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BGB-A317-SITRAVATINIB-301
AMENDMENT 1.0
SUMMARY OF CHANGES

Study Title: A Randomized Phase 3 Study of Tislelizumab in Combination With Sitravatinib in Patients With Locally Advanced or Metastatic Non-Small Cell Lung Cancer That Progressed on or After Platinum-Based Chemotherapy and Anti-PD-(L)1 Antibody

BeiGene, Ltd., has updated the BGB-A317-Sitravatinib-301 protocol from Original Protocol 0.0 (04 February 2021) to Protocol Amendment 1.0 (03 November 2021). The primary purpose of this amendment is to:

- Update the eligibility criteria by excluding patients with prior anticancer treatment that has a same mechanism of action as sitravatinib;
- Include intensive PK sample collection from 12 patients in Arm A for the analysis of sitravatinib malate salt and its active metabolite M10;
- Update clinical safety data of sitravatinib monotherapy and combination therapy with PD-1 a blocking agent according to the most recent version of the sitravatinib investigator's brochure (Version 8.1);
- Capture key updates in the tislelizumab Phase 3 study protocol template Version 4.0.

Key changes made from Original Protocol 0.0 to Protocol Amendment 1.0 are summarized in the table below.

Some minor updates were made to correct typos and improve clarity and readability.

~~Strikethrough~~ text indicates deleted text and **bold** text indicates newly added text.

Section	Key Changes	Rationale for the Change	Substantial Change (Y/N)	Potential Impact on the Safety of Patients, Study Conduct, or Expectedness of Suspected Serious Adverse Effects
Title Page	[redacted]	Updated the change in	N	NA

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Section	Key Changes	Rationale for the Change	Substantial Change (Y/N)	Potential Impact on the Safety of Patients, Study Conduct, or Expectedness of Suspected Serious Adverse Effects
	[redacted]	the medical monitor and contact information		
Investigator Signature Page	• **Instructions for Investigator:** Please SIGN and DATE this signature page ~~prior to~~**before** implementation of this sponsor-approved protocol. PRINT your name, title, and the name ~~and address~~ of the center in which the study will be conducted.	For consistency across all protocols	N	NA
Synopsis **3.1. Summary of Study Design**	• The study will be conducted at approximately ~~80 centers in the Asia-Pacific region~~ **100 centers globally**.	To allow for patient enrollment in more study sites	N	NA
Synopsis **2.1.2. Secondary Objectives**	• **To characterize the pharmacokinetics (PK) of sitravatinib when given in combination with tislelizumab, if data permit**	For better sitravatinib PK assessment with intensive sampling	N	NA
Synopsis **2.1.3. Exploratory Objectives**	• ~~To evaluate the PK of sitravatinib when given in combination with tislelizumab~~ • **To characterize the PK of the active metabolite M10 of sitravatinib when given in combination with tislelizumab, if deemed necessary** • To characterize ~~tislelizumab pharmacokinetics~~ **(the** PK~~)~~ and ~~host~~ immunogenicity ~~to~~ **of** tislelizumab when given in combination with sitravatinib	For better sitravatinib and M10 PK assessment with intensive sampling For clarity	N	NA
Synopsis **2.2.2. Secondary Endpoints**	• DOR, defined as the time from the first occurrence of a documented objective response to the time of ~~relapse~~ **the first occurrence of disease progression**, as determined by the IRC based on	For clarity and consistency	N	NA

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	RECIST v1.1, or death from any cause, whichever occurs first (**Section 9.2.2**); • **Plasma concentrations and the derived PK parameters of sitravatinib, if data permit**			
Synopsis **2.2.3. Exploratory Endpoints** **9.2.3. Exploratory Efficacy Analysis**	• DOR, defined as the time from the first occurrence of a documented objective response to the time of ~~relapse~~ **the first occurrence of disease progression**, as determined by the investigator based on RECIST v1.1, or death from any cause, whichever comes first; • ~~Summary of plasma concentrations for sitravatinib and serum concentrations for tislelizumab~~ • **Plasma concentrations and the derived PK parameters of M10 if data permit** • ~~Assessments of immunogenicity~~ **Serum concentrations** of tislelizumab **and** ~~by determining~~ the incidence of antidrug antibodies (ADAs)	For clarity and consistency	N	NA
Synopsis **2.2.3. Exploratory Endpoints**	• Potential biomarkers such as PD-L1 expression, gene expression profiling (GEP), ~~DNA mutation,~~ tissue and blood tumor mutation burden (tTMB/bTMB)**, and** microsatellite instability (MSI)**, and alterations in tissue** and circulating tumor DNA (ctDNA), and the association of biomarkers with disease status, and response/resistance to sitravatinib in combination with tislelizumab	For clarity and accuracy	N	NA
Synopsis **Study Schema (Figure 1)**	• Patients will be stratified by histological subtype (nonsquamous versus squamous), PD-L1 expression (< 1% TC versus ≥ 1% TC **by the**	For clarification	N	NA

