DESCRIPTION ON AMENDMENTS TO PROTOCOL CIBI308E301

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No	Section / page	Original protocol (V3.1)	Current protocol (V3.2)	Reason for changes
1	Cover, synopsis, and footer/P1，P3	**Version No./Date** ~~Dec. 30, 2020 Version 3.1~~	**Version No./Date** Jun 11, 2021 Version 3.2	Version revision
2	Cover, Sponsor's Signature Page/P1, P2	~~Medical Director~~	Executive Director of Medical Science	Position updates
3	Sponsor's Signature Page/ P2	Senior Director, Biostatistics	Executive Director of Biostatistics	Position updates
4	Synopsis, 3.1 Overall design/P3-4、P30	The primary endpoint of the study is the OS in the intention-to-treat (ITT) population or in the PD-L1 positive subjects (~~CPS ≥ 10~~)	The primary endpoint of the study is the OS in the intention-to-treat (ITT) population or in the PD-L1 positive subjects (CPS ≥ 5)	Modify the definition of PD-L1 positive population
5	Synopsis, statistical methods /P8-9	The primary endpoint of this phase III trial is OS~~. The OS in the overall population is evaluated with an α of 0.03 (two-sided), and OS in the PD-L1-positive subgroup is evaluated with an α of 0.02 (two-sided)~~ to strictly control the overall type I error for the hypothesis test of OS in the two populations. ~~For OS in the overall population, assuming that the hazard ratio (HR) of IBI308 to placebo, in combination with chemotherapy, is 0.75 (median OS is 14.6 months and 11 months, respectively), 505 OS events are required to provide about 85% power. It is estimated that approximately 38.5% of the overall population is PD-L1 positive. For OS in the PD-L1 positive~~	This study is a phase III clinical study. The primary efficacy endpoints are OS in PD-L1-positive population and OS in ITT population. The test will be performed in a fixed order. The test of OS in ITT population will be performed only when the PD-L1-positive population reaches statistically significant, so as to strictly control the overall type I error of hypothesis test on the two populations for OS efficacy endpoints. For OS in the PD-L1-positive population, assuming the hazard ratio (HR) of IBI308 to placebo, in combination with chemotherapy, is 0.7 (median OS is 15.7 and 11 months, respectively),	Modify the HR assumption for PD-L1 postitive population. modify the alpha allocation as fixed order. Modify the proportion of PD-L1 positive population

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		~~population, assuming that the HR of IBI308 to placebo, in combination with chemotherapy, is 0.65 (median OS is 16.9 and 11 months, respectively), 191 OS events are required to be observed at a level of 0.02 (two-sided) with 74.5% power.~~ The above calculations are based upon a 0.5% censoring rate of each month. The study will take 18 months to enroll 650 subjects, with 325 in each group. ~~505 OS events are estimated to be observed within 42 months~~. ~~As mentioned above, the type I error ratio between the OS in the overall population and OS in the PD-L1-positive subgroup is based on the assumption that the proportion of subjects who are PD-L1 positive is higher than 30%. If the proportion of PD-L1-positive subjects defined based on baseline tests is less than 30% of the overall subject population after the enrollment is completed, then the α is adjusted to 0.035 for the overall population and 0.015 for the PD-L1-positive subgroup.~~ ~~For OS, though the overall type I error rate is maintained by pre-specifying the α used for evaluating the overall population and the PD-L1-positive population, the latter is tested only if the former is not~~	287 OS events are required to be at a level of 0.05 (two sided) with 85% power. For OS in the ITT population, assuming that the HR of IBI308 to placebo, in combination with chemotherapy, is 0.75 (median OS is 14.7 and 11 months, respectively), 515 OS events are required to be at a level of 0.05 (two sided) with 90% power. The above calculations are based upon a 0.5% censoring rate of each month. The study will take 18 months to enroll 650 subjects, with 325 in each group. 515 OS events are estimated to be observed within 46 months. Based on the above assumptions, the PD-L1-positive population accounted for 56.2% (i.e., 365) of the ITT population with 287 OS events observed at the final analysis in the PD-L1-positive population. The enrollment rate and dropout rate observed as well as OS distribution when blinded will be used to predict and determine the cut-off time points for interim OS analysis and final OS analysis	

