perforation has been reported with inhibitors of VEGFR as an infrequent event (*Kamba, 2007*). The risk of gastrointestinal perforation with sitravatinib has not been fully characterized. However, such events have been reported with sitravatinib. Sitravatinib should be interrupted if gastrointestinal perforation is suspected and discontinued if confirmed.

7.2.2.12. Other Sitravatinib-Related Events

7.2.2.12.1 Pneumonitis

Pneumonitis has not been shown to occur among the common AEs observed in patients being administered sitravatinib as monotherapy; however, it is possible that sitravatinib may exacerbate or promote immune-mediated AEs when administered in combination with checkpoint inhibitors. Therefore, pneumonitis has been assessed as an expected SAR when given in combination with nivolumab, given that pneumonitis has been reported as a ‘suspected’ SAR more than once in subjects receiving sitravatinib in combination with nivolumab.

Pneumonitis (ILD) investigation

The following assessments, and additional assessments if required, will be performed to enhance the investigation and diagnosis of potential cases of pneumonitis. The results of the assessment will be collected.

- Physical examination
- Signs and symptoms (cough, shortness of breath and pyrexia, etc.) including auscultation for lung field will be assessed.
- Saturation of peripheral oxygen (SpO2)
- When pneumonitis (ILD) is suspected during study treatment, the following markers should be measured where possible:
    - ILD Markers (KL-6, SP-D) and β-D-glucan
    - Tumor markers: Particular tumor markers which are related to disease progression.
    - Additional Clinical chemistry: CRP, LDH

If new or worsening pulmonary symptoms (e.g. dyspnea) or radiological abnormality suggestive of pneumonitis/interstitial lung disease is observed, toxicity management as detailed in Table 2.The results of the full diagnostic workup (including high-resolution computed tomography (HRCT), blood and sputum culture, hematological parameters etc) will be captured in the eCRF. It is strongly recommended to perform a full diagnostic workup, to exclude alternative causes such as lymphangitic carcinomatosis, infection, allergy, cardiogenic edema, or pulmonary hemorrhage. In the presence of confirmatory HRCT

scans where other causes of respiratory symptoms have been excluded, a diagnosis of pneumonitis (ILD) should be considered and the aforementioned Dosing Modification and Toxicity Management Guidelines should be followed.

7.2.2.12.2 Nausea and Vomiting

The prevalence of nausea and vomiting in patients with advanced cancer is up to 70%, and these events result from several etiologies *(Harris 2010)*. Nausea and vomiting are also listed among the most common AEs observed in patients being administered other kinase inhibitors of VEGFR. Given that nausea and vomiting have each been reported as a 'suspected' SAR more than once, and corroboration with preclinical data and other VEGFR inhibitors exists, nausea and vomiting have been assessed as expected SARs of sitravatinib.

Other sitravatinib-related events include decreased appetite, dysphonia, fatigue and stomatitis. Management should be consistent with standard-of-care and sitravatinib dose modification as described in the protocol for each study.

7.2.2.12.3 Myocardial Infarction / Cerebrovascular Accident / Transient Ischemic Attack /Cerebral Infarction

The incidence rate of arterial thrombotic events (ATEs) in cancer subjects varies from 2% to 5% (Grover, 2021). In a cohort, population-based study of patients treated with VEGFR-targeted TKIs, ATEs occurred at a crude cumulative incidence of 4% (Vallerio, 2022). In a meta-analysis of 48 clinical studies, the use of VEGFR-TKIs was not found to significantly increase the risk of developing all-grade or high-grade VTEs but there was a significant increase in the risk of developing all-grade and high-grade ATEs, albeit with an overall low incidence of 2.7% and 0.6% respectively (Liu, 2017). Given that ATEs (myocardial infarction/cerebrovascular accident/transient ischemic attack/cerebral infarction) have been reported as 'suspected' SARs more than once, there is corroboration with other VEGFR inhibitors (Zhang, 2016), and these events are considered clinically significant, myocardial infarction/cerebrovascular accident have been assessed as expected SARs. Transient ischemic attack/cerebral infarction has been assessed as an expected SAR when given in combination with nivolumab or tislelizumab.

7.2.2.13. Evaluation of Potential for Increased Toxicities with Combination Use of Sitravatinib with Immune Checkpoint Inhibitors

Frequent AEs, such as fatigue, decreased appetite, nausea and diarrhea, which are non-specific and typical of cancer treatment regimens have been observed with checkpoint inhibitor therapies and with sitravatinib monotherapy. Potential exists for these AEs to be observed with increased severity or frequency during use of the agents in combination. Management of these effects in subjects receiving cancer therapy is well precedented.

Importantly, immune-related adverse events (irAEs) based on observed safety events using nivolumab or pembrolizumab monotherapy include pneumonitis, colitis, hepatitis, endocrinopathies, nephritis/renal dysfunction, rash/dermatitis, and encephalitis. Ipilimumab also includes rash/dermatitis. While sitravatinib may have immunostimulatory effects, significant autoimmune adverse effects have not been

recognized as class effects for this agent. The potential for sitravatinib to exacerbate or promote immune-mediated AEs when administered in combination with checkpoint inhibitors should be borne in mind.

As of 26 June 2022, a total of 1331 subjects with solid malignancies have received sitravatinib alone or in combination with the PD-1 checkpoint inhibitor nivolumab, in combination with nivolumab and ipilimumab, in combination with tislelizumab, or in combination with pembrolizumab and the ADC enfortumab vedotin-ejfv (pembro/EV). Subject numbers are estimated for ongoing studies where the study treatment is masked.

Among the 1279 subjects with solid malignancies who were treated with sitravatinib and included in the safety analysis, treatment-related irAEs, as assessed by the Investigator, have been reported for 451 subjects (35%). The most common treatment-related irAEs by preferred term reported in ≥ 2.0% subjects were hypothyroidism (129 subjects [10.1%]), diarrhea (88 [6.9%]), ALT increased (84 [6.6%]), AST increased (75 [5.9%]), fatigue (47 [3.7%]), blood thyroid stimulating hormone increased (43 [3.4%]), lipase increased (35 [2.7%]), pneumonitis (32 [2.5%]), decreased appetite (30 [2.3%]), rash (28 [2.2%]), rash maculo-papular and amylase increased (27 each [2.1%]), and pruritis (26 [2.0%]). .

7.2.2.13. Warnings, Precautions and Contraindications

Sitravatinib is contraindicated in persons with hypersensitivity to any component of the drug product. The composition of the drug product of formulations that may be used in clinical trials is described in Section 3.3 of the IB.

Sitravatinib is intended for investigational use by selected Investigators experienced in the use of anti-neoplastic agents and in conducting clinical trials with such agents in subjects with advanced malignancies.

The genotoxicity studies on sitravatinib indicate a lack of potential to induce point mutations, chromosomal aberrations, or to interact with or damage DNA, thus the risk for potential genotoxic effects is low.

7.2.2.14. Use During Pregnancy and Lactation

Based on the mechanism of action (inhibition of VEGF), effects of sitravatinib on the reproductive system are not unexpected. Sitravatinib is contraindicated in women who are pregnant or lactating. Women of childbearing potential and men receiving sitravatinib who are sexually active must employ an effective method of contraception throughout their period of treatment and for 6 months after their last treatment with sitravatinib.

8. RESTRICTIONS DURING THE STUDY AND CONCOMITANT TREATMENT(S)

8.1. RESTRICTIONS DURING THE STUDY

The following restrictions apply while the patient is receiving study treatment and for the specified times before and after:

8.1.1. Female patient of childbearing potential

- Female patients of childbearing potential who are not abstinent and intend to be sexually active with a non-sterilized male partner must use at least 1 **highly** effective method of contraception (***Table 6***) from the time of screening throughout the total duration of the drug treatment and the drug washout period (4 months after the last dose of Tislelizumab, and/or 6 months after the last dose of Sitravatinib or combination). Non-sterilised male partners of a female patient of childbearing potential must use male condom plus spermicide throughout this period. Cessation of birth control after this point should be discussed with a responsible physician. Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of birth control. Female patients should also refrain from breastfeeding throughout this period.

8.1.2. Male patients with a female partner of childbearing potential

- Non-sterilized male patients who are not abstinent and intend to be sexually active with a female partner of childbearing potential must use a male condom plus spermicide from the time of screening throughout the total duration of the drug treatment and the drug washout period of 4 months after the last dose of Tislelizumab, and/or 6 months after the last dose of Sitravatinib or combination). However, periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception. Male patients should refrain from sperm donation throughout this period.
- Female partners (of childbearing potential) of male patients must also use a highly effective method of contraception throughout this period (***Table 6***).

Females of childbearing potential are defined as those who are not surgically sterile (ie, bilateral salpingectomy, bilateral oophorectomy, or complete hysterectomy) or post-menopausal.

Women will be considered post-menopausal if they have been amenorrheic for 12 months without an alternative medical cause. The following age-specific requirements apply:

- Women <50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatments and if they have luteinizing hormone and follicle-stimulating hormone levels in the post-menopausal range for the institution.
- Women ≥50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of all exogenous hormonal treatments, had radiation-induced menopause with last menses >1 year ago, had chemotherapy-induced menopause with last menses >1 year ago.

Highly effective methods of contraception, defined as one that results in a low failure rate (ie, less than 1% per year) when used consistently and correctly are described in Table 5. Note that some contraception methods are not considered highly effective (e.g. male or female condom with or without spermicide; female cap, diaphragm, or sponge with or without spermicide; non-copper containing intrauterine device; progestogen-only oral hormonal contraceptive pills where inhibition of ovulation is not the primary mode of action (excluding Cerazette/desogestrel which is considered highly effective; and triphasic combined oral contraceptive pills).

Table 6. Highly Effective Methods of Contraception (<1% Failure Rate)

• Barrier/Intrauterine methods	• Hormonal Methods
• Copper T intrauterine device • Levonorgestrel-releasing intrauterine system (e.g., Mirena®)[a]	• Implants: Etonogestrel-releasing implants: e.g. Implanon® or Norplant® • Intravaginal: Ethinylestradiol/etonogestrel-releasing intravaginal devices: e.g. NuvaRing® • Injection: Medroxyprogesterone injection: e.g. Depo-Provera® • Combined Pill: Normal and low dose combined oral contraceptive pill • Patch: Norelgestromin/ethinylestradiol-releasing transdermal system: e.g. Ortho Evra® • Minipillc: Progesterone based oral contraceptive pill using desogestrel: Cerazette® is currently the only highly effective progesterone-based

[a] This is also considered a hormonal method

8.1.3. Blood donation

Patients should not donate blood while participating in this study, other than what is required for study procedures.

8.1.4. Effects on ability to drive and use machines

No studies to establish the effects of Sitravatinib and/or Tislelizumab on the ability to drive and use machinery have been conducted. Patients should be advised to use caution when driving or using machines if during the treatment with Sitravatinib and/or Tislelizumab they experience fatigue or any other treatment-related symptoms that may affect their ability to concentrate and react.

8.2. CONCOMITANT TREATMENT(S)

8.2.1 Tislelizumab

Information about clinical drug interactions with tislelizumab is not available. No dedicated drug-drug interaction studies are planned. The potential for drug-drug interaction between the study drugs (tislelizumab), standard chemotherapy, and small-molecule drug products is very low, given that tislelizumab is a therapeutic monoclonal antibody. Tislelizumab is unlikely to affect drug-metabolizing enzymes or transporters because it is expected to be degraded into amino acids and recycled into other proteins.

8.2.2 Sitravatinib

8.2.2.1. Effect of Sitravatinib on Cytochrome P-450 Substrates

In vitro experiments indicate that sitravatinib is a potential inhibitor of CYPs 2C8, 2C9, 2C19, 2D6, and 3A4. Medications that are sensitive substrates for CYPs 2C8, 2C9, 2C19, 2D6, or 3A4 with a narrow therapeutic index should be used with caution during treatment with sitravatinib.

8.2.2.2. Effect of Sitravatinib on Drug Transporter Substrates

Sitravatinib is an inhibitor of BCRP and P-gp transporters based on in vitro studies. Medications that are sensitive substrates for BCRP or P-gp transporters with a narrow therapeutic index should be used with caution during treatment with sitravatinib.

8.2.2.3. Effect of CYP Inhibitors or Inducers on Sitravatinib

In vitro experiments in microsomes and recombinant human P450 enzymes suggest that sitravatinib is metabolized by several cytochromes, including CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2D6, CYP2E1, and CYP3A4, with no single CYP enzyme contributed to more than 25% of the total metabolism of sitratavitib. Therefore, the risk of drug-drug interactions with inhibitors or inducers of CYP enzymes is low.

8.2.2.4. Effect of P-gp Inhibitors or Inducers on Sitravatinib

Sitravatinib is a substrate of P-gp in vitro. Inhibitors of P-gp (e.g., clarithromycin, itraconazole, propafenone, quinidine, ranolazine, ritonavir, verapamil) may increase sitravatinib exposure while inducers of P-gp (e.g., rifampin) may decrease sitravatinib exposure. Caution should therefore be used when administering sitravatinib to patients taking medications that inhibit or induce P-gp.

8.2.2.5. Medications that Prolong QTc

The risk of QTc prolongation in subjects receiving treatment with sitravatinib has not been fully characterized. Use of medications known to prolong QTc and pose risk of Torsades de Pointes should be avoided during treatment with sitravatinib.

8.2.2.6. Sitravatinib in Combination with Nivolumab or Other Monoclonal Antibodies

Sitravatinib administered in combination with nivolumab is unlikely to result in clinically relevant drug-drug interactions (DDI) based on absorption, metabolism/catabolism, or elimination. Nivolumab and other monoclonal antibodies are IV administered, whereas sitravatinib is an orally administered small molecule therapeutic; no absorption interactions are expected.

No studies on the metabolism of nivolumab have been reported in vitro or in humans. As a monoclonal antibody, nivolumab is expected to undergo catabolism (without CYP enzymes or drug transporters involvement) to peptides and amino acids in the same manner as endogenous IgG proteins without renal elimination. Therefore, sitravatinib is not expected to have any effect on the PK of nivolumab. There is no data suggesting that nivolumab has any effect on CYP enzymes and therefore it is not expected to have an effect on the PK of sitravatinib.

Like most therapeutic proteins, nivolumab is not expected to be metabolized by liver cytochrome P-450 (CYP) or other drug metabolizing enzymes and is unlikely to have an effect on CYPs or other metabolizing enzymes in terms of inhibition or induction.