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3.1. Study Design **3.3 Treatment Period** **9.1.1 Randomization Method**	**Ventana SP263 assay; patients whose tissues are unevaluable for PD-L1 expression will be included in the < 1% TC group**), and race (Asian versus non-Asian) to receive one of the 2 treatment regimens			
Synopsis **3.1. Study Design** **Study Schema (Figure 1)**	• Histologically confirmed NSCLC (Stage IIIB/ **IIIC** or Stage IV)	For clarity and consistency	N	NA
Synopsis **3.3. Treatment Period** **7.5. Tumor and Response Evaluations**	• A patient who discontinues study drugs early for reasons other than disease progression as assessed by the IRC (eg, toxicity, disease progression assessed by the investigator) will continue to undergo tumor assessments following the original plan until the patient experiences disease progression per RECIST v 1.1 as assessed by the IRC, withdraws consent, is lost to follow-up, **starts a new anticancer** treatment, or until death, or until the study terminates, whichever occurs first. • In the situation where the investigator believes the patient must urgently discontinue study treatment without waiting for the IRC's confirmation, the investigator ~~musts~~**should** contact the medical monitor to inform him/her of the decision of treatment discontinuation.	For clarification	N	NA
Synopsis **3.3. Treatment Period**	~~• Patients who discontinue treatment before disease progression (eg, due to unacceptable toxicity) will continue to be followed up radiologically until disease progression or withdrawal of consent.~~	To avoid redundancy	N	NA
Synopsis	• Added "**Patients in both arms will receive study**	To specify study	N	NA

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Section	Key Changes	Rationale for the Change	Substantial Change (Y/N)	Potential Impact on the Safety of Patients, Study Conduct, or Expectedness of Suspected Serious Adverse Effects
3.3. Treatment Period	**treatment until disease progression, intolerable toxicity, death, or withdrawal of consent, whichever occurs earlier**"	treatment discontinuation criteria		
Synopsis **3.3. Treatment Period**	• The duration of the study from the first enrolled patient to the final analysis for the ~~dual~~ primary endpoint ~~PFS and~~ OS is estimated to be approximately 32 months.	For clarity and consistency	N	NA
Synopsis **3.3. Treatment Period** **7.5. Tumor and Response Evaluations**	• In selected cases, patients **in Arm A** may continue treatment beyond radiologic progression if they continue to demonstrate clinical benefit, at the discretion of the investigator and with the sponsor's agreement. • Patients who could ~~derive~~ benefit from study treatment **in Arm A** after disease progression as assessed by the investigator **or IRC** per RECIST v1.1 criteria may continue treatment until loss of clinical benefit as assessed by the investigator, withdrawal of consent, unacceptable toxicity, study completion by the sponsor, start of a new anticancer therapy, or death, whichever occurs first. • After disease progression is assessed by the **investigator or** IRC per RECIST v 1.1, and at the investigator's discretion, a patient that would continue to benefit from the ~~combination therapy or tislelizumab monotherapy~~ **study treatment in Arm A** may continue their assigned treatment. **(Section 7.5)**	For clarity	N	NA
Synopsis **3.3. Treatment Period**	• In the event of unacceptable AEs potentially attributed to anti-PD-1 therapy and clearly not attributed to RTK inhibitor, sitravatinib can be	For clarity and accuracy	N	NA

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5.5.1. Dose Delay or Modification for Tislelizumab and/or Sitravatinib	continued as monotherapy at the discretion of **the** investigator. However, due to limited anticancer effect of rechallenging PD-(L)1 monotherapy after progression on PD-(L)1 inhibitor **or PD-(L)1-inhibitor-based therapy**, tislelizumab should not be used as monotherapy after permanent discontinuation of sitravatinib.			
Synopsis **9.1.2 Analysis Set**	• Added M10 PK Analysis Set	To define the PK Analysis Set for M10	N	NA
1.1. Background Information on Non-Small Cell Lung Cancer	• Added efficacy data from RATIONALE-304 (Study BGB-A317-304)	Data update for rationale justification	N	NA
1.4.4. Prior Clinical Experience of Tislelizumab of Tislelizumab	• Updated per Tislelizumab IB edition 9.0	Per latest Tislelizumab IB information	N	NA
1.4.4.2.3. Study BGB-A317-303 **1.6.1. Rationale for Tislelizumab in the Treatment of NSCLC**	• Updated data from interim analysis of Study BGB-A317-303 (with a data cutoff of 10 August 2020)	Data update for rationale justification	N	NA
1.5.1. Pharmacology **1.5.2. Toxicology** **1.5.3. Clinical Pharmacology** **1.5.4.1. Safety Assessment of Monotherapy Study** **1.5.4.2. Safety Assessment of Combination Study** **1.6.3. Rationale for Selection**	• Updated wordings and/or clinical safety data of sitravatinib per sitravatinib IB version 8.1	Per latest Sitravatinib IB information	N	NA

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of Sitravatinib Dose **1.7. Benefit-Risk Assessment**				
1.5.3. Clinical Pharmacology	• **Sitravatinib underwent multiple biotransformation reactions following single oral administration to healthy male volunteers, with metabolism mediated via oxidation, and oxidative O- and N-dealkylation, as well as secondary sulfation, demethylation, dehydrogenation, deamination, and reduction. Sitravatinib was the most abundant circulating component in human plasma, accounting for > 56% of the total drug-related exposure. M10 was the only major metabolite, accounting for approximately 19% of the total drug-related exposure. M10 was evaluated in nonclinical studies, and the data suggested M10 was pharmacologically active against sitravatinib RTK targets**.	Background information update for sitravatinib M10	N	NA
1.5.4.4. Efficacy Assessment of Sitravatinib Combination with PD-1 Blocking Agent **1.6.5. Rationale for Combination of Tislelizumab and Sitravatinib in the Treatment of NSCLC**	• Updated efficacy data from Study MRTX-500 • Updated efficacy data from Study BGB-900-103 for Cohort A and Cohort F where patients with anti-PD-(L)1 therapy refractory/resistant, non-squamous and squamous metastatic NSCLC were enrolled (with a data cutoff date of 13 October 2020)	Data update for rationale justification	N	NA
1.6.2. Rationale for Selection of Tislelizumab Dose	• Updated per tislelizumab Phase 3 study protocol template version 4.0	To provide a clear rationale for the selection of 200 mg Q3W dosage for tislelizumab	N	NA

