BGB-A317-SITRAVATINIB-301

AMENDMENT 2.0

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 study protocol from Protocol Amendment 1.0 (03 November 2021) to Protocol Amendment 2.0 (20 May 2022). The primary purpose of this amendment is to expand the patient population to include additional patients who progressed on anti-programmed cell death protein-1 (PD-1)/programmed cell death ligand-1 (PD-L1) (anti-PD-[L]1) antibody and chemotherapy and who may benefit from the investigational treatment (ie, tislelizumab in combination with sitravatinib).

Patients who progressed on or after prior anti-PD-(L)1 and platinum-based doublet chemotherapy in the following prior treatment conditions for NSCLC are allowed for enrollment in the PA 2.0:

- Anti-PD-(L)1 antibody administered before platinum-based chemotherapy or
- Anti-PD-(L)1 antibody as consolidation treatment following definitive chemoradiation for unresectable Stage III NSCLC, if the disease progression occurred within 6 months after the end of platinum-based chemotherapy component of the definitive chemoradiation therapy;
- Anti-CTLA-4 used in combination with anti-PD-(L)1.

Changes made from Protocol Amendment 1.0 to Protocol Amendment 2.0 are summarized in the table below. Some minor updates were made to correct typos for the improvement of 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	• **EudraCT Number: 2022-001779-15**	• Added the clinical trial number registered in Europe	Y	N
Synopsis **3.1. Summary of Study Design** **4.1. Inclusion Criteria #6**	• Patients with locally advanced or metastatic NSCLC who have disease progression following platinum-based chemotherapy and anti-PD-(L)1 antibody, with the anti-PD-(L)1 antibody administered in combination with ~~or following~~, **or sequentially before or after** platinum-based chemotherapy (also in **Figure 1**) • In addition, 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. **If anti-PD-(L)1-containing therapy is not the most recent systemic treatment, patients should also have radiographic progression per RECIST v1.1 on or after the most recent systemic treatment.**	• There is a high unmet medical need in patients with advanced NSCLC who had disease progression following platinum-based chemotherapy and anti PD-(L)1 antibody • Considering the functional mechanism of sitravatinib, it's assumed that the sequence of prior platinum-based chemotherapy and anti-PD-(L)1 antibody may not impact the efficacy of tislelizumab in combination with sitravatinib treatment • Anti-PD-(L)1 antibody monotherapy is recommended as the first-line treatment for NSCLC with high PD-L1 expression in guidelines and widely accepted in clinical practice.	Y	N
Synopsis **3.1. Summary of Study Design** **4.1. Inclusion Criteria #6b**	• If chemoradiation is followed by planned systemic therapy without documented progression between chemoradiation and systemic therapy, the entire treatment course counts as 1 line of therapy (~~patients with unresectable Stage III NSCLC who~~	• There is an unmet medical need in the patients who had disease progression following definitive chemoradiation and anti-PD-(L)1 antibody consolidation treatment for unresectable Stage III NSCLC	Y	N

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	~~received anti-PD-(L)1 antibody as consolidation after definitive chemoradiation are not allowed~~ **Patients who received anti-PD-[L]1 antibody as consolidation treatment following definitive chemoradiation for unresectable Stage III NSCLC can be enrolled immediately after disease progression, if the disease progression occurred within 6 months after the end of platinum-based chemotherapy component of the definitive chemoradiation**).	• Patients who have disease progression within 6 months after end of platinum-based chemotherapy is considered resistant to prior chemotherapy and will receive next line chemotherapy including docetaxel		
Synopsis **3.1. Summary of Study Design**	• Patients with known *EGFR* or *BRAF* **sensitizing** mutation, or *ALK* or *ROS1* rearrangement are ineligible for the study (also in **Figure 1**) • In locally advanced and unresectable NSCLC, disease progression on or within 6 months ~~of end~~ **after the end of systemic therapy as part of** prior curatively intended multimodal therapy will be counted as a prior line of systemic therapy (also in **Section 4.1** #6b).	For consistency and accuracy	N	NA
Synopsis **3.1. Summary of Study Design**	• Patients with histologically **or cytologically** confirmed locally advanced or metastatic (Stage IIIB/IIIC or Stage IV) NSCLC (also in **Figure 1**)	For accuracy	N	NA
4.1. Inclusion Criteria #3	• Metastatic or unresectable locally	For accuracy	N	NA