8.3. Permitted concomitant medications

Table 7. Supportive Medications

Supportive medication/class of drug	Usage
Concomitant medications or treatments (e.g., acetaminophen or diphenhydramine) deemed necessary to provide adequate prophylactic or supportive care, except for those medications identified as “prohibited,” as listed above	To be administered as prescribed by the Investigator
Best supportive care (including antibiotics, nutritional support, correction of metabolic disorders, optimal symptom control, and pain management [including palliative radiotherapy to non-target lesions, etc.)	Should be used, when necessary, for all patients
Inactivated viruses, such as those in the influenza vaccine, Covid-19 vaccines	Permitted

8.4. Excluded concomitant medications

Table 8. Prohibited Concomitant Medications

Prohibited medication/class of drug	Usage

Any investigational anticancer therapy other than those under investigation in this study	Should not be given concomitantly whilst the patient is on study treatment
mAbs against PD-1, or PD-L1 other than those under investigation in this study	Should not be given concomitantly whilst the patient is on study treatment
Any concurrent chemotherapy, radiotherapy, immunotherapy, or biologic or hormonal therapy for cancer treatment other than those under investigation in this study	Should not be given concomitantly whilst the patient is on study treatment. (Concurrent use of hormones for non-cancer-related conditions [e.g., insulin for diabetes and hormone replacement therapy] is acceptable. Local treatment of isolated lesions, excluding target lesions, for palliative intent is acceptable [e.g., by local surgery or radiotherapy])
Immunosuppressive medications including, but not limited to, systemic corticosteroids at doses exceeding 10 mg/day of prednisone or equivalent, methotrexate, azathioprine, and tumor necrosis factor-α blockers	*Should not be given concomitantly, or used for premedication prior to the infusions. The following are allowed exceptions:* ● *Use of immunosuppressive medications for the management of IMP-related AEs, short-term premedication for patients receiving combination agent where the prescribing information for the agent requires the use of steroids for documented hypersensitivity reactions* ● *Use in patients with contrast allergies. In addition, use of inhaled, topical, and intranasal corticosteroids is permitted.* *A temporary period of steroids will be allowed if clinically indicated and considered to be essential for the management of* non-immunotherapy related events experienced by *the patient (e.g., chronic obstructive pulmonary disease, radiation, nausea, etc.).*
Other TKIs and/or angiogenic drugs (other than Sitravatinib)	Should not be given concomitantly. Should be used with caution in the 90 days post last dose of Tislelizumab. Increased incidences of pneumonitis (with third generation EGFR TKIs) and increased incidence of transaminase increases (with 1st generation EGFR TKIs) has been reported when Tislelizumab has been given concomitantly.

Live attenuated vaccines	Should not be given through 30 days after the last dose of IMP (including SoC)
Herbal and natural remedies which may have immune-modulating effects	Should not be given concomitantly unless agreed by the sponsor

9. STUDY PROCEDURES

9.1. SCHEDULE OF STUDY PROCEDURES

Before study entry, throughout the study, and following study drug discontinuation, various clinical and diagnostic laboratory evaluations are outlined. The purpose of obtaining these detailed measurements is to ensure adequate safety and tolerability assessments. Clinical evaluations and laboratory studies may be repeated more frequently if clinically indicated. The Schedules of Assessments during the screening and treatment period is provided following the protocol synopsis:

- Efficacy (RECIST) assessment dates are not affected by dose delays and remain as originally scheduled, as they are based on the date of enrollment (not the date of therapy).

- All other scheduled assessments must be performed relative to the start of the dosing cycle such that all laboratory procedures, etc. required for dosing should be performed within 3 days prior to dosing.

- Patients may delay dosing under certain circumstances:
  - Dosing may be delayed per Toxicity Management Guidelines, due to either an immune or a non-immune-related AE.
  - If dosing must be delayed for reasons other than treatment-related toxicity, dosing will resume as soon as feasible.

9.1.1. Screening phase

Screening procedures will be performed up to 28 days before Day 1, unless otherwise specified. All patients must first read, understand, and sign the IEC-approved ICF before any study-specific screening procedures are performed. After signing the ICF, completing all screening procedures, and being deemed eligible for entry, patients will be enrolled in the study. Procedures that are performed prior to the signing of the ICF and are considered standard of care may be used as screening assessments if they fall within the 28-day screening window.

The following procedures will be performed during the Screening Visit:

- Informed Consent
- Review of eligibility criteria
- Medical history and demographics
- Complete physical exam
- ECOG Performance Status
- Vitals signs, weight and height
- 12-lead ECG (in triplicate [2-5 minutes apart])
- ECHO/MUGA
- Fresh tumor tissue from liver biopsies

- Peripheral blood sample (serum, plasma and cryopreserved lymphocytes) at baseline, along with image tests and disease progression. For translational research and ctDNA measurements.
- Newly acquired tumor biopsy formalin fixed and embedded in paraffin (for PD-L1 status)
- Review of prior/concomitant medications
- AE/SAEs assessment
- Imaging by CT or MRI
- Clinical laboratory tests for:
    - Hematology (within 7 days of cycle 1 day 1)(see Table 9)
    - Clinical chemistry (within 7 days of cycle 1 day 1)(see Table 10)
    - TSH (free T3 or free T4 will only be measured if TSH is abnormal or if there is clinical suspicion of an AE related to the endocrine system) (within 7 days of cycle 1 day 1)
    - Coagulation (PT, PTT, INR)
    - Creatinine Clearance
    - Creatinine Kinase (CK). CK-MB will be done in case CK is increased.
    - Serum pregnancy test (for women of childbearing potential only)
    - Hepatitis serologies
    - Urinalysis (see Table 11)

9.1.2. Treatment phase

Procedures to be conducted during the treatment phase of the study are presented in the Schedule of Assessments. Screening procedures performed within 72 hours of Cycle 1 Day 1 (C1D1) do not need to be repeated on C1D1.

- Targeted physical exam
- ECOG Performance Status
- Vitals signs, weight
- 12-lead ECG (as clinically indicated)
- ECHO/MUGA (Cycle 3 day 1 and as clinically indicated)
- Concomitant medications
- AE/SAEs assessment
- Clinical laboratory tests for:
    - Hematology (see Table 9)
    - Clinical chemistry (see Table 10)
    - TSH (free T3 or free T4 will only be measured if TSH is abnormal or if there is clinical suspicion of an AE related to the endocrine system)
    - Coagulation (PT, PTT, INR)
    - Creatinine Clearance
    - Serum pregnancy test (for women of childbearing potential only)
    - Urinalysis (see Table 11)
    - CK (in each cycle) and CK-MB will be done in case CK is increased in any cycle
- Tumor evaluation (CT or MRI): q6w ± 1w for the first 48 weeks (relative to the inclusion date), and then q12w ± 1w thereafter until confirmed objective disease progression/death (whichever

comes first). The schedule of q6w ± 1 week for first 48 weeks and then q12w ±1 w thereafter MUST be followed regardless of any delays in dosing

- Fresh tumor tissue from liver biopsies: New tumor biopsy will be mandatory and performed before 3rd cycle (around day +42 or week 6).
- Peripheral blood sample (serum, plasma and cryopreserved lymphocytes) at baseline, along with image tests and disease progression. For translational research and ctDNA measurements. q6w ± 1w for the first 48 weeks (relative to the inclusion date), and then q12w ± 1w thereafter along with tumor evaluation by image, until confirmed objective disease progression/death (whichever comes first). The schedule of q6w ± 1 week for the first 48 weeks and then q12w ±1 w thereafter MUST be followed regardless of any delays in dosing.

9.1.3. End of treatment

End of treatment is defined as the last planned dosing visit. The end of treatment is considered the last visit where the decision is made to discontinue all study treatment (Tislelizumab and/or Sitravatinib, whichever is later). All required procedures may be completed within 30±7 days of the end of treatment visit.

- Targeted physical exam
- ECOG Performance Status
- Vitals signs, weight
- 12-lead ECG (as clinically indicated)
- ECHO/MUGA
- Concomitant medications
- AE/SAEs assessment
- Clinical laboratory tests for:
    - Hematology(see Table 9)
    - Clinical chemistry (see Table 10)
    - TSH (free T3 or free T4 will only be measured if TSH is abnormal or if there is clinical suspicion of an AE related to the endocrine system)
    - Coagulation (PT, PTT, INR)
    - Creatinine Clearance
    - Serum pregnancy test (for women of childbearing potential only)
    - Urinalysis (see Table 11)
    - CK. CK-MB will be done in case CK is increased
- Tumor evaluation (CT or MRI): q6w ± 1w for the first 48 weeks (relative to the inclusion date), and then q12w ± 1w thereafter until confirmed objective disease progression/death (whichever comes first). The schedule of q6w ± 1 week for the first 48 weeks and then q12w ±1 w thereafter MUST be followed regardless of any delays in dosing. Repeated tumor evaluation is not required at the end of treatment if previously performed within 30 days prior to the end of treatment visit.
- Peripheral blood sample (serum, plasma and cryopreserved lymphocytes) at baseline, along with image tests and disease progression. For translational research and ctDNA measurements.

The collection of tumor biopsies at the time of progression is optional but strongly encouraged.

9.1.4. Safety follow-up

Safety follow-up visits will be scheduled 30 days after the last study drug administration. The procedures to be performed are the same as that for EOT visit except that CT scan should not be performed at this visit, unless clinically indicated at the discretion of the PI or as per normal practice.

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, given the potential risk for delayed immune-related toxicities. The extended safety follow-up beyond 30 days after last study drug administration may be performed either via a site visit or via a telephone call with subsequent site visit requested in case any concerns noted during the telephone call.

9.1.5. Long-term follow-up

After the safety follow-up visit, all patients will be followed for survival until the end of the study regardless of further treatments, or until the sponsor ends the study.

The long-term follow up may be performed either via a site visit or via a telephone call with subsequent site visit requested in case any concerns noted during the telephone call.

9.2. DESCRIPTION OF STUDY PROCEDURES

9.2.1. Medical history and physical examination, electrocardiogram, weight, and vital signs

Findings from medical history (obtained at screening) and physical examination shall be given a baseline grade according to the procedure for AEs. Increases in severity of pre-existing conditions during the study will be considered AEs, with resolution occurring when the grade returns to the pre-study grade or below.

- **Physical examination**

Physical examinations will be performed on study days noted in the Schedule of Assessments.

A complete physical examination will be performed and will include an assessment of the following (as clinically indicated): general appearance, respiratory, cardiovascular, abdomen, skin, head and neck (including ears, eyes, nose and throat), lymph nodes, thyroid, musculoskeletal (including spine and extremities), genital/rectal, and neurological systems and at screening only, height.

- **Electrocardiograms**
    - Resting 12-lead ECGs will be recorded at screening and as clinically indicated throughout the study. ECGs should be obtained after the patient has been in a supine position for 5 minutes and recorded while the patient remains in that position.
    - In case of clinically significant ECG abnormalities, including a QTcF value >470 ms, 2 additional 12-lead ECGs should be obtained over a brief period (eg, 30 minutes) to confirm the finding.
    - Situations in which ECG results should be reported as AEs are in section 11.1.1
    - At Screening, a single ECG will be obtained on which QTcF must be <470 ms.

- In case of clinically significant ECG abnormalities, including a QTcF value >470 ms, 2 additional 12-lead ECGs should be obtained over a brief period (e.g., 30 minutes) to confirm the finding.

- **ECHO/MUGA**

Echocardiography or MUGA for LVEF Assessment to be performed at screening, and after 3 cycles of treatment, if clinically indicated afterwards, and at end of treatment.

A multigated acquisition (MUGA) scan creates video images of the lower chambers of the heart to check whether they are pumping blood properly. It shows any abnormalities in the size of the chambers (called “ventricles") and in the movement of blood through the heart. Other names for this test include cardiac blood pooling imaging, nuclear heart scan, nuclear ventriculography, and radionuclide ventriculography. MUGA scans may be useful as follow-up care to find potential long-term heart side effects, or late effects of treatment.

- **Vital signs**

Vital signs (blood pressure [BP], pulse, temperature, and respiration rate) will be evaluated according to the assessment schedules. Body weight is also recorded at each visit along with vital signs.

- **First infusion**

On the first infusion day, patients will be monitored and vital signs collected/recorded in eCRF prior to, during and after infusion of IMP as presented in the bulleted list below.

- BP and pulse will be collected from patients before, during, and after each infusion at the following times (based on a 60-minute infusion):
  - Prior to the beginning of the infusion (measured once from approximately 30 minutes before up to 0 minutes [i.e., the beginning of the infusion])
  - Approximately 30 minutes during the infusion (**halfway** through infusion)
  - At the end of the infusion (approximately 60 minutes)
- If the infusion takes longer than 60 minutes, then BP and pulse measurements should follow the principles as described above or be taken more frequently if clinically indicated. A 1-hour observation period is recommended after the first infusion of Tislelizumab.

- **Subsequent infusions**

BP, pulse and other vital signs should be measured, collected/recorded in eCRF prior to the start of the infusion. Patients should be carefully monitored and BP and other vital signs should be measured during and post infusion as per institution standard and as clinically indicated. Any clinically significant changes in vital signs should be entered onto an unscheduled vital signs CRF page.

9.2.2. Clinical laboratory tests

The following clinical laboratory tests will be performed (see the Schedule of Assessments):

- Coagulation parameters: Prothrombin time, activated partial thromboplastin time and International normalized ratio to be assessed at baseline and currently.
- Pregnancy test (female subjects of childbearing potential only)

    - Urine human chorionic gonadotropin
    - Serum beta-human chorionic gonadotropin (at screening only)
- Thyroid Stimulating Hormone
- Free T3 and free T4 only if TSH is abnormal
- CK (at baseline, each cycle and EOT visit). CK-MB will be done in case CK is increased at any time
- Other laboratory tests
    - Hepatitis B surface antigen, hepatitis C antibody
    - HIV antibody

Table 9. Hematology Laboratory Tests

Basophils	Mean corpuscular volume
Eosinophils	Monocytes
Hematocrit	Neutrophils
Hemoglobin	Platelet count
Lymphocytes	Red blood cell count
Mean corpuscular hemoglobin	Total white cell count
Mean corpuscular hemoglobin concentration	

Note: [a] Can be recorded as absolute counts or as percentages. Absolute counts will be calculated by DM if entered as percentage. Total white cell count therefore has to be provided.

Table 10. Clinical Chemistry (Serum or Plasma) Laboratory Tests

Albumin	Glucose
Alkaline phosphatase	Lactate dehydrogenase
Alanine aminotransferase	Lipase
Amylase	Magnesium

Aspartate aminotransferase	Potassium
Bicarbonate	Sodium
Calcium	Total bilirubin[a]
Chloride	Total protein
Creatinine	Urea or blood urea nitrogen, depending on local practice
Gamma glutamyltransferase[b]	Uric acid
CK. CK-MB will be done in case CK is increased (above ULN)	

Tests for ALT, AST, alkaline phosphatase, and total bilirubin must be conducted and assessed concurrently.