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1.6.3. Rationale for Selection of Sitravatinib Dose	• **In Study BGB-Sitravatinib-101, the relative bioavailability between the malate formulation manufactured by BeiGene and the free-base formulation was assessed in healthy volunteers. The results showed that the exposures (geometric means of $AUC_{0-\infty}$, AUC_{0-t} and C_{max}) after a single dose of 100-mg malate formulation were numerically lower than those observed with the 120-mg free-base formulation, with a difference of approximately 12%. This difference was not expected to be clinically meaningful as the PK exposures for the 120-mg free-base formulation were more varied and contained that of the 100-mg malate salt formulation.**	Data update for rationale justification	N	NA
Synopsis **4.1. Inclusion Criteria**	• #2. Age ≥ 18 years on the day of signing the informed consent form (or the legal age of consent **if > 18** in the jurisdiction in which the study is taking place)	For clarity	N	NA
Synopsis **3.1 Summary of Study Design** **4.1. Inclusion Criteria**	• #6. Furthermore, patients must have had radiographic progression per RECIST v1.1 on or after anti-PD-(L)1 containing therapy as the most recent **systemic** treatment for locally advanced and unresectable or metastatic NSCLC. • #6. #a. Adjuvant or neo-adjuvant chemotherapy will count as a prior line of chemotherapy if the disease progressed on or within 6 months ~~between the last dose and the date of recurrence~~ **after the completion of the last dose.** • #6. #d. No other prior immunotherapies **with**	For clarity	N	NA

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	antibody or drug specifically targeting T-cell costimulation or checkpoint pathways, including but not limited to anti-CTLA-4, anti TIGIT, anti-OX40, and anti-CD137.			
Synopsis **3.1. Study Design** **4.1. Inclusion Criteria**	• #6. **No prior anticancer therapy having the same mechanism of action as sitravatinib (eg, tyrosine kinase inhibitor with a similar target profile or VEGF- or VEGFR inhibitor) will be allowed.**	To exclude the population who may not benefit from sitravatinib treatment due to prior exposure of anticancer therapy having the same mechanism of action as sitravatinib	N	NA
Synopsis **3.3 Treatment Period**	• Tumor assessment will be conducted (by magnetic resonance imaging [MRI] and/or ~~contrast-enhanced~~ computed tomography [CT] **(with oral and/or intravenous contrast, unless contraindicated)** during screening (within 28 days of randomization); every 6 weeks from Cycle 1 Day 1 (± 7 days) (at Weeks 7, 13, 19, 25, 31, 37, 43, and 49), and then at 9-week intervals (± 7 days) thereafter, until disease progression, withdrawal of consent, lost to follow up, **start of a new anticancer therapy,** or death, whichever occurs earlier.	For clarity and consistency	N	NA
Synopsis **3.3 Treatment Period**	• Added "**Tumor assessment should continue as planned in patients receiving study treatment beyond initial investigator-assessed progression. Tumor assessment in such patients should continue until study treatment discontinuation.**"	To request tumor assessment for patients receiving study treatment beyond disease progression	N	NA
Synopsis	• **Generally,** a maximum of 2 dose reductions are	For consistency and	N	For consistency

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5.2.2. Sitravatinib	allowed before the patient must be permanently withdrawn from the study drug. **Dose reduction below 50 mg once daily may be undertaken after discussion with the sponsor**. • Capsules should be taken with at least 200 mL (**approximately** 1 cup) of water.	clarity		
Synopsis **5.2.2. Sitravatinib**	• **If a patient forgets to take sitravatinib for more than 12 hours, he/she should skip the dose and resume taking the drug the next day**.	Provide guidance to patient if he/she forgets to take sitravatinib for more than 12 hours	N	NA
3.3. Treatment Period	• Continuation of study therapy beyond 2 years must be explicitly approved by the sponsor and will be contingent on the continued availability of tislelizumab, **and/or sitravatinib**. The study assessment and procedure schedule will remain the same. • If a patient has evidence of PD within 1 year of treatment interruption, the investigator can consider restarting tislelizumab and~~/or~~ sitravatinib therapy **(or sitravatinib alone)** after discussion with the sponsor, contingent on the continued availability of the study drug(s). • When a patient **in Arm A** reaches 2 years of treatment (as measured from Cycle 1 Day 1): - Patients may continue on study therapy beyond 2 years if the investigator considers this to be in the best interest of the patient based on an assessment of clinical benefit and potential risks;	For clarity	N	NA

