Research Protocol for the Phase I Clinical Study of the Recombinant Fully Human Anti-PD-L1 Monoclonal Antibody Socazolimab

An Open, Dose-Escalation and Expansion, Phase I Clinical Study in Patients with Recurrent or Metastatic Cancer upon Administration Every Two Weeks

Protocol Number: NTL-LEES-2017-02

Protocol Date: 2020.2.20

Version Number: 5.0

Zhaoke (Guangzhou) Oncology Pharmaceutical Ltd.

TABLE OF CONTENTS

ABBREVIATIONS

AUC	Area Under Concentration-Time Curve
BOR	Best Overall Response
CR	Complete Response
CRF	Case Report Form
CT	Computer Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DCR	Disease Control Rate
DLT	Dose-Limiting Toxicity
DOR	Duration of Response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic Data Capture System
GCP	Good Clinical Practice
irAEs	Immune-Related Adverse Events
i.v.	Intravenous Injection
iBOR	Immune-Related Best Overall Response
iORR	Immune-Related Overall Response Rate
iCR	Immune-Related Complete Response
iPD	Immune-Related Progressive Disease
iPR	Immune-Related Partial Response
iSD	Immune-Related Stable Disease
iRECIST	Immune-Related Response Evaluation Criteria in Solid Tumours
IRB/IEC	Institutional Review Board/Independent Ethics Committee
IRC	Independent Review Committee
MRI	Magnetic Resonance Imaging
MTD	Maximum-Tolerated Dose
NCI	National Cancer Institute
ORR	Overall Response Rate
PD	Progressive Disease
PD-1	Programmed Cell Death-1
PD-L1	Programmed Cell Death- Ligand 1
PD-L2	Programmed Cell Death- Ligand 2
PFS	Progression-Free Survival
PK	Pharmacokinetics
PR	Pharmacodynamics
RECIST	Response Evaluation Criteria in Solid Tumours
RR	Response Rate
SD	Stable Disease
SOP	Standard Operating Procedures
ULN	Upper Limits of Normal

ABSTRACT

Study Name	An Open, Dose-Escalation and Expansion, Phase I Clinical Study in Patients with Recurrent or Metastatic Cancer upon Administration Every Two Weeks
Clinical Phase	Phase I
Indication	Recurrent or Metastatic Cervical Cancer Patients that had previously failed or had been intolerant to first-line platimum-containing regimens
Study Aims	**Dose-Escalation Phase** **Primary Endpoints**: • To evaluate the safety and tolerability of Socazolimab in patients with recurrent or metastatic cervical cancer, when administered once every two weeks; • To determine the maximum-tolerated dose (MTD), dose-limiting toxicity (DLT), and the recommended dose for future clinical studies as a single-agent. **Secondary Endpoints**: • Overall Response Rate (ORR); • Overall Survival (OS); • Pharmacokinetic (PK) Characteristics; • Immunogenicity; • Receptor Occupancy (Pharmacodynamics, PD); • T Cell Function and Cytokine Expression Levels **Dose-Expansion Phase** **Primary Endpoints:** • To evaluate the safety and ORR of Socazolimab in patients with recurrent or metastatic cervical cancer, when administered with the recommended 5mg/kg dose, once every two weeks. **Secondary Endpoints:** • Progression-Free Survival (PFS); • Duration of Response (DOR);

	• Overall Survival (OS); • Best Overall Response (BOR)
Study Design	This study is an open, dose-escalation and expansion, phase I clinical study, which evaluates the safety, tolerability and pharmacokinetic characteristics of an intravenous infusion of Socazolimab (recombinant fully human anti-PD-L1 monoclonal antibody) in patients with recurrent or metastatic cervical cancer once every two weeks. The study is divided into four phases: - the screening period (up to 28 days); - the single dose (PK analysis) period; - the treatment period (multiple doses in a row, up to 24 cycles or 1 year, whichever occurs first); - and the follow-up period. For each dose-escalation treatment group, a single-dose lead-in period was performed 28 days before the start of multiple consecutive doses, and the dose was analyzed for pharmacokinetics. The duration of the single-dose (PK analysis) period, PK blood sampling time points, and the dose and/or administration interval of subsequent multiple doses will be adjusted according to the observed exposure (AUC) (the total number of PK sampling points will not increase). These can be adjusted when necessary. Multiple administrations of the study drug can last for up to 24 cycles or 1 year, until disease progression (evaluated by RECIST version 1.1); no evidence of clinical benefit; or intolerable toxicity. If the investigator suspects that the patient has spurious progression or there is evidence to prove a mixed effect, the patient may continue to receive the study drug at the decision of the investigator.

Study Procedure	**<u>Dose-Escalation Phase</u>** This study adopts the traditional 3+3 design and is carried out in 3 doses: 5, 10, 15 mg/kg/time, 14 days (2 weeks) as a treatment cycle. Patients were assigned to the corresponding treatment group according to the order of entry. The first patient in the first treatment group received the 5mg/kg dose. DLTs were monitored within 28 days of the first administration, and separately for single and multiple administrations. Patients of the next dose should not be enrolled earlier than 28 days after the last patient in the current treatment group has been administered with Socazolimab. At least 3 patients are included in each dose group. According to the occurrence of DLTs, 3 or 6 patients are included in each dose group. If 3 patients in a certain dose group do not have DLT, 3 patients will be included in the next higher dose group; if one of the 3 patients has experienced DLT, 3 more patients will be included in this dose group, and it will be expanded to 6 patients; if only 1 of 6 patients produces DLT, 3 patients will be entered in the next dose; if 2 of 6 patients develop DLT, then the dose is higher than the MTD (MTD is defined as the highest dose that does not exceed 1 of 6 patient's DLT), and new patients will be included in the previous lower dose (tolerated dose) group, until the lower dose group reaches 6 patients. If 0 or 1 of 6 patients develop DLT, the lower-dose group is designated as MTD. Both single and multiple administrations will be investigated for DLT. If there are more than 2 patients with delayed DLT (DLT that occurs during the treatment period) in a dose-escalation group, further inclusion of patients in this treatment group will be suspended, until investigator and sponsor approval; and ethics committee and CFDA notification. If a patient withdraws for reasons other than DLT within the first two treatment cycles, the patient can be replaced by another. A total of 6 patients received the maximum-tolerated dose (if the

	maximum-tolerated dose was not reached, the optimal dose is selected after comprehensive consideration of pharmacokinetics, safety results of each treatment group, and preliminary efficacy determination). Evaluations will be carried out on 28 days, and the dose-expansion phase should not commence before the end of the evaluation. If the first 5 patients do not develop DLT within 28 days, the dose-expansion phase can be started immediately after the 6th patient is enrolled (PK blood samples are not required for the dose-expansion phase). When a total of 15 patients are enrolled in the dose-escalation and expansion phase, an interim analysis will be carried out. According to the analysis results, it can be decided whether to increase the total number of patients to 60. In the dose-expansion phase, if a patient withdraws from the study due to reasons apart from DLT within 28 days (2 cycles) after dosing, another patient can be replaced. If the patient withdrew due to early disease progression, they will be included in the total efficacy analysis set according to the protocol. If the DLT incidence in the first 6 patients is ≥33% (including patients in the dose-escalation group),patient enrollment will be suspended. If a treatment group is undergoing safety assessment due to the occurrence of DLT, but a patient has already started the treatment, treatment does not need to be stopped as long as there is evidence of drug tolerance, unless it is deemed necessary. After the investigator and sponsor have completed the safety analysis and evaluation, they will decide whether to re-enroll patients at this dose, or decide to start a new lower-dose-expansion phase (15 patients). For late-onset DLT, the selection criteria are the same as DLT. ● Treatment Cycle Continuation The study treatment is usually up to 24 cycles (or 1 year), whichever occurs first, but for patients who have been on the drug for 24 cycles or 1 year can continue based on investigator decision. At the end of Cycles 4, 8, 12, 16, 20, and 24 (every 8 weeks), or

	according to clinical needs, anti-tumor efficacy is evaluated to decide whether treatment can be continued. Unless the patient has a CTCAE ≥ grade 3 or other adverse conditions related to Socazolimab and cannot continue to receive treatment, the patient will continue to receive treatment until confirmed disease progression (PD) occurs or voluntary withdrawal. See Section 3.3 for details. Patients who fulfil the below criteria can continue: · If the patient Best Overall Response comprises Complete Response (CR), Partial Response (PR) or Stable Disease (SD), they can continue to receive the next treatment cycle until the first occurrence of the following: 1) Clinical deterioration, which implies that further treatment is likely not to bring more clinical benefits; 2) Meet the Study Termination Criteria, refer to Section 7.2 (Dose-Limiting Toxicity, DLT) and Section 11 (Research Termination); 3) Intolerance to Treatment; 4) Maximum Number of Treatment Cycles reached. In instances of confirmed disease progression, but with no clinical deterioration, and showing a stable or improved clinical state, patients should continue to receive treatment until further progression or clinical deterioration. **Follow-Up Period** The longest follow-up is 1 year. All patients should complete Follow-Up Visit 1. The completion of follow-up visits depends on the status of the patient at the end of treatment. Apart from discontinuation due to disease progression (PD), all patients completed the follow-up period until recurrence, starting a new treatment, or finished the follow-up period of one year, whichever comes first. Patients who terminated the study due to PD were followed up

	for 3 months (Visit 1 and 2); Follow-Up 2 (for such patients only) included only pharmacokinetic and immunogenicity assessment, and collection of adverse events. For patients who are still alive, a survival follow-up (vai telephone) was conducted every 60 days until known confirmed death.
Study Period	The longest treatment period is 24 cycles or 1 year, whichever comes first. Treatment period can be extended should the investigator believes that patients can still benefit and can continue to take the drug. The patients usually participate in the study for 2 years. For patients who are still receiving study drug treatment for more than 2 years, we will continue to followup in accordance with the protocol and collect information on efficacy and safety.
Sample Size	101 patients with recurrent or metastatic cervical cancer.
Dosage	Socazolimab is given by intravenous infusion once every two weeks (q2w) for up to 24 cycles or 1 year. Escalating doses at 5, 10, 15 mg/kg. Socazolimab was infused intravenously at the dose specified in the plan using a positive displacement pump equipped with a 0.2μm online filter. It cannot be administered as an intravenous bolus. When the infusion is completed, flush the infusion catheter with normal saline. Dilute to a final volume of 250 ml with 0.9% sodium chloride. Complete intravenous infusion in 60-90 minutes (except for infusion reaction).
Safety Evaluations	During the screening period and throughout the study period (once every 2 weeks), safety assessments are conducted, through vital signs, laboratory tests, pregnancy tests, Eastern Cooperative Oncology Group (ECOG) physical status assessment, imaging

	diagnosis, physical examination, electrocardiogram, and the frequency and severity of adverse events to assess safety. Safety assessment also includes immune serum and immunogenicity checks. The last evaluation was performed 90 days after the last dose. **Dose-Limiting Toxicity (DLT):** DLT is defined as a grade 3 or higher adverse event related to the study drug that occurred within 28 days after the first dose (Excluding burning tumor reaction, which is characterized by local pain, irritation, or rash at the known or suspected tumor site, or transient (releasing within 6 hours) grade 3 infusion adverse events). Adverse events were assessed according to the National Cancer Institute (NCI) CTCAE version 4.0.3. Unless there are other clear and well-documented explanations, DLT is generally considered to be related to the study drug. Late-onset DLT is an adverse event that meets the DLT criteria but occurs during the treatment period. The estimation of MTD during dose escalation does not involve late-onset DLT. Researchers and sponsors continuously collect and evaluate late-onset DLT during the research process. **Main Safety Endpoints:** • Incidence of dose-limiting toxicity; • The attributes of dose-limiting toxicity; **Secondary Safety Endpoint:** • Maximum tolerated dose (MTD); • The incidence of adverse events (evaluation to 90 days after the last treatment, or to the start of a new anti-tumor treatment, whichever occurs first);

	• The severity of the adverse event (evaluated to 90 days after the last treatment, or to the start of a new anti-tumor treatment, whichever occurs first); • The nature of the adverse event (evaluation to 90 days after the last treatment, or to the start of a new anti-tumor treatment, whichever occurs first); • Changes in Vital Signs; • Change of 12-Lead ECG; • Changes in laboratory test values (blood routine, blood biochemistry, urine routine, immune safety test); • The number of subjects who developed anti-Socazolimab antibodies (evaluated every 8 weeks, up to 10 weeks after the last dose). Evaluate the potential immunogenicity of Socazolimab by the number and percentage of subjects with detectable anti-drug antibodies (ADAs); • Changes in T cell function and cytokine expression levels.
Efficacy Evaluations	Patients will undergo scheduled tumor assessment at baseline , every 8 weeks or clinical needs. Assessments must include CT scans or magnetic resonance imaging (MRI) of the chest, abdomen, and pelvis, and a brain scan and performed during the last week of the dosing cycle and before the start of the next treatment cycle. Patients who terminate the treatment for reasons other than disease progression, tumor assessments shall continue until disease progression, other systematic antitumor treatment, or death. **Endpoints:** • Immune related best overall response (iBOR) and best overall response (BOR) were evaluated by modified RECIST 1.1 for immune based therapeutics (iRECIST) and RECIST 1.1; • Immune related progression free survival (iPFS) and progression free survival (PFS) were evaluated by iRECIST and RECIST 1.1;

	• The duration of response (DOR) was evaluated by iRECIST and RECIST 1.1(from the time when the tumor was first evaluated as CR or PR to the time when it was first evaluated as PD or death from any cause); • Overall survival (from enrollment to death).
Pharmacokinetic Parameters	$AUC_{(0-T)}$、$AUC_{(INF)}$、C_{max}、Tmax、$T_{1/2}$、V_{ss}、CL_T and $C_{min.}$
Inclusion Criteria	Patients will be considered eligible for this study if **ALL** of the following conditions are met: 1. Voluntarily participation through written informed consent. 2. Female patients aged≥18 years. 3. Diagnosed with cervical cancer by histology/cytology. Patients with recurrent or metastatic cervical cancer who have had failed or intolerance after receiving at least first-line of platinum-based chemotherapy. Definition of first-line failure: progression during adjuvant treatment or within 6 months after the end of treatment, first progression after palliative treatment. 4. Patients must have at least 1 measurable disease on imaging based on RECIST version 1.1. 5. ECOG performance status of 0-1 and have a life expectancy of at least 3 months. 6. Adequate hematologic, liver and kidney function indicated by the following laboratory values: • absolute neutrophil count (ANC) > 1.5 x 109/L • platelet ≥ 80x109/L • hemoglobin ≥ 90g/L • serum albumin ≥ 28g/L • bilirubin ≤ 1.5 ULN • AST and ALT ≤ 1.5 × ULN , for patients with hepatic metastases, AST and ALT < 5.0 × ULN

	• creatinine ≤ 1.25 × ULN or measured or calculated creatinine clearance ≥ 50 mL/minute using Cockcroft-Gault formula 7. If of childbearing potential, patients must be willing to use effective barrier methods throughout the study, starting with the screening visit through 120 days after the last dose of study treatment；Patients of childbearing potential are those who have not been surgically sterilized should have a negative urine or serum pregnancy test within 72 hours at screening.
Exclusion Criteria	Patients must be excluded if: 1. There is a known active or suspected autoimmune disease. Those who are in a stable state and do not need systemic immunosuppressive therapy can be enroll； 2. The patient is being treated with immunosuppressive agents, or systemic or absorbable topical corticosteroids for immunosuppressive purposes (dose>10mg/day prednisone or equivalent), and 2 weeks before enrollment is still in use； 3. Have received any form of organ transplantation, including allogeneic stem cell transplantation; 4. Known to have been allergic to macromolecular protein inhibitors, or known to be allergic to any component of Socazolimab; 5. Have suffered from other malignant tumors other than the research target diseases of this study within 5 years, except for skin basal and squamous cell carcinoma; 6. Central nervous system metastasis with clinical symptoms (such as cerebral edema, brain metastasis requires corticosteroid intervention). Previously received treatment for brain or meningeal metastases, such as clinically stable (MRI) for less than 2 months, or systemic corticosteroid therapy (dose>10mg/day prednisone or equivalent) was discontinued for less than 2 weeks;

	7. Cardiac clinical symptoms or diseases that are not well controlled, such as: NYHA level 2 or higher heart failure, unstable angina, myocardial infarction within 1 year, clinically significant supraventricular or ventricular arrhythmia requiring treatment or intervention in patients with echocardiography, the left ventricular ejection fraction at rest is less than 50%; 8. Previously received radiotherapy, chemotherapy, major surgery or molecular targeted therapy, less than 4 weeks after the completion of the treatment and before the study medication; 9. Any active infection that requires systemic anti-infection treatment occurs within 14 days before the first administration; 10. Human immunodeficiency virus (HIV) test positive, Treponema pallidum test positive, untreated active hepatitis (hepatitis B surface antigen positive and peripheral blood HBV-DNA titer test ≥ 500IU/ml or reach the copy number tested by the research center Positive value; positive for hepatitis C virus antibody); 11. Have a history of active tuberculosis within 1 year before enrollment; 12. The patient is participating in other clinical studies, or it is less than 4 weeks since the end of the previous clinical study; 13. Patients may receive other systemic anti-tumor treatments during the study period; 14. Received blood transfusion, hematopoietic stimulating factors, such as colony stimulating factor, erythropoietin, thrombopoietin and other treatments within 14 days before screening; 15. The patient has previously received other PD-1 and/or PD-L1 or CTLA-4 antibody therapy, or other drug therapy for immunomodulatory receptor preparations; 16. Have received live vaccine treatment within 4 weeks before screening; 17. The patient is known to have a history of psychotropic drug abuse, alcohol abuse or drug abuse; 18. Pregnant or breastfeeding women;

	19. Any mental condition that hinders understanding or providing informed consent; 20. According to the judgment of the investigator, the patient has other factors that may cause the study to be terminated halfway, such as other serious diseases or severe laboratory abnormalities or other factors that will affect the safety of the patients, or the collection of test data and samples. Family or social factors.