[a] If total bilirubin is ≥2 × upper limit of normal (and no evidence of Gilbert's syndrome) then fractionate into direct and indirect bilirubin.

[b] It is preferable that both amylase and lipase parameters are assessed. For sites where only 1 of these parameters is routinely measured then either lipase or amylase is acceptable.

[c] Bicarbonate (where available), chloride, creatinine clearance, gamma glutamyltransferase, and magnesium testing are to be performed at baseline, on Day 0 (unless all screening laboratory clinical chemistry assessments are performed within 3 days prior to Day 0), and if clinically indicated.

[d] Creatinine Clearance will be calculated by data management using Cockcroft-Gault (using actual body weight).

[e] If TSH is measured within 14 days prior to Day 1 (first infusion day), it does not need to be repeated at day Free T3 or free T4 will only be measured if TSH is abnormal or if there is a clinical suspicion of an AE related to the endocrine system

Table 11. Urinalysis Tests[a]

Bilirubin	pH
Blood	Protein
Glucose	Specific gravity
Ketones	Colour and appearance

[a] Microscopy should be used as appropriate to investigate white blood cells and use the high-power field for red blood cells

If a patient shows an AST or ALT ≥3 x ULN together with total bilirubin ≥2 x ULN, refer to section 11.3.11.2 for further instructions on cases of increases in liver biochemistry and evaluation of Hy's Law. These cases should be reported as SAEs if, after evaluation, they meet the criteria for a Hy's law case or if any of the individual liver test parameters fulfill any of the SAE criteria.

All patients should have further chemistry profiles performed at 30 days (±3 days), 2 months (±1 week) and 3 months (±1 week) after permanent discontinuation of IMP.

Any clinically significant abnormal laboratory values should be repeated as clinically indicated and recorded on the eCRF. Situations in which laboratory safety results should be reported as AEs are described in Section 11.3.5.

All patients with Grade 3 or 4 laboratory values at the time of completion or discontinuation from IMP must have further tests performed until the laboratory values have returned to Grade 1 or 2, unless these values are not likely to improve because of the underlying disease.

9.3. BIOLOGICAL SAMPLING PROCEDURES

9.3.1. Biomarker/pharmacodynamic sampling and evaluation methods

9.3.1.1. Peripheral blood

Information about peripheral blood studies will be included in the informed consent form (ICF).

Blood samples for biomarker analysis will be acquired at baseline and every q6w ± 1w for the first 48 weeks (relative to the inclusion date), and then q12w ± 1w thereafter along with tumor evaluation by image, until confirmed objective disease progression/death (whichever comes first). The schedule of q6w ± 1 week for the first 48 weeks and then q12w ±1 w thereafter MUST be followed regardless of any delays in dosing.

9.3.1.2. Blood Samples

Every peripheral blood sample extraction for translational studies will consist of 2 whole blood tubes for peripheral blood mononuclear cells (PBMCs) isolation, 2 plasma tubes and 1 serum tube. A manual with the detailed procedures of extraction and manipulation of samples will be sent to each site. Plasma and serum tubes will be kept at -80ºC and shipped to the Translational Research Laboratory 1 at the Institut Català d'Oncologia (ICO) periodically. Whole blood for PBMCs will be frozen using FBS and DMSO, if this procedure is not available at the site, samples will be sent to the central laboratory in less than 24 hours.

9.3.1.3. Fresh tumor biopsies

Liver biopsies to be collected mandatory on baseline, before 3rd cycle (week 6 or day 42) and optionally but strongly encouraged, at disease progression.

Three core biopsies are to be collected at each timepoint:

- 1 core biopsy should be processed to FFPE in a single block
- 1 core biopsy for obtaining RNA / DNA for Whole exome sequencing and RNA-sequencing

Additional information regarding biological samples collection and management for biomarkers are detailed in the corresponding laboratory manual.

9.3.2. Estimate of volume of blood to be collected

The total volume of blood that will be drawn from each patient in this study is as follows:

Table 12. Volume of Blood to be Drawn From Each Patient

Assessment		Sample volume (mL)	No. of samples	Total volume (mL)
Safety	Clinical chemistry	Local practice	Local practice	Local practice
	Hematology	Local practice	Local practice	Local practice
	Biomarker	45	12	180
Total				

9.3.3. Fresh tumor biopsies

To study spatial cell populations within the tumor we plan to perform Image Mass Cytometry.

A fresh liver biopsy sample will be required from every patient in the study entry before combination therapy. A fragment of tumor tissue of at least 1 g of weight will be frozen immediately using an optimal cutting temperature (OCT) compound, tubes will be kept at -80ºC and shipped to the central laboratory at the Institut Català d'Oncologia (ICO) periodically.

Additionally before D1C3 (on day +42 after initiating study treatment) and at PD (optional but strongly encouraged) a new liver metastasis fresh biopsy will be obtained and frozen and kept at -80ºC. Details for the processing, labelling and shipping of the samples will be given to each site in a manual.

Deep-frozen tissue will be processed according to standard laboratory procedures to isolate DNA and RNA.

9.3.4. Labelling and shipment of samples

The samples and data from this research will be coded and not labeled with any personal details. Each sample will be identified with the study and patient enrollment number. In this way biomarker data may be correlated with clinical data, samples destroyed in the event of withdrawal of consent and regulatory audit enabled.

However, only the investigator will be able to link the biomarker sample to the individual patient. The coded samples may be made available to organizations working with the Sponsor on this research. However, the samples and any results will remain the responsibility of the Sponsor at all times.

The Principal Investigator ensures that samples are labeled and shipped in accordance with the Laboratory Manual, provided in the ISF.

9.3.5. Sample disposition after study

The use of biological samples will be carried out for research purposes, following the Spanish Law 14/2007 of July 3rd, on biomedical research and the Royal Decree 1716/2011 of November 18th, which establishes the basic requirements for authorization and operation of biobanks for biomedical research purposes and the treatment of human biological samples, and regulates the functioning and organization of the National Register of Biobanks for Biomedical Research.

A full chain of custody is maintained for all samples throughout their life cycle, at each Centre, the Principal Investigator keeps full traceability of collected biological samples from the patients while in storage at the Centre until shipment or disposal (where appropriate) and keeps documentation of receipt of arrival.

The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment and keeps documentation of receipt of arrival.

The Sponsor keeps oversight of the entire life cycle through internal procedures, monitoring of study sites and auditing of external laboratory providers.

Samples retained for further use will be stored in the sample collection of ICO L'Hospitalet Translational Research during the entire study life cycle.

9.3.6. Withdrawal of informed consent for donated biological samples

If a patient withdraws consent to the use of donated samples, the samples will be disposed of/destroyed, and the action documented. As collection of the biological samples is an integral part of the study, then the patient is withdrawn from further study participation.

The Principal Investigator:

- Ensures that biological samples from that patient, if stored at the study site, are immediately identified, disposed of /destroyed, and the action documented.
- Ensures the laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed/destroyed, the action documented and the signed document returned to the study site.
- Ensures that the patient is informed about the sample disposal.

10. DISEASE EVALUATION AND METHODS

The response to immunotherapy may differ from the typical responses observed with cytotoxic chemotherapy including the following *(Wolchok et al. 2009, Nishino et al. 2013)*:

- Response to immunotherapy may be delayed
- Response to immunotherapy may occur after PD by conventional criteria
- The appearance of new lesions may not represent PD with immunotherapy
- SD while on immunotherapy may be durable and represent clinical benefit.

Based on the above-described unique response to immunotherapy and based on guidelines from regulatory agencies, e.g., European Medicines Agency's "Guideline on the evaluation of anticancer medicinal products in man" (EMA/CHMP/205/95/Rev.4) for immune modulating anticancer compounds, the study may wish to implement the following in addition to standard RECIST 1.1 criteria:

- RECIST will be modified so that PD must be confirmed at the next scheduled visit, preferably, and no earlier than 4 weeks after the initial assessment of PD in the absence of clinically significant deterioration. Treatment with Tislelizumab and/or Sitravatinib would continue between the initial assessment of progression and confirmation for progression.
- In addition, patients may continue to receive Tislelizumab and/or Sitravatinib beyond confirmed PD in the absence of clinically significant deterioration and if investigators consider that patients continue to receive benefit from treatment.

Modification of RECIST as described may discourage the early discontinuation of Tislelizumab and/or Sitravatinib and provide a more complete evaluation of its antitumor activity than would be seen with conventional response criteria. Nonetheless, the efficacy analysis will be conducted by programmatically deriving each efficacy endpoint based on RECIST 1.1 criteria.

Of note, clinically significant deterioration is considered to be a rapid tumor progression that necessitates treatment with anticancer therapy other than Tislelizumab and/or Sitravatinib or with symptomatic progression that requires urgent medical intervention (e.g., central nervous system metastasis, respiratory failure due to tumor compression, spinal cord compression).

10.1. PRIMARY EFFICACY VARIABLE

Objective Response rate (ORR) according to RECIST 1.1 criteria.

ORR is defined as the proportion of patients with at least one visit response of CR or PR that is confirmed at least 4 weeks later.

Where PR is at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters as long as criteria for PD are not met and CR is the disappearance of all target lesions. Any pathological lymph nodes selected as target lesions must have a reduction in the short axis to <10mm.

Following RECIST 1.1 criteria, for non-randomized trials where response is the primary endpoint, confirmation of PR and CR is required to ensure responses identified are not the result of measurement error. ORR defined in this manner is a direct measure of drug antitumor activity, which can be evaluated in a single-arm study, providing an accurate assessment of a surrogate efficacy endpoint.

Tumor evaluation (CT or MRI) will be performed every 6w ± 1w for the first 48 weeks (relative to the inclusion date), and then q12w ± 1w thereafter until confirmed objective disease progression/death (whichever comes first). The schedule of q6w ± 1 week for the first 48 weeks and then q12w ±1 w thereafter MUST be followed regardless of any delays in dosing.

RECIST assessments will be performed on images from CT or MRI of, each preferably with IV contrast of the chest, abdomen (including liver and adrenal glands) and pelvis (when applicable). Additional anatomy should be imaged based on signs and symptoms of individual patients at baseline and follow-up. Baseline assessments should be performed no more than 28 days before the date of inclusion and, ideally, should be performed as close as possible to and prior to the start of IMPs. Confirmation of CR and PR response is required, for that reason, criteria must be met again 4 weeks after initial documentation of response. Additionally, confirmatory scans for PD should be performed preferably at the next scheduled imaging visit and no less than 4 weeks after the prior assessment of PD (in the absence of clinically significant deterioration). If an unscheduled assessment was performed and the patient has not progressed, every attempt should be made to perform the subsequent assessments at their next scheduled visit.

10.2. SECONDARY EFFICACY VARIABLES

1. *Progression Free Survival (PFS) according to RECIST 1.1 criteria.*

For this protocol, PFS is defined as the time from the first dose of study treatment until objective tumor progression or death according to the following procedure.

Confirmation of progression guidelines are set for the following reasons:

- for patient management and treatment decisions
- in the absence of significant clinical deterioration, to promote the collection of additional scans after the first radiologic RECIST 1.1 assessment of progressive disease (PD) in order to distinguish pseudoprogression from true radiologic progression, also known as RECIST 1.1 modified for confirmation of progression
- when scans are evaluated by Investigator and by BICR, to reduce informative censoring by Investigator assessments (Investigator assesses PD at a time-point earlier than does BICR).

Confirmed objective disease progression refers to either of the following scenarios: 1. Clinical progression/deterioration followed by a radiologic verification scan (PD by RECIST 1.1); or 2. In the absence of significant clinical deterioration, radiologic PD by RECIST 1.1 followed by a second radiologic confirmation scan with PD assessed according to the specific confirmation of progression criteria listed below. RECIST 1.1 modified for confirmation of progression refers to the second scenario above. The confirmatory scan should occur preferably at the next scheduled imaging visit and no earlier than 4 weeks following the date of the immediate prior assessment of RECIST 1.1 PD.

Immediate prior radiologic progression would be considered confirmed if any the following criteria are met in the confirmatory scan:

- ≥20% increase in the sum diameters of target lesions (TLs) compared with the nadir at 2 consecutive visits, with an absolute increase of at least 5 mm in sum of diameters compared to nadir,
- and/or significant progression (worsening) of non-target lesions (NTLs) and/or of pre-existing new lesions at the confirmatory scan time-point compared with the immediate prior time-point (Note: Pre-existing new lesions are evaluated as NTLs at the confirmatory scan time-point),
- and/or additional new unequivocal lesions at the confirmatory scan time-point.

NOTE: In order to have confirmed objective disease progression, there should be two consecutive assessments meeting the PD definition: the first PD by RECIST 1.1 and the second PD using the confirmation of progression criteria (above). If the first assessment fulfilling the PD definition by RECIST 1.1 is not confirmed, continue with assessments until the next PD by RECIST 1.1, which in turn will need its own immediate subsequent confirmation scan. In the absence of significant clinical deterioration, treatment with study drugs may continue between the initial assessment of progression and the scan to confirm progression.

If the confirmation scan confirms progression, then the date of the prior scan with PD should be declared as the date of progression.

If progression is not confirmed, in the absence of significant clinical deterioration, then the patient should continue study drug and on-treatment assessments until the next PD which will also require a follow-up confirmation scan. **If the first PD is not confirmed by the immediate next scan, then the Investigator should not change the PD assessment of the first scan.**

If a patient discontinued treatment (and/or receives a subsequent anticancer therapy) prior to radiologic progression, then the patient should still continue to be followed until confirmed objective disease progression. Those patients that do not present a progression or death event or are lost to follow up will be censored at the date of the last tumor imaging evaluation.

2. *Overall Survival (OS).*

Overall Survival is defined as the time from the first dose of study treatment until death from any cause. 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.

11. ASSESSMENT OF SAFETY

The Principal Investigator is responsible for ensuring that all staff involved in the study is familiar with the content of this section.

11.1. SAFETY PARAMETERS

11.1.1. Definition of adverse events

The International Conference on Harmonization (ICH) Guideline for Good Clinical Practice (GCP) E6 defines an AE as:

Any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product or to study assessments, whether or not considered related to the medicinal product.

An AE includes but is not limited to any clinically significant worsening of a patient's pre-existing condition. An abnormal laboratory finding (including ECG finding) that requires an action or intervention by the investigator, or a finding judged by the investigator to represent a change beyond the range of normal physiologic fluctuation, should be reported as an AE.

Adverse events may be treatment emergent (i.e., occurring after initial receipt of investigational product) or non-treatment emergent. A non-treatment-emergent AE is any new sign or symptom, disease, or other untoward medical event that begins after written informed consent has been obtained but before the patient has received an investigational product. Mitigation measures and management of potential adverse events related to study assessments (venipuncture, biopsies, or image determinations) will be performed according to Sites local practice.