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		~~statistically significant.~~ The enrollment rate and dropout rate observed as well as OS distribution when blinded will be used to predict and determine the cut-off time points for interim OS analysis and final OS analysis.		
6	Synopsis, Hypothesis test/P9	The primary efficacy endpoints are the OS in the ~~overall~~ population and in the PD-L1-positive population	The primary efficacy endpoints are the OS in the ITT population and in the PD-L1-positive population	Wording modification
7	Synopsis, Interim analysis/P9	~~This study is designed with one futility interim analysis at the time point when 200 PFS events are observed. In this analysis, the conditional probability is calculated based on the estimated OS HR corrected via PFS weighting. If this probability is higher than 55%, the sponsor will continue the trial based on safety data until a specified number of OS events are observed. This interim analysis is non-binding.~~	In this study, hypothesis tests will be performed in a fixed order. The superiority test will be performed on the OS of PD-L1 positive population first, and the OS test will be performed on the ITT population after the OS of PD-L1 positive population reaches statistically significance. This study plans to conduct an interim analysis of OS in both the PD-L1-positive population and the ITT population when the number of OS events is at least 70% (i.e., 361 in the ITT population and 201 in the PD-L1-positive population), and the test level will follow the Lan-Demets approach to approximate the O'Brien-Fleming boundary. At the interim analysis, with a nominal test of 0.0148, the minimum detectable difference (MDD) in OS was HR = 0.709 in the	Interim analysis plan updates

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			PD-L1-positive population and HR = 0.774 in the ITT population. At the final analysis, the nominal test level was 0.0455 with MDD for OS of HR = 0.790 for the PD-L1 positive population and HR = 0.838 for the ITT population. The exact alpha value of the OS analysis will be adjusted according to the Lan-DeMets approximation of the O'Brien-Fleming boundary based on the number of OS events that occur in real time to ensure an overall OS detection level of $\alpha = 0.05$. At the same time, this study plans to conduct an interim analysis of safety data at 200 PFS events to monitor the overall safety of clinical trial subjects.	
8	Synopsis, Biomarker/P9	Expression levels and distribution of PD-L1 ~~and other biomarkers~~ as well as transcriptomic characteristics of tumor tissues are subject to descriptive statistics and explored for their association with efficacy.	Expression level and distribution of PD-L1 is subject to descriptive statistics and explored for its association with efficacy	Updates biomarker analysis content
9	Table 1 Schedule of visits/P14	Subjects are required to provide at least 5 slices of archival or new tumor tissue samples (within 6 months prior to screening and signing of ICF) during screening to test PD-L1 expression.	Subjects are required to provide at least 5 slices of archival or new tumor tissue samples (within 6 months prior to screening and signing of ICF and 3 months of section) during screening to test PD-L1 expression	Clarification for sample requirement

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10	3.2.2 Rationale for a CPS ≥ 5 as the defined PD-L1 positivity/P31	In current studies of PD-1 monoclonal antibodies, immunohistochemistry is commonly used to detect the level of PD-L1 expression. However, the threshold for positivity varies because the detection reagents used are different. For example, 22C3 is used to identify PD-L1-positive patients for treatment with pembrolizumab, with 1% or 50% as the threshold for PD-L1 positivity. The relationship between PD-L1 expression and treatment efficacy in lung cancer has been confirmed in prospective clinical studies. The threshold for PD-L1 positivity in GC has not been defined yet. ~~According to the results of KEYNOTE-061 clinical study involving subjects with advanced GC, patients with a CPS ≥ 10 are more likely to benefit from the PD-1 antibody treatment. Thus the efficacy of IBI308 in combination with chemotherapy in advanced GC patients with a PD-1 CPS ≥ 10 will be explored, and the PD-L1 positivity is pre-defined as CPS ≥ 10 for this study.~~	In current studies of PD-1 monoclonal antibodies, immunohistochemistry is commonly used to detect the level of PD-L1 expression. However, the threshold for positivity varies because the detection reagents used are different. For example, 22C3 is used to identify PD-L1-positive patients for treatment with pembrolizumab, with tumor proportion score (TPS) ≥ 1% or 50% as the threshold for PD-L1 positivity in lung cancer. The relationship between PD-L1 expression and treatment efficacy in lung cancer has been confirmed in prospective clinical studies. The threshold for PD-L1 positivity in GC has not been uniformed yet. The advanced gastric cancer clinical study KEYNOTE-059 included patients with a combined positive score (CPS) ≥ 1, and both KEYNOTE-061 and KEYNOTE-062 suggested that patients with CPS ≥ 10 appeared to benefit from anti-PD-1 monoclonal antibody; while CPS ≥ 5 was used as the primary study endpoint in another CheckMate-649 study for advanced gastric cancer, and it was confirmed that the PD-L1-positive population benefited more than the whole population.	Provide additional information to support primary population change