STUDY DIAGRAM

Table 1. Single-Dose Period and First Treatment Cycle

Follow-Up[1]	Screening Period	Single-Dose Administration Period[2]	Follow-Up Period		Treatment Cycle		Follow-Up Period[1]			
					1st Administration (+1 day)		Follow-Up			Survival Follow-Up[23]
					C1:1[3]	C1:2	1	2	3-5	
Study Period (days)	-28 to 1 days	Day 1	Day 8	Day 15	1	8	Last Follow-Up (+1-7 days)	Previous Follow-Up +84 days (±7 days)	Previous Follow-Up +84 days (±7 days)	Every 60 days (±7 days)
Informed Consent[4]	X									
Inclusion Criteria	X									
Demograhics/ Medical History [5,6]	X									
Diagnosis/Staging	X									
Tumor-Related Treatment History	X									
Pregnancy Tests [7]	X	X			X		X			
Blood Sampling (Immunogenicity Test)[8]		Refer to Table 3					X	X		
Blood Sampling (PK)[8]		Refer to Table 3					X	X		
Vital Signs[9]	X	X	X	X	X	X	X	X	X	

ECOG Score[10]	X	X	X	X	X	X	X	X	X	
Physical Fitness Tests[11]	X	X	X	X	X	X	X	X	X	
Tumor imaging examination (including chest, abdomen, pelvic cavity, CT/MRI）[12]	X[13]						X[15]	X	X	X[24]
Brain CT Scan/MRI [12,14]	X[13]						X[15]	X[15]	X[15]	X[24]
12-Lead ECG[16]	X	X			X		X	X	X	
Echocardiogram [17]	X									
Blood Test [18/19]	X		X	X	X	X	X	X	X	
Blood Biochemistry[18/19]	X		X	X	X	X	X	X	X	
Immune Safety Test[18]	X				X		X	X		
HBV (Hepatitis B), HCV Antibody, HIV Antibody and Syphilis Antibody Test	X									
HBV-DNA[20]	X									
Tumor PD-L1 Expression[21]	X									
Urine Test	X				X	X	X	X	X	
CD4+，CD8+[22]		X			X					
Cytokine Test (TNF-α, IFN-γ，IL-2，IL-6，IL-10，IL-12) [22]		X			X					
Socazolimab Infusion		X			X					
Combination Therapy	X	X	X	X	X	X	X	X	X	

Adverse Events		X	X	X	X	X	X	X	X	
Follow-Up Anti-Tumor Treatment							X	X	X	X
Overall Survival State										X

Note: Table 1 is applicable to the dose-escalation phase and the first phase of the dose-expansion phase (the first phase of the dose-expansion phase does not carry out single dosing and follow-up, and the visit on the 8th day of the first cycle is not carried out).

1. If the patient cannot enter the second cycle of treatment, the visit on the first day of the second cycle will not be performed, but follow-up visit 1 will be started. If the patient needs to terminate the treatment of the study drug, but does not withdraw from the study, it is necessary to complete the CRF form for the termination of the study drug and indicate the reason for the termination of the drug. Patients need to complete other visits in the cycle (including the collection of a single pharmacokinetic blood sample at the appropriate visit), and then enter the follow-up period. If the patient terminates the study because of PD and/or clinical deterioration, all assessments of follow-up visit 1 are completed, and only pharmacokinetic and immunogenic assessments of pharmacokinetics and immunogenicity are performed on follow-up visits, as well as a record of adverse events. If the patient remains in the study, follow-up visits will continue until the disease progresses/clinically worsens, new anti-tumor drugs are used, or 1 year of follow-up (after follow-up 1), whichever is completed first. For those who are still alive, follow-ups will be conducted every 60 days (phone follow-up is possible) until a confirmed death is known.
2. The final time course of the single-dose PK analysis period, the PK blood sample time point, and the dose and/or dosing interval of subsequent multiple doses will be adjusted according to the exposure (AUC) obtained during the lead-in period (PK sampling points will be adjusted according to the actual blood sampling situation, but the total number of points will not increase).
3. Examinations within 28 days before the administration used as the evaluation baseline.
4. Patients must voluntarily sign an informed consent form before administering any study drugs and conducting any research process.
5. Collect information on past and current medical history, as well as past medications and combined medications (from the signing of the ICF to the end of the screening period).
6. The adverse events that occurred after signing the informed consent and before the administration of SOCAZOLIMAB should be recorded in the medical history/current medical condition section of the CRF.
7. Blood/urine β-HCG pregnancy test should be performed on women of childbearing age during the screening period, single dose (-7~1 days) and the designated time of the treatment period, and the follow-up period. It was confirmed that the pregnancy test was negative before the study drug infusion.
8. Blood sample collection according to Table 3.
9. The vital signs examination includes body temperature, heart rate, breathing, resting systolic and diastolic blood pressure. On the day of each infusion, check the vital signs before the start of the infusion, every 15 ± 3 minutes during the infusion, and after the infusion (15, 30, 60 minutes, time window ± 3 minutes). In addition, in a single administration, vital signs must be recorded 120 ± 10 minutes and 240 ± 20 minutes after the infusion. If it is necessary to reduce the rate of administration or restart the infusion due to an infusion reaction, it should be every 15 ± 3 minutes during the infusion period (or according to the time point recommended by the investigator), and 15, 30, 60 minutes after the infusion, The time window is ±3 minutes (if necessary, the monitoring time can be extended according to the researcher's recommendation) to monitor the vital signs once until the patient's condition is stable.
10. Perform ECOG performance assessment before each infusion and during the follow-up period.
11. Perform physical examination and record abnormal findings, as well as new or worsening signs. A full set of physical examinations must be completed before a single dose and each cycle of infusion. Height measurement is only performed during the screening period. Weight measurement is performed during the screening period and before each infusion, but the measurement frequency can be increased according to the requirements of the research center.
12. Computed tomography (CT) is the first choice to obtain tumor imaging. When CT is contraindicated or when imaging the brain, magnetic resonance imaging should be used. CT or MRI can be selected according to the situation when imaging the pelvic cavity. The imaging method of the same patient should be consistent throughout the study (in terms of

mode and use of contrast agents). Bone ECT should be added to areas suspected of bone metastasis. For other areas suspected of metastasis, such as cervical lymph nodes, CT scan of the neck should be performed.

13. Accept the patient's baseline imaging examination (brain scan can use the results within 56 days) and the 12-lead ECG result during the routine examination within 28 days before Socazolimab infusion. Baseline imaging and imaging examinations for efficacy evaluation should be carried out in the same research institution.
14. If the patient has not had a brain CT/MRI (priority MRI) examination within 56 days before SOCAZOLIMAB infusion, it must be done during the screening period. Only when the results of the screening period suggest that there are tumors in the brain, brain scans are required during the treatment and follow-up periods to confirm whether complete remission (CR) or partial remission (PR), or corresponding examinations based on clinical indications. If the previous medical history or positive results in the screening period suggest the need for a brain scan, check it out every four cycles and follow-up visits 2-5.
15. If it has not been performed 28 days before, proceed according to clinical indications.
16. Perform before and after the infusion.
17. Only in patients with clinically significant supraventricular or ventricular arrhythmia requiring treatment or intervention.
18. During the screening period, hematology and blood biochemical examinations are required, and the examination results shall be carried out and reviewed before a single dose (7 days). Immune safety and virological examination results within 14 days before receiving a single dose.
19. Hematology and blood biochemical examinations are required during the treatment period, and the examination results shall be carried out and reviewed before each administration (7 days). Any abnormal laboratory results or changes of grade ≥3 that are related to possible irAE (relative to disease progression), such as increased liver function tests, electrolyte fluctuations, and blood deterioration, should be assessed for the risk of continued treatment and administration.
20. Patients with positive hepatitis B surface antigen need to complete the HBV-DNA examination to exclude hepatitis B activity.
21. For patients who can obtain pathological biopsy specimens, further detect the expression of PD-L1 in tumor tissues.
22. The response of CD4+ and CD8+ cells to tumors and the frequency of cytokine detection are set on the first day (before administration), the second day (24-36 hours after administration), and the first day of each cycle thereafter. One day (before administration).
23. Survival visits are followed up every 60 days ± 7 days, and can be followed up by telephone.
24. If the disease has not progressed after the last follow-up visit, it is necessary to collect the imaging examination results closest to each survival follow-up as far as possible.

Table 2. 2nd to 24th Treatment Cycle

	Treatment Cycle		Follow-Up Period[1]			
	2nd to 24th Treatment Cycle (±2 days)		Follow-Up Period			Survival Follow-Up Period
Follow-Up	Cn:1	Cn:2	1	2	3-5	
Study Period (days)	1[2]	14[3]	Last Follow-Up (+1-7 days)	Previous Follow-Up +84 days (±7 days)	Previous Follow-Up +84 days (±7 days)	Every 60 days (±7 days)[16]
Pregnancy Test [4]	X		X			
Vital Signs Test[5]	X		X	X	X	
ECOG Score[6]	X		X	X	X	
Physical Fitness Test[7]	X		X	X	X	
Tumor imaging examination (including chest, abdomen, pelvic cavity, CT/MRI）[8]		X	X[9]	X	X	X[17]
Brain CT Scan/MRI [8,10]		X	X[9]			X[17]
Efficacy Evaluation[11]		X	X	X	X	
12-Lead ECG [12]	X		X	X	X	
Blood Test[13]	X		X	X	X	
Blood Biochemistry[13]	X		X	X	X	
Immune Safety Test [13]	X		X	X		
Urine Test	X		X	X	X	
Echocardiogram[14]	X					

CD4+，CD8+[15]	X					
Cytokine Test (TNF-α, IFN-γ，IL-2，IL-6，IL-10，IL-12)[15]	X					
Blood Sampling (Immunogenicity Test)	Refer to Table 3					
Blood Sampling (PK)	Refer to Table 3					
Socazolimab Infusion	X					
Combination Therapy	X	X	X	X	X	
Adverse Events	X	X	X	X	X	
Follow-Up Anti-Tumor Treatment			X	X	X	X
Overall Survival State						X

Note: Table 2 applies to the dose-escalation phase and the first phase of the dose-expansion phase.

1. When the patient terminates the study drug treatment but does not withdraw from the study, he should fill in the relevant part of the CRF and indicate the reason, and complete the remaining visits in the treatment cycle (excluding drug infusion, and only collect one pharmacy Kinetic blood sample), then enter the follow-up period, and follow-up visit 1 will replace the first day of the next treatment cycle. If the patient terminates the study because of PD and/or clinical deterioration, all assessments of follow-up visit 1 are completed, and only pharmacokinetic and immunogenic assessments of pharmacokinetics and immunogenicity are performed on follow-up visits, as well as a record of adverse events. If the patient remains in the study, follow-up visits will continue until the disease progresses/clinically worsens, new anti-tumor drugs are used, or 1 year of follow-up (after follow-up 1), whichever is completed first. Patients who are still alive will then undergo a follow-up visit every 60 days (telephone follow-up) until the confirmed death is known.
2. An assessment is made at the end of the cycle to decide whether to enter the next cycle of treatment. See section 3.3 for details.
3. The purpose of this visit is for the investigator to conduct radiological evaluation and evaluate the corresponding results (evaluation of efficacy). Radiological evaluation and efficacy evaluation should be done between days 8-14 and before the next cycle of administration.
4. Women of childbearing age must confirm a negative pregnancy test before infusion of study drug.
5. The vital signs examination includes body temperature, respiration, heart rate, resting systolic and diastolic blood pressure. On the day of each infusion, perform a vital sign check before the start of the infusion and within 30 minutes after the end of the infusion. If it is necessary to reduce the rate of administration or restart the infusion due to an infusion reaction, it should be every 15 ± 3 minutes during the infusion (or according to the time point recommended by the investigator), and 15, 30, 60 minutes after the infusion (± 3 minutes) (if necessary, the monitoring time can be extended according to the researcher's recommendation) monitor the vital signs once until the patient's condition is stable.
6. Perform ECOG performance status assessment before each infusion.
7. Perform physical examination (not including height), record abnormal findings, and new or worsening signs or symptoms. A full set of physical examinations must be completed before the start of each cycle of infusion. Weight measurement is performed during the screening period and before each cycle of infusion, but the measurement frequency can be increased according to the requirements of the research center.

8. Computed tomography (CT) is the first choice for tumor imaging. When CT is contraindicated or brain imaging is performed, magnetic resonance imaging should be used. CT or MRI can be selected according to the situation when imaging the pelvic cavity. The imaging method of the same patient should be consistent throughout the study (in terms of mode and use of contrast agents). At the end of cycles 4, 8, 12, 16, 20 and 24 (ie every 8 weeks), or according to clinical needs. Bone ECT should be added to areas suspected of bone metastasis. For other areas suspected of metastasis, such as cervical lymph nodes, CT scan of the neck should be performed.
9. The follow-up period is based on clinical indications or imaging examinations every 12 weeks.
10. Only when the results of the screening period suggest that there are tumors in the brain, brain scans are required during the treatment and follow-up periods to confirm whether complete remission (CR) or partial remission (PR), or corresponding examinations based on clinical indications.
11. At the end of cycles 4, 8, 12, 16, 20, and 24 (ie every 4 cycles), evaluate the efficacy of the tumor and decide whether to continue treatment.
12. Perform before and after infusion.
13. During treatment, hematology, blood biochemistry and immune safety inspections are required, and the inspection results shall be carried out and reviewed before each administration (7 days). Any abnormal laboratory results or changes of grade $\geqslant$3 that are related to possible irAE (relative to disease progression), such as increased liver function tests, electrolyte fluctuations, and blood deterioration, should be assessed for the risk of continued treatment and administration.
14. Check only in patients with clinically significant supraventricular or ventricular arrhythmias that require treatment or intervention, and recheck in cycles 6, 12, 18, and 24, respectively.
15. CD4+, CD8+ cell response to tumor and cytokine detection, on the first day of each cycle (before administration).
16. Survival visits are followed up every 60 days ± 7 days, and can be followed up by telephone.
17. If there is no disease progression after the last follow-up visit, it is necessary to collect the imaging examination results closest to each survival follow-up as far as possible.

Table 3. Dose-Escalation Phase: Blood Sampling (PK), Receptor Occupancy, Immunogenicity, Cytokine Flow Cytometry Assays

Study Day [a]	Time (relative to dosing) [a]	Window Time	PK Blood Sampling	Receptor Occupancy Blood Sampling [e]	Immunogenecity	Cytokine Flow Cytometry Assays
Single Administration						
Day 1	0 (before administration) [b]	- 30 min	X	X	X	X
	1.0 (EOI) [c]	± 5 min	X			
	EOI + 30 min	± 5 min	X			
	EOI + 60 min	± 10 min	X			
	EOI + 120 min	± 10 min	X			
	EOI + 240 min	± 15 min	X			
Day 2	24 h	± 1 h	X			X [f]
Day 3	48 h	± 1 h	X			
Day 4	72 h	± 1 h	X			
Day 8	168 h	± 1 h	X			

Day 15	336 h	± 1 h	X		X	
Day 20	456 h	± 1 h	X		X	
Day 25	576 h	± 1 h	X		X	
Multiple Administrations						
Cycle 1 – 5 Day 1	0 (before administration)	- 30 min	X	X	X	X
Cycle 6 Day 1	0 (before administration)	- 30 min	X	X	X	X
	1.0 (EOI) [c]	± 5 min	X			
	EOI + 30 min	± 5 min	X			
	EOI + 60 min	± 10 min	X			
	EOI + 120 min	± 10 min	X			
	EOI + 240 min	± 15 min	X			
Cycle 6 Day 2	24 h	± 1 h	X			X [f]
Cycle 6 Day 3	48 h	± 1 h	X			

Cycle 6 Day 4	72 h	± 1 h	X			
Cycle 6 Day 8	168 h	± 1 h	X			
Cycle 6 Day 15	336 h	± 1 h	X		X	
Every 3 cycles Day 1 for next year or discontinuation	0 (before administration)	- 30 min	X	X	X	X [g]
Follow-up 1 [d]	0	± 1 h	X	X	X	
Follow-up 2 [d]	0	± 1 h	X		X	

Notes:

a. If a subject permanently discontinues study drug treatment, or is not receiving an infusion at a given visit either due to an AE or due to the alternate dose schedule, a single blood sample will be taken at that visit.

b. Predose samples will be drawn within 30 minutes before infusion.

c. EOI: End of infusion. Samples should be taken within 5 minutes after the end of the infusion.

d. A single sample will be taken at Follow-up Visits 1 and 2.

e. Collect peripheral blood before administration in each cycle and Follow-up 1 to detect receptor occupancy of PD-L1 on CD3+ T cells.

f. Detect on the second day (24-36 h after administration).

g. Detect before administration on the first day of each cycle.

Table 4. Second Phase of the Dose-Expansion Phase

Visit	Screening	Treatment		Follow-up period [17]		
		Cycle 1 – 24 (± 7 days)		Follow-up		Follow-up of survival
		Cn : 1	Cn : 2	1	2 - 5	
Study time (day)	- 28 day ~ 1 day	1	14	Last visit + (1-7 days)	Previous Follow-up visit + 84 days (± 7 days)	Once every 60 days (± 7 days) [15]
Informed consent [1]	X					
Inclusion Criteria	X					
Demographics/Medical History	X					
Diagnosis/Stage [2]	X					
Physical Fitness Tests [3]	X	X		X	X	
Vital Signs Test [3]	X	X		X	X	
ECOG Score[3]	X	X		X	X	
Pregnancy test [4]	X	X		X	X	
Tumor imaging examination (including chest, abdomen, pelvic cavity, CT/MRI) [5]	X	X		X	X	X [16]

Brain CT scan/MRI [6]	X			X	X	X [17]
12-Lead ECG [7]	X	X		X	X	
Echocardiography [8]	X	X				
Blood Test [9]	X	X		X	X	
Blood Biochemistry [9]	X	X		X	X	
Urine Test [9]	X	X		X	X	
CEA, CA125, SCC [10]	X	X		X	X	
HBV (Hepatitis B), HCV Antibody, HIV Antibody and Syphilis Antibody Test [11]	X					
HBV DNA test [11]	X				X	
Immunogenicity Test [12]	Refer to Table 3					
Immune safety assays [13]	X	X		X	X	
CD4+, CD8+ [14]		X				
Cytokine Test (TNF-α, IFN-γ, IL-2, IL-6, IL-10, IL-12) [14]		X				
Tumor PD-L1 Expression	X					

Socazolimab Infusion		X				
Combination Therapy	X	X	X	X	X	
Adverse Events		X	X	X	X	
Follow-Up Anti-Tumor Treatment						X
Overall Survival State						X

Notes:

1. Informed consent must be signed before the initiation of any study drug administration or procedures.
2. Record the information of concomitant medications 1 month before signing the informed consent.
3. ECOG Performance Status, physical examination (including weight), and vital signs are performed during the screening period, within 7 days before each infusion, and during the follow-up period (1-5).
4. During the screening period, childbearing-aged women must confirm that the blood/urine β-HCG pregnancy test is negative before each infusion of the study drug, and during the follow-up period (2-5).
5. Computed tomography (CT) is the first choice to obtain tumor imaging. When CT is contraindicated or brain imaging is performed, magnetic resonance imaging should be used. CT or MRI can be selected according to the situation when imaging the pelvic cavity. The imaging method of the same subject should be consistent throughout the trial period (in terms of mode and use of contrast agents). At the end of the 4th, 8, 12, 16, 20 and 24 cycles (ie every 4 cycles), as well as the follow-up period or according to clinical needs. Accept the subject's baseline imaging examination during the routine examination within 28 days before ZKAB001 infusion (brain scan can use the results within 56 days). Baseline imaging and imaging examinations for efficacy evaluation should be performed at the same research institution. Bone ECT should be added to areas suspected of bone metastasis. Other areas suspected of metastasis, such as cervical lymph nodes, should be treated with cervical CT.
6. If the subject has not had a brain CT/MRI (priority MRI) examination within 56 days before Socazolimab infusion, it must be done during the screening period. Only when the results of screening period suggest that there are tumors in the brain, brain scans are required during the treatment and follow-up periods to confirm whether complete remission (CR) or partial remission (PR), or corresponding examinations based on clinical indications. If the previous medical history or positive results in the screening period suggest that a brain scan is needed, check it out every 4 cycles and during the follow-up period. The ECG is performed within 28 days of the first administration, which will be completed within 7 days before each cycle and during the follow-up period (1-5).
7. The ECG should be performed within 28 days of the first administration, and the follow-up period (1-5) will be completed within 7 days before each cycle.