Elective treatment or surgery or pre-planned treatment or surgery (that was scheduled prior to the patient being enrolled into the study) for a documented pre-existing condition that did not worsen from baseline, is not considered an AE (serious or non-serious). An untoward medical event occurring during the pre-scheduled elective procedure or routinely scheduled treatment should be recorded as an AE or SAE.

The term AE is used to include both serious and non-serious AEs.

11.1.2. Definition of serious adverse events

A serious adverse event is an AE occurring during any study phase (i.e., screening, run-in, treatment, wash-out, follow-up), at any dose of the study drugs that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity

- Is a congenital abnormality or birth defect in offspring of the patient
- Is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above.

Medical or scientific judgment should be exercised in deciding whether expedited reporting is appropriate in this situation. Examples of medically important events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalizations; or development of drug dependency or drug abuse.

The causality of SAEs (their relationship to all study treatment/procedures) will be assessed by the investigator(s) and communicated to Mirati and BeiGene.

11.2. ASSESSMENT OF SAFETY PARAMETERS

The safety objective of this trial is to characterize the safety and tolerability of Tislelizumab in combination with Sitravatinib in subjects with mUM. The safety analysis will be based on subjects who experienced toxicities as defined by CTCAE, v5.0 the attribution to drug, time-of-onset from the first dose and last dose, duration of the event, its outcome, and any concomitant medications administered will be recorded. AEs will be analyzed including but not limited to all AEs, SAEs, fatal AEs, and laboratory changes.

11.2.1. Assessment of severity

Assessment of severity is one of the responsibilities of the investigator in the evaluation of AEs and SAEs. Severity will be graded according to the NCI CTCAE v5.0.
The determination of severity for all other events not listed in the CTCAE should be made by the investigator based upon medical judgment and the severity categories of Grade 1 to 5 as defined below.

Grade 1 (mild)	An event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
Grade 2 (moderate)	An event that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the patient.
Grade 3 (severe)	An event that requires intensive therapeutic intervention. The event interrupts usual activities of daily living, or significantly affects the clinical status of the patient.
Grade 4 (life-threatening)	An event, and/or its immediate sequelae, that is associated with an imminent risk of death or with physical or mental disabilities that affect or limit the ability of the patient to perform activities of daily living (eating, ambulation, toileting, etc).

Grade 5 (fatal)	Death (loss of life) as a result of an event.

It is important to distinguish between serious criteria and severity of an AE. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 11.1.2. A Grade 3 AE need not necessarily be considered an SAE. For example, a Grade 3 headache that persists for several hours may not meet the regulatory definition of an SAE and would be considered a non-serious event, whereas a Grade 2 seizure resulting in a hospital admission would be considered an SAE.

11.3. RECORDING OF ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

AEs and SAEs will be collected from the time of the patient signing the informed consent form until the follow-up period is completed (90 days after the last dose of Sitravatinib and 150 days after the last dose of Tislelizumab). If an event that starts post the defined safety follow up period noted above is considered to be due to a late onset toxicity to study drug then it should be reported as an AE or SAE as applicable.

During the course of the study, all AEs and SAEs should be proactively followed up for each patient for as long as the event is ongoing. Every effort should be made to obtain a resolution for all events, even if the events continue after the patient has discontinued study drugs or the study has completed.

Any AEs that are unresolved at the patient's last visit in the study are followed up by the Investigator for as long as medically indicated, but without further recording in the eCRF. Mirati and Beigene retain the right to request additional information for any patient with ongoing AE(s)/SAE(s) at the end of the study, if deemed necessary.

The following variables will be collected for each AE:

- AE (verbatim)
- The date when the AE started and stopped
- The maximum CTCAE grade reported
- Changes in CTCAE grade
- Whether the AE is serious or not
- Investigator causality rating against the IMPs (yes or no)
- IMPs batch number
- Action taken with regard to IMPs
- Administration of treatment for the AE
- Outcome

In addition, the following variables will be collected for SAEs:

- Date the AE met criteria for SAE
- Date the Investigator became aware of the SAE
- Seriousness criteria fulfilled
- Date of hospitalization
- Date of discharge

- Probable cause of death
- Date of death
- Whether an autopsy was performed
- Causality assessment in relation to study procedure(s)
- Causality assessment in relation to other medication, as explained in Section 11.3.2
- Description of the SAE

The grading scales found in the NCI CTCAE version 5.0 will be utilized for all events with an assigned CTCAE grading. For those events without assigned CTCAE grades, the recommendation in the CTCAE criteria that converts mild, moderate, and severe events into CTCAE grades should be used. A copy of the CTCAE version 5.0 can be downloaded from the Cancer Therapy Evaluation Program website (http://ctep.cancer.gov).

Events, which are unequivocally due to disease progression, should not be reported as an AE during the study.

11.3.1. Study recording period and follow-up for adverse events and serious adverse events

Adverse events and serious adverse events will be recorded from time of signature of informed consent, throughout the treatment period and including the follow-up period (90 days after the last dose of Sitravatinib and 150 days after the last dose of Tislelizumab).

During the course of the study all AEs and SAEs should be proactively followed up for each patient. Every effort should be made to obtain a resolution for all events, even if the events continue after discontinuation/study completion.

If a patient discontinues from treatment for reasons other than disease progression, and therefore continues to have tumor assessments, drug or procedure-related SAEs must be captured until the patient is considered to have confirmed PD and will have no further tumor assessments.

The investigator is responsible for following all SAEs until resolution, until the patient returns to baseline status, or until the condition has stabilized with the expectation that it will remain chronic, even if this extends beyond study participation.

11.3.2. Causality collection

Relationship of adverse events with study drugs will be assessed by investigators based on the toxicity profile described for each study drug (see investigator brochure) and medical judgment. The Investigator's assessment of causality must be provided for all AEs (serious and non-serious); the Investigator must record the causal relationship in the eCRF, as appropriate, and report such an assessment in accordance with the serious adverse reporting requirements if applicable.

The Investigator will assess the causal relationship between the IMPs and each AE and answer “yes” or “no” to the question “Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?”

For SAEs causal relationships will also be assessed for other medication and study procedures (see section 11.3.3). Note that for SAEs that could be associated with any study procedure, the causal relationship is implied as “yes” (see section 11.3.3).

If the Investigator does not know whether or not the study treatment caused the event, then the event will be handled as “related to study treatment” for reporting purposes.
If the Investigator's causality assessment is “unknown but not related to study treatment”, this should be clearly documented on study records.

11.3.3. Relationship to protocol procedures

The Investigator is also required to provide an assessment of the relationship of SAEs to protocol procedures on the SAE report form. This includes both non-treatment–emergent (i.e., SAEs that occur prior to the administration of IMP) and treatment-emergent SAEs. A protocol-related SAE may occur as a result of a procedure or intervention required during the study (e.g., blood collection). The following guidelines should be used by Investigators to assess the relationship of SAEs to the protocol:

- **Protocol related:** The event occurred due to a procedure or intervention that was described in the protocol for which there is no alternative etiology present in the patient’s medical record.
- **Not protocol related:** The event is related to an etiology other than the procedure or intervention that was described in the protocol. The alternative etiology must be documented in the study patient’s medical record.

11.3.4. Adverse events based on signs and symptoms

All AEs spontaneously reported by the patient or reported in response to the open question from the study personnel: “Have you had any health problems since the previous visit/you were last asked?” or revealed by observation will be collected and recorded in the eCRF. When collecting AEs, the recording of diagnoses is preferred, when possible, to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

11.3.5. Adverse events based on examinations and tests

The results from protocol-mandated laboratory tests and vital signs measurements will be summarized in the patient records. Deterioration as compared to baseline in protocol-mandated laboratory values and vital signs should therefore only be reported as AEs if they fulfill any of the SAE criteria or are the reason for discontinuation of treatment with the IMPs.

If deterioration in a laboratory value or vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result or vital sign will be considered as additional information. Whenever possible, the reporting Investigator should use the clinical rather than

the laboratory term (e.g., anemia versus low hemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AEs.

Deterioration of a laboratory value that is unequivocally due to disease progression should not be reported as an AE/SAE.

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE.

11.3.6. Hy's Law

Cases where a patient shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT ≥3 × ULN together with total bilirubin ≥2 × ULN may need to be reported as SAEs. Please contact Coordinating Investigator [redacted]) for further instruction on cases of increases in liver biochemistry and evaluation of Hy's law.

11.3.7. Disease progression

Disease progression can be considered as a worsening of a patient's condition attributable to the disease for which the IMP is being studied. It may be an increase in the severity of the disease under study and/or increases in the symptoms of the disease. The development of new or progression of existing metastasis to the primary cancer under study should be considered as disease progression and not an AE. Events that are unequivocally due to disease progression should not be reported as an AE during the study.

11.3.8. New cancers

The development of a new cancer should be regarded as an SAE. New primary cancers are those that are not the primary reason for the administration of the IMP and have been identified after the patient's inclusion in this study.

11.3.9. Deaths

All deaths that occur during the study treatment period, or within the protocol-defined (whichever occurs the later, 90 days after the last dose of Sitravatinib and 150 days after the last dose of Tislelizumab) safety follow-up period after the administration of the last dose of study drug, must be reported as follows:

- Death clearly resulting from disease progression should be reported to the Study Monitor/Physician at the next monitoring visit and should be documented in the eCRF in the Statement of Death page. It should not be reported as an SAE.
- Where death is not due (or not clearly due) to progression of the disease under study, the AE causing the death must be reported to the appropriate CRO representative as a SAE within 24 hours (see Section 11.3.10 for further details). It should also be documented in the Statement of Death page in the eCRF. The report should contain a comment regarding the co involvement of PD, if appropriate, and should assign main and contributory causes of death.
- Deaths with an unknown cause should always be reported as an SAE. It should also be documented in the Statement of Death page in the eCRF. A post mortem may be helpful in the assessment of the

cause of death, and if performed, a copy of the post-mortem results should be available for the sponsor or its representative within the usual timeframes.

Deaths that occur following the protocol-defined 90 days after the last dose of Sitravatinib and 150 days after the last dose of Tislelizumab (whichever occurs later) safety follow-up period will be documented in the eCRF, but will not be reported as an SAE. However, if an investigator learns of any SAEs, including death, at any time after the patient has been permanently withdrawn from study, and he/she considers there is a reasonable possibility that the event is related to study treatment, the investigator should notify the Study Sponsor as a SAE.

Mirati/BeiGene retain the right to request additional information through the Sponsor for any patient with ongoing AE(s)/SAE(s) at the end of the study, if deemed necessary.

11.3.10. Follow-up of unresolved adverse events

Any AEs that are unresolved at the patient's last visit in the study are followed up by the investigator for as long as medically indicated, but without further recording in the eCRF. After 90 days after the last dose of Sitravatinib and 150 days after the last dose of Tislelizumab (whichever occurs later), only patients with ongoing investigational product-related SAEs will continue to be followed for safety.

11.3.11. Post-study events

After the patient has been permanently withdrawn from the study, there is no obligation for the investigator to actively report information on new AE or SAEs occurring in former study patients after the 90 days after the last dose of Sitravatinib and 150 days after the last dose of Tislelizumab (whichever occurs later). However, if an investigator learns of any SAEs, including death, at any time after the patient has been permanently withdrawn from study, and he/she considers there is a reasonable possibility that the event is related to study treatment, the investigator should notify the study sponsor who will inform Mirati/BeiGene.

11.3.12. Reporting of serious adverse events

All SAEs will be reported, whether or not considered causally related to the investigational product, or to the study procedure(s). The reporting period for SAEs is the period immediately following the time that written informed consent is obtained through 90 days after the last dose of Sitravatinib and 150 days after the last dose of Tislelizumab (whichever occurs later) or until the initiation of alternative anticancer therapy. The Sponsor representative is responsible for reporting to the Regulatory Authorities of the SAE as per local requirements. A copy of the report must be sent by email to Mirati/BeiGene at the time the event is reported to the Competent Authorities. It is the responsibility of the investigator to compile all necessary information. It is the responsibility of the Sponsor to ensure that the Competent Authorities receive a report according to the regulatory agencies and competent authorities reporting requirement timelines and to ensure that these reports are also submitted to Mirati and Beigene at the same time.

***** A ***cover page*** should accompany report indicating the following:

- "Notification from an Investigator Sponsored Study"
- The investigator IND number assigned by the regulatory agencies and competent authorities
- The Sponsor name and address
- The trial name/title
- BeiGene ISR #: ISR-CL-BGBA317-NonBGNE-0052
- Mirati ISR #: 516-ISR-005

***** Sponsor must also indicate, either in the SAE report or the cover page, the ***causality*** of events ***in relation to all study medications*** and if the SAE is ***related to disease progression***, as determined by the principal investigator.

Site staff should send SAE report and accompanying cover page by fax or email to sponsor/CRO's designated mailbox:

DEPARTAMENTO DE INVESTIGACIÓN
MFAR Clinical Research
[redacted]

**** A CRO representative will send a SAE report, the CIOMS report from Eudravigilance and accompanying cover page to*** Mirati/BeiGene according to the procedure agreed with each of the Lab. If a non-serious AE becomes serious, this and other relevant follow-up information must also be provided to Mirati/BeiGene.

11.3.12.1. Expedited Reporting to Health Authorities, Investigators, Institutional Review Boards, and Independent Ethics Committees

The Investigator Sponsor will promptly assess all SAEs against cumulative study drug experience to identify and expeditiously communicate new safety findings to regulatory authorities, investigators, IRBs, and IECs based on applicable legislation.

To determine the reporting requirements for individual SAEs, the Investigator Sponsor will assess the expectedness of the SAEs using the following reference safety information (RSI) documents:

- Tislelizumab Investigator's Brochure
- Sitravatinib Investigator's Brochure

11.3.12.2. Investigator Sponsor Reporting Responsibilities to BeiGene (Tislelizumab) and Mirati (Sitravatinib)

Investigator Sponsor will report all Serious Adverse Events (as defined in the Protocol) to the applicable regulatory authorities and the appropriate ethics committee as required by the Protocol and applicable law and/or regulation within the requisite applicable timeframes. Investigator Sponsor will conduct follow-up activities with respect to Adverse Events as required by the Protocol and applicable law and/or regulation. Investigator Sponsor will report Serious Adverse Events (as such term is defined in the Protocol)

requiring expedited reporting to applicable regulatory authorities via an CIOMS I report form or other locally required form, as applicable, and concurrently provide a copy of such report to Mirati and BeiGene.

For expedited reports, Investigator Sponsor will send the report to Mirati and BeiGene no later than seven (7) days for initial or follow-up life-threatening and death reports, and fifteen (15) days for all other initial or follow-up serious and unexpected suspected adverse reactions (SUSARs), from the time of receipt of the SAE by Investigator.