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3.4. End of Treatment/Safety Follow-up **Study Schema (Figure 1)** **Appendix 1 Former Footnote #5**	• Patients who discontinue treatment for any reason will be asked to return to the clinic for the EOT Visit (to occur ~~within~~ 30 days [± 7 days] after the last dose of study drug (s), or before the initiation of a new anticancer treatment, whichever occurs first)	Updated per tislelizumab Phase 3 study protocol template version 4.0	N	NA
3.5. Survival Follow-up	• Patients will be followed for survival and to obtain information on subsequent anticancer therapy after discontinuation of study treatment via telephone calls, patient medical records, and/or clinic visits approximately every 3 months (± 14 days) after the EOT **Visit** or as directed by the sponsor until death, withdrawal of consent, lost to follow-up, or end of study. ~~All patients will be followed for survival and subsequent anticancer therapy information unless a patient requests to be withdrawn from follow-up.~~	For clarity To avoid redundancy	N	NA
3.7. End of Study	• Added a bullet under "The sponsor has the right to terminate this study at any time. Reasons for terminating the study early may include, but are not limited to, the following:" - **"A rollover study becomes available"**	Updated per tislelizumab Phase 3 study protocol template version 4.0 and for clarity	N	NA
4.1. Inclusion Criteria	• #4. Able to provide archival/fresh tumor tissues for biomarker analysis to assess PD-L1 expression and other biomarkers. **Tumor tissues should be of good quality and acceptable sample type (See Section 7.7.1 for details). Written informed consent is required prior to performance of fresh tumor biopsies**.	For clarity To avoid redundancy	N	NA

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	• #5. No known *EGFR* or *BRAF* **sensitizing** mutation, or *ALK* rearrangement or ROS1 rearrangement: #a. Documentation of ~~wild-type~~ *EGFR* status **with no sensitizing mutation** by tissue-based test must be provided for patients with nonsquamous NSCLC before enrollment (also in **Section 7.7.1**; **Appendix 1 Footnote #17**). • Removed #7. ~~Recovery from adverse effects of prior therapy to baseline or Grade 1 (excluding alopecia).~~			
4.1. Inclusion Criteria	• #10. #a. #ii. Platelets ≥ ~~75~~ **100** x 10^9/L; • #10. #d. Aspartate aminotransaminase (AST) and alanine aminotransferase (ALT) ≤ 2.5 x ULN, or AST and ALT ≤ 5.0 x ULN for patients with documented liver metastases. ~~Docetaxel should not be given if bilirubin > ULN, or if AST and/or ALT > 1.5 x ULN concomitant with alkaline phosphatase > 2.5 x ULN~~ **If AST and/or ALT > 1.5 x ULN, alkaline phosphatase should be ≤ 2.5 x ULN.** • #10. #e. Serum total bilirubin ≤ ~~1.5~~ **1** x ULN ~~(total bilirubin must be < 3 x ULN for patients with Gilberts syndrome)~~. • #11. ~~Females of childbearing potential must be willing to use a highly effective method of birth control for the duration of the study, and for ≥ 120 days after the last dose of tislelizumab or sitravatinib, or within 180 days after the last dose of docetaxel, and have a negative serum pregnancy~~	To ensure patients' safety if allocated to receive chemotherapy treatment; For clarity	N	NA

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	~~test ≤ 7 days prior to randomization~~ **Females of childbearing potential must be willing to use a highly effective method of birth control when being on study treatment, and within 180 days after the last dose of study drug(s), and have a negative serum pregnancy test ≤ 7 days before randomization.** (**Section 8.8.6**). • #12. Nonsterile males must be willing to use a highly effective method of birth control for the duration of the study and for ≥ ~~120~~**180** days after the last dose of study drug(s): - Added bullet point: **"A nonsterile male that has a partner of non-childbearing potential may not be required to use a highly effective method of birth control."**			
4.2. Exclusion Criteria	• #4. #b. Measurable ~~and/or evaluable~~ disease outside the CNS • # 5. Active autoimmune diseases or history of autoimmune diseases that may relapse. Note: Patients with the following diseases are not excluded and may proceed to further screening: #c. ~~Controlled~~Celiac disease controlled **by diet alone.** • #9. History of interstitial lung disease, noninfectious pneumonitis or uncontrolled **lung** diseases, including pulmonary fibrosis and acute lung diseases. • #12. Untreated chronic hepatitis B or chronic hepatitis B virus (HBV) carriers with HBV DNA ~~>~~≥ 500 IU/mL **or 2500 copies/mL,** or active	Updated per tislelizumab Phase 3 study protocol template version 4.0 and for clarity	N	NA

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	hepatitis C virus (HCV) carriers. **Note:** Inactive hepatitis B surface antigen (HBsAg) carriers, treated and stable hepatitis B (HBV DNA < 500 IU/mL **or 2500 copies/mL**) patients, and cured hepatitis C patients can be enrolled. Patients with detectable HBsAg or detectable HBV DNA should be managed per treatment guidelines. Patients receiving antivirals at screening should have been treated for > 2 weeks before randomization. (also in **Section 6.2.1.2**). • #23. Patient was administered a live vaccine ≤ 28 days before randomization. Note: **Vaccines for COVID-19 are allowed except for any live vaccine that may be developed**. Seasonal vaccines for influenza are generally inactivated vaccines and are allowed. Intranasal vaccines are live vaccines and are not allowed. • #32. **Known COVID-19 antigen positive by a licensed test during the screening period.** • #33. **Uncontrollable pleural effusion, pericardial effusion, or ascites requiring frequent drainage (recurrence ≤ 14 days after intervention)**			
4.2. Exclusion Criteria	• #10. Severe chronic or active infection (including tuberculosis infection, etc) requiring systemic antibacterial, antifungal, or antiviral therapy **(not including antiviral therapy for hepatitis)** within 14 days ~~prior to~~**before** randomization.	For clarity and consistency	N	NA
4.2. Exclusion Criteria	• #15. - ~~#b. Symptomatic pulmonary embolism~~	For consistency with Exclusion Criteria #20;	N	NA