8. Echocardiography is only examined in patients with clinically significant supraventricular or ventricular arrhythmias that require treatment or intervention.
9. Blood, biochemical, and urine tests are carried out during the screening period, within 7 days before the administration of each cycle, and during the follow-up period (1-5). Laboratory indicators that do not meet the selection/exclusion criteria of the program are allowed to be retested during the screening period.
10. Abbreviations: carcinoembryonic antigen (CEA), cancer antigen 125 (CA-125), squamous cell carcinoma (SCC). CEA, CA125, and SCC will be tested within 14 days before the first medication, which will be performed at the same frequency as the imaging evaluation thereafter.
11. Virology should be tested within 14 days before the first medication. HBV-infected patients should be tested for HBV-DNA to determine whether they are in the active phase.
12. The immunogenicity should be sampled within 30 minutes before the administration of 1-6 cycles, and then should be sampled within 30 minutes before the administration of every 3 cycles.
13. Immune safety inspection shall be carried out within 14 days before the first administration, and then 7 days before the administration of each cycle during the follow-up period (1-2). Laboratory indicators that do not meet the selection/exclusion criteria of the program are allowed to be retested during the screening period.
14. CD4+, CD8+ cells to tumor and cytokine detection frequency, complete sampling within 30 minutes before administration of each cycle.
15. Patients who can obtain pathological biopsy specimens should further detect the expression of PD-L1 in tumor tissues.
16. Survival visits are followed up every 60 days ± 7 days and can be followed up by telephone.
17. When a subject will discontinue study drug treatment, but remain in the study, the Study Drug Discontinuation Case Report Form (CRF) should be completed including the reason for study drug discontinuation. All remaining visits of that treatment cycle should be completed (without infusions at applicable visits), and the subject should enter the Follow-up Period. Subjects who will discontinue the study due to PD and/or clinical deterioration will complete all Follow-up Visit 1 evaluations and will complete only immunogenic evaluations and collection of adverse events for Follow-up Visit 2. If a subject remains in the study, subsequent follow-up visits will continue until disease progression/clinical deterioration, initiation of a new anti-tumor therapy, or a total of 1 year follow-up (following Follow-up Visit 1) has been completed, whichever occurs first.

Table 5. Dose-Expansion Phase: Receptor Occupancy, Immunogenicity, Flow Cytometry, and Cytokine Blood Sampling Plan

Study Period	Time (relative administration time)	Dosing Window	Receptor Occupancy Blood Sampling [a]	Immunogenicity	Flow cytometry and cytokine detection
1st – 6th Treatment Cycle Day 1	0 (before administration)	-30min	X	X	X
Every 3 Treatment Cycles thereafter on the Day 1 until 1 year or the end of the study	0（(before administration)	-30min	X	X	X[b]
Follow-Up 1			X	X	
Follow-Up 2				X	

a. Receptor Occupancy is only tested in the first phase of the Dose-Expansion Phase.

b. Collected before each Treatment Cycle.

1. INTRODUCTION

1.1 Background of Research

Tumors are the exogenous tissues in human. Therefore, cancer immunotherapy can effectively attack tumors by enhancing immune recognition. Immune surveillance prevents tumor progression due to the expression of tumor-specific antigens in many tumors. Currently, immune evasion is well-recognized obstacle in cancer treatment. In tumor patients, the high expression of PD-L1 promotes tumor metastasis, thereby resulting in the rise of patient's mortality. Hence, PD-L1 serves as a prognostic marker in cancer patients (Pedoeem, Azoulay-Alfaguter et al. 2014).

Studies showed that PD-L1 is highly expressed in multiple cancer cell lines, including melanoma, non-small cell lung cancer, ovarian cancer, renal cell carcinoma, etc. Tumor cells highly express PD-L1 upon the action of various cytokines, which is associated with tumor immune evasion. However, in the *in vitro* environment, the expression level of PD-L1 is relatively lower, indicating that PD-L1 expression is closely related to tumor microenvironment. Moreover, tumor-infiltrating CD8+ T cells are also affected by tumor microenvironment. In that scenario, PD-1 is highly expressed more than T cells in peripheral blood and then interacts with PD-L1 on the surface of tumor to inhibit T cells activation and proliferation, consequently leading to lose functions of T cells in killing tumor cells (Mamalis, Garcha et al. 2014). Thus, anti-PD-1 monoclonal antibodies block binding of PD-1 and its ligands while anti-PD-L1 monoclonal antibodies impede the interactions of PD-L1 with PD-1 and CD80, thereby contributing to restore and enhance T cell functions in killing tumors (Wang, Luo et al. 2015). Based on the mechanism of immunotherapy, anti-PD-L1/PD-1 therapy exerts their effects via activating immune response in heterogenous tumors rather than only in a certain type of tumors.

Cervical cancer is one of malignant tumors that commonly occurs in women all over the world, which is only second to breast cancer. According to statistics worldwide, there are approximately 500,000 new cases of cervical cancer each year, accounting for 5% of all new cases of cancer, 80% of which are from developing countries (Zhang and Gui, 2008). It was reported from GLOBOCAN 2012 that the number of new cases of cervical cancer in China is 61,691 per year, and the number of deaths is 29,526 per year. Approximately 29-38% of cervical cancer patients have relapse or uncontrolled cases after treatment (Zhang and You, 2014). Surgery and radiotherapy are the two main treatments. However, the therapeutic effects in treating advanced cervical cancer are still poor so far, from which the long-term survival rate is less than 40%. And the survival rate after recurrence is low, not more than 30%. 5-Fu and DDP are commonly employed as novel adjuvant treatments, but merely 50% of patients have effective

response to them. Radiotherapy in combination with chemotherapy can reduce the risk of recurrence and death by 40-60% and 30-50% respectively, but their toxicity is relatively high (Wang, Sui, et al. 2010).

Hence, there is still an unmet need for medications of cervical cancer in China, suggesting that it is necessary to continue developing the novel treatment to bring benefits to patients. This phase I clinical study aims to select cervical cancer for research.

1.2 PD-1/PD-L1 Signalling and The Immune Reponse

Immune evasion is well-recognized obstacle in treating tumors. Tumor-specific CD8+ T cells are activated at the early stage. In response to constitutively increased secretion of IFN-γ by CD8+ T cells, tumors eventually develop resistance.

Early tumor-specific CD8+ T cells are activated; as the secretion function of interferon-γ (IFN-γ) continues to increase, tumors also develop resistance. Among them, PD-L1 protein has become the main target for study in recent years.

PD-L1 is widely expressed in in antigen presenting cells, activated T cells and B cells, macrophages, placental trophoblasts, myocardial endothelium and thymic cortical epithelial cells. In many human tumor tissues, PD-L1 can be detected and the expression level of PD-L1 is significantly upregulated in comparison with that in normal tissues. PD-L1 expression has been examined by using immunohistochemical analysis in human tumor tissues, such as breast cancer, lung cancer, gastric cancer, bowel cancer, esophageal cancer, ovarian cancer, cervical cancer, kidney cancer, bladder cancer, pancreatic cancer, glioma, melanoma, etc. And the expression level of PD-L1 is closely related to the clinical features and prognosis of patients.

PD-L1 (B7-H1) belongs to the B7 family, containing IgV- and IgC-like domains, transmembrane domains, and cytoplasmic tails. PD-L1 interacts with PD-1, its receptor on T cells. The PD-1/PD-L1 signaling pathway inhibits activation of antigen-specific T cells, then downregulating T cell-mediated immune response. The PD-1/PD-L1 pathway plays a critical role in the negative regulation of immune response, meanwhile resulting in tumor escape from the autoimmune attack.

Socazolimab can strongly bind to human PD-L1 protein. Socazolimab attenuates tumor immune escape via targeting PD-L1 and blocking the PD-1/PD-L1 signaling pathway, thereby normally inducing

the antitumor immune response mediated by T cells to inhibit tumor growth. Socazolimab also possesses the intact Fc domain of human lgG1, which can be easily recognized by the Fc receptor on NK cells. Once Fc receptors binds to Fc domains of IgG, NK cells release cytokines (like IFN-γ) and cytotoxic factors, including perforin and granzymes etc, then triggering the antibody-dependent cell-mediated cytotoxicity (ADCC). Conclusively, Socazolimab binds to PD-L1 on the surface of tumor cells and exercises ADCC-mediated antitumor effect by its Fc domain-induced NK cells to tumor sites.

1.3 Socazolimab Introduction

The current application is a recombinant fully human anti-PD-L1 monoclonal antibody injection (Socazolimab) for the treatment of patients with locally advanced and metastatic solid tumors, which is a class 1 domestic biological product. The detailed information of this product is listed below:

- Product Name: Recombinant fully human anti-PD-L1 monoclonal antibody injection
- Code of Company: Socazolimab
- Molecular Weight: 146 kDa
- Strength: 100 mg/4mL/vial
- Conditions of Storage: Store at 2 – 8ºC

Socazolimab is screened from the world's largest human G-MAB^{TM} antibody library, which has the significantly high specificity and affinity against human PD-L1. Socazolimab binds to PD-L1 and effectively blocks the interaction of PD-L1 with its receptor, PD-1, then suppressing inhibition of T cells induced by the PD-L1/PD-1 pathway. Finally, T cells are activated, thereby exerting the anti-tumor growth effect via enhancing T cell-mediated autoimmunity.

Socazolimab is proposed to treat with recurrent or metastatic solid tumors.

Our company has proved the non-clinical effectiveness and safety of Socazolimab through a series of experiments of pharmacology, toxicology, and pharmacokinetics. The results of preclinical experiments are summarized as follows:

Highly-Specific Antibody-Antigen Binding Ability

Results of enzyme-linked immunosorbent assay (ELISA) and flow cytometry indicated that Socazolimab effectively binds to monkey and human PD-L1. In comparison with the positive control (Positive control is an antibody manufactured by Crown Bioscience International, which is produced according to the amino acid sequence of Atezolizumab, an anti-PD-L1 monoclonal antibody from Roche), Socazolimab shows a better relative binding efficacy. The binding ability of Socazolimab is specific, which can only bind to human and monkey PD-L1, but no significant binding ability against dog, rat,

and mouse. Socazolimab enables inhibiting human and monkey PD-L1 that binds to PD-1. And Socazolimab dose-dependently binds to the surface protein of PD-L1 in many human cancer cells.
Dual mechanisms of action of anti-tumor growth

Socazolimab monoclonal antibody has the primary and secondary mechanisms of action of anti-tumor growth. The primary mechanism is to block the PD-1/PD-L1 signaling pathway, then activating T cells to attack against tumors. In addition, Socazolimab monoclonal antibody conserves the intact Fc region, hence it also kills cancer cells through traditional antibody-dependent cell-mediated cytotoxicity (ADCC).

We tested the effects of Socazolimab on the downstream of PD-1/PD-L1 signaling pathway by using the PD-1/PD-L1 Blockade Bioassay provided by Promega. Results demonstrated that Socazolimab significantly impeded the downstream of PD-1/PD-L1 signaling pathway and induced the gene expression of NFAT. NFAT is a direct downstream regulator of T cell receptors. T cells further promote NFAT-mediated expression of other cytokines like interleukin-2 (IL-2), consequently leading to activate T cells. Moreover, our results of the allogeneic mixed lymphocyte reaction (MLR) showed that Socazolimab dose-dependently enhanced the secretion of IL-2 and IFN-γ.

We detected the ADCC effect of Socazolimab monoclonal antibody by using the antibody-dependent cell-mediated cytotoxicity experiment and ELISA. Due to the fact that anti-PD-1 monoclonal antibodies available in the market act on T cells, the ADCC effect must be removed when designing anti-PD-1 monoclonal antibodies, otherwise T cells are subjected to autoimmune attack. The anti-PD-L1 antibody acts on tumor cells, and ADCC has no effect on T cells, whereas it causes the additional efficacy on killing tumor cells.

Under the dual mechanisms of action, 1mg/kg of Socazolimab monoclonal antibody significantly inhibited the tumor growth in humanized mouse model, which inhibitory rate against tumor growth was 68.4%.

High levels of tolerability and safety

The Socazolimab monoclonal antibody showed no significant adverse events in the acute toxicities (the highest dose was 225 mg/kg) and the 4-week repeated dose toxicities studies (the highest dose was 150 mg/kg) in cynomolgus monkeys.

In the experiments of chronic toxicities in cynomolgus monkeys and pharmacokinetic study, the anti-drug antibody (ADA) was detected in all samples. Nevertheless, the experimental results indicated no significant adverse events after administration. We therefore consider that the presence of ADA has no effect on safety. And we will pay close attention to ADA in future clinical trial and further evaluate its safety and efficacy in humans.

Neither Socazolimab injection nor its vehicle has no hemolytic and sensitizing reactions. And only slight or obvious redness and swelling at the injection site were observed in the administration group (also observed in the vehicle group), demonstrating no relevance with Socazolimab administration.

1.4 Dose Selection

Results of the toxicological study in cynomolgus monkeys showed that NOAEL dose was equal to or more than 150 mg/kg, which human equivalent dose (HED) is 48.8 mg/kg. According to "Anti-tumor Drug Clinical Trial Technical Guidelines" stipulated by CFDA, 1/5 or higher dose of the NOAEL (No Observed Adverse Effect Level) obtained from non-clinical rodents can be set at the starting dose of single administration in phase I clinical studies due to the relatively lower toxicities of some non-cytotoxic anticancer drugs. 1/5 of 48.8 mg/kg is approximately 9.8 mg/kg. In the meantime, we referred to the starting dose of clinical trials of anti-PD-L1 antibodies in domestic and foreign countries and the effective dose of anti-PD-L1 antibodies in the market. The initial dose of single and multiple administrations in this phase I clinical trial was set at 5 mg/kg, and a dose-escalation study was planning for 3 doses, 5, 10, 15 mg/kg/time.

1.5 Increase in Sample Size

Since January 2020, due to impacts of the COVID-19 pandemic, the road traffic was controlled in all countries, especially in Hubei province. Many research centers have been temporarily requisitioned and cannot timely provide medications in treating cancer patients, thus affecting the time of treatment and the assessment of therapeutic efficacy among many subjects enrolled in this study. Hence, due to impacts of the pandemic, subjects who exceed the time window of treatment (14+7 days) will not be included in case analysis of the efficacy as supplement of case number.

For those subjects whose imaging evaluation are not confirmed to progress, the sponsor decides to continue providing the compassionate drug use, from which the relevant data are tentatively included in the safety analysis. According to statistics, among all subjects currently enrolled in this study, there are

approximately 33 subjects who have exceeded the time window of treatment due to impacts of the pandemic. Therefore, after multi-party communication and discussion, it is decided that 35 subjects are temporarily supplemented on basis of original 66 subjects.

Owing to the dynamic change of the pandemic, the sponsor will decide whether the total number is going to expand 101 cases or not based on results of the efficacy evaluation of these 33 subjects.

2. RESEARCH OBJECTIVES

2.1 Primary Objectives of the Dose-Escalation Phase

The primary objectives are to assess the safety and tolerability of Socazolimab when administered once every two weeks to subjects with recurrent or metastatic cervical cancer; and to determine the maximum tolerated dose (MTD) and dose limiting toxicity (DLT); and to explore the recommended phase II dose of Socazolimab as a single agent for administration.

2.2 Secondary Objectives of the Dose-Escalation Phase

1) To evaluate the preliminary efficacy based on objective responses and overall survival (OS) in subjects treated with Socazolimab;
2) To assess the pharmacokinetic properties of Socazolimab as a single agent for administration;
3) Immunogenicity of Socazolimab;
4) Receptor occupancy of Socazolimab;
5) The effect of Socazolimab on T cell function and the expression levels of cytokines;
6) To evaluate the relationship between the expression levels of PD-L1 and the clinical efficacy, and the toxicities.

2.3 Primary Objectives of the Dose-Expansion Phase

The primary objective is to assess the safety and ORR of Socazolimab when administered at the dose of 5 mg/kg once every two weeks to subjects with recurrent or metastatic cervical cancer.

2.4 Secondary Objectives of the Dose-Expansion Phase

1) Progression-free survival (PFS)
2) Duration of response (DOR)
3) Overall survival (OS)
4) Best overall response (BOR)

3. STUDY DESIGN

This is an open-label, dose-escalation phase I clinical trial, aiming to investigate the safety, tolerability, and pharmacokinetic properties of Socazolimab (a recombinant fully human anti-PD-L1 monoclonal antibody) intravenously administered as a single agent once every two weeks in subjects with recurrent or metastatic cervical cancer.

This study consists of 4 periods: Screening (up to 28 days), Single dosing PK analysis, Treatment (continuous dosing, up to 24 cycles or 1 year, whichever occurs first), and Follow-up. Each dose-escalation group is given as a single dosing for 28 days before the start of treatment of continuous dosing, of which the single dosing is conducted for pharmacokinetic analysis. The final time course of the single dosing PK analysis, the time point of PK blood samples, and the dose and/or dosing interval of subsequent continuous dosing will be adjusted according to the acquired exposure (AUC) (PK sampling points are adjusted based on real conditions, but the total number of points does not increase). Treatment of continuous dosing is up to 24 cycles or 1 year, until as per investigator's opinion, subjects experience disease progression (evaluated by RECIST 1.1), no clinical benefit, or intolerable toxicity. If investigators suspect subjects experience pseudoprogression or have evidence to prove as mixed response, subjects can continue to accept treatment as investigator decided.