For non-expedited SAE reports (i.e., unrelated to Study Drug or listed/expected event), Investigator Sponsor will send a quarterly line listing to Mirati and BeiGene within 10 days after the start of each quarter (e.g., April 10th for Quarter 1 data due each year).

11.3.13. Other events requiring reporting

11.3.13.1. Overdose

Use of Tislelizumab or Sitravatinib in doses in excess of that specified in the protocol is considered to be an overdose. There is currently no specific treatment in the event of overdose of Tislelizumab or Sitravatinib, and possible symptoms of overdose are not established.

- An overdose with associated AEs will be recorded as the AE diagnosis or symptoms in the relevant AE modules of the eCRF.
- An overdose without associated symptoms will only be reported in the eCRF.

If an overdose occurs in the course of the study, then the Investigator or other site personnel will inform appropriate CRO representatives immediately, or **no later than 24 hours** of when he or she becomes aware of it.

The designated sponsor representative will work with the Investigator to ensure that all relevant information is provided to Mirati/BeiGene.

For overdoses associated with an SAE, the standard reporting timelines apply, see Section 11.3.10. For other overdoses, reporting must occur within 30 days.

11.3.13.2. Hepatic function abnormality

Hepatic function abnormality that fulfills the biochemical criteria of a potential Hy's Law case in a study patient, with or without associated clinical manifestations, is required to be reported as "hepatic function abnormal" ***within 24 hours of knowledge of the event*** to the sponsor who will inform Mirati and Beigene Patient Safety using the designated Safety e-mailbox (see Section 11.3.10 for contact information), unless a definitive underlying diagnosis for the abnormality (e.g., cholelithiasis or bile duct obstruction) that is unrelated to investigational product has been confirmed. The criteria for a potential Hy's Law case is Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) ≥3x Upper Limit of Normal (ULN) together with Total Bilirubin (TBL) ≥2xULN at any point during the study following the start of study medication irrespective of an increase in Alkaline Phosphatase (ALP).

- If the definitive underlying diagnosis for the abnormality has been established and is unrelated to the investigational product, the decision to continue dosing of the study patient will be based on the clinical judgment of the investigator.

- If no definitive underlying diagnosis for the abnormality is established, dosing of the study patient must be interrupted immediately. Follow-up investigations and inquiries must be initiated by the investigational site without delay.

Each reported event of hepatic function abnormality will be followed by the investigator and evaluated by the sponsor and Mirati/BeiGene.

11.3.13.3. Pregnancy

a) Maternal exposure

If a patient becomes pregnant during the course of the study, the IMPs should be discontinued immediately.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the IMP under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities or birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) should be followed up and documented even if the patient was discontinued from the study.

If any pregnancy occurs in the course of the study, then the Investigator or other site personnel should inform the appropriate Sponsor representatives within 1 day, i.e., immediately, but **no later than 24 hours** of when he or she becomes aware of it.

The designated Sponsor representative will work with the Investigator to ensure that all relevant information is completed within 1 to 5 calendar days for SAEs and within 30 days for all other pregnancies. The same timelines apply when outcome information is available.

b) Paternal exposure

Male patients should refrain from fathering a child or donating sperm during the study and 90 days after the last dose of Sitravatinib and 150 days after the last dose of Tislelizumab (whichever occurs later).

Pregnancy of the patient’s partner is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) occurring from the date of the first dose until 90 days after the last dose of Sitravatinib and 150 days after the last dose of Tislelizumab (whichever occurs later).

When a report of pregnancy is received, prior to obtaining information about the pregnancy, the Investigator must obtain the consent of the patient’s partner. Therefore, the local study team should adopt

the generic ICF template in line with local procedures and submit it to the relevant Ethics Committees (ECs)/Institutional Review Boards (IRBs) prior to use.

11.3.14. Medication error

For the purposes of this clinical study a medication error is an unintended failure or mistake in the treatment process for a study drug (Tislelizumab and/or Sitravatinib) that either causes harm to the patient or has the potential to cause harm to the patient.

A medication error is not a lack of efficacy of the drug, but rather a human or process related failure while the drug is in control of the study site staff or patient.

Medication error includes situations where an error

- Occurred
- Was identified and intercepted before the patient received the drug
- Did not occur, but circumstances were recognized that could have led to an error

Examples of events to be reported in clinical studies as medication errors:

- Drug name confusion
- Dispensing error e.g. medication prepared incorrectly, even if it was not actually given to the patient
- Drug not administered as indicated, for example, wrong route or wrong site of administration
- Drug not taken as indicated e.g. tablet dissolved in water when it should be taken as a solid tablet
- Drug not stored as instructed e.g. kept in the fridge when it should be at room temperature
- Wrong patient received the medication (excluding IVRS/IWRS errors)
- Wrong drug administered to patient (excluding IVRS/IWRS errors)

Examples of events that **do not** require reporting as medication errors in clinical studies:

- Errors related to or resulting from IVRS/IWRS - including those that lead to one of the above listed events that would otherwise have been a medication error
- Patient accidentally missed drug dose(s) e.g. forgot to take medication
- Accidental overdose (will be captured as an overdose)
- Patient failed to return unused medication or empty packaging
- Errors related to concomitant and rescue medication, or standard of care medication in open label studies

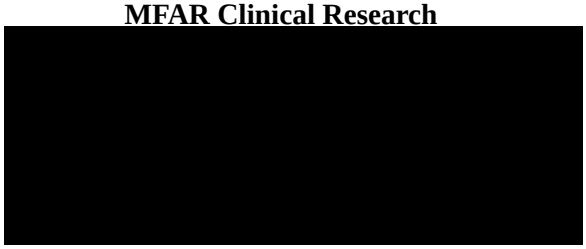
Medication errors are not regarded as AEs but AEs may occur as a consequence of the medication error.

If a medication error occurs in the course of the study, then the Investigator or other site personnel informs the appropriate Sponsor representatives within 1 day i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated Sponsor representative works with the Investigator to ensure that all relevant information is completed within 1 or 5 calendar days if there is an SAE associated with the medication error (see Section 11.3.12) and within 30 days for all other medication errors. Mirati/BeiGene should be informed in parallel.

The designated sponsor representative and CRO for the trial is:

MFAR Clinical Research



12. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

12.1. DESCRIPTION OF ANALYSIS SETS

12.1.1. Safety analysis set

The safety analysis set will include all patients who receive at least 1 dose of study treatment. The safety analysis set will be the primary population for evaluating treatment administration/compliance and safety.

12.1.2. Efficacy analysis set

The analysis sets will be defined as follows:

- **Full Analysis Set (FAS):** will include all enrolled subjects who received at least one dose of the study drugs. 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 tumour evaluations.
- **Per Protocol Analysis Set:** will include those subjects in FAS who had no major protocol deviations.

Efficacy endpoints (ORR, PFS and OS) will be evaluated for both, full and per protocol analysis sets.

12.1.3. Translational analysis set

The translational analysis set will consist of all enrolled subjects who received at least one dose of the study drugs and have at least an analizable sample collected at any time point.

Translational substudies will be evaluated for both, full analysis and translational analysis sets.

12.2. METHODS OF STATISTICAL ANALYSES

Descriptive summary will be provided for all baseline variables, efficacy variables, and safety variables, as appropriate. Continuous variables will be summarized with mean, standard deviation, range, and median. Categorical variables will be summarized with frequency and percentage.

The primary efficacy analysis will be performed using descriptive statistics, frequency counts and percentage of patients within each category will be provided. Ninety-five percent confidence intervals (95% CI) may be presented, as appropriate.

Survival analysis will be performed to analyse PFS and OS, Kaplan-Meier curves will be presented and possible comparisons among patient subgroups (i.e. stratification by prognostic factors) will be tested using the log-rank test or the Cox proportional hazard model for multivariate analysis, hazard ratios (HR) and their 95% CI will be provided.

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 tumour evaluations.

12.2.1. Demographic and other baseline characteristics

Demographic and other baseline characteristics will be summarized and listed. For continuous demographic/baseline variables including age, weight, and vital signs, results will be summarized and presented as n, number of not available data (NA), mean, standard deviation, median, and minimum and maximum values. For categorical variables such as race/ethnicity, the number and percentage of subjects will be used.

Prior and concomitant medications will be summarized and listed by drug and drug class.

12.2.2. Safety analyses

Patient assessed safety analysis will be collected at every visit. AEs will be analysed including but not limited to all AEs, SAEs, fatal AEs, toxicities, substantial clinical and laboratory changes. Specific immune-related adverse events (irAEs) will be collected and designated as immune related events of clinical interest (ECIs).AEs and toxicities will be summarized with frequency and percentage. Toxicities will be graded according to NCI CTCAE, Version 5.0. Safety will be continuously monitored and statistically analyzed for the safety analysis set by the time of the completion of first stage (16 patients enrolled) and when data are mature to be representative of the result of the trial, expected after 6 months after the last patient in.

12.2.3. Efficacy analyses

The analysis of the primary efficacy variable (ORR) will be performed by the time of the completion of first stage (16 patients enrolled) and when data are mature to be representative of the result of the trial, expected after 6 months of the last patient in. ORR will be based on the investigator assessment. Efficacy analysis is described in Table 13.

Table 13. Efficacy analyses

Objectives	Variable	Analysis	Analysis population
Primary: ORR	Proportion of patients with at least one visit response of CR or PR that is confirmed at least 4 weeks later	Proportion estimation with a 95% confidence interval	Full Analysis, and Per protocol sets
Secondary: PFS	PFS is defined as the time from the first dose of study treatment until objective tumor progression or death according to section 10.2.1.	Kaplan-Meier estimation of median PFS with a 95% confidence interval	Full Analysis, and Per protocol sets
Secondary: Overall survival	Time from the first dose of study treatment to death according to section 10.2.2 .	Kaplan Meier estimation of median overall survival with a 95 % confidence interval	Full Analysis, and Per protocol sets
Exploratory: Biomarkers and laboratory objectives	Descriptive		Full Analysis,, and

			Translational analysis sets

12.2.3. Interim analyses

No formal interim analyses is planned, after recruiting 16 patients Mirati/BeiGene will be contacted to purpose different alternatives to follow-up with the projects depending on different scenarios:

- Response rate ≥20%: Mirati/BeiGene will be approached to expand the cohort of patients to increase the number to 34 patients to demonstrate an increase in median PFS from 2.4 months to 5 months (one-sided; alpha error 0.05, and power 80%, accrual 9m, and follow up 12m)(https://stattools.crab.org/Calculators/oneNonParametricSurvival.htm). The null hypothesis was estimated in 2.4 months and the alternative hypothesis in 5 months based on the results from previous clinical trials that described a median PFS ranging from 2.1 (dabacarbacine)(*Carvajal D. et al. 2018*)(*Algazi et al. 2016*) to 5.5 months (*Piulats et al. 2020*)(*Pelster et al. 2021*). .
- Response rate <20%: The patient enrollment will be considered closed.

12.2.4. Determination of sample size

Previous trials in mUM with TKIs have reported no responses to treatment (*Carvajal D. et al. 2018*)*(Buder et al. 2013, Daud et al. 2017, Scheulen et al. 2017),* whereas the largest retrospective study reported an ORR of 3% (*Algazi et al. 2016*). Recent prospective clinical trials with Nivolumab plus ipilimumab reported an ORR of up to 18% (*Piulats et al. 2020*)(*Pelster et al. 2021*). Finally, a phase II trial with adoptive cell therapy has shown an ORR of 35% (*Chandran et al. 2017*). Thus, we expect a response rate of 2% or less for the null hypothesis and a response rate equal or higher than 20% for the alternative hypothesis. Based in the Exact-proportion, difference from constant (binomial test, one sample case), assuming a constant proportion p0=0.02 in the population and an effect size g=0.18 (i.e. p1=0.02 + 0.18=0.2), a power of a one-sided test of 80% and alpha=0.05, a total sample size of N=14 will be required (G*Power Version 3.1.9.6. Franz Faul, Universität Kiel, Germany,Copyright © 1992-2020). Assuming a 10% attrition rate, the total required sample size is 16 patients to ensure the inclusion of at least 14 evaluable patients. We could reject the null hypothesis if in 2 out of the first 14 evaluable patients the relevant event is observed.

If the response rate ≥20%, Mirati/BeiGene will be approached to expand the cohort of patients to increase the number to 34 patients to demonstrate an increase in PFS from 2.4 months to 5 months (one sided; alpha error 0.05, and power 80%, accrual 9 months and follow-up 12 months) based on the non-parametric estimate of the survival distribution using One Arm Survival (https://stattools.crab.org/Calculators/oneNonParametricSurvival.htm), which is an interactive program for calculating either estimates of accrual or power for null and alternative survival functions based on either design specifications of survival probability or median survival. We expect a median PFS of 2,4 months or less for the null hypothesis and a median PFS equal or higher than 5 months for the alternative hypothesis based on the results from previous clinical trials that described a median PFS ranging from 2.1 (dabacarbacine)(*Carvajal D. et al. 2018*)(*Algazi et al. 2016*) to 5.5 months (*Piulats et al. 2020*)(*Pelster et al. 2021*).

13. ETHICAL AND REGULATORY REQUIREMENTS

13.1. ETHICS COMMITTEE

It is the responsibility of the sponsor to have prospective approval of the study protocol, protocol amendments, informed consent documents, and other relevant documents, e.g., recruitment advertisements, if applicable, from the EC and Regulatory Authorities according to applicable legislation. All correspondence with the EC should be retained in the investigator and sponsor Trial Master File, when applicable according GCPs.

The only circumstance in which an amendment may be initiated prior to EC approval is where the change is necessary to eliminate apparent immediate hazards to the patients. In that event, the sponsor must notify the EC in writing immediately after the implementation.

13.2. ETHICAL CONDUCT OF THE STUDY

The current clinical trial will be conducted in accordance with the protocol, the principles established in the International Ethical Guidelines for Biomedical Research Involving Human Patients (Council for International Organizations of Medical Sciences 2002), the current revised version of the Declaration of Helsinki (64th WMA General Assembly, Fortaleza, Brazil, October 2013) and the applicable regulatory requirements, particularly the ICH: E6-R2: Guideline for good clinical practice - Step 5 (2017) - Adopted by CHMP, 15 December 2016, issued as EMA/CHMP/ICH/135/1995, the Regulation (EU) 536/2014 relative to clinical trials on medicinal products for human use and the locally applicable regulations (e.g., In Spain, the Royal Decree on Clinical Trials 1090/2015).

In addition, the study will be conducted in accordance with the protocol, and applicable local regulatory requirements and laws.

13.3. ETHICS AND REGULATORY REVIEW

The protocol, ICF, and appropriate related documents must be reviewed and approved by an EC constituted and functioning in accordance with ICH E6, Section 3, and any local regulations.