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	~~≤ 28 days before randomization~~ - #~~g. QTc ≤ 470 msec in females and ≤ 450 msec in males (based on average of screening triplicates). Note: If any patient has QTc interval > 450 msec in males or > 470 msec in females on initial ECG, a follow-up ECG will be performed to confirm the result~~**QT interval corrected by Fridericia's method (QTcF) > 470 msec in females and > 450 msec in males** **Note: If a patient has QTcF interval > 450 msec for males or > 470 msec for females on an initial ECG, a follow-up ECG will be performed to confirm the result**. - #h. Cardiac left ventricular ejection fraction < ~~40%~~**50%** or lower limit of normal as assessed by echocardiography or multigated acquisition (MUGA). The same modality used at baseline must be applied for subsequent evaluations.	Correction of a typo as this study intends to exclude patients who have long QTc interval at baseline. To ensure patient safety		
4.2. Exclusion Criteria	• #18. Patients ~~with bleeding or thrombotic disorders or~~ who use anticoagulants such as warfarin or similar agents requiring therapeutic INR monitoring. • #19. ~~Patients with any signs or medical history of bleeding, regardless of the severity; within~~**Within** 4 weeks ~~prior to allocation~~ **before randomization**, patients with **active bleeding disorder or** any bleeding events ≥ CTCAE level 3, unhealed wounds, ulcers, or fractures. • #20. Patients with **a history of** artery/~~venous~~**deep vein** thrombosis ~~that occurred~~ within 6 months before ~~allocation~~ **randomization**, such as	To avoid redundancy and for clarity		

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	cerebrovascular incident (including temporary ischemic attack), deep vein thrombosis, and pulmonary embolism. • #21. Patients treated with any Chinese herbal medicine or Chinese patent medicines used to control cancer within 14 days of ~~Day 1~~**randomization.** • #22. #b. ≥ Grade 2 imAE associated with anti-PD-(L)1 unless the AE resolved or was well controlled by withholding the anti-PD-(L)1 treatment and/or treatment with steroids, with the exception of prior colitis, encephalitis, myocarditis, hepatitis, ~~uveitis,~~ and pneumonitis, which are exclusionary			
4.2. Exclusion Criteria **6.2.1. Permitted Concomitant Medications/Procedures** **6.3. Potential Interactions Between the Study Drugs and Concomitant Medications** **Appendix 11. Medications or Substances to Be Avoided or Used With Caution During Treatment With Sitravatinib**	• #28. ~~Patients requiring treatment with gastric pH-modifying medications including proton pump inhibitors and/or H2 antagonist medications. Patients may switch to use of antacids.~~ • Removed ~~Proton pump inhibitors and H2 antagonists should be avoided during sitravatinib treatment but are not exclusionary. Switching from use of proton pump inhibitors or H2 antagonists to antacids is preferred. Use of antacids should be avoided 4 hours before and 2 hours after administration of the study drug(s) (Section 6.2.1)~~ • Section 6.3: Updated DDI data for sitravatinib • Appendix 11: - Updated appendix title: Medications or Substances to be Avoided or Used With Caution During Treatment With ~~Sitravatinib~~**Study Drugs** - Updated DDI data	Updated per latest DDI data suggesting no impact of PPI on sitravatinib PK	N	NA

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5.1.2. Sitravatinib	• Sitravatinib **malate formulation** will be provided as 50 mg and 35 mg capsules.	For consistency	N	NA
5.2.3. Docetaxel	• Added "**Before each cycle of docetaxel,** - **Liver function tests (LFTs) should be reviewed, and docetaxel should not be given if bilirubin > 1x ULN, or if AST and/or ALT > 1.5 × ULN concomitant with alkaline phosphatase > 2.5 × ULN.** - **Blood counts should be reviewed, and docetaxel should not be given if neutrophil counts are < 1500 cells/mm^3**.	To keep consistency with docetaxel's label	N	NA
5.4. Study Drug Accountability **12.4. Drug Accountability**	• Patients enrolled in ~~the study~~**Arm A** will be provided with patient diaries.	For clarity	N	NA
5.5.1. Dose Delay or Modification for Tislelizumab and/or Sitravatinib	• Patients may temporarily suspend ~~study treatment~~ **1 component of the study treatment or both,** if they experience toxicity that is considered related to study drugs and requires a dose to be withheld. • If the administration of sitravatinib is interrupted for reasons other than **sitravatinib-related** toxicity, then treatment with the study drug(s) may be resumed at the same dose. • Sitravatinib can be interrupted for up to 28 consecutive days. If the treatment with sitravatinib is delayed for ≥ 14 days, then resumption at a reduced dose should be considered. If the drug is planned to be interrupted for ~~≥~~ > 28 days, the medical monitor should be contacted before permanent patient discontinuation from the	For clarification	N	NA