3.1 Dose-Escalation Phase

The traditional 3+3 design is utilized for the dose escalation of this phase I study. Three dose levels, planned as 5, 10, 15 mg/kg/dose, will be administered every 14 days (2 weeks) as a treatment cycle. Subjects will be assigned to a dose level in the order of study entry. The first cohort of subjects will receive Socazolimab at the 5mg/kg dose level. Dose limiting toxicity (DLT) will be observed for 28 days after first dose of Socazolimab and needs to be observed in a single dosing and multiple dosing periods.

Enrollment into the next cohort cannot begin until 28 days have elapsed since the last subject's first dose in the previous cohort. 3 or 6 subjects treated at each dose level depending upon the incidence of DLTs.

If no DLTs occur in a cohort of 3 subjects, a new cohort of 3 subjects will be treated at the next higher dose level. If 1 of 3 subjects in a cohort experiences a DLT, that cohort will be expanded to 6 subjects. If only 1 of the 6 subjects experiences a DLT, then the next cohort of 3 subjects will be treated

at the next higher dose level. If 2 or more DLTs occur within a cohort, then that dose level will be above the MTD (the highest dose tested where no more than 1 of 6 subjects has experienced a DLT), and new subjects will be enrolled at the previous lower (tolerated) dose level until that cohort has 6 subjects. If no more than 1 of 6 subjects have experienced a DLT, this relatively lower dose level is defined as MTD. And DLT needs to be observed both at a single dosing and multiple dosing escalation treatment period.

If 2 or more delayed DLTs, i.e., DLTs that occur during treatment period, are noted within a dose-escalation cohort, accrual will be held pending safety analysis and will be restarted only with investigator and sponsor approval (and subsequent IRB and CFDA notification). A subject who is withdrawn from the study during Cycle 1 and 2 for reasons other than a DLT will be replaced.

3.2 Dose-Expansion Phase

A total of 6 subjects must be enrolled at the MTD (if MTD is not reached, the optimized dose level will be selected, based on comprehensive evaluation of pharmacokinetics, safety results at each dose level, and preliminary efficacy) and evaluated at the end of 28 days before any subject is dosed in the expansion cohorts. If none of the first 5 subjects have a DLT by the end of 28 days, enrollment to the expansion cohorts can begin immediately following the enrollment of the sixth subject (PK blood samples in the expansion cohorts will not be collected).

A total of 15 subjects (dose escalation plus expansion cohort) will be enrolled for an interim analysis, of which the results determine if the total of 60 subjects will be expanded. According to statistical analysis, if 2 or more responses mentioned above are observed in 15 subjects of cervical cancer, 45 subjects will be more included (total sample size reaches 60 subjects). We will start the expansion at a dose of 5mg/kg and conduct a multi-center clinical study to further observe the safety and effectiveness of the subjects. DLT will not be observed during the expansion period. In each cohort, a subject who is withdrawn from the study before the completion of 28 days for a reason other than a DLT will be replaced. If they were withdrawn for early progression, they will be counted in the per protocol estimate of overall efficacy.

Enrollment may be held in any expansion cohort if the rate of DLTs is ≥33% after enrollment of the first 6 subjects in that indication (including subjects from the dose-escalation cohort at the expansion dose). Subjects who are tolerating study drug at a dose level that is being reviewed due to the occurrence of a DLT in another subject will not be automatically precluded from continued dosing during the safety

review and will be allowed to continue dosing for as long as study drug is tolerated unless directed otherwise as a result of the safety review. After safety analysis by the investigators and the sponsor), a decision will be made whether to resume enrollment at the current dose or initiate a new expansion cohort (15 subjects) at a lower dose.

For late-onset DLTs, enrollment will be held and/or restarted using the same rules as those for DLTs.

3.3 Administration of Additional Treatment Cycles

The maximum duration of study therapy to be administered to an individual subject in this study is 24 cycles (or 1 year). But for subjects who have been administered for 24 cycles or 1 year, the investigator believes that they can still benefit and can continue to be administered. By the end of treatment cycle 4, 8, 12, 16, 20 and 24 (every 8 weeks), or as clinically needed, the decision to treat a subject with additional cycles of Socazolimab will be based on tumor assessment.

Subjects usually participate in the study for up to 2 years. We will continue to follow up and collect information on the efficacy and safety of subjects who are still receiving the treatment for more than 2 years. Subjects will continue to receive treatment until confirmed progressive disease (PD) or subjects voluntarily withdraw unless experience > grade 3 CTCAE or other AE related to Socazolimab. If treatment is delayed for more than 14 days due to toxicity (immune-related adverse reactions have not recovered to ≤ level 1, skin and endocrine lesions have not recovered ≤ level 2), no additional cycles will be administered. If subjects in the expansion cohort are treated with toxicity or adverse events, dosing can be delayed, but not more than 4 weeks. If the infusion of Socazolimab cannot be performed on the scheduled date due to other reasons, the infusion should be completed within 7 days. No subjects will be permitted dose escalations or de-escalations.

Subjects who meet the following conditions will be treated with additional cycles:

- Subjects with a best overall response (BOR) of complete response (CR), partial response (PR) or stable disease (SD) will continue to receive Socazolimab treatment until the first occurrence of either: 1) clinical deterioration suggesting that no further benefit from treatment is likely; 2) meets criteria for discontinuation of study therapy as outline in sections 7.2 (Dose Limiting Toxicity) and 11 (Research Termination); 3) other intolerability to therapy; or 4) receipt of the maximum number of cycles.
- CR, PR and SD: patients will continue to receive study drug, until experience confirmed PD, or

toxicity, or the maximum number of cycles allowed have been administered. The patients will then follow-up period.

- PD: Accumulating evidence indicates that the emergence of objective responses to agents that activate anti-tumor immune responses follows delayed kinetics of weeks or months, and can be preceded by initial apparent radiological progression, or the appearance of new lesions or some enlarging lesions while certain target lesions are regressing ("mixed response"). It is thus reasonable, in the absence of clinical deterioration, to continue to treat these subjects until radiologic progression is both confirmed and found to have worsen at a subsequent imaging evaluation. Evidence of PD will be based on a comparison with baseline (or nadir) scans, in which there is either an increase of 20% or more in the sum of the longest diameters (SLD) of target lesions taking as reference the smallest sum of the longest diameters (nadir) recorded since Screening, and/or unequivocal progression of non-target lesions, with or without the development of 1 or more new lesions. PD should be confirmed by repeat scans at the next scheduled imaging evaluation 8 weeks later (but no sooner than 4 weeks).

Subjects with PD should be managed in the study as follows:

- PD at the end of Cycle 2: In the absence of clinical deterioration, subjects may continue treatment. In the presence of clinical deterioration, the decision whether to stop treatment should be discussed by investigator and sponsor.
- PD at the end of Cycle 4 or later: Subjects with stable or improved clinical status will continue to be treated with study drug until their next scheduled imaging evaluation.

Development of a ≥ Grade 3 (CTCAE) intolerability or adverse event related to Socazolimab that precludes further treatment with the study drug, but subject does not have worsening progression: Subjects will complete the remaining visits of their current treatment cycle (without infusions) if possible. Subjects will then enter the Follow-up period.

3.4 Follow-Up Period

The maximum duration of follow-up will be 1 year. All subjects should complete Follow-up Visit 1. Completion of subsequent follow-up visits will depend on the status of the subject at the end of the Treatment Period. Except for subjects who discontinue due to PD (as described above), all subjects will be followed from the last visit until relapse, initiation of a new therapy, or a total of 1 year follow-up, whichever occurs first. Subjects who discontinue study drug due to PD will be followed for 3 months (Follow-up Visits 1 and 2); Follow-up Visit 2 (for these subjects only) will only include immunogenic

evaluations and adverse event (see section 12 for AE report) collection. For subjects who are still alive, Follow-up will be conducted every 60 days (Follow-up by phone is possible) until a confirmed death is known.

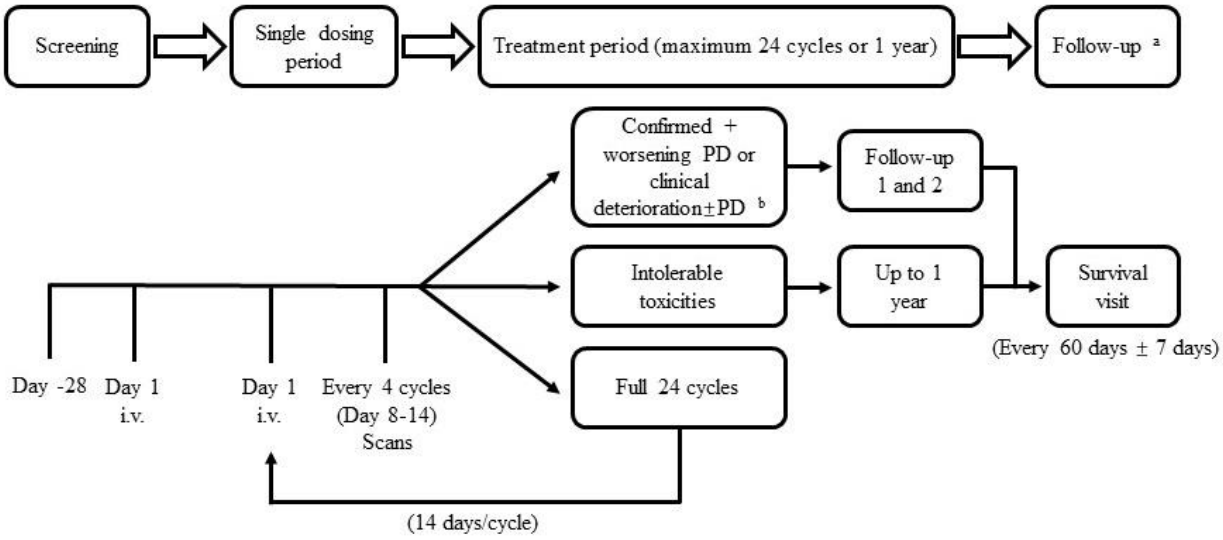

Figure 2: Individual subject flow of 3+3 cohort (Up to 24 cycles or 1 year treatment, up to 1 year Follow-up)

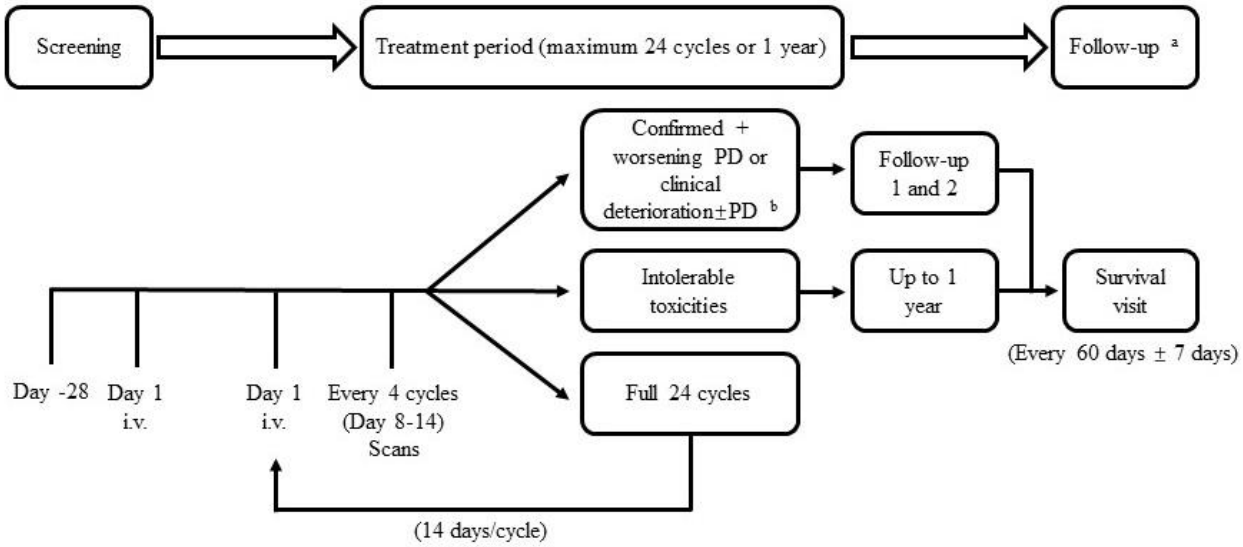

Figure 3: Subject flow of expansion cohort (Up to 24 cycles or 1 year treatment, up to 1 year Follow-up)

Note: PD = Progressive disease

a. For subjects who discontinue from the study within 90 days after the administration of the last dose of study drug, the subject should be followed to resolution/stabilization for all adverse events. Only study drug-related serious adverse events will be collected > 90 days after the last administration of study drug.

b. PD that has been confirmed and then worsens or there is clinical deterioration at a subsequent visit. Follow up visits should be done unless precluded by disease progression or clinical deterioration.

3.5 Research Termination

3.5.1 Dose-Escalation Termination

The dose-escalation schema will proceed based upon the occurrence of a greater than or equal to Grade 2 study drug-related adverse event and DLTs experienced within the first cycle. If 4 or more subjects experience delayed DLTs, accrual will be held pending safety analysis and will be restarted only with investigator and sponsor approval (and subsequent IRB and CFDA notification).

3.5.2 Dose-Expansion Termination

Enrollment may be held in any expansion cohort if the rate of DLTs is ≥ 33% after enrollment of the first 6 subjects in that indication (including subjects from the dose-escalation cohort at the expansion dose). Subjects who are tolerating study drug at a dose level that is being reviewed due to the occurrence of DLTs in another subject will not be automatically precluded from continued dosing during the safety review and will be allowed to continue dosing for as long as study drug is tolerated unless directed otherwise as a result of the safety review. After safety analysis by the investigator and sponsor, a decision will be made whether to resume enrollment at the current dose or initiate a new expansion cohort of 15 subjects in 1 or more indications at a lower dose. For delayed DLTs, enrollment will be held and/or restarted using the same rules as those for DLTs.

3.5.3 Termination due to Clinical Deterioration

Under normal circumstances, we use RECIST 1.1 as the main method to evaluate tumor remission and the time to disease progression as the basis for all programs related to the disease status. After study centers first obtains the results of imaging examination showing PD, RECIST 1.1 is applied to confirm the occurrence of progressive disease (PD). The investigator should be contacted immediately. And iRECIST will be used to assess tumor remission and progression, then make treatment decisions.

To consider that some subjects may have a temporary tumor increase in the first few months after starting immunotherapy, and then the disease will be remitted. Hence, after the first imaging progression, subjects clinically stable are allowed to continue receiving treatment until the imaging examination results are obtained again (≥4 cycles later). Clinical stability is defined as follows:

1) There are no clinically significant symptoms and signs that indicate disease progression;
2) The ECOG performance status score has not deteriorated;
3) No rapid disease progression;
4) There are no advanced tumors (such as spinal cord compression) in important anatomical parts that require other emergency medical intervention. However, subjects who are judged to be clinically

unstable will stop receiving treatment from the first confirmation of imaging and do not need to pass repeated imaging examinations.

Subjects undergoing re-imaging review, if any of the following occurs, is confirmed to have PD:

1) The sum of the diameters of the target lesions is increased by ≥5mm from the lowest value
2) Deterioration of the initial PD lesions
3) New lesions have appeared since the last evaluation

If any of the above conditions occurs during repeated imaging examinations, leading to confirmation of PD, the subject will be discontinued from the study treatment.

4. INCLUSION/EXCLUSION CRITERIA

During the screening period and baseline period before the start of treatment, patients were screened based on whether they were able to meet the inclusion and exclusion criteria.

4.1 Inclusion Criteria

Once the patient has considered participating in this clinical study, prior to commencing any research operations, the researcher will introduce the patient to the research and ask the patient to sign an informed consent form. After signing the informed consent, the patients will be evaluated during the screening period for compliance with the study's inclusion and exclusion criteria.

Patients will be considered eligible for this study if **ALL** of the following conditions are met:

1. Voluntarily participation through written informed consent.
2. Female patients aged≥18 years.
3. Diagnosed with cervical cancer by histology/cytology. Patients with recurrent or metastatic cervical cancer who have had failed or intolerance after receiving at least first-line of platinum-based chemotherapy. (Definition of first-line failure: progression during adjuvant treatment or within 6 months after the end of treatment, first progression after palliative treatment.)
4. Patients must have at least 1 measurable disease on imaging based on RECIST version 1.1.
5. ECOG performance status of 0-1 and have a life expectancy of at least 3 months.
6. Adequate hematologic, liver and kidney function indicated by the following laboratory values:
   - absolute neutrophil count (ANC) > 1.5 x 109/L
   - platelet ≥ 80x109/L
   - hemoglobin ≥ 90g/L
   - serum albumin ≥ 28g/L

- bilirubin ≤ 1.5 ULN
- AST and ALT ≤ 1.5 × ULN , for patients with hepatic metastases, AST and ALT < 5.0 × ULN
- creatinine ≤ 1.25 × ULN or measured or calculated creatinine clearance ≥ 50 mL/minute using Cockcroft-Gault formula

7. If of childbearing potential, patients must be willing to use effective barrier methods throughout the study, starting with the screening visit through 120 days after the last dose of study treatment； Patients of childbearing potential are those who have not been surgically sterilized should have a negative urine or serum pregnancy test within 72 hours at screening

4.2 Exclusion Criteria

If the patient meets any of the following criteria, they will be excluded from the study:

1）There is a known active or suspected autoimmune disease. Those who are in a stable state and do not need systemic immunosuppressive therapy can be enroll；

2）The patient is being treated with immunosuppressive agents, or systemic or absorbable topical corticosteroids for immunosuppressive purposes (dose>10mg/day prednisone or equivalent), and 2 weeks before enrollment is still in use；

3） Have received any form of organ transplantation, including allogeneic stem cell transplantation;

4） Known to have been allergic to macromolecular protein inhibitors, or known to be allergic to any component of Socazolimab;

5） Have suffered from other malignant tumors other than the research target diseases of this study within 5 years, except for skin basal and squamous cell carcinoma;

6） Central nervous system metastasis with clinical symptoms (such as cerebral edema, brain metastasis requires corticosteroid intervention). Previously received treatment for brain or meningeal metastases, such as clinically stable (MRI) for less than 2 months, or systemic corticosteroid therapy (dose>10mg/day prednisone or equivalent) was discontinued for less than 2 weeks;

7） Cardiac clinical symptoms or diseases that are not well controlled, such as: NYHA level 2 or higher heart failure, unstable angina, myocardial infarction within 1 year, clinically significant supraventricular or ventricular arrhythmia requiring treatment or intervention in patients with echocardiography, the left ventricular ejection fraction at rest is less than 50%;

8） Previously received radiotherapy, chemotherapy, major surgery or molecular targeted therapy, less than 4 weeks after the completion of the treatment and before the study medication;

9） Any active infection that requires systemic anti-infection treatment occurs within 14 days before the first administration;

10）Human immunodeficiency virus (HIV) test positive, Treponema pallidum test positive, untreated active hepatitis (hepatitis B surface antigen positive and peripheral blood HBV-DNA titer test ≥500IU/ml or reach the copy number tested by the research center Positive value; positive for hepatitis C virus antibody);

11）Have a history of active tuberculosis within 1 year before enrollment;

12）The patient is participating in other clinical studies, or it is less than 4 weeks since the end of the previous clinical study;

13）Patients may receive other systemic anti-tumor treatments during the study period;

14）Received blood transfusion, hematopoietic stimulating factors, such as colony stimulating factor, erythropoietin, thrombopoietin and other treatments within 14 days before screening;

15）The patient has previously received other PD-1 and/or PD-L1 or CTLA-4 antibody therapy, or other drug therapy for immunomodulatory receptor preparations;

16）Have received live vaccine treatment within 4 weeks before screening;

17）The patient is known to have a history of psychotropic drug abuse, alcohol abuse or drug abuse;

18）Pregnant or breastfeeding women;

19）Any mental condition that hinders understanding or providing informed consent;

20）According to the judgment of the investigator, the patient has other factors that may cause the study to be terminated halfway, such as other serious diseases or severe laboratory abnormalities or other factors that will affect the safety of the patients, or the collection of test data and samples. Family or social factors.