Any protocol amendment and/or revision to the ICF will be resubmitted to the EC for review and approval, except for changes involving only logistical or administrative aspects of the study (e.g., change in CRA[s] or change of telephone number[s]). Documentation of EC compliance with ICH and any local regulations regarding constitution and review conduct will be provided to the sponsor.

A signed letter of study approval from the EC Chairman must be obtained prior to study start and the release of any study drug to the site by the sponsor or its designee. If the EC decides to suspend or terminate the study, the sponsor will immediately send the notice of study suspension or termination by the EC to the investigators. Study progress is to be reported to the EC annually (or as required) by the sponsor. If the investigator is required to report to the EC, he/she will forward a copy to the sponsor at the time of each periodic report. The sponsor will submit periodic reports and inform the EC of any

reportable adverse events according to local legislation. Upon completion of the study, the investigator will provide the EC and the regulatory authorities with a brief report of the outcome of the study

13.4. INFORMED CONSENT

All parties will ensure protection of patient personal data and will not include patient names on any sponsor forms, reports, publications, or in any other disclosures, except where required by laws.

When study data are compiled for transfer to the sponsor and other authorized parties, patient names, addresses, and other identifiable data will be replaced by a numerical code based on a numbering system provided by the sponsor in order to de-identify study patients. The study site will maintain a confidential list of patients who participated in the study, linking each patient's numerical code to his or her actual identity. In case of data transfer, the sponsor will maintain high standards of confidentiality and protection of patient's personal data consistent with applicable privacy laws.

The informed consent document must be in compliance with ICH GCP, local regulatory requirements, and legal requirements, including applicable privacy laws.

The informed consent document(s) used during the informed consent process must be reviewed by the sponsor, approved by the IEC before use, and available for inspection.

An approved informed consent form will be provided by the sponsor to participating sites. The written Informed Consent Form (ICF) should be prepared in the local language(s) of the potential subject population. In obtaining and documenting informed consent, the Investigator should comply with the applicable regulatory requirements, and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. The consent form and any revision(s) should be approved by the Ethics Committee prior to being provided to potential subjects.

Before a subject's participation in the study, it is the Principal Investigator's (or their designee) responsibility to obtain freely given consent in writing, from the subject after adequate explanation of the aims, methods, anticipated benefits, and potential risks of the study and before any protocol-specific screening procedures or any study drugs are administered. Subjects must have the opportunity to ask questions and receive answers and will have adequate time to decide whether or not to participate in the study. Once the Investigator is assured that the subject understands the implications of participating in the trial, the subject will be asked to give consent to participate in the trial by signing the informed consent. The ICF should be signed and personally dated by the subject and by the physician who conducted the informed consent discussion (Principal Investigator or designee). The subject's written informed consent should also be documented in the subject's medical records.

If the informed consent is revised during the course of the trial, all active participating subjects must sign the revised form approved by the Ethics Committee.

The investigator should record the informed consent process in the patient records, the recommended text is detailed below: *"On XX/XXX/XXXX the patient has been correctly informed by XXXX about the risk and benefits of his/her participation in the SITISVEAL trial (EudraCT: XXXXXXX). He/she had the time*

and chance to ask as many questions as he/she considered necessary and has accepted to participate by signing the ICF version XX from XX/XXX/XXXX."

The Investigator shall provide a copy of the signed informed consent to the subject. A second original form shall be maintained in the Investigator study file at the site. If the informed consent is revised during the course of the trial, all active participating subjects must sign the revised form approved by the Ethics Committee. The subject participating in a clinical trial, or his/her legal representative, may withdraw consent at any time without giving any reason and without this involving any penalty or prejudice for the participating subject.

13.5. CHANGES TO THE PROTOCOL AND INFORMED CONSENT FORM

There are to be no changes to the protocol without written approval from the sponsor. Protocols will be followed as written. Any change to the protocol requires a written protocol amendment or administrative change that must be approved by the sponsor before implementation. Amendments affecting the safety of subjects, the scope of the investigation, or the scientific quality of the study require submission to Health Authorities as well as additional approval by the EC. These requirements should in no way prevent any immediate action from being taken by the investigator, or by the sponsor, in the interest of preserving the safety of all subjects included in the study. If an immediate change to the protocol is felt by the investigator to be necessary for safety reasons, the sponsor's appropriate study team member must be notified promptly and the EC for the site must be informed immediately. A protocol change intended to eliminate an immediate hazard may be implemented immediately, provided that the Health Authorities and EC are subsequently notified by protocol amendment.

Changes affecting only administrative aspects of the study do not require formal protocol amendments or EC approval, but the EC (if regionally required, the heads of the medical institutions) must be kept informed of such changes. In these cases, the sponsor will send a letter to the EC (if regionally required, the heads of the medical institutions) detailing such changes. Documentation of any non-substantial amendments will be available on request for inspection at the trial site or the sponsor premises as appropriate.

13.6. AUDITS AND INSPECTIONS

In addition to routine monitoring procedures, the sponsor's Clinical Quality Assurance department conducts audits of clinical research activities in accordance with the sponsor's Standard Operating Procedures (SOPs) to evaluate compliance with the principles of ICH GCP and all applicable local regulations. A government regulatory authority may also wish to conduct an inspection (during the study or after its completion). If an inspection is requested by a regulatory authority, the investigator must inform the sponsor immediately that this request has been made.

The investigators and institutions will allow the monitoring, auditing and inspection activities related to this clinical trial including direct access to source data and documents.

13.7. CONFIDENTIALITY

The contents of this protocol and any amendments and results obtained during the course of this study will be kept confidential by the investigator, the investigator's staff, and the EC and will not be disclosed in whole or in part to others or used for any purpose other than reviewing or performing the study without the written consent of the sponsor. No data collected as part of this study will be utilized in any written work, including publications, without the written consent of the sponsor. These obligations of confidentiality and non-use shall in no way diminish such obligations as set forth in the Confidentiality Agreement between the sponsor and the investigator.

All persons assisting in the performance of this study must be bound by the obligations of confidentiality and non-use set forth in the Confidentiality Agreement between the investigator and sponsor (provided by the sponsor).

All laboratory specimens, evaluation forms, reports, and other records will be identified with patient code (clinical trial number) to maintain subject confidentiality throughout the trial. Each Investigator will ensure that all site personnel involved will respect the confidentiality of any information about trial subjects. Management of personal data from subjects participating in the trial, particularly as regards consent, will comply with the EEA General Data Protection Regulation (GDPR) 2016/679 and the Spanish implementation: Ley Orgánica 3/2018, de 5 de diciembre, de Protección de Datos Personales y garantía de los derechos digitales.

At each site, all records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the subject. Subject identity is confidential and may only be known by the Investigator, trial personnel, appointed auditors and monitors, and Health Authorities.

Each Investigator and all employees and coworkers involved with this trial may not disclose or use for any purpose other than performance of the trial, any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the trial. Prior written agreement from the sponsor or its designee must be collected for the disclosure of any said confidential information to other parties.

13.8. INSURANCE

The sponsor has contracted an insurance policy to cover the responsibilities of the investigator and other parties participating in the study, according to the applicable Spanish legislation.

- Insurance company: QBE Europe SA/NV Sucursal en España
- Policy Number: 065 0000056

13.9. PUBLICATIONS

As stated in article 42 of RD 1090/2015 of clinical trials, the Sponsor is obliged to publish both positive and negative results of the authorized clinical trials in scientific journals and with mention to the Ethical Committee of Clinical Research that approved the study.

After completion of the trial, the clinical publication will be carried out by the Coordinating Investigator in collaboration and Principal Investigators. The order of authors will strictly depend on the contribution to the study. Coordinating investigator, will be first and last authors, and the number of the rest of the authors will depend on the above rule and the requirements of the congresses and/or journals.

The first publication will include the results of the analysis of the primary end-point and will include data from all trial sites that provided evaluable data. The Investigator will inform the Sponsor in advance about any plans to publish or present data from the trial. Any publications and presentations of the results (abstracts in journals or newspapers, oral presentations, etc.), either in whole or in part, by Investigators or their representatives will require written authorization by the Sponsor before submission.

The anonymity of the source subjects of the data and biological samples will be maintained at all times. The results or conclusions of the study will be communicated primarily in scientific publications before being released to the non-health public. No efficacy study outcome will be reported prematurely or sensationalistically. Participating investigators should not publish any patient data that is directly related to the study objectives until the trial report is published.

The trial will be registered in the Spanish Registry of Clinical Studies (REEC - Registro Español de Estudios Clínicos) and Clinical trials.gov before including the first patient.

14. STUDY MANAGEMENT

14.1. TRAINING OF STUDY SITE PERSONNEL

- The study will be performed in centers with multidisciplinary teams with wide experience in uveal melanoma trained in GCP's.
- The principal investigator will maintain a record of all center staff involved in the clinical trial (Co-Investigators, nurses and other staff involved) ensuring that they receive appropriate training to perform the study, and that any new information of relevance to the study will be transmitted to them.
- Researchers will be instructed about the documents (Protocol, ICF, IB, etc.) procedures of the trial (selection, inclusion, treatment, safety, notifications, eCRF, among others) during the initiation visits made by monitors to each participating center prior to the study start.

14.2. MONITORING OF THE STUDY

The CRO in charge of monitoring this trial is:

MFAR Clinical Research

The sponsor's or representative (e.g., CRO's CRA) will maintain contact with the investigator and designated staff by telephone, and/or letter, and/or email between study visits. Monitoring visits to each investigational site will be conducted by the assigned CRA as described in the monitoring plan. The investigator (if regionally required, the heads of the medical institutions) will allow the CRA to inspect the clinical, laboratory, and pharmacy facilities to assure compliance with Good Clinical Practices, MFAR Clinical Research SOPs and local regulatory requirements.

The eCRFs and subject's corresponding original medical records (source documents) are to be fully available for review by the sponsor's representatives at regular intervals.

These reviews verify adherence to the study protocol and data accuracy in accordance with federal regulations. All records at the investigational site, including source documents, are subject to inspection by the regulatory authorities and to review by the Ethical Committee.

14.2.1. Source data

Source data are defined as all data in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial that are necessary for the reconstruction and evaluation of the trial.

The Investigator must keep a file (medical file, original medical records) on paper or electronically for every subject in the trial. It must be possible to identify each subject by using this subject file. This file will contain the demographic and medical information for the subject listed below and should be as complete as possible.

- Subject's full name, date of birth, sex, height, weight
- Medical history and concomitant diseases
- Prior and concomitant therapies (including changes during the trial)
- Trial identification, that is, the Sponsor trial number for this clinical trial, and subject number
- Dates for entry into the trial (informed consent) and visits to the site
- Any medical examinations and clinical findings predefined in this clinical trial protocol
- All AEs
- Date that the subject left the trial including any reason for early withdrawal from the trial or IMP (if applicable).

All documents containing source data must be filed, including, but not limited to CT or MRI scan images, ECG recordings, and laboratory results. Such documents must bear the subject number and the date of the procedure. If possible, this information should be printed by the instrument used to perform the assessment or measurement. As necessary, medical evaluation of such records should be performed; all evaluations should be documented, signed, and dated by the Investigator.

Electronic subject files will be printed whenever the Monitor performs source data verification. Printouts must be signed and dated by the Investigator, countersigned by the Monitor and kept in a safe place at the site.

14.2.2. Non-compliances

Protocol deviations are unintended and/or unanticipated departures from the procedures and/or processes in the protocol as approved by the sponsor, the CA and IEC, and agreed to by the Investigator.

Minor deviations usually have a limited impact on study outcomes and do not involve ICH E6-R2 guidelines, inclusion/exclusion criteria or primary endpoint criteria.

Major deviations are those that may adversely affect the rights, safety or welfare of subjects and / or quality and integrity of data.

Critical deviations are those that adversely affect the rights, safety or welfare of subjects and / or quality and integrity of data.

Each study site Investigator must document and explain in the subject's source documentation any deviations from the approved protocol. Investigators may implement a deviation from the protocol to eliminate an immediate hazard to trial subjects without prior IEC informed consent approval, but the deviation must be reported to the monitor/CRA within 1 working day. Such incidents will be evaluated for potential safety hazards of the ongoing study, and if deemed appropriate, a protocol amendment will be issued.

The monitor/CRA will document protocol deviations throughout the course of monitoring visits. The monitor will notify the Investigator during a visit and a “Protocol Deviation Form” is completed and signed by the investigator and by the monitor.

14.3. STUDY TIMETABLE AND END OF STUDY

Expected Study Duration:

- Trial Initiation: 3Q 2022
- First Patient In: 3Q 2022
- Last Subject In: 2Q 2023
- Last Patient Last Visit: 1Q 2024
- Publication of results : 2Q 2024

End of Study Declaration:

Last Patient Last Visit, expected on 1Q 2024

Early study termination

Sites level:

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 to the Sponsor and CRO 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

Study Level:

This study can be terminated prematurely if in the opinion of the sponsor there is a reasonable and sufficient cause. The investigator will receive a written notification in which the sponsor motivates the interruption of the study. Reasons that justify are as follows, but not limited to:

- Finding unforeseen, considerable or unacceptable risks for the patients.
- Impossibility to include an acceptable number of patients.
- Insufficient compliance with protocol requisites.
- Plans to modify, halt or discontinue the development of study drugs.

Health Authorities and Independent Ethics Committees (IECs)/Institutional Review Boards (IRBs) will be informed about the discontinuation of the trial in accordance with applicable regulations.

In case of early termination of the study, all the study material must be returned to the Sponsor.

15. DATA MANAGEMENT

The Data Management Plan (DMP) defines and documents the procedures necessary to ensure data quality. These activities must be followed to ensure data are properly entered, validated, coded, integrated, reconciled and reviewed.

SAP will include:

- Data source strategy
- Analysis of objectives
- Analysis of sets/ populations/subgroups
- Endpoints and covariates management
- Handling of missing values and other data conventions
- Statistical methodology

Database (DB) elaboration and validation plan will include:

- Data management plan
- DB and syntaxes elaboration and validation procedure
- Clinical coding (medication, AE, LNR) with client-specific dictionaries
- Reviewing procedure and consolidation management
- Project management of data, data validation and query resolution
- SAE Reconciliation
- Quality Assurance Audit and Quality Control Procedures

Statistical report

- Elaboration according SAP and client-specific requirements
- Reviewing process
- Final validation process

Data required by the protocol are collected on an electronic Case Report Form (eCRF) and entered into a validated data management system which is compliant to all regulatory requirements. As defined by ICH Guidelines, ‘the Case Report Form (CRF) is a printed, optical, or electronic document designed to record all of the protocol required information to be reported to the sponsor on each trial subject’. In this study, CRF should refer to electronic data collection form. Data collected on the CRF must follow the instructions described in the CRF Completion Guidelines. The Investigator has ultimate responsibility for the collection and reporting of all clinical, safety and laboratory data entered on the CRF.

