Clinical research project of Union Hospital Affiliated to Tongji Medical College, Huazhong University of Science and Technology

Project name	A Phase II clinical study of Candonilimab (AK104) combined with chemotherapy in PD-1 inhibitor-resistant nasopharyngeal carcinoma
Scheme number	AK104-IIT
Version number	V1.0
Release date	2022.9.18
Principal investigator	Yang Kunyu
Specialized department	Department of Head and Neck Oncology, Wuhan Union Cancer Cente

Estimated starting and ending date	2022.9.22-2025.9.22

Scheme signature page

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Version number/Version date: V1.0

I have read and understood the research plan, confirmed that the plan includes the necessary contents for the research implementation, and made clear the responsibilities of the researcher related to the research plan.As the principal investigator, I will provide copies of this protocol and all relevant information to all researchers who participate in this study.I will discuss this information with them to ensure that they fully understand how the research protocol will be implemented.I agree and will perform my duties strictly in accordance with the applicable laws and regulations, Helsinki Declaration, clinical trial quality management practice and this study protocol.

Principal Investigator's Signature (print) :

Principal Investigator's Signature/Date:

Clinical Research Unit:

catalogue

scenario summary	
Research name	A Phase II clinical study of calbenizimumab (AK 104) plus chemotherapy for PD-1 inhibitor-resistant nasopharyngeal carcinoma
Research profile	AK 104 is a humanized immunoglobulin G1 (IgG 1) bispecific antibody (BsAb) with crystalliable fragment (Fc) mutations to eliminate the Fc-receptor and complement-mediated cytotoxic effects. AK 104 is able to bind both programmed cell death receptor-1 (PD-1) and cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) and block the interaction of PD-1 / programmed cell death ligand-1 (PD-L1), PD-1 / PD-L2, CTLA-4 / B7.1, and CTLA-4 / B7.2. AK 104 is a tetravvalent IgG-ScFv bispecific antibody. AK 104 contains a point mutation in its constant region that prevents the binding of the complement protein C1q and the Fc γ receptor involved in the cytotoxic effect. AK 104 is expressed in a Chinese hamster ovary cell line with a total molecular weight including oligosaccharides of about 200 kDa.
purpose of research	**fundamental purpose** • To evaluate the safety and efficacy of carbenilizumab plus chemotherapy (platinum-based) second-line treatment of PD-1 inhibitor-resistant NPC based on RECIST v l.1 Objective response rate (ORR) and PFS as assessed. **Secondary purpose**

	• To evaluate DoR, DCR, TTR, TTP, and OS in PD-1 inhibitor-resistant NPC with capradilimumab plus chemotherapy (platinum-based). • To evaluate the pharmacokinetics of carradilizumab plus chemotherapy (Pharmacokinet ics, PK). • To assess the immunogenicity of caldradilizumab in combination with chemotherapy. • To evaluate the correlation of PD-Ll expression with efficacy in immunohistochemical detection of tumor samples. • To evaluate the association of EB virus (EBY) DNA copy number in blood and antitumor activity of caadilimumab in subjects with advanced NPC. To assess health-related quality of life (HRQoL) in subjects treated with carradiniilizumab plus chemotherapy
research design	This study is a Phase II clinical study of carradilimumab (AK 104) plus chemotherapy for PD-1 inhibitor-resistant nasopharyngeal cancer to evaluate the safety and efficacy of carradilimumab plus chemotherapy as second-line and above treatment for PD-1 inhibitor-resistant nasopharyngeal cancer. This study is a single-arm, phase II clinical study with approximately 30 PD-1 inhibitor-resistant NPC subjects scheduled to be enrolled. PD-Ll CPS (<50% vs> 50%, subjects whose PDLl expression was not evaluated were classified as <50%) were used as the stratification factor. The study will have a safe lead-in period of approximately 6 PD-1 inhibitor-resistant subjects, and the investigator will conduct an preliminary safety assessment. If the safety and