5. RANDOMIZATION AND BLINDING

This study is an open phase I clinical study, so there is no blinding. Patients in the dose-escalation group are assigned to the corresponding dose group according to the order of entry, and because the expansion phase study only involves one dose group, this clinical study does not randomize all patients.

6. DOSAGE AND DOSING SCHEDULE

6.1 Overview of Study Drugs

Socazolimab injection (25mg/ml) is packaged in a 6ml vial. Each vial contains 100mg (4ml) of Socazolimab. The solution is colorless, transparent to slightly milky white, and basically contains no visible particles.

6.2 Packaging and Labeling

Socazolimab injection is packaged in a 6ml vial with a specification of 25.0 mg/ml, and contains 4ml liquid. The composition of the preparation is recorded in the product manual of Socazolimab injection and the Investigator's Brochure.

The packaging and labeling of research drugs must comply with the current Good Manufacturing Practices (GMP). The label includes at least the following information: study drug name, specifications, date of manufacture or expiration, batch number, name and address of the sponsor, and storage conditions.

6.3 Provision of Study Drugs

The research center will receive enough research drugs, infusion pumps, infusion catheters and other required research related items. The study drug will be entrusted to a third-party logistics company for 2-8°C cold chain transportation. In addition, if necessary, the research center can fill in the application form and email it to **Zhaoke (Guangzhou) Oncology Pharmaceutical Ltd.,** with the email address: michael.wong@leespharm.com, to apply for the required research-related items.

6.4 Storage

All study drug must be stored at 2-8 °C . Wear gloves and laboratory clothes when preparing and handling Socazolimab injection.

If the glass bottle is broken, the study drug is discolored or other damages are found, the study drug must not be used, and the sponsor must be contacted immediately.

6.5 Preparation and Dosing Schedule of Study Drugs

Dilute 25mg / ml of Socazolimab injection with 0.9% sodium chloride to 250ml final volume. Socazolimab was infused intravenously at the dose specified in the plan using a positive displacement pump equipped with a 0.2μm filter. It cannot be administered as an intravenous bolus. 90 minutes ≥ intravenous infusion time ≥ 60 minutes (except for infusion reactions), and the infusion rate is ≤4.2ml/min . The infusion time can be extended according to section 7.3 due to infusion reactions. When the infusion is completed, flush the infusion catheter with saline.

The preparation ratio of Socazolimab injection diluted with 0.9% sodium chloride to different specified doses is shown below:

	Socazolimab Dose (mg/kg)		
	5	10	15
Volume of Socazolimab injection [a] (ml)	12	24	36
Socazolimab injection bottle number (n)	3	6	9
0.9% sodium chloride injection volume (ml)	238	226	214

a. 25mg / ml of Socazolimab injection bottle 4ml, a total of 100mg / vial.

The specific steps are as follows:

1) Before preparation, take out the required number of Socazolimab injection vials and let them stand at room temperature for 5 minutes to confirm that the injection is clear, colorless, and visually free of particulate matter.

2) Under aseptic operation, use a syringe to draw out the excess volume of normal saline (0.9% sodium chloride), and use the remaining normal saline to prepare Socazolimab injection.

3) Under aseptic operation, use a syringe to extract the required amount of Socazolimab injection, and inject it into the normal saline infusion bag of mentioned in Step 2 (Note: Do not draw the Socazolimab injection multiple times from the vial. Do not use the glass syringe to extract the Socazolimab injection), the final formulated 250ml final volume.

4) Invert the infusion bag several times and mix gently. Do not shake.

5) Visually inspect the prepared solution. If the prepared solution is turbid, or there is a suspected deposit, please change the study drug (as described in section 6.8) and record it in the study drug count table.

6) Indicate the preparation time and dosage of Socazolimab on the infusion bag .

7) Connect the prepared Socazolimab solution to the infusion catheter, 0.2μm filter, and volumetric pump.

8) 90 minutes ≥ intravenous infusion time ≥ 60 minutes (except for infusion reactions), and the infusion rate is ≤ 4.2ml/min .

It is recommended to use it within 4 hours (including intravenous infusion time) under normal temperature and static state after preparation, so as to avoid excessive exposure at room temperature. If the drug needs to be delayed due to special circumstances, the diluted drug can be stored at 2-8 ℃ for up to 12 hours.

6.6 Drug Count

The research center receives the research drugs and stores them in a safe place, and only the researcher and designated personnel can get these drugs. After receiving the medicine, it needs to be stored according to the instructions of Socazolimab. Distribute research-related items according to the plan.

Drug labeling should comply with relevant regulations. The content of the label contains storage conditions, but does not display the patient's information.

The investigator needs to accurately record the transportation and distribution quantity of the study drug in the drug record. The CRA in charge records the drug quantity during each center visit and when the study is completed.

At the end of the study or during the study period, the investigator shall return all used and unused study drugs, packaging, drug labels and copies of drug quantity records to **Zhaoke (Guangzhou) Oncology Pharmaceutical Ltd.** (see each address Researcher's folder in the research center).

6.7 Dose Adjustment, Delayed Infusion Time and Missed Dosing

If the patient meets the conditions for continuing to receive Socazolimab treatment, the start of the next cycle should not be earlier than 12 days after the previous cycle. In the dose-escalation stage, patients with not alleviate toxicity and delayed Socazolimab treatment for 14 days or more (immune-related adverse events did not recover to ≤ 1 grade skin and endocrine disease is not restored ≤ 2 level), is discontinued from the Socazolimab treatment. If the Socazolimab infusion cannot be performed on the established date, it should be given as soon as possible. If there is a delay infusion of 2 or more days, Socazolimab infusion is considered to be missed and should be given in the next administration cycle. Participants in the expansion phase can delay dosing, but not more than 4 weeks, if they are dealing with toxic reactions. If the infusion of Socazolimab cannot be performed on the scheduled date due to other reasons , the infusion should be completed within 7 days.

6.8 Destruction of Study Drugs

If it is necessary to destroy the study drug in this study at the research center, the investigator shall be responsible for ensuring that the drug is properly handled, ensuring that the entire process complies with relevant regulations and the research center's standard operating procedures (SOP), and making relevant records. The unused study drugs can be destroyed only after inspection and coordination by the sponsor.

6.9 Return of Study Drug

All unused and/or partially used study drugs will be collected by the sponsor.

7. MANAGEMENT OF TOXICITY

7.1 Dose-Escalation Study

This clinical study adopts the traditional 3+3 design and is planned to be carried out in 3 doses: 5, 10, 15 mg/kg/ time, every 14 days (2 weeks) as a treatment cycle. Patients were assigned to the corresponding dose group according to the order of entry. The first patient in the first dose group received a dose of 5 mg/kg. Observe DLT within 28 days of the first Socazolimab administration, and observe DLT separately for single and multiple administrations .

The patients of the next dose should not be enrolled earlier than 28 days after the last patient in the current dose group received Socazolimab. At least 3 patients are included in each dose group. According to the occurrence of DLT, 3 or 6 patients are included in each dose group.

If there is no DLT occurs in the 3 patients of any of the dose groups, it will enter into the next higher dose and recruit 3 new patients in that higher dose. If 1 out of 3 patients experiences DLT, then 3 more patients needs to be recruited (total of 6 patients); if only 1 of the 6 patients after the expansion experiences DLT , then enter the next higher dose to include 3 patients; if the 6 patients after the expansion have ≥ 2 patients experience DLT, then that particular dose is regarded as higher than MTD (MTD is defined as the highest dose that does not exceed 1/6 of the patient experiences DLT), and new patients will be included in the previous lower dose (tolerated dose) group, until the lower dose group reaches 6 patients . If ≤1/6 patients experience DLT , this lower-dose group is designated as MTD . According to the toxicity of the drug, the intermediate dose can be increased through program revision. DLT was observed within 28 days of the first administration of Socazolimab.

If 2 or more cases of delayed type of DLT present in any of the doses during dose-escalation (DLT occurs after the second cycle), the recruitment should be temporally stopped. The re-initiation of recruitment can only be started again after the approval of the investigator and the sponsor (and inform the ethics committee and NMPA).

If the patient withdrew during the first two cycles of administration due to non-DLT reasons, it can be replaced by another patient.

7.2 Dose-Limiting Toxicity (DLT)

DLT is defined as a grade 3 or higher adverse event related to the study drug that occurred within 28 days after the first dose (Excluding burning tumor reaction, which is characterized by local pain, irritation, or rash at the known or suspected tumor site, or transient (releasing within 6 hours) grade 3 infusion adverse events). Adverse events were assessed according to the National Cancer Institute (NCI) CTCAE version

4.0.3. Unless there are other clear and well-documented explanations, DLT is generally considered to be related to the study drug.

Blood-related DLT includes:

- Grade 4 neutropenia;
- Grade 3 neutropenia with fever;
- Grade 4 thrombocytopenia (platelets < 25,000/mm ^{3}) lasts for 48 hours or more, or grade 3 thrombocytopenia with bleeding tendency;

Non-blood related DLTs include:

- Grade 3 or 4 clinically significant non-hematological toxicity (except for nausea, vomiting, constipation, alopecia, etc., diarrhea still > Grade 3 should be considered as DLT after appropriate supportive treatment) ;
- Grade 3 or 4 immune-mediated pneumonia;
- Grade 3 or 4 immune-mediated enteritis;
- Grade 3 or 4 immune-mediated hepatitis;
- Immune-mediated endocrine disease
  - Grade 4 hypophysitis
  - Grade 3 or 4 adrenal insufficiency
  - Grade 3 or 4 hypothyroidism / thyroiditis or hyperthyroidism
  - Type 1 diabetes with grade 4 hyperglycemia
- Grade 4 immune-mediated nephritis and renal insufficiency
- Grade 3 or 4 immune-mediated adverse skin reactions
- Grade 3 or 4 immune-mediated encephalitis

Late-onset DLT is an adverse event that meets the DLT criteria but occurs during the treatment period. The estimation of MTD during dose-escalation does not involve late-onset DLT. Researchers and sponsors continuously collect and evaluate late-onset DLT during the research process.

All unanticipated toxicity that meets the DLT definition and is ≥ Grade 3 must be reported to the sponsor within 24 hours through the same rapid procedure as the reporting of serious adverse events (SAE).

7.3 Infusion Reaction

The infusion site reactions were graded according to the description of allergic reactions / hypersensitivity reactions in CTCAE version 4.0.3. Signs and symptoms of an infusion reaction include, but not limited to, fever, chills, headache, rash, itching, joint pain, hypotension / hypertension, bronchospasm, and other symptoms.

Severe infusion reactions require immediate interruption and permanent termination of the study drug. Appropriate medications should be prepared, including epinephrine, glucocorticoids, intravenous antihistamines, bronchodilators, and oxygen. In the event of the above, the patients' signs and symptoms should be closely observed until complete relief.

For each infusion reaction that occurs, the investigator should try to give the best appropriate medical practice. The following are the recommended treatment guidelines for the program:

CTCAE Level 1:

Reduce the drug infusion rate to 50% and monitor closely for further deterioration. If the infusion reaction still exists at this infusion rate, it is necessary to further reduce the infusion rate. The maximum infusion time is 3 hours (180 minutes).

CTCAE Level 2:

Stop the study drug infusion. According to medical indications, administer adrenaline, glucocorticoids, intravenous antihistamines, bronchodilators, and / or oxygen. If the infusion reaction is relieved or the severity is reduced to CTCAE level 1, the infusion can be restarted at 50% of the original infusion rate, and at the same time, whether any deterioration has occurred is closely monitored. If the infusion reaction occurs again at this infusion rate, the infusion rate can be further reduced. The longest infusion time is 3 hours (180 minutes).

CTCAE level 3 or 4:

Immediately stop the study drug infusion and disconnect the infusion catheter from the patient. According to medical indications, administer adrenaline, glucocorticoids, intravenous antihistamines, bronchodilators, and / or oxygen. Notify the sponsor and record it as SAE. No further study drugs will be given afterwards.

Restart Socazolimab treatment after infusion reaction. Once the infusion rate is reduced due to an infusion reaction (for example, CTCAE grade 1 or 2 infusion reaction), all subsequent drug infusion rate

will be reduced. If the patient still has an infusion reaction at that rate, the infusion rate should be further reduced and the infusion time should be extended further. After two consecutive extension of infusion time, if the patient shows good tolerance, it can be restored to the shorter infusion time. If the patient still has an infusion reaction after reducing the infusion rate, corticosteroids can be given for intervention.

7.4 Principles for Handling Immune-Related Adverse Events

According to the severity of the adverse reaction, Socazolimab treatment should be suspended. When the severity of AE returns to grade 1 or lower, Socazolimab tretament can be considered again. When serious grade 3 or life-threatening grade 4 adverse reactions occur, treatment should be permanent disabled.

The treatment of immune-related adverse reactions should be carried out in accordance with the medical practice and guidelines of the research institution. The following are the treatment recommendations for immune-related adverse reactions (see the table below) for reference. For the treatment of common adverse reactions, see Appendix 4.

CTCAE Classification	Clinical Treatment	Socazolimab Treatment
Grade 1 (mild)	Close observation, symptomatic and supportive treatment	continue
Level 2 (moderate)	Close monitoring, symptomatic and supportive treatment, oral or intravenous steroids, 0.5-1mg/kg/day, prednisone equivalent	Suspend the medication, re-administer the medication when ≤1 grade; except for skin and endocrine lesions, continue medication
Grade 3 (severe)	Recommend hospitalization; Intravenous or oral 1-2mg/kg/day, prednisone equivalent If steroid therapy is ineffective for 3-5 days, consider adding other immunosuppressive agents Suggest a specialist consultation	Suspension of medication: Whether to restart medication should be decided after comprehensive consideration of the risk/benefit ratio and discussion
Level 4 (life-threatening)	Intravenous injection of 1-2 mg/kg methylprednisolone If steroid treatment is ineffective for 3-5 days, consider adding other immunosuppressive agents	Permanently deactivate

7.5 Criteria for Delayed Administration

When the following situations occur, the administration should be delayed:

- Any non-skin and non-endocrine adverse events ≥ Grade 2 drug-related, except for Grade 2 drug-related fatigue or abnormal laboratory tests;
- Any grade 3 drug-related skin adverse events;
- Any grade 3 drug-related adverse endocrine events;
- Any grade 3 drug-related laboratory abnormalities, except for grade 3 amylase or lipase abnormalities that are not related to pancreatitis symptoms and clinical manifestations ;
- Any adverse events, laboratory abnormalities, complicated diseases, the investigator judges that the drug needs to be delayed

Patients who need to delay dosing should be rechecked and monitored weekly, and the frequency of monitoring should be increased when there are clinical indications. When the criteria for resuming medication are met (see 7.6.), study drug can be resumed .

Tumor assessments for all patients still need to continue as required by the protocol, regardless of whether the drug is delayed or not.

7.6 Restoring Medication Standards

When the drug-related AEs return to ≤ Grade 1 or the baseline status, the study treatment can be restarted, except for:

- The patient with grade 2 fatigue not recovered can be restarted for the treatment.
- Grade 2 Skin AE can continue to be treated;
- Drug-related endocrine lesions can be fully controlled if only physiological dose hormone replacement is required, and treatment can be resumed.

The study drug is allowed to be delayed for a maximum of 4 weeks, calculated from the time of the last administration. If after a delay of 4 weeks, the patient has not yet reached the standard for resuming study drug, the study treatment needs to be permanently terminated (refer to 7.7.)

7.7 Standards for Permanent Discontinuation

Study drug must be permanently terminated in the following situations:

- Any grade 3 drug-related non-skin AE , duration> 7 days, with the following exceptions:

- Any grade 3 drug-related uveitis, pneumonia, bronchospasm, hypersensitivity or infusion reactions must be terminated in the study treatment;

- Grade 3 drug-related endocrine disease, only physiological dose of hormone replacement therapy can be fully controlled, and there is no need to terminate the treatment;

- Abnormal grade 3 drug-related laboratory tests do not require termination of treatment. However, if grade 3 thrombocytopenia occurs> 7 days or related to bleeding , the study medication must be terminated.

- Any grade 4 drug-related AE or laboratory abnormality, except for the following:

- Grade 4 neutropenia < 7 days;

- Grade 4 lymphopenia or leukopenia;

- Isolated grade 4 amylase or lipase elevation, not accompanied by pancreatitis symptoms or clinical manifestations. The sponsor shall be notified if there is an increase in grade 4 amylase or lipase.

- Isolated Grade 4 electrolyte imbalance / abnormality that is not accompanied by clinical sequelae and can be corrected by supplementation / appropriate treatment within 72 hours after its occurrence ;

- For grade 4 drug-related endocrine lesions, only physiological doses of hormone replacement therapy are needed and the air separation is controllable, and the treatment does not need to be terminated.

- A treatment delay of > 4 weeks is required , and the study treatment must be terminated, except for the following:

- When dealing with drug-related adverse events, it is allowed to postpone the administration of cortisol for more than 4 weeks due to the need to gradually reduce the dose. Discuss with the sponsor before resuming dosing. During the postponement of dosing, tumor evaluation should continue as required by the protocol. Safety visits and laboratory examinations should also be carried out at the original frequency or more frequently when there is clinical correction.

- Due to non-study drug-related reasons, the administration needs to be delayed> 4 weeks. Before resuming the administration, the decision must be made after discussion with the sponsor. During the postponement of dosing, tumor evaluation should continue as required by the protocol. Safety visits and laboratory examinations should also be carried out at the original frequency or more frequently when there is clinical correction.