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	advanced histologically **or cytologically** confirmed NCSLC, not amenable to treatment with curative intent			
Synopsis **3.1. Summary of Study Design** **4.1. Inclusion Criteria #6d**	• Maintenance therapy following platinum-based chemotherapy is not considered as a separate line of therapy. No other prior immunotherapies with 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, will be allowed (**prior anti-CTLA-4 used in combination with anti-PD-[L]1 is permitted**).	• Anti-CTLA4 antibody in combination with anti-PD-(L)1 antibody-based treatment has been approved by the FDA as the first-line treatment for NSCLC • High myeloid-derived suppressor cell (MDSC) in tumor microenvironment is a potential resistance mechanism in anti-CTLA-4 or anti-PD-(L)1 therapy, which could be targeted by sitravatinib	Y	NA
Synopsis **5.2.3. Docetaxel**	• Premedication with ~~dexamethasone~~**oral corticosteroids** will be required in accordance with regional standards.	For clarity	N	NA
1.1. Background Information on NSCLC **1.2. Current Treatment of NSCLC and Unmet Clinical Needs**	• Updated the background information on the treatment of NSCLC	For clarify and to provide updated information	N	NA
1.4.3. Clinical Pharmacology	• Updated the clinical pharmacology data of tislelizumab	To provide updated information in support of the study design	N	NA
1.5.3. Clinical Pharmacology	• Updated the clinical pharmacology data of sitravatinib	To provide updated information in support of the study design	N	NA

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1.5.4.2. Safety Assessment of Combination Study	• Added the safety data from Study BGB-900-103	To provide more safety data in support of the investigational treatment	N	NA
1.6.2. Rationale for Selection of Tislelizumab Dose	• Updated the rationales for the selection of tislelizumab dose	To provide more detailed data justifying the dose selection	N	NA
1.6.3. Rationale for Selection of Sitravatinib Dose	• Updated the rationales for the selection of sitravatinib dose	To provide more detailed data justifying the dose selection	N	NA
1.6.4. Rationale for Dose Selection of Sitravatinib and Tislelizumab in Combination Treatment	• Split from **Section 1.6.3** to a new **Section 1.6.4**, with minor updates in wordings for clarity	For clarity	N	NA
1.6.6. Rationale for Combination of Tislelizumab and Sitravatinib in the Treatment of NSCLC	• In both of these studies, anti-PD-(L)1 therapy was required to be the most recent prior treatment. As patients who have disease progression on or after the upfront anti-PD-(L)1 therapy that was followed by chemotherapy are also refractory/resistant to anti-PD-(L)1 therapy, based on the mechanism of sitravatinib, it is speculated that sitravatinib in combination with a checkpoint inhibitor is beneficial to those patients, just as to the subset of patients who received anti PD-(L)1 therapy as the most recent prior treatment.	To provide more rationale for the study patient population	N	NA
1.7. Benefit-Risk Assessment	• ~~However, the risk:benefit assessment for this combination has not yet been established.~~ • More than ~~1000~~ **3000** patients have been treated with tislelizumab as monotherapy	• Removed because the risk-benefit assessment had been addressed • Updated per tislelizumab Investigator Brochure Edition 9.0	N	NA

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	at clinically relevant doses (≥ 2 mg/kg) **or**~~and~~ in combination with other drugs.			
4.1. Inclusion Criteria #10b	• ~~Serum creatinine ≤ 1.5 x upper limit of normal (ULN) or estimated~~**Estimated** glomerular filtration rate (GFR) ≥ ~~60~~**45** mL/min/1.73 m^2 by Chronic Kidney Disease Epidemiology Collaboration equation	• An isolated serum creatinine concentration is unsatisfactory for the evaluation of renal function as it depends on creatinine production, which is related to muscle mass, as well as on renal elimination of creatinine, so serum creatinine alone is removed as an eligibility criterion for renal function • Docetaxel is predominantly eliminated by hepatobiliary extraction. Renal excretion is minimal (~6%); therefore, the need for dosage adjustments for renal dysfunction is unlikely, so the criterion for GFR is revised to expand the study population with no expected increase in the risk of renal toxicity	N	NA
4.2. Exclusion Criteria #4	• Active leptomeningeal disease for metastatic NSCLC**,** or uncontrolled~~,~~ **or** untreated brain metastasis.	For clarity	N	NA
4.2. Exclusion Criteria #21	• ~~Patients treated with any Chinese herbal medicine or Chinese patent medicines used to control cancer within 14 days of randomization~~ **Received any Chinese herbal medicine or Chinese patent**	For safety considerations, to minimize the likelihood of developing post-radiation pneumonitis	N	NA

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	medicine for the treatment of NSCLC within 14 days before randomization, or received palliative radiation within 28 days before randomization for the lung, or within 14 days before randomization for other organs.			
4.2. Exclusion Criteria #22b	• ≥ 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, and pneumonitis, which are exclusionary.	Exclusion criterion #22c defines CNS or ocular AE of any grade related to anti-PD-(L)1 as unacceptable toxicity on prior anti-PD-(L)1 treatment, which covered ≥ Grade 2 encephalitis	N	NA
5.1.3. Docetaxel	• Management (ie, handling, storage, ~~administration,~~ and disposal) of docetaxel will be in accordance with the relevant local guidelines and/or prescribing information.	For clarity	N	NA
7.4.4. Laboratory Safety Tests	• If laboratory tests at screening are ~~not~~ performed within 7 days before randomization, these tests ~~should~~ **(hematology, clinical chemistry, coagulation, urinalysis, and pregnancy test, if applicable) do not have to** be repeated and **the test results must be** reviewed before ~~administration~~**the first dose** of study drug(s).	For clarity	N	NA
7.7.1. Tissue Biomarkers Appendix 1 Schedule of	• Archival tumor tissues (FFPE blocks or approximately 15 [~~≥ 5~~**at least 5 slides for**	For clarity	N	NA