	tolerance are good and initial efficacy signals are observed, the extended enrollment phase will enter. Efficacy analysis will be performed for approximately 15 subjects. If 6 of the 15 subjects are not tolerated, subject enrollment may be stopped after the investigator discussion. After poor safety, the investigator decided to revise or stop the study. For 4-6 cycles, the use of calduilizumab until the investigator determines that there is no clinical benefit (based on the comprehensive judgment of RECISTv1.1 imaging assessment and clinical symptoms), toxicity intolerance, completion of 24 months of treatment, or satisfaction of other criteria for treatment termination in the regimen, whichever occurs first. • Subject treatment protocol: • Caradilizumab (200 mg, administered on Day 1, Q3W until no longer clinical benefit) + platinum-based chemotherapy, Q3W, 4-6 cycles), treatment cycle every 3 weeks (21 days).
Total number of enrolled patients	30 Cases
Number of research groups **Number of control groups**	The number of the study group was 30 cases
diagnose	nasopharyngeal darcinoma
Selection criteria	Selection criteria: Subjects must meet all of the following inclusion criteria to be enrolled in the study:

	Voluntary signed the written ICF. 1) Age was over 18 and 75 at the time of enrollment, acceptable for both men and women. 2) The Eastern Cooperative Oncology (ECOG) physical performance score was 0 or 1. 3) Expected survival is greater than 3 months. 4) Histologically or cytologically confirmed nasopharyngeal carcinoma. 5) The subject had previously failed treatment with PD-1 inhibitor and had no indication for radical local treatment. 6) According to the efficacy evaluation criteria of solid tumors RECIST v l. And l with at least one measurable lesion.
Exclusion criteria	
Research intervention	This study is a Phase II clinical study of carradilimumab (AK 104) plus chemotherapy for PD-1 inhibitor-resistant nasopharyngeal cancer to evaluate the safety and efficacy of carradilimumab plus chemotherapy as second-line and above treatment for PD-1 inhibitor-resistant nasopharyngeal cancer. AK 104 has been approved for marketing and is not approved for nasopharyngeal cancer. The reasons for this study intervention in NPC are as follows: 1. Clinically, more and more NPC patients develop PD-1 inhibitor resistance.2. A large amount of research evidence shows that the combination of PD-1 antibody and CTLA-4 antibody avoids the dark side of PD-1 antibody to some extent and effectively reduces the occurrence of PD-1 inhibitor resistance in

	tumors. PD-1 and CTLA-4 complement each other and do not repeat in regulating immune responses, with mechanisms preventing T cell depletion and promoting T cell activation, respectively. When the PD-1 pathway and CTLA-4 modulation target the two pathways (Pardoll, 2012), they have more effective anti-tumor activity than single-agent therapy.
evaluation criterion: **Main end point:** **Secondary end point:** **safety evaluation:**	Main end point Safety: Incidence and severity of adverse events (AEs), clinically significant abnormal laboratory findings. Based on the following data in RECIST v i. The ORR as assessed by the I. Based on the following data in RECIST v i. I of the assessed PFS. Secondary end point According to the RECIST vi. The DoR, DCR, TTR, TTP, and OS as assessed by I. PK characteristics: including serum concentrations of cadadiniilimumab at different time points after cadadinibizumab administration. Immunogenicity assessment: Number and percentage of subjects presenting with detectable antimicrobial antibodies (ADA). To evaluate the correlation of PD-Ll expression with efficacy in immunohistochemical detection of tumor samples. To evaluate the association of EB virus (EBY) DNA copy number in blood and antitumor activity of caadilimumab in subjects with advanced NPC.