- In the event of clinical adverse events, abnormal laboratory tests, or concurrent diseases, according to the investigator's judgment, continued research and medication will bring significant risks to the patients. Even if the medication is discontinued, the patient must continue the tumor evaluation as required by the protocol.

8. COMBINED MEDICATION

All drugs used by the patients in the 28 days before the start of the study and during the study (except for solvents, such as saline, glucose injection, etc.) will be recorded in the relevant part of the eCRF table, and the reason for use and details of use must be indicated .

a) Preventive antiemetics, except corticosteroids (only allowed for infusion reactions), are not used before the first treatment.

b) Granulocyte colony stimulating factor or granulocyte - macrophage colony stimulating factor is not allowed to be used for prevention.

c) It is not allowed to use proprietary Chinese medicines or herbal medicines with anti-tumor effects, other commercially available anti-cancer chemotherapy or immunotherapy drugs, or any other drugs under development (drugs for any indication that have not been approved for marketing).

d) It is not allowed to use any other new chemotherapy or immunotherapies except the research drug.

e) Palliative care or therapy (eg, local radiation therapy to relieve pain, thoracentesis to reduce discomfort) can be performed after the investigator's judgment.

f) During the study period, the use of live vaccines is prohibited, but inactivated vaccines for influenza prevention can be used at any time. The inactivated vaccines used to prevent other infectious diseases can be used according to the situation according to the judgment of the investigator, but it is necessary to consider increasing the washout period before and after the medication. All vaccines used during the study must be recorded in the patient’s medical records and CRF .

g) Oral or enteral corticosteroids with immunosuppressive effects should be gradually reduced (>10mg/ day of prednisone or equivalent drugs) two weeks before the first dose of SOCAZOLIMAB , and any immunosuppressive corticosteroids should not be taken during the study period. Inhibitory doses of these drugs (except for infusion reactions, irAEs , or other adverse events).

h) The use of denosumab is not allowed . Bisphosphonate drugs such as zoledronic acid can be used.

Patients need to use the same combination medication. During the study period, if a new concomitant medication needs to be added, or the current dose or dosing schedule of the concomitant medication needs to be adjusted, a record should be made in the appropriate part of the eCRF .

9. RESEARCH PROCESS OF DOSE-ESCALATION STAGE

9.1 Screening Period

Within 28 days before the single administration and after obtaining the written informed consent, the patients were evaluated during the screening period. If the patient has received routine imaging and

electrocardiography in the 28 days before the start of Socazolimab administration , it can be used as baseline data without repeating it.

The screening period visit includes the following items:

1) Obtain informed consent;
2) Demographic data;
3) Medical history (past and current medical history);
4) Combined medication (previous medication and medication used by patients in the screening period);
5) Diagnosis and tumor staging (pathological section, pathological report, and pathology used to diagnose recurrence or metastasis at the initial diagnosis);
6) Tumor-specific treatment history;
7) Confirmation of entry standards;
8) Blood / urine β-HCG test (for women of childbearing age, the blood / urine pregnancy test must be negative to continue this clinical study);
9) Vital signs detection (including body temperature, heart rate, breathing, and systolic / diastolic blood pressure at rest);
10)ECOG fitness score;
11)Physical examination (including height and weight);
12)Tumor imaging examination (CT/MRI examination of chest, abdomen, and pelvis). The same imaging method should be used throughout the research process;
13)Brain CT scan /MRI examination (MRI is preferred);
14)12- lead ECG ;
15)Echocardiogram (optional);
16)Tumor cell PD-L1 expression level;
17)Laboratory inspection:

- Routine blood examination: complete blood count (including absolute lymphocyte count), direct count of hemoglobin and platelets.
- Blood biochemical examination: albumin, aspartate aminotransferase (AST/SGOT), alanine aminotransferase (ALT/SGPT), bilirubin (direct bilirubin and total bilirubin), creatinine, glucose, lactate dehydrogenase (LDH)), total protein, urea nitrogen (BUN) / urea, uric acid
- Electrolytes: sodium, potassium, calcium.
- Urine routine examination: urine specific gravity, urine pH , urine protein, urine glucose, urine white blood cells, urine red blood cells.

- Immune safety analysis: rheumatoid factor, thyroid stimulating hormone, free T4 level, C- reactive protein.
- HBV (five items of hepatitis B), HCV antibody, HIV antibody and syphilis antibody examination. Positive hepatitis B surface antigen, perfect HBV-DNA examination.

9.2 Treatment Period (Single-Administration)

A single dose was given 28 days before multiple doses to explore PK parameters, which includes the following:

1) Pregnancy test
2) Vital signs detection (including body temperature, heart rate, breathing, and systolic / diastolic blood pressure at rest);
3) ECOG fitness score (day 1 , 8 , 15) ;
4) Physical examination (day 1 , 8 , 15);
5) 12- lead ECG (before and after infusion);
6) Laboratory testing. Blood routine and blood biochemical tests must be performed before infusion and administration, and the result evaluation must be completed. For any new laboratory abnormality test results ≥3 grade, or consistent with possible changes in irAE (relative to disease progression), such as high liver function test results, electrolyte imbalance, or blood disease deterioration, continue infusion should be performed Possible risk assessment of drug administration. The sampling site should be different from the intraday infusion site (eg, the contralateral arm).

--- Classified blood counts (days -7~1 , 8 , 15) (see section 9.1 for details)
--- Blood biochemistry (days -7~1 , 8 , 15) (see section 9.1 for details)
--- Urine routine examination (see section 9.1 for details)
--- Flow cytometry and cytokine check

7) Perform intravenous infusion of SOCAZOLIMAB ;
8) Pharmacokinetic blood samples and immunogenic blood samples are collected (see Table 3 for detailed sampling time points . The blood sample collection site after infusion should be different from the intraday infusion site, such as the contralateral arm);
9) Combination therapy;
10)Assessment of adverse events, including detailed symptom descriptions that may indicate irAEs

9.3 Treatment Period (Multiple Administration)

The patients received an infusion of Socazolimab every 14 days (1 cycle). At the end of cycles 4, 8, 12, 16, 20, and 24 (i.e. every 8 weeks), or according to clinical needs, evaluate the tumor status and to decide whether to continue treatment (see section 3.3 for details). Increasing or decreasing the dose within the individual is not allowed. The treatment duration is up to 24 cycles or 1 year (whichever comes first), but for patients who have taken the drug for 24 cycles or 1 year, if the investigator believes that they can still benefit from the treatment, the treatment can be continued.

The follow-up visit should be conducted in accordance with the time window specified in the plan as far as possible. For delayed infusion administration (e.g. 2 days or longer) or missed infusion time, see section 6.7. If the patient missed the drug infusion during the first cycle due to non-DLT reasons, another patient will replace it. This treatment phase procedure is also applicable to patients in the first phase of the expansion phase.

9.3.1 The First Treatment Cycle

Patients received an intravenous infusion of Socazolimab on the first day of the first cycle, 90 minutes ≥ infusion time ≥ 60 minutes (except for infusion reactions), and the therapeutic effect was evaluated between days 8-14 of the cycle . Only patients completed Socazolimab infusion therapy, and the tumor evaluation for the 1st cycle can be regarded as the completion of the 1st cycle. The completion of the 1st treatment cycle should record in the CRF table.

Follow Table 1 (the first cycle research flowchart), and fill in the following information into the CRF:

- Vital signs examination (measure body temperature, heart rate, respiration, and resting systolic / diastolic blood pressure before, after and on the 8th day of the infusion. For detailed time points, see the flow chart notes in Table 1)
- ECOG performance status (evaluated on the day before the infusion and on the 8th day)
- Physical examination, including weight (days 1 and 8)
- 12-Lead ECG
- Blood / urine pregnancy test (all women of gestational age should be performed before the infusion, and the study can be continued only if the result is negative)
- Blood sample collection for pharmacokinetic studies, receptor occupancy and immunogenicity tests (see Table 3 for detailed sampling time points . The blood sample collection site after infusion should be different from the intraday infusion site, such as the contralateral arm).

- Laboratory testing. Blood routine and blood biochemical tests must be performed before infusion and administration, and the result evaluation must be completed. For any new laboratory abnormality test results ≥3 grade, or consistent with possible changes in irAE (relative to disease progression), such as high liver function test results, electrolyte imbalance, or blood disease deterioration, continue infusion should be performed Possible risk assessment of drug administration. The sampling site should be different from the intraday infusion site (eg, the contralateral arm).

--- Classified blood counts (days -7~1 and 8) (see section 9.1 for details)

--- Blood biochemistry (days -7~1 and 8) (see section 9.1 for details)

--- Urine routine examination (days 1 and 8) (see section 9.1 for details)

--- Flow cytometry and cytokine check

- Immune safety analysis: rheumatoid factor, thyroid stimulating hormone, free T4 level, C- reactive protein.
- Perform intravenous infusion of SOCAZOLIMAB
- Combination therapy
- Assessment of adverse events, including detailed symptom descriptions that may indicate irAEs

9.3.2 The 2nd to 24th Treatment Cycle

After completion of the 1st cycle, if the patient is clinically stability, the patient may continue to receive additional Socazolimab treatment (cycles 2-24), until any of the following situations happen: confirmation of clinical deterioration, PD , ≥3 more stages of drug-related CTCAE , cannot tolerate the treatment or any other reason causing the patient to withdraw from the study. If the patient cannot enter the second cycle of treatment, the visit on the first day of the second cycle will not be performed, and follow-up will be carried out as described in Table 1 and Table 2.

In the second and subsequent treatment cycles, perform the following assessments according to the items in Table 2 and record them in the CRF table:

- Vital sign examination (measure body temperature, heart rate, breathing, and systolic / diastolic blood pressure in resting state , see the flow chart in Table 2 for details)
- ECOG fitness status
- Blood / urine pregnancy test (all women of gestational age should be performed before the infusion, and the study can be continued only if the result is negative)
- Physical examination (including weight)
- 12- lead ECG

- Tumor imaging evaluation (CT/MRI of chest, abdomen, pelvis), at the end of cycles 4, 8, 12, 16, 20, and 24 (ie every 4 cycles) on days 8-14 , and in the next cycle Before administration, or according to clinical needs.
- Brain CT scan /MRI (MRI is preferred). Only when the results of the screening period suggest that there are tumors in the brain, brain scans during the treatment and follow-up periods, or corresponding examinations based on clinical indications, are required.
- Blood sample collection for pharmacokinetic studies (see Table 3 for detailed sampling time points . The blood sample collection site after infusion should be different from the infusion site on the same day, such as the contralateral arm).
- Recipient occupancy rate blood sample collection (see Table 3).
- Blood sample collection for immunogenicity testing (see Table 3)
- Laboratory testing. Blood routine and blood biochemical tests must be performed before infusion and administration, and the result evaluation must be completed. For any new laboratory abnormality test results ≥3 grade, or consistent with possible changes in irAE (relative to disease progression), such as high liver function test results, electrolyte imbalance, or blood disease deterioration, continue infusion should be performed Possible risk assessment of drug administration. The sampling site should be different from the intraday infusion site (eg, the contralateral arm).

--- Classified blood count (see section 9.1 for details)

--- Blood biochemistry (see section 9.1 for details)

--- Immune safety test (see 9.2 for details)

--- Urine routine examination (see section 9.1 for details)

--- Flow cytometry and cytokine check

- Echocardiogram (optional)
- Perform intravenous infusion of SOCAZOLIMAB
- Combination therapy
- Efficacy evaluation (at the end of the 4th, 8, 12, 16, 20 and 24 cycles (ie every 4 cycles) on the 8-14th day, complete the tumor efficacy evaluation before the next cycle of administration, and decide whether to continue treatment)
- Assessment of adverse events, including detailed descriptions of symptoms that may indicate irAEs

9.4 Follow-Up Period

The follow-up period included 5 visits. The longest follow-up period is about 1 year. All patients should complete follow-up visit 1 (day 7 after the last visit of the last treatment cycle). The completion of

the remaining follow-up visits (2-5) should be based on the patient's condition after the last treatment. Except for patients who discontinued the study due to PD, all patients should be followed up for one year from the last visit until recurrence, starting a new treatment, or reaching one year of follow-up, whichever occurs first. For the patients who had PD and discontinued the study, they were followed up for 3 months (Visit 1 and 2), and the pharmacokinetics and immunogenicity were evaluated in visit 2, and adverse events were collected. For those who are still alive, follow-up visits will be conducted every 60 days (phone follow-up is possible) until a confirmed death is known.

Perform the following assessments based on the items in Tables 1 and 2 and record them in the CRF table:

- Blood / urine β-HCG test
- Collect blood for immunogenicity test (see Table 3 for details)
- Receptor occupancy rate detection (see Table 3 for details)
- Blood sample collection for pharmacokinetic studies (see Table 3 for details)
- Vital signs testing
- ECOG fitness status
- Physical examination
- 12- lead ECG
- Tumor imaging
- Laboratory examination
- Combination therapy
- Adverse events

9.5 Patient Compliance

If there is a violation of the dosing regimen during the study, the investigator must record it in the original record and record it in the eCRF as the source data. The first stage of the expansion phase: 15 patients (including the best tolerated 6 patients), if a patient withdraws from the study due to non-DLT reasons within 28 days after dosing, another patient can be replaced.

10. THE SECOND PHASE OF THE DOSE-EXPANSION PHASE

10.1 Screening Period

Within 28 days before the first administration and after obtaining the written informed consent, the patients will be evaluated during the screening period. If the patient has received routine imaging

examinations and electrocardiograms within 28 days before starting Socazolimab administration (the results within 56 days of receiving cranial MR), it can be used as baseline data without repeating it again. The screening period visit includes the following items:

1) Obtain informed consent;
2) Demographic data;
3) Medical history (past and current medical history);
4) Combined medication (collected within 1 month before the screening period);
5) Diagnosis and tumor staging (pathological section, pathological report);
6) Tumor-specific treatment history;
7) Confirmation of entry standards;
8) Blood / urine β- HCG test (for women of childbearing age, the blood / urine pregnancy test must be negative to continue this clinical study);
9) Vital signs detection (including body temperature, heart rate, breathing, and systolic / diastolic blood pressure at rest);
10)ECOG fitness score;
11)Physical examination (including height and weight);
12)Tumor imaging examination (CT/MRI examination of chest, abdomen, and pelvis). The same imaging method should be used throughout the research process;
13)Brain CT scan /MRI examination (MRI is preferred);
14)12- lead ECG ;
15)Echocardiogram (optional);
16)Tumor cell PD-L1 expression level;
17)Laboratory inspection:

- Routine blood examination: complete blood count (including absolute lymphocyte count), direct count of hemoglobin and platelets.
- Blood biochemical examination: albumin, aspartate aminotransferase (AST/SGOT), alanine aminotransferase (ALT/SGPT), bilirubin (direct bilirubin and total bilirubin), creatinine, glucose, lactate dehydrogenase (LDH)), total protein, urea nitrogen (BUN) / urea, uric acid
- Electrolytes: sodium, potassium, calcium.
- Urine routine examination: urine specific gravity, urine pH , urine protein, urine glucose, urine white blood cells, urine red blood cells.
- CEA , CA125 , SCC

- Immune safety analysis: rheumatoid factor, thyroid stimulating hormone, free T4 level, C- reactive protein.
- HBV (five items of hepatitis B), HCV antibody, HIV antibody and syphilis antibody examination. Positive hepatitis B surface antigen, perfect HBV-DNA examination.

10.2 Treatment Period

The following tests are included:

1) Pregnancy test;
2) Vital signs detection;
3) ECOG fitness score;
4) Physical examination
5) 12-Lead ECG ;
6) Laboratory testing. Blood routine and blood biochemical tests must be performed before infusion and administration, and the result evaluation must be completed.

--- Classified blood counts;
--- Blood biochemistry;
--- Urine routine examination;
--- Flow cytometry and cytokine inspection (within 30 minutes before each medication);
--- CEA , CA125 , SCC (synchronized with image evaluation);
--- Immune safety inspection

7) Tumor imaging examination (every 4 cycles or according to clinical needs);
8) Immunogenicity (at 1-6 prior to dosing period 30 within minutes after every 3 pre-dose period 30 within minutes)
9) Perform intravenous infusion of SOCAZOLIMAB ;
10) Combination therapy;
11)Assessment of adverse events, including detailed descriptions of symptoms that may suggest irAEs .

10.3 Follow-Up Period

The follow-up period included 5 visits. The longest follow-up period is about 1 year. All patients should complete follow-up visit 1 (day 7 after the last visit of the last treatment cycle). The completion of the remaining follow-up visits (2-5) should be based on the patient's condition after the last treatment.

Apart from patients who discontinued the study due to PD, all patients should be followed up for one year from the last visit until recurrence, starting a new treatment, or reaching one year of follow-up, whichever occurs first.

For the patients who had PD and discontinued the study, they were followed up for 3 months (Visit 1 and 2), and only during the visit 2, immunogenicity and adverse events were collected. For those who are still alive, follow-ups will be conducted every 60 days (phone follow-up is possible) until a confirmed death is known.

The following tests are included:

1) Pregnancy test;
2) Vital signs detection;
3) ECOG physical status;
4) Physical examination
5) 12-Lead ECG;
6) Tumor imaging;
7) Laboratory inspection
8) Combination therapy;
9) Adverse event
10) Follow-up anti-tumor therapy;
11) State of existence.

11. RESEARCH TERMINATION

11.1 Patient Withdrawal Criteria

Patients can voluntarily withdraw or be required to withdraw from the study and / or study drugs at any time for reasons including but not limited to:

1) The patient wishes to withdraw from this study;
2) The patient has experienced a serious or life-threatening AE , or the investigator believes that the patient needs to withdraw from the study in order to protect the safety of the patient;
3) pregnant;
4) The patient seriously violated the protocol;
5) Disease progression (as described in section 3.3);
6) Severe clinical deterioration;
7) The behavior of the patient may impair the correctness of the research results;

If the patient withdraws from the study early, follow-up visits 1 and 2 must be completed to monitor adverse events or other serious adverse events within 90 days after the last dose . If the patient withdraws from the study early due to an AE , the patient should be followed up until the investigator determines that the AE has been resolved (or reached a normal value or reached a baseline value) or stabilized. If the patient cannot undergo follow-up visits, they should be contacted at least once within 90 days after the last dose , and telephone visits can be accepted.

11.2 Study Termination Criteria

If the investigator and / or sponsor believes that the continued progress of the study may cause significant medical risks to the patients, the study should be stopped in time. This includes but is not limited to: serious, life-threatening or fatal AE , or AE in nature, unacceptable in severity or frequency of occurrence. In addition, the sponsor can terminate the study at any time for any reason.