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	study drug. • If the patient is unable to resume sitravatinib and/or tislelizumab within the permitted timeframe after the last dose of study drug(s), then the patient should be discontinued from the study drug(s). **Continuation/resumption of study drug(s) after an interruption of more than the permitted timeframe must be discussed with the medical monitor.** • When contribution to an unacceptable AE by either drug cannot be ruled out, both sitravatinib and tislelizumab should be held or ~~their doses~~ **the dose of sitravatinib** should be reduced according to dose modification guidelines. • Based on the known toxicity profiles of sitravatinib and tislelizumab, certain AEs are likely to be associated with one drug versus the other. For example, treatment-emergent hypertension or ~~proteinuria~~**palmar plantar erythrodysesthesia** are likely to be associated with sitravatinib rather than tislelizumab; • Therefore, early recognition and initiation of treatment is critical to reduce complications. Tislelizumab must be withheld for drug-related ~~toxicities and~~ severe or life-threatening AEs. See Appendix 8 for supportive care guidelines, including use of corticosteroids.			
5.5.2. Dose Delay, Interruption or Modifications for Docetaxel	• **Table 5**: Grade 3 skin/~~neuropathy/~~ major organ/non-hematologic toxicity. • Patients who develop~~> Grade3~~ **≥ Grade 3**	To keep consistency with docetaxel's label	N	NA

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	peripheral neuropathy should have docetaxel treatment discontinued entirely			
6.2.1.2. Hepatitis B Treatment	Patients with active hepatitis B, defined as HBV DNA ≥ 500 IU/mL **or 2500 copies/mL** at Screening, must initiate treatment 2 weeks before randomization and continue until 6 months after the last dose of study drug(s).	For clarity	N	NA
6.2.1.3. Hepatitis C Treatment	• The entire section was removed, as a result, the numbering of sections following it switched forward.	This section is not applicable to this study, as HCV carriers are not allowed to be enrolled in this study	N	NA
6.2.1.4. Radiation Therapy	• ~~It is not required to withhold study tislelizumab treatment~~ **Withhold of study treatment is required** during palliative radiotherapy	To ensure patient safety	N	NA
6.2.2. Prohibited Concomitant Medications/Procedures	• Live vaccines ≤ 28 days before randomization **for patients in both arms, during tislelizumab treatment** and ≤ 60 days after the last dose of **tislelizumab for patients in Arm A** ~~study drug(s)~~ are prohibited.	For clarity	N	NA
6.2.3. Restricted Concomitant Medications/Procedures	• Split the restrictions by "**Arm A only**" and "**Arm A and Arm B**" • The following medications are restricted during the study: #. **Surgeries, except:** **− To treat an AE (eg, appendectomy)** **In the event that major surgery is needed during study treatment, the patient should,**	For clarity Updated per tislelizumab Phase 3 study protocol template version 4.0	N	NA

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	if possible, interrupt dosing with study treatment 2 weeks in advance of the surgery and may resume dosing 2 weeks after the surgery.			
7.2.1. Confirmation of Eligibility	• Updated confirmation of eligibility language per BGB-A317 Phase 3 protocol template version 4.0	For consistency across company protocols	N	NA
7.4.5. Electrocardiograms **Appendix 1 Footnote**	• #8. When coinciding with blood draws at the same timepoint, ECG assessment should be **either** performed prior to blood draws~~.~~**, or at least 30 minutes after the blood draws.**	For better operation	N	NA
7.5. Tumor and Response Evaluations **Appendix 4**	• Revised tumor measurement/assessment instructions per tislelizumab Phase 3 study protocol template version 4.0	To improve consistency in how sites measure and assess tumors	N	NA
5.2. Dosage, Administration, and Compliance **7.6. Pharmacokinetic and Antidrug Antibody Testing** **Appendix 2**	• Added intensive PK sample collection from 12 patients in Arm A for the sitravatinib and M10.	For better sitravatinib and M10 PK assessment with intensive sampling	N	NA
5.5.1. Dose Delay or Modification for Tislelizumab and/or Sitravatinib	• Sitravatinib can be interrupted for up to ~~approximately~~ 28 consecutive days. If treatment with sitravatinib is delayed for ≥ 14 days, then resumption at a reduced dose should be considered.	For clarity and accuracy	N	NA
5.5.2. Dose Delay, Interruption or Modifications for Docetaxel	• Updated Table 5 Guidelines for Docetaxel Dose Modifications; • Patients who are dosed initially at 75 mg/m^2 and who experience either febrile neutropenia, neutrophils < 500 cells/mm^3 (Grade 4) > 1 week,	Provide more guidance on dose modification	N	NA

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	severe or cumulative cutaneous reactions, or other Grade 3/4 non-hematologic toxicities during docetaxel treatment should have treatment withheld until resolution of the toxicity and treatment then resumed at 55 mg/m^2. **Should these AEs occur after the first dose reduction, then a second dose reduction is permitted. During this study, local standard practice for docetaxel administration may be used. Patients requiring more than two dose reductions of docetaxel due to adverse events should discontinue treatment with docetaxel.** Patients who develop ≥ Grade 3 peripheral neuropathy should have docetaxel treatment discontinued entirely.			
7.7. Biomarker	• Create separate sections for Tissue and Blood Biomarkers (**Section 7.7.1** and **Section 7.7.2**, respectively); • **Section 7.7.1:** Fine-needle aspiration, brushing, cell pellets from pleural effusion, ~~and~~ lavage samples, **and bone/bone marrow aspirates** are not acceptable (**Appendix 1 Footnote #17**).	Update per tislelizumab Phase 3 study protocol template version 4.0	N	NA
7.7.1. Tissue Biomarkers **9.6.1. Exploratory biomarker analyses** **Appendix 1 Footnote #17**	• Analysis of the relationship of response to other exploratory biomarkers (eg, GEP, DNA ~~mutation,~~**alteration**, tTMB/bTMB, MSI, and ctDNA) may be carried out, depending on the adequacy of available data.	For accuracy	N	NA
7.7. Biomarker **Appendix 1 Table and Footnote #22**	• Peripheral blood samples will be collected for biomarker analysis, such as DNA ~~mutation~~**alteration**, bTMB, MSI, and ctDNA. • Approximately 10 mL of peripheral blood samples	For better assessment on biomarkers	N	NA