Any corrections to entries made on the CRF must be documented in a valid audit trail where the corrections must be dated, initiated, the reason for change stated, and original data not obscured. Only data required by the protocol for the purposes of the study should be collected.

The compliance with the 21 CFR11 and EU and local guidelines of the computerized systems used are guaranteed. The eCRF is a solution from Medical R&C, and the hardware infrastructure is hosted by

Claranet Inc., that ensures high availability and also implements all the security controls regarding access to the hardware hosting the eCRF.

The eCRF software implements all the internal security protocols and data entry recommendations, such as:

- Access limited to authorized individuals
- Audit trail
- Data encryption
- Data consistency
- Range checks and alerts.
- Backup system (systems necessary to avoid data loss and ensure data integrity)

A CRF is required and should be completed for each included patient. The Investigator has ultimate responsibility for the collection and reporting of all clinical, safety and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring and available when required.
The source documents are the hospital's or the physician's patient chart. In these cases, data collected on the CRFs must match the data in those charts.

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Appendix 1. Infusion-Related Reactions, Hypersensitivity Reactions and Immune-Mediated Adverse Events: Evaluation and Management

Management of Infusion-Related Reactions and Hypersensitivity Reactions

Management and treatment modifications for symptoms of infusion-related reactions associated with study drug(s) administration are provided in the table below.

If a hypersensitivity reaction occurs, the patient must be managed according to the best available medical practice, as described in the guideline for emergency treatment of anaphylactic reactions according to the Working Group of the Resuscitation Council (UK) (Soar et al 2008). Patients should be instructed to report any delayed reactions to the investigator immediately.

Treatment Modifications for Symptoms of Infusion-Related or Hypersensitivity Reactions Associated with Study Drug(s) Administration

NCI-CTCAE Grade	Treatment Modification for study drug(s)
Grade 1 - mild Mild transient reaction; infusion interruption not indicated; intervention not indicated.	Decrease infusion rate by 50%. Closely monitor for worsening signs or symptoms. Medical management as needed. Subsequent infusions should be given after appropriate premedication and at the reduced infusion rate.
Grade 2 - moderate Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, corticosteroids, and/or intravenous fluids); prophylactic medications indicated for ≤ 24 hours.	Stop infusion. Infusion may be resumed at 50% of previous rate once infusion-related reaction has resolved or decreased to Grade 1 in severity. Closely monitor for worsening signs or symptoms. Appropriate medical management should be instituted, as described below. Subsequent infusions should be given after premedication and at the reduced infusion rate.
Grade 3 – severe Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for observation or clinical management.	Immediately stop the infusion. Proper medical management should be instituted as described below. The patient should be withdrawn from study drug(s) treatment.
Grade 4 – life threatening Life-threatening consequences; urgent intervention indicated.	Immediately stop the infusion. Proper medical management should be instituted as described below. The patient should be withdrawn from study drug(s) treatment.

	Hospitalization is recommended.

Abbreviations: NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Event.

If the infusion rate of study drug(s) has been decreased by 50% or suspended due to an infusion-related reaction, this decreased rate must be maintained for all subsequent infusions and be administered with premedication. If the patient has a second infusion-related reaction (≥ Grade 2) on the slower infusion rate, infusion should be discontinued, and the patient should be withdrawn from tislelizumab treatment.

For the prophylaxis of mild events (eg, nasal congestion or flu-like symptoms), a dose of 25 mg indomethacin or a comparable dose of nonsteroidal anti-inflammatory drugs (eg, 600 mg ibuprofen or 500 mg naproxen sodium) may be administered 2 hours before and 8 hours after the start of each dose of study drugs(s) infusion. Alternative treatments for fever (eg, paracetamol) may be given to patients at the discretion of the investigator.

NCI-CTCAE Grade 1 or 2 infusion reaction: Proper medical management should be instituted as indicated per the type of reaction. This includes, but is not limited to, an antihistamine (eg, diphenhydramine), an antipyretic (eg, paracetamol), and if considered indicated, oral or intravenous glucocorticoids, epinephrine, bronchodilators, and oxygen. In subsequent cycles, the patient should receive oral premedication with an antihistamine (eg, diphenhydramine) and an antipyretic (eg, paracetamol), and should be closely monitored for clinical signs and symptoms of an infusion reaction.

NCI-CTCAE Grade 3 or 4 infusion reaction: Proper medical management should be instituted immediately, as indicated per type and severity of the reaction. This includes, but is not limited to, oral or intravenous antihistamines, antipyretics, glucocorticoids, epinephrine, bronchodilators, and oxygen.

In the event of a systemic anaphylactic/anaphylactoid reaction the infusion must be stopped immediately, and the patient discontinued from study treatment. Systemic anaphylactic/anaphylactoid reactions typically manifest within minutes following administration of the drug/antigen and are characterized by respiratory distress; laryngeal edema; and/or intense bronchospasm; and often followed by vascular collapse or shock without antecedent respiratory difficulty; cutaneous manifestations such as pruritus and urticaria (with or without edema); and gastrointestinal manifestations such as nausea, vomiting, crampy abdominal pain, and diarrhea.

The patient will be administered epinephrine injection and dexamethasone infusion if severe hypersensitivity reaction is observed. The patient should be closely monitored, and ICU should be alerted for possible transfer as indicated.

Evaluation of Immune-Mediated Adverse Events

The recommendations below for the diagnosis and management of any immune-mediated AE (imAE) are intended as guidance. This document should be used in conjunction with expert clinical judgement (by specialist physicians experienced in the treatment of cancer using immunological agents), and individual institutional guidelines or policies.

The recommendations for diagnostic evaluation and management of imAEs are based on European Society for Medical Oncology (ESMO) and American Society of Clinical Oncology (ASCO) guidelines (Haanen et al 2017, Brahmer et al 2018). For any AEs not included in the tables below, refer to the ASCO Clinical Practice Guideline (Brahmer et al 2018) for further guidance on diagnostic evaluation and management of immune-mediated toxicities.

Criteria used to diagnose imAEs include blood tests, diagnostic imaging, histopathology, and microbiology assessments to exclude alternative causes such as infection, disease progression, and adverse effects of concomitant drugs. In addition to the results of these tests, the following factors should be considered when making an imAE diagnosis:

- What was the temporal relationship between initiation of tislelizumab and the AE?
- How did the patient respond to withdrawal of tislelizumab?
- Did the event recur when tislelizumab was reintroduced?
- Was there a clinical response to corticosteroids?
- Is the event an autoimmune endocrinopathy?
- Is disease progression or an alternative diagnosis a more likely explanation?

When alternative explanations to autoimmune toxicity have been excluded, the imAE field associated with the AE in the eCRF should be checked. If further diagnostic evaluations change the assessment, the eCRF should be updated accordingly.

Recommended Diagnostic Tests in the Management of Possible Immune-Mediated Adverse Events

Immune-mediated Toxicity	Diagnostic Evaluation Guideline
Thyroid Disorders	Scheduled and repeated thyroid function tests (TSH and T4).
Hypophysitis	Check visual fields and consider pituitary endocrine axis blood profile. Perform pituitary and whole brain MRI in patients with headache, visual disturbance, unexplained fatigue, asthenia, weight loss, and unexplained constitutional symptoms. Consider consultation with an endocrinologist if an abnormality is detected.
Pneumonitis	All patients presenting with new or worsened pulmonary symptoms or signs, such as an upper respiratory infection, new cough, shortness of breath, or hypoxia should be assessed by high-resolution CT. Consider pulmonary function test including DLCO. Radiographic appearance is often nonspecific. Depending on the location of the abnormality, bronchoscopy and bronchoalveolar lavage or lung

	biopsy may be considered. Consult with a respiratory medicine physician for cases of uncertain cause.
Neurological Toxicity	Perform a comprehensive neurological examination and brain MRI for all CNS symptoms; review alcohol history and other medications. Conduct a diabetic screen and assess blood B12/folate, HIV status, TFTs, and consider autoimmune serology. Consider the need for brain/spine MRI/MRA and nerve conduction study for peripheral neuropathy. Consult with a neurologist if there are abnormal findings.
Colitis	Review dietary intake and exclude steatorrhea. Consider comprehensive testing, including the following: FBC, UEC, LFTs, CRP, TFTs, stool microscopy and culture, viral PCR, *Clostridium difficile* toxin, and cryptosporidia (drug-resistant organism). In case of abdominal discomfort, consider imaging, eg, X-ray, CT scan. If a patient experiences bleeding, pain, or distension, consider colonoscopy with biopsy and surgical intervention as appropriate.
Eye Disorders	If a patient experiences acute, new onset, or worsening of eye inflammation; blurred vision; or other visual disturbances, refer the patient urgently to an ophthalmologist for evaluation and management.
Hepatitis	Check ALT/AST/total bilirubin, INR/albumin; the frequency will depend on severity of the AE (eg, daily if Grade 3 to 4; every 2 to 3 days if Grade 2, until recovering). Review medications (eg, statins, antibiotics) and alcohol history. Perform liver screen including Hepatitis A/B/C serology, Hepatitis E PCR and assess anti-ANA/SMA/LKM/SLA/LP/LCI, iron studies. Consider imaging (eg, ultrasound scan for metastases or thromboembolism). Consult with a hepatologist and consider liver biopsy.
Renal toxicity	Review hydration status and medication history. Test and culture urine. Consider renal ultrasound scan, protein assessment (dipstick/24-hour urine collection), or phase-contrast microscopy. Refer to a nephrologist for further management assistance.
Dermatology	Consider other causes by conducting a physical examination. Consider dermatology referral for skin biopsy.
Joint or muscle inflammation	Conduct musculoskeletal history and perform complete musculoskeletal examination. Consider joint X-ray and other imaging as required to exclude metastatic disease. Perform autoimmune serology and refer to rheumatology for further management assistance. For suspected myositis/rhabdomyolysis/myasthenia include: CK, ESR, CRP, troponin, and consider a muscle biopsy.

Myocarditis	Perform ECG, echocardiogram, CK/CK-MB, troponin (I and/or T), and refer to a cardiologist.

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; ANA, antinuclear antibody; AST, aspartate aminotransferase; CK, creatine kinase; CK-MB, creatine kinase cardiac isoenzyme; CNS, central nervous system; CRP, C-reactive protein; CT, computed tomography; DLCO, diffusing capacity for carbon monoxide; ECG, electrocardiogram; ESR, erythrocyte sedimentation rate; FBC, full blood count; HIV, human immunodeficiency virus; INR, international normalized ratio; LCI, liver cytosolic antigen; LFT, liver function test; LKM, liver kidney microsomal antibody; LP, liver pancreas antigen; MRA, magnetic resonance angiogram; MRI, magnetic resonance imaging; PCR, polymerase chain reaction; SLA, soluble liver antigen; SMA, smooth muscle antibody; T4, thyroxine; TFT, thyroid function tests; TSH, thyroid-stimulating hormone; UEC, urea electrolytes and creatinine.

Management of Immune-Mediated Adverse Events

Immune-mediated AEs can escalate quickly. Study treatment interruption, close monitoring, timely diagnostic work-up, and treatment intervention as appropriate is required. Immune-mediated AEs should improve promptly after introduction of immunosuppressive therapy. If this does not occur, review the diagnosis, seek further specialist advice, and contact the study medical monitor.

If a toxicity does not resolve to ≤ Grade 1 within 12 weeks, study drug(s) should be discontinued after consultation with the sponsor. Patients who experience a recurrence of any event at the same or higher severity grade after restart of study drug should permanently discontinue treatment.

For some Grade 3 toxicities that resolve quickly, rechallenge with study drug may be considered if there is evidence of a clinical response to study treatment, after consultation with the study medical monitor.>

Steroid dosages in the table below are for oral or intravenous (methyl)prednisolone. Equivalent dosages of other corticosteroids can be substituted. For steroid-refractory imAEs, consider use of steroid-sparing agents (eg, mycophenolate mofetil [MMF]). Consider prophylactic antibiotics for opportunistic infections if the patient is receiving long-term immunosuppressive therapy.

Management of Immune-Mediated Adverse Events

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
Thyroid Disorders	**1-2** Asymptomatic TFT abnormality or mild symptoms	Replace thyroxine if hypothyroid, until TSH/T4 levels return to normal range. Thyrotoxic patients should be referred to an endocrinologist. In cases with systemic symptoms: withhold study treatment, treat with a beta blocker,	Continue study treatment or withhold treatment in cases with systemic symptoms.

		and consider oral prednisolone 0.5 mg/kg/day for thyroid pain. Taper corticosteroids over 2-4 weeks. Monitor thyroid function regarding the need for hormone replacement.	
	3-4 Severe symptoms, hospitalization required	Refer patient to an endocrinologist. If hypothyroid, replace with thyroxine 0.5-1.6 µg/kg/day (for the elderly or those with comorbidities, the suggested starting dose is 0.5 µg/kg/day). Add oral prednisolone 0.5 mg/kg/day for thyroid pain. Thyrotoxic patients require treatment with a beta blocker and may require carbimazole until thyroiditis resolves.	Hold study treatment; resume when resolved/improved to Grade 0-1. >
Hypophysitis	**1-2** Mild-moderate symptoms	Refer patient to an endocrinologist for hormone replacement. Add oral prednisolone 0.5-1 mg/kg/day for patients with pituitary inflammation. Taper corticosteroids over at least 1 month. If there is no improvement in 48 hours, treat as Grade 3-4.	Continue study treatment.
	3-4 Severe or life-threatening symptoms	Refer patient to an endocrinologist for assessment and treatment. Initiate pulse intravenous methylprednisolone 1 mg/kg for patients with headache/visual disturbance due to pituitary inflammation. Convert to oral	Hold study treatment for patients with headache/visual disturbance due to pituitary inflammation until resolved/improved to ≤ Grade 2. Discontinuation is usually not necessary.

		prednisolone and taper over at least 1 month. Maintain hormone replacement according to endocrinologist's advice.	
Pneumonitis	**1** Radiographic changes only	Monitor symptoms every 2-3 days. If appearance worsens, treat as Grade 2.	Consider holding study treatment until appearance improves and cause is determined.
	2 Symptomatic: exertional breathlessness	Commence antibiotics if infection suspected. Add oral prednisolone 1 mg/kg/day if symptoms/appearance persist for 48 hours or worsen. Consider *Pneumocystis* infection prophylaxis. Taper corticosteroids over at least 6 weeks. Consider prophylaxis for adverse steroid effects: eg, blood glucose monitoring, vitamin D/calcium supplement.	Hold study treatment. Retreatment is acceptable if symptoms resolve completely or are controlled on prednisolone ≤ 10 mg/day. Discontinue study treatment if symptoms persist with corticosteroid treatment.
	3-4 Severe or life-threatening symptoms: breathless at rest	Admit to a hospital and initiate treatment with intravenous methylprednisolone 2-4 mg/kg/day. If there is no improvement, or worsening after 48 hours, add infliximab 5 mg/kg (if no hepatic involvement). Convert to oral prednisolone and taper over at least 2 months. Cover with empiric antibiotics and consider prophylaxis for *Pneumocystis* infection and other adverse steroid effects, eg, blood glucose monitoring, vitamin D/calcium supplement.	Discontinue study treatment.