11.3 Research Center Withdrawal Criteria

The research center can withdraw from this research under the following circumstances:

1) The principal investigator requests to withdraw from the study;
2) The sponsor requires the center to withdraw from the research;
3) The center did not comply with Chinese regulations;
4) Violated the plan and refused to rectify;
5) The researcher change or equipment change of the center seriously affects the research progress.

12 Clinical Evaluation

12.1 Safety Assessment

Safety assessment is carried out by evaluating adverse events and abnormal results of laboratory inspections. The toxicity was evaluated according to CTCAE version 4.0.3 . For Socazolimab safety and tolerability assessments included: checking vital signs, laboratory tests, pregnancy testing, ECOG fitness tests, imaging tests, physical examination, the ECG , the occurrence of adverse events and the severity.

Due to the mechanism of Socazolimab, it is also necessary to detect immune-related adverse events (irAEs) caused by T cell activation , such as immune dermatitis, pneumonia, colitis, uveitis, arthritis, nephritis, etc. According to clinical indications, an eye examination is performed for signs and symptoms of uveitis. In addition, immune safety assessment (such as irAEs , or autoimmune serum laboratory tests), immunogenicity testing, T cell function and cytokine testing are also required.

12.1.1 Immune Safety

Immune safety refers to the detection of changes in laboratory tests due to autoimmunity or other due to Socazolimab stimulating the immune system. The generation of new reactivity is not necessarily related to clinical results, but safety monitoring is required in accordance with the protocol. The blood sampling time points for immunogenicity testing are shown in Table 3 . The sample is used to evaluate the production of anti-drug antibodies (ADA).

12.1.2 Immunogenicity

Immunogenicity refers to the body 's immune response to Socazolimab, that is, the body's anti-Socazolimab antibody. The production of this antibody will accelerate the clearance of Socazolimab in the blood, or increase the chances of patients experiencing an infusion reaction during treatment.

12.1.3 T Cells and Cytokines

Socazolimab can prevent the mutual recognition of PD-1 and PD-L1, restore the function of some T cells, so that T cells can kill tumor cells. At the same time, it stimulates the secretion of cytokines, activates lymphocytes, and regulates the body's immunity.

12.2 Efficacy Evaluation

According to RECIST1.1 (see Appendix 2), the tumor efficacy was evaluated. Different from traditional chemotherapy or targeted drugs, the clinical efficacy (objective response) of activating anti-tumor immune response drugs has a delayed effect, which usually occurs several weeks or months after administration.

During this period, some lesions will show enlargement (may be due to real tumor growth, or it may be due to an increase in inflammatory infiltration), this phenomenon is usually interpreted as disease progression, and then there are other lesions that show shrinkage or stability. However, after continuous treatment, the anti-tumor immune response will gradually mature, and all lesions may shrink or stabilize. In other words, before this, it is possible to detect the initial obvious imaging progress, or the emergence of new lesions, or the size of some lesions mixed with the enlargement of some lesions (called " mixed therapeutic effect ").

Therefore, in the case of patients showing early tumor volume increase and obvious early progress, if the clinical status is stable or improved, they can continue to receive a cycle of study drug treatment until the next plan provides imaging Assess the time point and determine the progress. In this clinical study, if the patient develops PD but is clinically stable, he can continue to receive study drug treatment.

In the absence of clinical deterioration, even if imaging progress is detected, the study drug is allowed to continue until further deterioration is proven at the next continuous imaging evaluation after definite imaging progress is produced. The investigator should make a comprehensive clinical judgment to consider whether the patient is clinically deteriorating and is unlikely to continue to benefit from the treatment.

In order to provide objective, neutral, and reproducible efficacy data, in addition to the investigator's evaluation, this study will establish a third-party Indempendent Radiology Review Committee (IRC) during the expansion phase to evaluate tumor efficacy. All images obtained at each center (including unplanned scans) will be reviewed by the IRC , and the evaluation results will be used as the supporting basis for the efficacy results. Clinical decisions related to efficacy evaluation will be based on the investigator's evaluation.

12.3 Pharmacokinetics (PK) and Receptor Occupancy Determination

The pharmacokinetic parameters include AUC (0-T) , AUC (INF), Cmax , Tmax , T1/2 , Vss , CLT and steady-state trough value Cmin . See Table 3 for the detailed schedule of PK blood sampling . The blood collection site should be different from the drug infusion site on the day (such as the contralateral arm). If the infusion is interrupted for some reason, the reason for the interruption should be noted in the CRF table. If the patient's baseline examination shows that the hemoglobin level is less than 10g/dl , intensive blood sampling should not be performed. Separate the monocytes in the peripheral blood before each cycle of single administration and multiple administrations, and measure the receptor occupancy rate of PD-L1 on CD3+ T cells.

13 ADVERSE EVENT REPORT

13.1 Adverse events (AE)

"Adverse events" (AE) refers to all adverse medical events that occur after clinical study patients receive the test drug. It can be manifested as symptoms, signs, diseases, or abnormal laboratory tests, but it may not be inferred to be related to the test drug. Clear causality. Therefore, an adverse event may be any discomfort and unconscious signs (for example: abnormal laboratory test results), symptoms or diseases. The AE is classified according to CTCAE version 4.0.3 . If the CTCAE classification does not apply to an adverse event, use mild, moderate, severe, fatal, and death to evaluate.

A disease or medical condition that occurred before the infusion of the study drug is considered as an adverse event only if it worsens after the infusion. If a medical event occurs before the administration

or after the ICF is signed , it will be recorded in the CRF as a past or current medical history. All abnormal laboratory inspection data are classified and recorded according to CTCAE version 4.0.3 .

After discovering abnormal data in laboratory inspections, if the following conditions are caused, they are classified as AE :

- Discontinue study drug;
- Need for therapeutic medical intervention;
- The investigator assessed it as an adverse event;
- The laboratory test results are clinically significant and meet the definition of AE

13.2 Serious Adverse Events (SAE)

1) A serious adverse event (SAE) refers to an AE that causes one of the following conditions in the patient after receiving the study drug :

- Cause death
- life threatening
- Cause the patient to be hospitalized or extend the planned hospital stay
- Cause permanent or significant disability
- Cause congenital abnormalities / birth defects
- Causing serious medical events or reactions that require medical or surgical intervention

" Life-threatening " refers to the fact that the researcher believes that the patient will soon be at risk of death after the event occurs, rather than the event becoming worse and leading to death.

2) Events that are not serious adverse events

- Emergency room visits
- Observation in hospital within 24 hours
- Inpatient for outpatient routine examinations (hospitalization time is less than 24 hours)

- The situation mentioned in the protocol: hospitalization for treatment administration, hospitalization due to the completion of the assessents required by the protocol.
- Hospitalization for social reasons: if the patient is hospitalized without care
- Surgery that is scheduled before the study starts, if the surgery requires hospitalization must be recorded in the source document and the screening part of the case record form (it will be considered as a SAE if the condition worsens and requires surgery)

- Hospitalized in rehabilitation institutions and nursing homes
- Routine physical examination and hospitalization
- Indications disease progression

When determining whether other medical events are serious adverse events, for example, an important medical event may not immediately threaten patient's life or cause death or hospitalization, but may endanger patients or may require relevant interventions to prevent the above adverse consequences. Any serious adverse events should be determined by strict professional medicine or science. For example, receiving intensive treatment in the emergency room or at home because of the occurence of allergic bronchospasm, malignant hematological changes, or convulsions without hospitalization, drug addiction, etc.

13.3 AE, SAE Reporting

From the clinical studys starts, until the 90 days after the last dose is administered, all AEs and SAEs should be captured in patient's medical chart and eCRF. If the patient terminates its participation within 90 days after the last dose is administered, then:

- If it is a adverse drug reaction (ADR, an drug-related AE), the AE should be recored and followed up by the investigator until it is resolved or stabilized
- If the AE result in the patient termination, then the AE should be followed up until it is resolved or stabilized
- If the patient is not able to attend the follow-up visit in the study site, it can be assessed via telephone

Only SADR (serious adverse drug reaction) and other AEs that is clinically significant (e.g., late onset irAEs) are required to follow-up at least 90 days after the last dose is administered.

All non-serious AEs should be captured when the first dose of study treatment is administered and draw an evaluation 90 days after the last dose is administered. All non-serios AEs should be followed up until it is resolved or stabilized. If an AE escalates to an SAE, then report as an SAE. If the non-serious AE result in study discontinuation or termination, it also needs to follow-up.

The AE events should be recorded in the eCRF which should include start date & time, end date & time, CTCAE grade (grade 1-5) or strength, severity, causality to the investigational drug, follow-up action, and outcome. AE should be reported by concise medical term. If certain symptoms or signs are associated with a concise medical diagnosis and syndrome, then the specific name of the diagnosed disease or syndrome should

be recorded in the eCRF, rather than simply recording its symptoms and signs.

13.4 AE and SAE Report by Investigators

All SAEs (expected or unexpected, related or not related to the investigational drug) should be captured within 90 days after the last dose is administered, or within 30 days after the last visit of screening failure. Moreover, the investigators should inform the pharmcovigilance team of sponsor **Zhaoke (Guangzhou) Oncology Pharmaceutical Ltd.** of the SAE in writing (sponsor email: zhaokeoncologypv@leespharm.com or fax to 39062888-8282) within 24 hours, any updates of an SAE has to report to the pharmcovigilance team within 24 hours also. If the SAE is related to the investigational drug, the SAE that occurred 90 days after the last dose is administered also needs to be collected and reported. Besides, investigators should report any SAEs to the National Medical Products Administrations (NMPA), National Health Commission, competent authority of each province, autonomous region, and direct-administered municipalities in accordance with the regulations and the ethics committee guidelines.

13.5 Pregnancy

According to the protocol, women of childbearing age should receive pregnancy tests during the entire study period. Its result should record in the eCRF. Only female patients with negative pregnancy test results can receive the next stage of study treatment. If a patient becomes pregnant during the study, patient is not allowed to receive Socazolimab. If a woman of childbearing age suspects that she is pregnant (missing or delaying her menstrual period) during the study and within 90 days after the last dose of study treatment, patient should contact the investigator immediately. If male patients discover that their partner is pregnant during the study period or within 180 days after the last dose of study treatment, they should contact the investigator immediately. The investigator should arrange a follow-up visit for their partner in order to observe their pregnancy condition, if possible.

After study treatment starts (including the 6 half-life periods after administration), if the female patient or the male patient’s partner is found to be pregnant, or suspected to be pregnant, the female patient’s participation should be permanently terminated (regarding to the safety concern, the drug dosage can be gradually reduced). End of study visits and follow-up visits will be arranged.

The investigator should inform the sponsor **Zhaoke (Guangzhou) Oncology Pharmaceutical Ltd.** of the pregnancy event in writing (email to zhaokeoncologypv@leespharm.com or fax to 39062888-8282) within 24 hours when the investigator/ study tea become aware of the event, and the repoting form will send to sponsor’s

pharmacovigilance team. The pharmacovigilance team will monitor the pregnant condition with the investigator every 3 months in order to collect pregnancy-related data, as long as reminding the investigator update the "pregnancy reporting form". The infant has to be monitored at least 8 weeks after delivery.

13.6 Other Special AE Reporting

Except SAEs, the investigators should inform the pharmacovigilance team of the sponsor of the following AEs in writing (email to zhaokeoncologypv@leespharm.com or fax to 39062888-82820) within 24 hours when the investigator/ study team becomes aware of the event.

- AEs that may fulfill the DLT standard
- AEs that may fulfill late-onset DLT criteria
- Grade 3, 4 of infusion reaction, regardless identified as DLT or not
- ≥Grade 2 of diarrhea/ ulcerative colitis
- Grace 3 of irAE (except diarrhea/ ulcerative colitis)
- Hy's Law (ALT/AST> 3 times the upper limit of normal (ULN) associated with total bilirubin> 2 times of ULN, no other possible causes)

14. STATISTICAL ANALYSIS

14.1 Sample Size Determination

This study is a Phase I dosage escalation stage study. The sample size is determined based on statistical considerations and determined by the actual toxicity. Each dose group will be included 3 or 6 patients.

For the expansion study, when 15 patients are included in the MTD dose, if 2 patients (13.3%) responded. The confidence interval is 80%, the objective effectiveness rate was (3.6%, 31.7%). If 3 patients (20.0%) patients responded, the objective effective rate was (7.6%, 39.3%). If 4 patients (26.7%) responded, the objective effective rate was (12.2%, 46.4%). If 5 patients (33.3%) responded, and the objective effective rate was (17.2%, 53.2%).

If the actual ORR of 15 cervical cancer patients is 15%, there is a 68.1% chance of observing at least 2 responses, a 39.6% chance of observing at least 3 responses, and a 31.9% chance of observing 0 or 1 response. (False negative rate). If more than 2 responses are observed in 15 cervical cancer patients, 45 more patients can be included (total sample size reaches 60), and the multi-center clinical study can be continued to further observe the safety and effectiveness of patients.

Due to the pandemic situation of the COVID-19, extra 35 patients were enrolled (66 patients were planned originally) after multiple communication and discussion with several parties. Further,

according to the evaluation results from the patients that the treatment was administered over the planned timeframe (due to the COVID-19 situation), the sample size was expanded to 101. (See 1.5 for more details)

14.2 Definition of Analysis Set

- Full Analysis Set (FAS)：The full analysis set includes all patients who have received at least one study drug/ treatment. The full analysis set will be used for the statistical description/analysis of the study population and the efficacy endpoint.
- Per-protocol Set (PPS)：The per-protocol set includes patients who did not have major protocol deviations during the entire study period. The FAS are used for the analysis of efficacy endpoints, FAS will mainly contribute to the efficacy endpoints analysis and PPS will be the second.
- Pharmacokinetic Analysis Concentration Set（PKCS）：the Pharmacokinetic Analysis Concentration Set includes all patients who have received at least once study drug/ treatment and at least one blood drug concentration data is collected.
- Pharmacokinetics Parameter. Set (PKPS）：The pharmacokinetic analysis set is a subset of FAS, it includes all patients who had collected at least one calculable PK parameter and have no major protocol deviations that may affect PK evaluation. The patients data excluded from the PK analysis set due to major protocol deviations will be discussed at the data review meeting and finalized the included patient data before the database is locked. The analysis and evaluation of PK parameters will be based on PKS.
- DLT analysis set：The DLT analysis set includes all patients in FAS who developed DLT or completed the prescribed medication within 28 days after the first treatment is administered, and used for DLT analysis.
- Safety Set （SS）：The safety analysis set includes all patients who had received the study drug/treatment administration for the analysis of safety and immunogenicity data.

14.3 Endpoints

14.3.1 Safety Endpoints

- Adverse evnets：includes all adverse events starting from the first day of the study treatmend to the 90 days after the last dose is administered, or until the end of the study (not includes any serious adverse events). All SAEs start after the signing of informed consent to the 90 days after the last dose is administered, or until the end of the study.

- Occurrence of DLT（first 28 days）。
- Abnormal lab result, including hematology, biochemistry (until the end of the study)
- Vital Sign Assessment, including blood pressure, heart rate, and its mean values changes from the baseline

14.3.2 Efficacy Endpoints

The objective response rate (ORR) of each dose level was evaluated during the initial study phase and the follow-up period. ORR is defined as the proportion of patients who achieve the best objective response rate (PR or CR).

14.3.3 Pharmacokinetic Endpoints

Estimate and report $AUC_{(0\text{-}T)}$, $AUC_{(INF)}$, C_{max}, T_{max}, $T_{1/2}$, Vss, V_{ss} and the bottom value C_{min} at steady state.

14.3.4 Immunogenicity Endpoints

From baseline, patients have increased frequency of anti-drug antibody levels (throughout the study period)。

14.3.5 Receptor Occupancy

According to different doses, the PD-L1 receptor occupancy rate on CD3+ T cells in circulating peripheral blood when Socazolimab is administered to trough concentrations for multiple times.

14.3.6 T Cells and Cytokines

The response of CD4+ and CD8+ cells to the tumor at baseline and after each administration was detected by the method of flow cytometry.

Detect the levels of TNF-α, IFN-γ, IL-2, IL-6, IL-10 and IL-12 in serum at baseline and after each administration.

14.4 Analysis

14.4.1 General Rules

All statistical programming will be completed using SAS 9.2 or revised version.

Continuous variables will be statistically described using the number of cases, mean, standard deviation (SD), median, maximum and minimum. The categorical variables will be summarized using

the frequency and percentage of each category.

The data is mainly used for descriptive statistics, without any formal hypothesis testing, but some statistical methods may be used to explore, analyze and better understand the data. Unless otherwise stated, all statistical tests will use a two-sided test of $\alpha = 0.05$, with a two-sided 95% confidence interval (CI).

Unless otherwise specification, all missing data will be treated as missing, and no hypothetical value will be used for filling.

14.4.2 Demographics and baseline measurement

Demographic and baseline characteristics, including age, gender, ethnicity, race, height, weight, and ECOG status, all data was summarized by dose group with descriptive statistics.

14.4.3 Safety Analysis

Calculate the incidence of DLT in each dose group. According to the Med DRA dictionary, the system organizes the classification of adverse events, the coding of preferred terms, and the most serious CTC classification is a list of dose groups. The incidence of adverse events will also be listed, and their clinical importance and potential significance will be reviewed. Vital signs and laboratory test results are summarized in a list of dose groups. List the clinically significant physical examination results and laboratory test results. The researcher will evaluate the ECG results, and if there are any abnormalities, they will also be listed. Immune-related adverse events (irAE) and non-death-related inflammatory events (IERC) will be listed separately.

14.4.4 Efficacy Analysis

Calculate the objective response rate (ORR) and disease control rate (DCR) and the corresponding two-sided 95% accurate confidence interval according to the dose group. ORR is defined as the ratio of the number of patients receiving PR or CR to the total number of patients receiving treatment. DCR is defined as the ratio of the number of patients with PR or CR or SD $\geqslant$ 12 weeks to the total number of patients receiving treatment.

The duration of response is defined as the time from the first remission to the time of disease progression or death, whichever occurs first; the duration of response is calculated in patients with the

best response of CR or PR. The response time is defined as the time from the first treatment to the first remission; the response time is calculated in patients whose best response is CR or PR. PFS is defined as the time from the first treatment to the first occurrence of disease progression or death, whichever comes first; PFS is calculated in all patients with measurable lesions at baseline. The Kaplan-Meier method was used to calculate the median value of response duration, response time and progression-free survival and its 95% confidence interval.

Efficacy analysis is based on the revised RECIST criteria (see Appendix 2), based on tumor evaluation data collected during the initial treatment period and follow-up period until tumor progression. Other efficacy analysis is based on immune-related response criteria, iRECIST (see Appendix 3), using immune-related efficacy evaluation criteria, such as immune-related BOR (iBOR), immune-related PFS (iPFS) and immune-related DCR (iDCR).

