BGB-A317-SITRAVATINIB-301
PROTOCOL AMENDMENT 3.0
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 Protocol Amendment 2.0 (20 May 2022) to Protocol Amendment 3.0 (09 August 2022). The primary purposes of this amendment are to:

- Add the dose modification & toxicity management for palmar-plantar erythrodysesthesia (PPE) associated with sitravatinib;
- Revise the language for dose modification in Section 8.9 to improve clarity;
- Revise the exclusion criteria to include patients with well-controlled HIV;
- Revise the exclusion criteria regarding QT interval corrected by Fridericia's method (QTcF);
- Revise to avoid concomitant medications that have potential interactions with sitravatinib;
- Revise to include electrocardiogram (ECG) monitoring around T_{max} of sitravatinib after the first dose and at steady state;
- Revise to collect additional PK samples for sitravatinib PK and exposure-response analysis;
- Remove PFS by investigator and DCR from alpha-controlled secondary efficacy endpoints;
- Update treatment eligibility review (TER) process.

Overall, changes have been made to correct typos and to enhance clarity and readability.

Key changes made from Protocol Amendment 2.0 to Protocol Amendment 3.0 are summarized in the table below.

~~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	• Updated sponsor address	Incorporate administrative and regulatory study updates	N	NA
Synopsis	• The protocol synopsis was updated to match the body of the protocol	For internal consistency with the protocol	N	NA
4.2. Exclusion Criteria Bullet 10 and 11	• Severe chronic or active infection (including tuberculosis infection, etc) requiring systemic antibacterial, antifungal, or antiviral therapy (not including antiviral therapy for hepatitis **or HIV**) within 14 days before randomization • **Untreated HIV infection, if known. Patients with a known HIV infection are eligible if the following criteria are met:** **b. Stable on antiretroviral therapy for ≥ 4 weeks before randomization** **c. Patient agrees to adhere to antiretroviral therapy per World Health Organization (WHO) guidelines**	To include patients with well-controlled HIV in this study	Y	Impact on conduct of the study

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	d. No documented multidrug resistance that would prevent effective antiretroviral therapy **e. Viral load of < 400 copies per mL at screening** **f. CD4+ T-cell count ≥ 350 cells/µL at screening** **g. No history of an AIDS-defining opportunistic infection ≤ 12 months before randomization unless eligibility is agreed to by the medical monitor after consultation** **h. If prophylactic antimicrobial drugs are indicated, patients may still be eligible upon agreement with the medical monitor** **For sites in Germany, patients with a known history of HIV infection or if HIV status is unknown, a positive HIV test at screening are excluded**			

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4.2. Exclusion Criteria Bullet 15. f.	• 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.	Based on available nonclinical and clinical data, the risk of QTc prolongation is low for sitravatinib. This criterion is updated to allow enrollment of male patients with QTcF longer than 450 msec, but no longer than 470 msec.	Y	Impact on conduct of the study
5.2.3. Docetaxel	• Premedication with ~~oral~~ corticosteroids will be required in accordance with regional standards.	For clarity	N	NA
6.3. Potential Interactions Between the Study Drugs and Concomitant Medications	• Concomitant medications that are sensitive substrates or substrates with a narrow therapeutic index for these CYP enzymes (examples listed in Appendix 11) should be ~~used with caution~~ **avoided** during sitravatinib treatment. • ~~Caution should therefore be used~~**Concomitant medications**	For clarity	Y	Impact on conduct of the study and safety of patients

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	that inhibit or induce P-gp should be avoided when administering sitravatinib to patients ~~taking medications that inhibit or induce P-gp~~. Concomitant medications that are sensitive substrates or substrates with narrow therapeutic indices for P-gp and/or BCRP transporters (examples listed in Appendix 11) should be ~~used with caution~~ **avoided** during sitravatinib treatment.			
7.2.1. Confirmation of Eligibility	• Removed Treatment Eligibility Form language Added that sponsor verification of patient eligibility will be managed by source data verification in accordance with ICH E6	Update per sponsor's current legal language Update per regulatory requirement	Y	Potential impact to the conduct management of the study
7.4.5. Electrocardiograms **Appendix 1, Footnote 9**	• **For patients in Arm A, ECG assessments will be performed at pre-dose (within 30 minutes before pre-dose PK sample collection of sitravatinib) and approximately 6 hours post dose (within 30 minutes before post-dose PK**	To include ECG monitoring around T_{max} of sitravatinib after the first dose and at steady state and for clarity	Y	Impact on conduct of the study