Neurological Toxicity	**1** Mild symptoms	–	Continue study treatment.
	2 Moderate symptoms	Treat with oral prednisolone 0.5-1 mg/kg/day. Taper over at least 4 weeks. Obtain neurology consultation.	Hold study treatment; resume when resolved/improved to Grade 0-1.
	3-4 Severe/life-threatening symptoms	Initiate treatment with oral prednisolone or intravenous methylprednisolone 1-2 mg/kg/day, depending on symptoms. Taper corticosteroids over at least 4 weeks. Consider azathioprine, MMF, cyclosporine if no response within 72-96 hours.	Discontinue study treatment.
Colitis/Diarrhea	**1** Mild symptoms: ≤ 4 liquid stools per day over baseline and feeling well	Symptomatic management: fluids, loperamide, avoid high fiber/lactose diet. If Grade 1 persists for > 14 days, manage as a Grade 2 event.	Continue study treatment.
	2 Moderate symptoms: 4-6 liquid stools per day over baseline, or abdominal pain, or blood in stool, or nausea, or nocturnal episodes	Oral prednisolone 0.5 mg/kg/day (non-enteric coated). Do not wait for any diagnostic tests to start treatment. Taper steroids over 2-4 weeks. Consider endoscopy if symptoms are recurring.	Hold study treatment; resume when resolved/improved to baseline grade.
	3 Severe symptoms: ≥ 7 liquid stools per day over baseline, or if episodic within 1 hour of eating	Initiate intravenous methylprednisolone 1-2 mg/kg/day. Convert to oral prednisolone and taper over at least 4 weeks. Consider prophylaxis for adverse steroid effects, eg, blood glucose	Hold study treatment; retreatment may be considered when resolved/improved to baseline grade and after discussion with the study medical monitor.

	4 Life-threatening symptoms	monitoring, vitamin D/calcium supplement. If no improvement in 72 hours or symptoms worsen, consider infliximab 5 mg/kg if no perforation, sepsis, TB, hepatitis, NYHA Class III/IV CHF or other immunosuppressive treatment: MMF or tacrolimus. Consult gastroenterologist to conduct colonoscopy/ sigmoidoscopy.	Discontinue study treatment.
Skin reactions	**1** Skin rash, with or without symptoms, < 10% BSA	Avoid skin irritants and sun exposure; topical emollients recommended.	Continue study treatment.
	2 Rash covers 10%-30% of BSA	Avoid skin irritants and sun exposure; topical emollients recommended. Topical steroids (moderate strength cream once a day or potent cream twice a day) ± oral or topical antihistamines for itch. Consider a short course of oral steroids.	Continue study treatment.
	3 Rash covers > 30% BSA or Grade 2 with substantial symptoms	Avoid skin irritants and sun exposure; topical emollients recommended. Initiate steroids as follows based on clinical judgement: For moderate symptoms: oral prednisolone 0.5-1 mg/kg/day for 3 days then taper over 2-4 weeks. For severe symptoms: intravenous methylprednisolone 0.5-1 mg/kg/day; convert to oral prednisolone and taper over at least 4 weeks.	Hold study treatment. Re-treat when AE is resolved or improved to mild rash (Grade 1-2) after discussion with the study medical monitor.

	4 Skin sloughing > 30% BSA with associated symptoms (eg, erythema, purpura, epidermal detachment),	Initiate intravenous methylprednisolone 1-2 mg/kg/day. Convert to oral prednisolone and taper over at least 4 weeks. Admit to a hospital and seek urgent dermatology consultation.	Discontinue study treatment.
Hepatitis	**1** ALT or AST > ULN to 3 x ULN	Check LFTs within 1 week and before the next dose; check LFTs to verify that there has been no worsening. If LFTs are worsening, recheck every 48-72 hours until improvement is seen.	Continue study treatment if LFTs are unchanged or improving. Hold study treatment if LFTs are worsening until improvement is seen.
	2 ALT or AST >3 x to 5 x ULN	Recheck LFTs every 48-72 hours. For persistent ALT/AST elevation: consider oral prednisolone 0.5-1 mg/kg/day for 3 days, then taper over 2-4 weeks. For rising ALT/AST: start oral prednisolone 1 mg/kg/day and taper over 2-4 weeks; re-escalate dose if LFTs worsen, depending on clinical judgement.	Hold study treatment; treatment may be resumed when resolved/improved to baseline Grade and prednisolone tapered to ≤ 10 mg.
	3 ALT or AST >5 x to 20 x ULN	ALT/AST < 400 IU/L and normal bilirubin/INR/albumin: Initiate oral prednisolone 1 mg/kg and taper over at least 4 weeks. ALT/AST > 400 IU/L or raised bilirubin/INR/low albumin: Initiate intravenous (methyl)prednisolone 2 mg/kg/day. When LFTs improve to Grade 2 or lower, convert to oral prednisolone and	If ALT and AST ≤ 10 x ULN: Hold study treatment until improved to baseline grade; reintroduce only after discussion with the medical monitor. If ALT or AST > 10 x ULN: Discontinue study treatment.

		taper over at least 4 weeks.	
	4 ALT or AST > 20 x ULN	Initiate intravenous methylprednisolone 2 mg/kg/day. Convert to oral prednisolone and taper over at least 6 weeks.	Discontinue study treatment.
	Worsening LFTs despite steroids: ● If on oral prednisolone, change to pulsed intravenous methylprednisolone. ● If on intravenous methylprednisolone, add mycophenolate mofetil (MMF) 500 to 1000 mg twice a day. ● If worsens on MMF, consider addition of tacrolimus. Duration and dose of steroid required will depend on severity of event.		
Nephritis	**1** Creatinine 1.5 x baseline or > ULN to 1.5 x ULN	Repeat creatinine weekly. If symptoms worsen, manage as per criteria below.	Continue study treatment.
	2 Creatinine > 1.5-3 x baseline or > 1.5-3 x ULN	Ensure hydration and review creatinine in 48-72 hours; if not improving, consider creatinine clearance measurement by 24-hour urine collection. Discuss with nephrologist the need for kidney biopsy. If attributed to study drug, initiate oral prednisolone 0.5-1 mg/kg and taper over at least 2 weeks. Repeat creatinine/U&E every 48-72 hours.	Hold study treatment. If not attributed to drug toxicity, restart treatment. If attributed to study drug and resolved/improved to baseline grade: Restart study drug if tapered to < 10 mg prednisolone.
	3 Creatinine > 3 x baseline or > 3-6 x ULN	Hospitalize patient for monitoring and fluid balance; repeat creatinine every 24 hours; refer to a nephrologist and discuss need for biopsy. If worsening, initiate intravenous (methyl)prednisolone 1-2 mg/kg. Taper corticosteroids over at	Hold study treatment until the cause is investigated. If study drug suspected: Discontinue study treatment.

		least 4 weeks.	
	4 Creatinine > 6 x ULN	As per Grade 3, patient should be managed in a hospital where renal replacement therapy is available.	Discontinue study treatment.
Diabetes/ Hyperglycemia	**1** Fasting glucose value ULN to 160 mg/dL; ULN to 8.9 mmol/L	Monitor closely and treat according to local guideline. Check for C-peptide and antibodies against glutamic acid decarboxylase and islet cells are recommended.	Continue study treatment.
	2 Fasting glucose value 160-250 mg/dL; 8.9-13.9 mmol/L	Obtain a repeat blood glucose level at least every week. Manage according to local guideline.	Continue study treatment or hold treatment if hyperglycemia is worsening. Resume treatment when blood glucose is stabilized at baseline or Grade 0-1.
	3 Fasting glucose value 250-500 mg/dL; 13.9-27.8 mmol/L	Admit patient to hospital and refer to a diabetologist for hyperglycemia management. Corticosteroids may exacerbate hyperglycemia and should be avoided.	Hold study treatment until patient is hyperglycemia symptom-free, and blood glucose has been stabilized at baseline or Grade 0-1.
	4 Fasting glucose value > 500 mg/dL; > 27.8 mmol/L	Admit patient to hospital and institute local emergency diabetes management. Refer the patient to a diabetologist for insulin maintenance and monitoring.	Hold study treatment until patient is hyperglycemia symptom-free, and blood glucose has been stabilized at baseline or Grade 0-1.
Ocular Toxicity	**1** Asymptomatic eye examination/test abnormality	Consider alternative causes and prescribe topical treatment as required.	Continue study treatment.
	2 Anterior uveitis or mild symptoms	Refer patient to an ophthalmologist for assessment and topical	Continue study treatment or hold treatment if symptoms worsen or if there are symptoms of

		corticosteroid treatment. Consider a course of oral steroids.	visual disturbance.
	3 Posterior uveitis/panuveitis or significant symptoms	Refer patient urgently to an ophthalmologist. Initiate oral prednisolone 1-2 mg/kg and taper over at least 4 weeks.	Hold study treatment until improved to Grade 0-1; reintroduce only after discussion with the study medical monitor.
	4 Blindness (at least 20/200) in the affected eyes	Initiate intravenous (methyl)prednisolone 2 mg/kg/day. Convert to oral prednisolone and taper over at least 4 weeks.	Discontinue study treatment.
Pancreatitis	**2** Asymptomatic, blood test abnormalities	Monitor pancreatic enzymes.	Continue study treatment.
	3 Abdominal pain, nausea and vomiting	Admit to hospital for urgent management. Initiate intravenous (methyl)prednisolone 1-2 mg/kg/day. Convert to oral prednisolone when amylase/lipase improved to Grade 2 and taper over at least 4 weeks.	Hold study treatment; reintroduce only after discussion with the study medical monitor.
	4 Acute abdominal pain, surgical emergency	Admit to hospital for emergency management and appropriate referral.	Discontinue study treatment.
Arthritis	**1** Mild pain with inflammation, swelling	Management per local guideline.	Continue study treatment.
	2 Moderate pain with inflammation, swelling, limited instrumental (fine motor) activities	Management as per local guideline. Consider referring patient to a rheumatologist. If symptoms worsen on treatment, manage as a Grade 3 event.	Continue treatment or, if symptoms continue to worsen, hold study treatment until symptoms improve to baseline or Grade 0-1.
	3	Refer patient urgently to a	Hold study treatment

	Severe pain with inflammation or permanent joint damage, daily living activity limited	rheumatologist for assessment and management. Initiate oral prednisolone 0.5-1 mg/kg and taper over at least 4 weeks.	unless improved to Grade 0-1; reintroduce only after discussion with the study medical monitor.
Mucositis/ stomatitis	**1** Test findings only or minimal symptoms	Consider topical treatment or analgesia as per local guideline.	Continue study treatment.
	2 Moderate pain, reduced oral intake, limited instrumental activities	As per local guidelines, treat with analgesics, topical treatments, and oral hygiene care. Ensure adequate hydration. If symptoms worsen or there is sepsis or bleeding, manage as a Grade 3 event.	Continue study treatment.
	3 Severe pain, limited food and fluid intake, daily living activity limited	Admit to hospital for appropriate management. Initiate intravenous (methyl)prednisolone 1-2 mg/kg/day. Convert to oral prednisolone when symptoms improve to Grade 2 and taper over at least 4 weeks.	Hold study treatment until improved to Grade 0-1.
	4 Life-threatening complications or dehydration	Admit to hospital for emergency care. Consider intravenous corticosteroids if not contraindicated by infection.	Discontinue study treatment.
Myositis/ Rhabdomyolysis	**1** Mild weakness with/without pain	Prescribe analgesics. If CK is significantly elevated and patient has symptoms, consider oral steroids and treat as Grade 2.	Continue study treatment.
	2 Moderate weakness with/without	If CK is 3 x ULN or worse, initiate oral prednisolone 0.5-1 mg/kg	Hold study treatment until improved to

	pain	and taper over at least 4 weeks.	Grade 0-1.
	3-4 Severe weakness, limiting self-care	Admit to hospital and initiate oral prednisolone 1 mg/kg. Consider bolus intravenous (methyl)prednisolone and 1-2 mg/kg/day maintenance for severe activity restriction or dysphagia. If symptoms do not improve, add immunosuppressant therapy. Taper oral steroids over at least 4 weeks.	For Grade 3: Hold study treatment until improved to Grade 0-1. Discontinue upon any evidence of myocardial involvement.
Myocarditis[a]	**< 2** Asymptomatic but significantly increased CK-MB or increased troponin OR clinically significant intraventricular conduction delay	Initiate cardiac evaluation under close monitoring with repeat serum testing and including ECG, cardiac ECHO/MUGA, and/or other interventions per institutional guidelines; consider referral to a cardiologist. If diagnosis of myocarditis is confirmed, treat as Grade 2.	Hold study treatment. If a diagnosis of myocarditis is confirmed and considered immune mediated, permanently discontinue study treatment in patients with moderate or severe symptoms. Patients with no symptoms or mild symptoms may not restart tislelizumab unless cardiac parameters have returned to baseline and after discussion with the study medical monitor.
	2 Symptoms on mild-moderate exertion	Admit to hospital and initiate oral prednisolone or intravenous (methyl)prednisolone at 1-2 mg/kg/day. Consult with a cardiologist and manage symptoms of cardiac failure according to local guidelines. If no immediate response, change to pulsed doses of (methyl)prednisolone 1 g/day and add MMF, infliximab, or anti-thymocyte globulin.	
	3 Severe symptoms with mild exertion		
	4 Life-threatening		

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BSA, body surface area; CHF, congestive heart failure; CK, creatine kinase; CK-MB, creatine kinase cardiac isoenzyme; ECG, electrocardiogram; INR, international normalized ratio; LFT, liver function test; MMF, mycophenolate mofetil;

MUGA, multigated acquisition scan; NYHA, New York Heart Association; T4, thyroxine; TB, tuberculosis; TFT, thyroid function test; TSH, thyroid-stimulating hormone; U&E, urea and electrolytes; ULN, upper limit of normal.

[a] If clinically significant cardiac enzyme abnormalities are detected during laboratory assessment and serial cardiac enzyme assessments pose logistical hardship for the patient, then patient hospitalization should strongly be considered until immune-mediated myocarditis has been ruled out.