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	will be collected at baseline (predose on Cycle 1 Day1)~~,~~ **and predose on Cycle 3 Day 1;** • For patients who have confirmed CR/PR **(± 14 days)** or PD ~~as assessed by the investigator~~, additional blood samples (approximately 10 mL) will be collected upon each ~~time~~**confirmation**.			
7.9. Visit Windows	• If the timing of a protocol-mandated study visit coincides with a holiday, weekend, or other event, the visit should be scheduled on the nearest feasible date (the visit window is provided in Appendix 1), with subsequent visits conducted according to the planned schedule every 3 weeks from Day 1 of ~~Cycle 1~~ **the previous cycle**.	For clarity	N	NA
8.7. Management of Adverse Events Potentially Associated With Either or Both of Sitravatinib and Tislelizumab	• For example, hypertension, arterial thrombotic events, ~~proteinuria~~**palmar plantar erythrodysesthesia,** and hemorrhagic events are known risks for sitravatinib treatment, while imAEs are risks for tislelizumab treatment. • Removed ~~Section 8.7.1 Timing of Adverse Event Onset~~ • If an AE is suspected to be treatment related and is severe/life threatening at the time of onset or is rapidly worsened, action including interrupting or holding both drugs, initiating treatment with a corticosteroid (with exception of hypothyroidism, type I diabetes mellitus) **to treat an imAE,** and other supportive care should be taken promptly.	For consistency and clarity of AE management	N	NA
8.9.2. Management of Hematological Toxicities of	• In addition, dose reduction **of sitravatinib** at the discretion of **the investigator**~~sitravatinib~~ should be	Correction of typos	N	NA

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Sitravatinib	implemented in the following cases.			
8.9.4. Hypertension	• Hypertension, including Grade ~~3~~**4** events, has been reported with sitravatinib.	For accuracy	N	NA
Synopsis **9.1.2. Analysis Sets**	• ~~The Per-Protocol (PP) Analysis Set includes all randomized patients who received ≥ 1 dose of the assigned study drug and had no critical protocol deviations that significantly impact efficacy or safety evaluation. Critical protocol deviations will be determined and documented before the database lock for the primary analysis.~~ • The Safety Analysis Set includes all patients who received ≥ 1 dose of **any of** the study drugs; it will be the analysis set for the safety analyses.	Removed the PP Analysis Set; its inclusion could lead to selection bias and therefore is not suggested by ICH E9(R1) guideline; For clarity.	N	NA
9.2.1.1. Overall Survival	• Added "**The primary analysis of OS will treat death due to COVID-19 as an OS event and will be performed regardless of any other COVID-19-related intercurrent events. COVID-19-related sensitivity/supplementary analyses will be specified in the SAP. "** • **The COVID-19-related sensitivity/supplementary analyses of PFS may be considered and will be specified in the SAP.**	For clarification of analysis plan	N	NA
9.2.2. Secondary Efficacy Analysis	• **DCR by IRC is defined as the proportion of patients whose best overall response (BOR) is CR, PR or stable disease as determined by the IRC based on RECIST v1.1 in the ITT Analysis Set**	For consistency across sections	N	NA

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9.2.2. Secondary Efficacy Analysis	• Clinically meaningful changes post baseline (percentage of patients with a 10-point improvement or worsening, or to be defined in the SAP) for global health scores and physical function of the QLQ-C30 and dyspnoea, coughing, haemoptysis, peripheral neuropathy, pain in the arms and shoulders, and pain in the chest of LC13 will be calculated by timepoint and compared between the treatment arms **using the mixed models which include baseline score, prespecified stratification factors, treatment arm, visit, and treatment arm by visit interaction as fixed effects with visit as a repeated measure with an unstructured covariance structure**.	Add MMRM model for between treatment arms comparison	N	NA
9.2.2. Exploratory Efficacy Analysis	• ~~Patient-reported outcomes of health-related quality of life and lung cancer-specific symptoms evaluated by the EQ-5D and QLQ-LC13 questionnaire will be summarized and compared between arms. The detailed analysis method will be discussed in the SAP.~~	Deleted because of duplication with QoL analysis in the secondary efficacy analysis section	N	NA
9.3.2. Adverse Events	• For the treatment arm, ~~the TEAE classification also applies to~~ imAEs ~~that~~ are recorded up to 90 days after discontinuation from tislelizumab, regardless of whether the patient starts a new anticancer therapy. Only those AEs that were treatment emergent will be included in summary tables **of TEAE**. All AEs, treatment-emergent or otherwise, will be presented in patient data listings.	Global TEAE definition update	N	NA