	Health-related Quality of Life Assessment HRQoL-as measured using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTCQLQ-C30) and EORTCQLQ-H & N35.
statistical method: **sample capacity:** **analytic set:** **Primary Efficacy Endpoint:** **Safety end:**	A total of 30 subjects are planned to be enrolled as a single-arm, phase II clinical study. This study used historical data as a control with no formal statistical hypothesis. **efficiency analysis** The primary study endpoint of this study was according to the RECIST v l. And l the ORR and PFS assessed. Analysis of the primary endpoint was performed after the last subject who met the statistical and imaging assessment requirements had completed at least 24 weeks of follow-up (or disease progression). The ORR and OCR analyses will be performed based on the full analysis set, with their 95% exact two-sided confidence intervals estimated by the Clopper Pearson method. The time to reach the event endpoint (OOR, PFS, and OS) was analyzed by the Kaplan-Meier method. The PFS and OS analyses will be performed based on the randomized analysis set. The graphical analysis will include a spider map of the percent change in target lesion tumor load from baseline over time, and a waterfall plot of the best percentage of change in target lesion tumor load from baseline. **safety** The safety analysis will be based on the safety analysis set, which includes all enrolled subjects who have received any study drug. Summary statistics for AEs will be summarized for all adverse events, adverse events related to study drug,

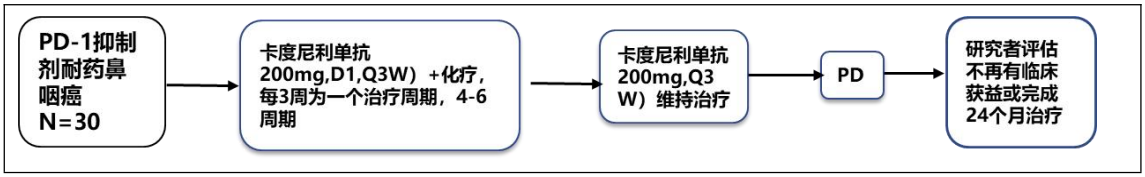
	serious adverse events (SAEs) and for AEs and AESIs leading to discontinuation. Will be based to the National Cancer Institute Common Terminology Criteria for Adverse Events (National Cancer Inst i tute Common Tem1inology Criteria for Advers e Events, NCI CTCAE) Version 5.0 grades the AEs, And adopt the International Medical Dictionary for Regulatory Activities (Medical Dictionary for Regulatory Activities, Med DRA) For encoding. Laboratory abnormal findings and toxicity levels will be summarized per version NC I CTCAE 5.0. In the cross table of clinical laboratory examinations, the change in baseline CTCAE grade and highest-severity grade after baseline will be shown and grade CTCAE 3 or 4 clinical laboratory abnormalities will be listed.
Study duration	Three years
Participation time of the subjects	Three years
Study unit / site	Department of Head and Neck Oncology, Cancer Center, Union Hospital, Huazhong University of Science and Technology

Principal Investigator Data

Name, qualification, and contact information of the principal investigator

- Qualifications include physician practicing license, or pharmacist qualification certificate, nurse practitioner practicing license and other professional technical certificates, professional title certificate, GCP certificate, and other clinical trial related training certificates

Flow chart of the study



Acronym table	
abbreviation	**The full text of Chinese**
AASLD	, The American Society for the Study of Liver Diseases
ADA	Anti-drug antibodies
AE	adverse event
AESI	Adverse events, and of special interest
ALP	alkaline phosphatase
ALT	glutamic-pyruvic transaminase
ANC	Absolute neutrophil count
AST	glutamic-oxalacetic transaminase
AUC	Area under the concentration-time curve
BCLC	The Barcelona liver cancer clinical staging system
CI	confidence interval
CL	clearance
CNS	C. N. S
CR	complete remission
CRA	Clinical study monitor
CRO	contract research organization
CrCl	CC
CT	computerized tomographic scanning
DCR	Disease control rate
DLT	dose-limiting toxicity