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			Taking into account the published clinical data in gastric cancer studies and the distribution of PD-L1 expression levels in the Chinese population, we sought to explore the efficacy of the combination of chemotherapy with sintilimab in these patients with PD-L1 expression CPS ≥ 5 in advanced gastric cancer, and this study defined PD-L1CPS ≥ 5 as the positive cut-off value.	
11	5.1.1 IBI308/P40	Administer with a 0.2~~–1.2 μm~~ in-line filter (suggested infusion time is 30–60 min). Document the start and stop time of infusion.	Administer with a 0.2~5.0 μm in-line filter (suggested infusion time is 30–60 min). Document the start and stop time of infusion	Updates based on CMC requirement
12	9.2 Hypothesis and Sample Size Calculation/P79-80	~~OS in the overall population is evaluated with an α of 0.03 (two-sided), and OS in the PD-L1-positive subgroup is evaluated with an α of 0.02 (two-sided)~~ to strictly control the overall type I error for the hypothesis test of OS in the two populations. For OS in the overall population, assuming that the hazard ratio (HR) of IBI308 to placebo, in combination with chemotherapy, is 0.75 (median OS is ~~14.6~~ months and 11 months, respectively), ~~505 OS events~~ are required to provide ~~about 85% power~~. It is estimated that approximately 38.5% of the overall population is PD-L1 positive. For OS in the PD-L1 positive population, ~~assuming that the HR of IBI308 to placebo, in combination with chemotherapy, is 0.65 (median OS~~	This study is a phase III clinical study. The primary efficacy endpoints are OS in PD-L1-positive population and OS in ITT population. The test will be performed in a fixed order. The test of OS in ITT population will be performed only when the PD-L1-positive population reaches statistically significant, so as to strictly control the overall type I error of hypothesis test on the two populations for OS efficacy endpoints. For OS in the PD-L1-positive population, assuming the hazard ratio (HR) of IBI308 to placebo, in combination with chemotherapy, is 0.7 (median OS is 15.7 and 11 months, respectively), 287 OS events are required to be at a level of 0.05	Statistical analysis plan updates

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		~~is 16.9 and 11 months, respectively), 191 OS events are required to be observed at a level of 0.02 (two-sided) with 74.5% power.~~ The above calculations are based upon a 0.5% censoring rate of each month. The study will take 18 months to enroll 650 subjects, with 325 in each group. ~~505 OS events are estimated to be observed within 42 months.~~ ~~A futility interim analysis will be performed, based on PFS and OS in the overall population, when about 200 PFS events are observed in the study. In this analysis, the conditional probability is calculated based on the estimated OS HR corrected via PFS weighting. If this probability is higher than 55%, the sponsor will continue the trial based on safety data until a specified number of OS events are observed.~~ ~~As mentioned above, the type I error ratio between the OS in the overall population and OS in the PD-L1-positive subgroup is based on the assumption that the proportion of subjects who are PD-L1 positive is higher than 30%. If the proportion of PD-L1-positive subjects defined based on baseline tests is less than 30% of the overall subject population after the enrollment is completed, then the α is adjusted to 0.035 for the overall population and 0.015 for the PD-L1-~~	(two sided) with 85% power. For OS in the ITT population, assuming that the HR of IBI308 to placebo, in combination with chemotherapy, is 0.75 (median OS is 14.7 and 11 months, respectively), 515 OS events are required to be at a level of 0.05 (two sided) with 90% power. The above calculations are based upon a 0.5% censoring rate of each month. The study will take 18 months to enroll 650 subjects, with 325 in each group. 515 OS events are estimated to be observed within 46 months. Based on the above assumptions, the PD-L1-positive population accounted for 56.2% (i.e., 365) of the ITT population with 287 OS events observed at the final analysis in the PD-L1-positive population. In this study, hypothesis tests will be performed in a fixed order. The superiority test will be performed on the OS of PD-L1 positive population first, and the OS test will be performed on the ITT population after the OS of PD-L1 positive population reaches statistical significance. This study plans to conduct an interim analysis of OS in both the PD-L1-positive population and the ITT population when the number of OS events is at least 70% (i.e., 361 in the ITT population and 201 in the PD-L1-positive population), and the test level will follow the Lan-Demets approach to	