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9.4. Pharmacokinetic Analysis	• Updated and specified PK parameters to be evaluated for sitravatinib and M10	For better sitravatinib and M10 PK assessment with intensive sampling	N	NA
9.8 Interim Analysis	• The non-binding futility boundary is specified at HR = ~~1.021~~ **1.076**, as is determined by an HSD beta spending function with parameter 1.	Calculation error correction	N	NA
10.2. Independent Data Monitoring Committee	• The first IDMC safety review will occur after ≥ 20 patients have been randomized to study treatment (ie, approximately 10 patients per treatment arm) and have been on treatment for ≥ 1 month in order to determine if the proposed dosing schedule of tislelizumab **and sitravatinib combination therapy** is safe and tolerable.	For clarity	N	NA
13.4. Patient and Data Confidentiality	• Data generated during this study must be available for inspection upon request by representatives of the **European Medicines Agency (EMA),** US Food and Drug Administration (FDA), the China National Medical Products Administration (NMPA), and all other national and local health authorities; by sponsor monitors, representatives, and collaborators; and by the IRBs/IECs for each study center, as appropriate.	For completeness	N	NA
13.4. Patient and Data Confidentiality	• Added rationales for race/ethnicity data collection	Justify collection of race/ethnicity data	N	NA
15. Reference	• Mirati Therapeutics, Inc. Investigator's Brochure, Sitravatinib. ~~Version 7.0, August 2020~~ **Version 8.1, August 2021**	Most recent version of sitravatinib IB was referenced to	N	NA

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Appendix 1	• Added superscript/footnote #2. "**Includes age or year of birth, gender, self-reported race/ethnicity, smoking history, and drinking history; history of treatment for the primary diagnosis, including prior medication, loco-regional treatment(s), and surgical treatment(s). Information on radiographic studies performed before study entry may be collected for review by the investigator. Pre-existing AEs at baseline should be recorded as medical history**";	For clarity	N	NA
Appendix 1	• Removed "Adverse events" evaluation from Survival follow-up	For consistency across document	N	NA
Appendix 1	• Footnote #8. If an ECG has been performed within ~~3 days of the first dose of study drug(s) and~~ **7 days prior to randomization or prior to** the EOT visit, the test does not need to be repeated on Cycle 1 Day 1, and the EOT visit**, respectively**.	For better operation	N	NA
Appendix 1	• Footnote #15. All measurable and ~~evaluable~~**nonmeasurable** lesions should be assessed and documented; **Screening assessments and each subsequent assessment of the tumor must include CT scans (with oral/intravenous contrast, unless contraindicated) or MRI of the chest, abdomen, and pelvis. Other known or suspected sites of disease must be included in the imaging assessments (neck, brain, etc). Imaging of the brain (preferably MRI) at baseline is required for all screened patients. Bone scans (Technetium-99m [Tc-99m]) or PET should be performed at Screening if clinically**	For easy reference; Update per tislelizumab Phase 3 study protocol template version 4.0	N	NA

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	indicated. If bone metastases are present at Screening and cannot be seen on CT or MRI scans, Tc-99m or PET bone scans should be repeated when a CR is suspected in target lesion or when progression in bone is suspected. ~~MRI scan of brain should be performed if clinically indicated.~~ • Tumor assessments are required to be performed on schedule regardless of whether study treatment has been administered or held. The same imaging technique should be used throughout the study for each patient. After the first documentation of response (CR or PR), confirmation of tumor response should occur ≥ 4 weeks after the first response or at the next scheduled assessment timepoint. ~~Progressive disease suspected as pseudoprogression needs to be confirmed by repeated imaging ≥ 4 weeks later but not exceeding 8 weeks from the date of initial documentation of PD. Patients who stop treatment prior to Patients who stop treatment before documentation of PD will undergo repeated imaging for tumor response assessments~~ (see **Section 7.5** for details).			

Abbreviations: AE, adverse event; ALK, anaplastic lymphoma kinase; AUC, area under the plasma or serum concentration-time curve; BOR, best overall response; C_{max}, maximum concentration that a drug achieves in tested area after the drug has been administrated; CR, complete response; CT, Computed Tomography; DCR, disease control rate; DDI, drug-durg interaction; DOR, duration of response; ECG, electrocardiogram; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EORTC QLQ-LC13, European Organisation for Research and Treatment of Cancer lung cancer module questionnaire; EOT, End of Treatment; EQ-5D-5L, European Quality of Life 5-Dimension 5-Level; HR, hazard ratio; HSD, Hwang-Shih-DeCani; IB, investigator's brochure; ICH, International Council for Harmonisation; IRC, independent review committee; ITT, Intent-to-Treat; MD, doctor of medicine; MMed, master of medicine; MMRM, mixed model repeated measures; MRI, magnetic resonance imaging; N, no; NA, not applicable; OS, overall survival; PD, progressive disease; PD-1, programmed cell death protein-1; PD-L1, programmed cell death protein ligand-1; PD-(L)1, programmed cell death protein-1/programmed cell death protein ligand-1; PET, positron emission tomography; PFS, progression-free survival; PK, pharmacokinetics; PP, Per-Protocol; PPI, proton-pump inhibitors; PR, partial response; QTc, corrected QT Interval; QTcF, Fridericia's correction formula for QT interval;

RECIST, Response Evaluation Criteria in Solid Tumors; SAP, statistical analysis plan; TC, tumor cells; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor; Y, yes.

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