dMMR	Mismatch repair-defective type
DoR	Relieve duration
ECG	electrocardiogram
ECOG	The Eastern US Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data acquisition
EFS	Event-free survival
Fc	FC
FDA	The US Food and Drug Administration
FFPE	Formalin was fixed fixed and embedded in paraffin wax
GCP	Practice management of drug clinical trials
GLP	Good Laboratory Practice for Drug Non-clinical Studies
HBV	HBV
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HIV	human immunodeficiency virus
ICF	informed consent
ICH	International Conference on coordination requirements for human medicines
IEC	Independent ethics committee
Ig	immunoglobulin
IgG1	Immunoglobulin G1
IHC	immunohistochemistry
irAE	Immune-related adverse events
IRB	The Institutional Review Board
IV	I.V
IVIG	Intravenous immunoglobulin was administered
LFT	liver function test

LLN	lower limits of normal
mAb	monoclonal antibody
MedDRA	The International Medical Dictionary for Regulatory Activities
MRI	nuclear magnetic resonance
MSI-H	Height microsatellite instability type
NCI CTCAE	US National Cancer Institute Common Terminology Criteria for Adverse Events
NHC	The National Health and Family Planning Commission of the People's Republic of China
NMPA	The National Medical Products Administration
NSAID	non-steroid anti-inflammatory drug
NSCLC	nonsmall-cell lung cancer
ORR	Objective mitigation rate
OS	Overall survival
PD	PD
PD-1	Programmed cell death-1
PD-L1	Promed cell death ligand-1
PD-L2	Promed cell death ligand-2
PFS	Progression-free survival
PK	pharmacokinetics
PR	partial remission
Q2W	Once every 2 weeks
QTcB	QT interval corrected by heart rate using the Bazett formula
QTcF	QT interval corrected by heart rate using the Fridericia formula
RECIST	Criteria for efficacy evaluation in solid tumors
RO	Receptor share
SAE	Serious adverse events
SAP	Statistical analysis plan
SD	stable disease

SID	Subjects number
$t_{1/2}$	half-life period
TTR	To ease the time
TBil	total bilirubin
TIL	TIL
TSH	TSH
ULN	Upper limit of normal value
WHO-DD	The World Health Organization Dictionary of Drugs

1. foreword

1.1 research background

1.1.1 General overview (must)

AK 104 is a humanized immunoglobulin G1 (IgG 1) bispecific antibody (BsAb) with crystalliable fragment (Fc) mutations to eliminate the Fc-receptor and complement-mediated cytotoxic effects. AK 104 is able to bind both programmed cell death receptor-1 (PD-1) and cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) and block the interaction of PD-1 / programmed cell death ligand-1 (PD-L1), PD-1 / PD-L2, CTLA-4 / B7.1, and CTLA-4 / B7.2.

AK 104 is a tetravvalent IgG-ScFv bispecific antibody. AK 104 contains a point mutation in its constant region that prevents the binding of the complement protein C1q and the Fc γ receptor involved in the cytotoxic effect. AK 104 is expressed in a Chinese hamster ovary cell line with a total molecular weight including oligosaccharides of about 200 kDa.

Therefore, this study aimed to evaluate the efficacy and safety of cadradinilizumab combination chemotherapy in patients with PD-1 inhibitor-resistant NPC and to determine its PK and immunogenicity characteristics to provide evidence for subsequent studies.

1.1.2 The existing preliminary research basis of this study (if any)

AK 104 in Australia enrolled subjects with advanced solid tumors that failed standard therapy, and dose escalation decisions followed a "3 + 3 + 3" design. Phase AK104 Ia / Ib clinical study was AK 104 first used in human study. As of 30 April 2020, the phase AK104 Ia study has enrolled 92 subjects with advanced solid tumors after the standard treatment failure, Including NSCvarious tumor types LC, gastric cancer, pancreatic cancer, mesothelioma, triple-negative breast cancer, neuroendocrine cancer, endometrial cancer and so on, The lowest dose of AK 104 treatment was 0.2 mg / kg Q2W, The ascending doses of 0.5mg / kg Q2W, 1mg / kg Q2W, 2mg / kg Q2W, 4mg / kg Q2W, 6mg / kg Q2W, 10mg / kg Q2W, A fixed dose of 450mg Q2W and 15mg / kg Q3W. Of these, 18 subjects were enrolled at 10mg / kg Q2W and 3 subjects at 15mg / kg Q3W.