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Assessments Footnote #17	**PD-L1 assessment**] freshly cut unstained FFPE slides from each block) must be collected (if available) for biomarker analysis to assess PD-L1 expression (mandatory) and, if tissue samples are sufficient, to assess biomarkers such as GEP, DNA alteration, tTMB and MSI (optional).			
8.1.1. Risks Associated With Tislelizumab and Sitravatinib	• Tislelizumab and sitravatinib are investigational agents that are currently in clinical development. **Across studies, the safety profile of tislelizumab is consistent with the therapeutic class of the drug. When combined with another investigational agent, the safety profile of the combination is generally consistent with the safety profiles of each drug given as monotherapy.** • Limited safety data for sitravatinib ~~and~~**in combination with** tislelizumab in patients are available, and the full safety profiles have not been characterized. • The guidelines for management of potential AEs more specific to treatment with sitravatinib or agents in the same class of cancer treatment are presented in Section ~~8.8~~ **8.9.**	• Updated the safety profile of tislelizumab according to the ociperlimab/tislelizumab Phase 3 protocol template; • For clarity; • Correction of typo	N	NA
9.3.2. Adverse Events	• A TEAE is defined as an AE that had an onset date or a worsening in severity from	Updated the new TEAE definition for tislelizumab	N	NA

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	baseline (pre-treatment) on or after the first dose of study drug and up to 30 days following study drug discontinuation or initiation of new anticancer therapy, whichever occurs first. **Only those AEs that were treatment emergent will be included in summary tables of TEAEs.** • **Immune-mediated AEs will be identified from all AEs that had an onset date or a worsening in severity from baseline (pretreatment) on or after the first dose of tislelizumab and up to 90 days from the last dose of tislelizumab, regardless of whether the patient starts a new anticancer therapy.**~~For the treatment arm, imAEs 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 TEAEs.~~			
9.4. Pharmacokinetic Analysis	• Cmax (~~μg~~**ng**/mL) • C_{τ} (~~μg~~**ng**/mL) • $AUC_{(0\text{-}t)}$ (~~μg~~**ng**•h/mL)	Switch to a more appropriate unit	N	NA
13.4. Patient and Data Confidentiality	• Updated the patient and data confidentiality language per the latest updates in the corporate statement	To enhance the protection for patient and data confidentiality	N	NA

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Appendix 1. Schedule of Assessments Footnote #14	• Thyroid function tests **for FT3, FT4, and TSH** will be performed at Screening and every 3 cycles (ie, Day 1 of Cycles 4, 7, 10, etc), and at the EOT Visit. **If test for FT3 or FT4 is not available, TT3 or TT4 should be tested instead.**	For clarity	N	NA
Appendix 10	• < 55 years of age with no spontaneous menses for ≥ 12 months AND with postmenopausal follicle-stimulating hormone (FSH) concentration > 30 **m**IU/mL and all alternative medical causes for the lack of spontaneous menses for ≥ 12 months have been ruled out, such as polycystic ovarian syndrome, hyperprolactinemia, etc.	Correction of typo	N	NA

Abbreviations: AE, adverse event; ALK, anaplastic lymphoma kinase; $AUC_{(0\text{-}t)}$, area under the plasma concentration-time curve from time zero to the last measurable timepoint calculated by log-linear trapezoidal summation; BRAF, B-Raf proto-oncogene; CTLA-4, cytotoxic T-lymphocyte associated protein 4; C_{max}, observed maximum plasma concentration during a sample interval; Cτ, observed trough concentration at steady state; eGFR, estimating glomerular filtration rate; EGFR, epithelial growth factor receptor; EOT, end of treatment; EudraCT, European Union drug regulating authorities clinical trials database; FDA, food and drug administration; FT3, free triiodothyronine; FT4, free thyroxine; GEP, gene expression profile; ICH, International Council for Harmonisation; imAE, immune-mediated adverse event; MSI, microsatellite instability; N, no; NA, not applicable; NSCLC, non-small cell lung cancer; OX40, TNF receptor superfamily member 4; 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; RECIST, Response Evaluation Criteria in Solid Tumors; ROS1, ROS proto-oncogene 1; TEAE, treatment-emergent adverse event; TIGIT, T cell immunoreceptor with Ig and ITIM domains; tTMB, tissue tumor mutation burden; TT3, serum total triiodothyronine, TT4, serum total thyroxine; TSH, thyroid stimulating hormone; ULN, upper limit of normal; Y, yes.