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		~~positive subgroup. For OS, though the overall type I error rate is maintained by pre-specifying the α used for evaluating the overall population and the PD-L1-positive population, the latter is tested only if the former is not statistically significant~~.	approximate the O'Brien-Fleming boundary. At the interim analysis, with a nominal test of 0.0148, the minimum detectable difference (MDD) in OS was HR = 0.709 in the PD-L1-positive population and HR = 0.774 in the ITT population. At the final analysis, the nominal test level was 0.0455 with MDD for OS of HR = 0.790 for the PD-L1 positive population and HR = 0.838 for the ITT population. The exact alpha value of the OS analysis will be adjusted according to the Lan-DeMets approximation of the O'Brien-Fleming boundary based on the number of OS events that occur in real time to ensure an overall OS detection level of α = 0.05. At the same time, this study plans to conduct an interim analysis of safety data at 200 PFS events to monitor the overall safety of clinical trial subjects.	
13	9.4.1.1 Analysis of primary efficacy endpoint/P81	The primary endpoint is OS of overall population or PD-L1-positive subjects. • OS of overall population or OS-PD-L1-positive population，……。	The primary endpoint is OS of ITT population or PD-L1-positive subjects • OS of ITT population or OS-PD-L1-positive population，……。	Wording modification
14	9.4.5 Interim analysis /P84	~~A futility interim analysis will be performed, based on PFS and OS in the overall population, when about 200 PFS events are observed in the study. In this analysis, the conditional probability is calculated based on the~~	In this study, hypothesis tests will be performed in a fixed order. The superiority test will be performed on the OS of PD-L1 positive population first, and the OS test will be performed	Statistical analysis plan updates

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		~~estimated OS HR corrected via PFS weighting. If this probability is higher than 55%, the sponsor will continue the trial based on safety data until a specified number of OS events are observed. This interim analysis is non-binding.~~ The interim analysis is conducted in blinded form. Unblinded data is only accessible to the iDMC. Refer to Section **Error! Reference source not found.** for details regarding the iDMC. ~~Calculating the conditional probability based on the estimated OS HR corrected via PFS weighting is detailed in the iDMC manual.~~	on the ITT population after the OS of PD-L1 positive population reaches statistical significance.This study plans to conduct an interim analysis of OS in both the PD-L1-positive population and the ITT population when the number of OS events is at least 70% (i.e., 361 in the ITT population and 201 in the PD-L1-positive population), and the test level will follow the Lan-Demets approach to approximate the O'Brien-Fleming boundary.At the interim analysis, with a nominal test of 0.0148, the minimum detectable difference (MDD) in OS was HR = 0.709 in the PD-L1-positive population and HR = 0.774 in the ITT population.At the final analysis, the nominal test level was 0.0455 with MDD for OS of HR = 0.790 for the PD-L1 positive population and HR = 0.838 for the ITT population.The exact α value of OS analysis will be adjusted according to the number of OS events occurring in real time to approximate the O'Brien-Fleming boundary according to the Lan-DeMets method, so as to ensure the overall detection level of OS α = 0.05.At the same time, this study plans to conduct an interim analysis of safety data at 200 PFS events to monitor the overall safety of clinical trial subjects.The interim analysis will be performed under blind conditions, and the unblinded results	

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			will only be delivered to the iDMC. Refer to Section **Error! Reference source not found.** for details regarding the iDMC.	
15	9.4.7 Multiple comparisons and adjustments/P84	~~In order to maintain an overall α of 0.05 (two-sided), OS in the overall population is evaluated with an α of 0.03 (two-sided), and OS in the PD-L1-positive subgroup is evaluated with an α of 0.02 (two-sided) to strictly control the overall type I error for the hypothesis test of OS in the two populations.~~ ~~If the proportion of PD-L1-positive subjects defined based on baseline tests is less than 30% of the overall subject population after the enrollment is completed, then the α is adjusted to 0.035 for the overall population and 0.015 for the PD-L1-positive subgroup.~~ ~~In this study, OS in PD-L1-positive population is tested only if the OS in the overall population is not statistically significant.~~	In this study, a fixed order test will be used to control the overall α of 0.05 (two sided). The superiority test will be performed on the OS of PD-L1 positive population firstly, and then the OS test will be performed on the ITT population after the OS of PD-L1 positive population reaches statistical significance. The overall type I error for hypothesis testing on both populations for the efficacy endpoints of OS was tightly controlled through a fixed order testing approach. The final multiplicity comparison strategy will also be defined and specified in the statistical analysis plan and iDMC charter prior to database lock (under blind data) to ensure that the overall test level with an α of 0.05 (two sided).	Statistical analysis plan updates
16	9.4.9Exploratory analysis /P85	…… ~~To evaluate the correlation between biomarkers in tumor tissue and efficacy, including PD-L1 expression level and transcriptomic characteristics of tumor tissues~~	…… To descriptive statistic the expression level and distribution of PD-L1, and explore the potential relationship between PD-L1 expression and efficacy	Biomarker analysis updates

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17	9.5.2 Blinding maintenance evaluation/P85	…… In this study, iDMC is set for the ~~interim~~ and final OS analysis。……	…… In this study, iDMC is set for the interim analysis of safety, the interim and final OS analysis。……	Clarification for interim analysis