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	sample collection of sitravatinib) on Cycle 1 Day 1 and Cycle 2 Day 1. For other ECG assessments, when coinciding with blood draws at the same timepoint, ECG assessment should be performed either before blood draws or at least 30 minutes after blood draws. Patients should rest in semirecumbent supine position for at least 10 minutes before ECG collection. **If an ECG has been performed within 7 days before randomization (for patients in Arm B) or before the EOT visit (for all patients), the test does not need to be repeated on Cycle 1 Day 1, and the EOT visit, respectively.** ECG collection may be done at other timepoints as clinically indicated.			
7.4.8. Hepatitis B, Hepatitis C, and HIV Testing **Appendix 1, Footnote 15**	• **HIV serology is required at screening for patients in Germany with an unknown HIV status and will include antigen and/or antibodies. Viral load assessment (HIV RNA) and CD4+ T-cell count tests will be conducted at screening for patients outside Germany with a known HIV infection.**	To align with IC/EC	Y	Impact on conduct of the study

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8.9. Management of Sitravatinib-specific Adverse Events	• Revised language to more clear instructive language for all dose modifications	For clarity and consistency	N	NA
8.9.3. Dose Modification Guidelines for Sitravatinib-Specific AEs	• Added a table for the dose modification and toxicity management of sitravatinib for PPE • Clarified sitravatinib dose modification for increased blood pressure and increased hepatic transaminase	For clarity	N	NA
9.1.3. Multiplicity	• By using the graphic approach of Bretz et al 2009, if the PFS or OS hypotheses are both rejected, the corresponding alpha will be shifted to the hypothesis test~~s~~ of the secondary efficacy endpoint **ORR per RECIST v1.1 assessed by the IRC**~~s (ie, PFS assessed by investigator, DCR and ORR per RECIST v1.1 assessed by the IRC), which will be tested sequentially. The inferential test will be stopped at the first nonsignificant endpoint~~.	Removed PFS by investigator and DCR from alpha-controlled secondary efficacy endpoints in response to health authority request	N	NA
9.7. Sample Size Consideration	• The ~~censoring~~**dropout** rate for OS is assumed to be 5% per year.	For clarity	N	NA

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9.8. Interim Analyses	• **Final analysis of PFS will be performed at the time of the interim analysis of OS. No interim analysis of PFS for efficacy is planned.**	For clarity	N	NA
Appendix 2. Schedule of Pharmacokinetics/ Antidrug Antibody Assessments **Sitravatinib and M10 PK (Only for patient from Arm A)**	• Updated to collect pre-dose PK samples for sitravatinib and M10 on C9D1 and C17D1 from all patients of Arm A.	For adequate population in PK and exposure-response analysis	Y	Impact on conduct of the study
Appendix 2. Schedule of Pharmacokinetics/ Antidrug Antibody Assessments **Tislelizumab PK/ADA (Only for patients from Arm A)**	• Revised the allowable window for EOT visit to 30 (± 7) days after last dose	For clarity	N	NA

Abbreviations: ADA, antidrug antibody; AE, adverse event; ECG, electrocardiogram; EOT, end-of-treatment; HIV, human immunodeficiency virus; IC/EC, inclusion criteria/ exclusion criteria; ICH, International Council for Harmonization; IRC, independent review committee; N, no; NA, not applicable; ORR, overall response rate; OS, overall survival; PD-(L)1, programmed cell death protein-1/programmed cell death protein ligand-1; PFS, progression-free survival; PK, pharmacokinetics; PPE, palmar-plantar erythrodysesthesia; QTcF, QT interval corrected by Fridericia's method; RNA, ribonucleic acid; TER, treatment eligibility review; Y, yes.