14.4.5 Immunogenicity Analysis

The proportion of patients with at least one positive ADA assessment during the clinical study period and the proportion of patients whose ADA level increased from baseline were calculated by dose group.

14.4.6 Pharmacokinetic Analysis

The pharmacokinetic parameters of the sixth cycle of single dose and multiple doses will be listed by dose group. The geometric mean and coefficient of variation of $C_{max,}$ CLT, $AUC_{(0-T)}$, $AUC_{(INF)}$ will be reported. T_{max} reports the median, minimum, and maximum value. The mean and standard deviation of $T_{1/2}$ and V_{ss}will be reported. To describe the dose dependence, a scatter plot of C_{max}, $AUC_{(0-T)}$, and $AUC_{(INF)}$ versus dose will be provided.

The bottom (C_{min}) concentration of Socazolimab and the concentration at the end of infusion (EOI) will be listed by dose group and study days. In order to evaluate the steady state achieved, the geometric mean of the C_{min} value and the number of study days will be plotted separately for each dose group.

The evaluation of dose ratio will use the power model to estimate the slope of Socazolimab linear regression, the slope of log(C_{max}) on log(dose) and the slope of log($AUC_{(INF)}$) on log(dose). The point estimate of the dose ratio parameter (the slope of the linear regression) and the 90% confidence interval

will be calculated.

Data describing plasma concentrations at different time points will be reported separately for subsequent population pharmacokinetic evaluation.

14.4.7 Receptor occupancy Analysis

Using descriptive statistics to summarize the receptor occupancy rate by dose group; for the comparison of receptor occupancy rates between different groups, use analysis of variance or Kruskal-Wallis test according to the normality of the data.

14.4.8 T Cell Function and Cytokine Analysis

The changes in T cell function and serum cytokines from baseline (percentage changes) will be statistically described according to group and visit period to evaluate the pharmacodynamic effects. In addition, the time course of T cell function serum cytokines will be studied with graphs, such as general graphs (such as box plots) or graphs of individual changes over time. The possible relationship between changes in biomarkers and exposure to pharmacokinetics will also be explored.

14.4.9 Biomarker Analysis

The possible relationship between clinical outcome (such as tumor response) and biomarkers including different changes in serum cytokines (baseline value or relative baseline changes) will be explored based on available data using patients with evaluable responses Analyze potential predictive markers. Analysis methods such as but not limited to logistic regression will be used to explore these relationships. Depending on the availability of data, measurement of markers based on selectable samples, such as tumor-based markers, will be presented. The relationship between these measurements and meaningful security events (such as irAE) will also be mapped and explored based on the available data.

15、REGULATIONS AND RESPONSIBILITIES OF THE ETHICS COMMITTEE

15.1 Regulations

The clinical study conduction is in accordance with GCP guidelines and all current regulations. During the study period, the sponsor will prepare an annual safety report and submit it to the GCP department and EC. During the study period, any other requirements from current regulations, regulatory authorities or ethics committee (EC) also need to comply.

15.2 Informed Consent Form (ICF)

Only patients who had the signed on a written nformed consent form (signed in person) and the nformed consent form was approved by the ethics committee (or an informed consent form signed by a legal representative) can enrolled in this study. Only after obtaining the informed consent form from the patients, patients can receive relevant research assessments (ie all the assessments required by the protocol). The process of obtaining informed consent should be recorded in the original medical record of the patient.

The informed consent form provided to the research site must follow the GCP principles and current regulatory requirements, and be consistent with this research. If the investigator proposes to make any amendments to the informed consent form, it must be approved by **Zhaoke (Guangzhou) Oncology Pharmaceutical Ltd.** before submitting the amendments to the ethics committee. Besides, a copy of the ethics committee's approval must be submitted to **Zhaoke (Guangzhou) Oncology Pharmaceutical Ltd.**

15.3 Responsibilities of Investigators and Independent Ethics Committee

Before the start of the clinical study, both the protocol and the informed consent must be reviewed and approved by the ethics committee, and a signed and dated statement (declaring that the ethics committee has approved the protocol and the informed consent) must be submitted to **Zhaoke (Guangzhou) Oncology Pharmaceutical Ltd.**. Before the start of the clinical study, the investigator is required to sign the signature page of the protocol, proving that he/she agrees to conduct the clinical study in accordance with the protocol requirements and research-related materials, and is willing to submit all relevant data to the inspector for inspection.

The investigator should be aware that they need to to avoid any protocol deviations/ protocol violations. Under no circumstances should the investigators allow the sponsors or other third parties to approve the deviation/ violation of the protocol, because any protocol deviations/ violations are not allowed. If the investigator believes that a protocol deviation/ protocol violation may help to the clinical study process, then the protocol should be revised, and the protocol revision can be implemented only after the approval of **Zhaoke (Guangzhou) Oncology Pharmaceutical Ltd.** and the approived by the ethics committee. All major protocol deviations/ protocol violations shall be recorded in the final clinical study report (CSR).

15.4 Confidentiality of Patient Data

All medical information related to this study must be kept confidential. **Zhaoke (Guangzhou)**

Oncology Pharmaceutical Ltd., regulatory authorities and relevant ethics committees can inspect the medical data of all patients in this study. The investigators can submit the medical information of the patient to the representative or agent of the sponsor, the ethics committee or the regulatory authority in order to review the accuracy and integrnity of the data. All patients are coded with corresponding numbers, and the names of any patients will not be disclosed when the study result is published.

16. ADMINISTRATIVE AND LEGAL DUTIES

16.1 Protocol Amendments and End of Study

Any amendments or additions on the protocol is only allowed by written protocol revision, and it must be approved by **Zhaoke (Guangzhou) Oncology Pharmaceutical Ltd.**, the rehulatory authority (if required) and the ethics committee.

Only the amendment is related to the patient safety can be implemented before approved by the ethics committee. Although the protocol amendment needs to be formally approved, if it helps to ensure the safety of the patients, the investigator should take corresponding measures immediately (even if the measures is deviated from the protocol). Under this circumstance, the investigator should inform **Zhaoke (Guangzhou) Oncology Pharmaceutical Ltd.** and the ethics committee within 10 working days.

Amendments that require approval:

- Increase the dose or time of study treatment administration, or greatly increase the sample size
- Significant changes in the study design (such as adding or removing the control group)
- Adding more assessments to patients
- Adding or eliminating patients/s assessments in order to have a better monitor on patient safety

Zhaoke (Guangzhou) Oncology Pharmaceutical Ltd. has the right to terminate the study based on a clinical agreement.

16.2 Study Record and Data Archiving

Investigators should keep research records in accordance with GCP principles, for at least 5 years after the completion of the research. If the storage location of the research data is changed, the investigator must notify **Zhaoke (Guangzhou) Oncology Pharmaceutical Ltd.** in advance.

16.3 Monitoring and Data Collection

Before the clinical study starts, the representative of **Zhaoke (Guangzhou) Oncology Pharmaceutical Ltd.** and the investigators should discuss and review on the protocol and cCRF in the

site initiation visit and meetings.

During the entire clinical study period, the monitors will visit the study site regularly to verify the completion of the patient's records, the accuracy of eCRF data and its compliance with the protocol and GCP, the screening process. Besides, the monitor should ensure the storage, distribution and inventory of the study drugs are complied with the requirements. The investigator must be present ans coorperate with the monitor during the monitoring visit.

The investigators need to keep the patient's source document, including medical records and visit records (hospital or clinical medical records), which include any demographics, medical history records, laboratory examinations, echocardiograms, and other examination results or evaluations. All information in the eCRF must be traceable from the source medical record.

The investigators shall keep the original informed consent form signed by each patient (a copy of the informed consent form is given to the patient). The investigator needs to provide all relevant original data to the monitor in order to confirm the data is consistent with the eCRF. The monitor shall fully confirm whether the informed consent has been carried out, whether it meets the entry and discharge standards, the SAE record, and all the major endpoints and safety assessments. In addition, the monitor has to confirm the original data is consistent with the eCRF according to the monitoring plan. The original medical record should not contain any patient information.

16.4 Quality Control and Quality Assurance

After the starts of the clinical study, in order to ensure the quality of the study, the monitors will perform regular monitoring visit, regular auditing, due-cause auditing and coordinated auditing by the project manager will be carried out.

17. REFERENCES

1. Mamalis, A., Garcha, M., & Jagdeo, J. (2014). Targeting the PD-1 pathway: a promising future for the treatment of melanoma. Arch. Dermatol. Res 306, 511-519
2. Pedoeem, A., Azoulay-Alfaguter, I., Strazza, M., et al. (2014). Programmed death-1 pathway in cancer and autoimmunity. Clin. Immunol 153, 145-152
3. Zibelman, M., & Plimack, E. R. (2016). Checkpoint Inhibitors and Urothelial Carcinoma: The Translational Paradigm. Clin Oncol (R Coll Radiol) 30，160-162
4. Zhang, Z., & You, Z. (2014). Research progress of recurrent cervical cancer. NM Med J 6, 699-701. [Chinese Translation: Inner Mongolia Medical Journal]
5. Zhang, X. & Gui, S. (2008). Research progress in the pathogenesis of cervical cancer. Chinese J. Women Child Health Res 19, 56-59 [Chinese Translation: Chinese Journal of Woman and Child Health Research]
6. Wang, X. & Liang, N. (2010) Progress in the treatment of cervical cancer. J. North China. Coal Med. Coll 12(2), 183-185 [Chinese Translation: Journal of North China Coal Medical College]
7. Wang, S., Luo, L., Lui, M., et al. (2015). PD-1/PD-L1 signaling pathway and its application in tumors. J. Int. Pharm. Res 42, 143-147

Appendix 1：ECOG Performance Status Evaluation

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work
2	Ambulatory and capable of all selfcare, confined to bed or chair more than 50% of walking hours
3	Capable of only limited selfcare, confined to bed or hair more than 50%of waking hours
4	Completely disabled. Cannot carry on any selfcare. Tatally confined to bed or chair
5	Dead

Appendix 2: Response Evaluation Criteria in Solid Tumours (RECIST1.1) (Revision)

Definitions

Measurable lesions	Lesions that can be accurately measured in at least one dimension, the longest diameter to be recorded as ≥20 mm, or spiral CT ≥10mm by clinical exam
Non-measurable lesions	All other lesions (including small lesions, i.e., the longest diameter< 20 mm or spiral CT <10 mm by clinical exam). Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses and cystic lesions that cannot be diagnosed by imaging are considered as non-measurable.
Target Lesions	>1 Measurable lesions under baseline assessment, all lesions should be recorded and measured, and up to a maximum of 5 lesions total (not more than 2 per organ). Target lesions should be selected on the basis of size and measurable repeatable assessment. The sum of the lengths of all target lesions is used as the reference baseline for effective remission records. Lymph nodes with a short diameter ≥ 15 mm in CT scans can be used as pathologically significant measurable target lesions, and the total number of target lesions can be included in the evaluation of curative effect. Criteria for mitigation: ● Complete response（CR）：the disappearance of all targets lesions, the short axis value of any pathological lymph node (including target lesion or non target lesion) must be less than 10mm. ● Partial response（PR）：using the sum of diameter as a reference, the total diameter of target lesions is reduced by at least 30%. ● Progressive disease（PD）：Based on the minimum value of the total diameter of all target lesions measured during the

	experimental study, the total diameter should be increased by at least 20% (take the baseline as the reference if the baseline measurement value is the smallest value), and the absolute value of the total diameter increase must be greater than 5mm , or the appearance of new lesions ● Stable disease（SD）：Taking the minimum value of the sum of the diameters of the target lesions measured in the study as a reference, the reduction did not reach PR or increased but did not reach PD. PD needs to be confirmed in this study, unless the patient has a rapidly progressing clinical deterioration.
Non-target Leision	Except target leision, any other lesions, including pathological lymph nodes is considered as a non-target lesions without further assessments, but it should be recorded in the baseline assessment. For example, "existence", "absence" or in rare cases "clear progress". Extensive target lesions can be recorded with target organs (such as a large number of enlarged pelvic lymph nodes or large-scale liver metastases) Complete response（CR）：the disappearance of all non target lesions, and the level of tumor markers returned to normal levels. All lymph nodes are non-pathological (ie, the short axis value is less than 10 mm). Non-complete response/ non-progressive disease：the continuous existence of >1 non-target lesions, and/or the level of tumor markers continues to be higher than normal. Progressive disease（PD）：One or more new lesions and/or existing non-target lesions have clearly progressed. PD needs to be confirmed in this study, unless the patient has a rapidly progressing clinical deterioration.
Best Overall Response Rate	From the beginning of treatment to disease progression or recurrence, the smallest measurement value measured, and the valus is verified at least 4 weeks later, CR or PR is the best confirmed therapeutic effect. The measurement is carried out with

	a ruler or a measuring instrument and recorded in international units.

●Total Evaluation

Target Lesion	Non-target Lesion	New lesion	Total evaluation
CR	CR	No	CR
CR	Non- CR/non- PD	No	PR
CR	Cannot be assessd	No	PR
PR	Non- PD or cannot be fully assessed	No	PR
SD	Non- PD or cannot be fully assessed	No	SD
Cannot be fully assessed	Non- PD	No	NE
PD	any	Yes/ No	PD
any	PD	Yes/ No	PD
any	any	Yes	PD

Remarks：CR，complete response；PR，compete response；SD，stable disease；PD，progressive disease；NE，not evaluated

- Efficacy Evaluation

  Patients evaluated as CR or PR should repeat the evaluation again at least 4 weeks later. In this study, the time interval for evaluating tumor efficacy meets this standard. Patients who are evaluated as SD should repeat the evaluation again after a specific interval written in the protocol (generally no less than 6-8 weeks).

Total efficacy at the first time point	Total efficacy at subsequent time points	Best Overall Response Rate
CR	CR	CR
CR	PR	SD, PD 或 PR[a]
CR	SD	If SD lasts for sufficient time, it considered as SD. Otherwise, considered as PD

CR	PD	If SD lasts for sufficient time, it considered as SD. Otherwise, considered as PD
CR	NE	If SD lasts for sufficient time, it considered as SD. Otherwise, considered as NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	If SD lasts for sufficient time, it considered as SD. Otherwise, considered as PD
PR	NE	If SD lasts for sufficient time, it considered as SD. Otherwise, considered as NE
NE	NE	NE

Remarks：CR，complete response；PR，partial response；SD，stable disease；PD，progressive disease；NE，not evaluated

a. If CR is reached at the first time point, any diseases observed at subsequent time points, even if it meets the PR criteria relative to the baseline, it will be assessed as PD (because the disease reappears after reaching CR). The Best Overall Response Rate depends on the time that a SD lasts for. Sometimes, it is evaluated as CR during assessment at the first time point, but in fact there are small lesions. Therefore, it should be evaluated as the a PR instead of CR at the first time point. In this cicumstance, the originally evaluated CR will be changed to PR and the best response will be PR.

Appendix 3. Immune-related Response Evaluation Criteria In Solid Tumors （iRECIST）

1. Measurable and non-measurable lesions：

- Measurable lesions:： ⩾10mm non-pathological lymph nodes, pathological lymph nodes with the short axis ⩾15mm at CT with section thickness ≤ 5mm
- Non-measurable lesions：
  - Measurable lesions that are non-target lesions
  - small lesions (longest diameter <10 mm or pathological lymph nodes with short axis >10 but <15 mmm, and other undetectable lesions.
  - Leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses and cystic lesions that cannot be diagnosed by imaging are considered as non-measurable.

2. Target and non-target lesions：

- Target Lesions：>1 Measurable lesions under baseline assessment, all lesions should be recorded and measured, and up to a maximum of 5 lesions total (not more than 2 per organ)/ Target lesions should be selected on the basis of size (the longest diameter). It must be representative of all organs involved, and the measurement must be repeatable.
- Non-target leiosns：includes all lesions but excepting all target lesions. The target and non-target lesions evaluation should perform at the same time.

3. Sum of the longest diameters（SLD）

The sum of the diameters of all target lesions (including the longest diameter of non-lymph node lesions and the shortest diameter of lymph node lesions) will be the sum of the baseline diameters. The combined baseline diameter will be used as a reference value for the baseline level of the disease.

Baseline SLD：The sum of the baseline target lesion diameters before the first dose

SLD during the tumor evaluation：During the study, imaging-based tumor SLD assessment was performed according to the protocol or clinical indications.

Minimal SLD：performing ≥1 tumor assessments after baseline assessments, perform subsequent tumor evaluation on the reference of minimal SLD

4. Immune-Related Best Overall Response Definitions:

immune-related Complete Response（iCR）：The non-lymph node lesions were

completely disappeared for at least 4 weeks, and the short axis of the lymph node <10mm, and no new lesions

immune-related Partial Response（iPR）：≥30% drop in tumor burden from baseline and persists for at least 4 weeks

immune-related Stable Disease（iSD）：excludes from iCR/iPR/iUPD/iCPD criteria

mmune-related Progressive Disease（iPD）：divides into iUPD and iCPD。

iUPD- includes new measurable/non-measurable lesions, or the tumor burden increases by ≥20% relative to the lowest point, and the non-target lesions are clearly progressing

iCPD-（iUPD≥4 weeks double confirmation. The size of target lesions or new target lesions increased by ≥ 5 mm, and the number of non-target lesions or new non-target lesions increased or the number of new lesions increased.

Remarks：

1. New measurable lesions can be evaluated as target lesions (up to a maximum of 5 lesions total with not more than 2 organs). It will not be included in the original total tumor burden baseline; other measurable and non-measurable new lesions are called new non-target lesions.
2. After the first assessment of iUPD, there are two conditions for confirmation: the original iUPD lesions have further deteriorated or the non-iUPD lesions have progressed to meet the RECIST 1.1 standard. For the target lesion, when it meets the PD written in RECIST1.1 standard, it can be assessed as iUPD. When the target lesion increases by ≥5mm during the re-evaluation, it can be assessed as iCPD . When the original iUPD lesion has further deteriorated; non-target lesions or new lesions are clear during the re-evaluation progress (according to the RECIST 1.1), or the appearance of other new lesions can be evaluated as iCPD. Therefore, the progress of non-iUPD lesions that had met the RECIST 1.1 criteria.
3. The evaluation of non-target lesions is similar to the evaluation of target lesions
4. For new lesions, iUPD can be assessed as long as they appear during the first evaluation. During the re-evaluation, iCPD can be confirmed by an increase in the size of new lesions (the total increase of new target lesions ≥ 5 mm or any increase in new non-target lesions) or the appearance of other new lesions.
5. Immune-related best verall response (iBOR)

   iBOR is evaluated by the response appeared during the entire treatment period.

When iCPD is not confirmed, the best response is assessed as iBOR, and when iCPD occurs, it is assessed as iBOR.