In terms of safety, as of 30 April 2020, at all dose levels, only one dose of 1.0mg / kg dose subject experienced a dose-limiting toxicity (DLT) event: Grade 3 AST increase. Among them, 18 subjects were treated with 10mg / kg Q2W, the incidence of grade 3 / 4 TRAE was 22.2%, respectively fever, hyperthyroidism, polyneuropathy, nephritis, all occurred in 1 subject; currently AK 104 in China is undergoing 10mg / kg Q2W dose climbing, no DLT events. Three subjects were on 15mg / kg Q3W and did not develop grade 3 TRAEs; TRAEs included anemia (grade 2), facial rash (grade 1), and thyroid dysfunction (grade 1). In terms of efficacy, as of 30 April 2020, the ORR and DCR reached 56.9% in 51 subjects.

Including two phase Ib / II clinical studies, both were multicenter, open-label, phase Ib / II clinical studies conducted in China. One was to evaluate the safety, tolerability, PK profile, immunogenicity, pharmacodynamics, and antitumor activity of AK 104 alone in advanced solid tumors and AK 104 in combination with oxaliplatin and capecitabine (mXELOX) in the first-line treatment of locally advanced or metastatic gastric adenocarcinoma or gastric esophageal adenocarcinoma. The study consisted of 3 phases, namely, dose escalation and extension Phase (Phase I) and dose confirmation Phase (Phase II). To evaluate the safety and efficacy of AK 104 monotherapy (6mg / kg, 10mg / kg, 450mg Q2W) for advanced solid tumors and

AK 104 (4mg / kg, 6mg / kg and 10mg / kg Q2W) combined with mXELOX in first-line treatment for advanced gastric cancer or gastric esophageal adenocarcinoma. As of 30 April 2020,107 solid tumors were received AK 104 monotherapy (6mg / kg and 450mg Q2W), of whom 15 of them were advanced NSCLC who failed systemic therapy. For safety, see the AK 104 safety summary below. In terms of efficacy, as of April 30,2020, the ORR and 63.6% in 44 subjects with standard treatment failure. In the cohort of AK 104 combined with mXELOX for advanced gastric cancer or gastroesophageal adenocarcinoma, of 19 evaluable subjects, 2 CR, 11 PR, 5 SD, ORR reached 68.4% and 9 DCR reached 94.7%.

Another phase Ib / II clinical study of AK 104 in China was to evaluate the efficacy of efficacy, safety, PK characteristics, immunogenicity, and relevant biomarkers of AK 104 in selected patients with advanced or metastatic solid tumors. Subjects will be classified into the following cohort: Cohort A: locally advanced or metastatic non-small-cell lung cancer with failed systemic therapy and without immunotherapy; Cohort B: locally advanced or metastatic non-small-cell lung cancer with failed systemic therapy and refractory to PD-1 / PD-L1 antibodies; Cohort C: Locally advanced or metastatic non-small-cell lung cancer that relapsed after failed systemic therapy and anti-PD-1 / PD-L1 antibodies; Cohort D: local progression or metastatic melanoma after failure of standard therapy. All the subjects received AK104 6 mg / kg Q2W. As of 30 April 2020, cohort A has enrolled 19 subjects with locally advanced or metastatic NSCLC with systemic treatment failure and without immunotherapy. Safety is described below. In terms of efficacy, considering the above two studies in China, 34 (15 + 19) Chinese subjects with systematically failed advanced NSCLC received 6mg / kg Q2W or 450mg Q2W, with an ORR of 16.0% (4 / 25) of 25 evaluable subjects.

Combined with the above three clinical trials in Australia and China, as of 30 April 2020 in all subjects receiving AK 104 alone (N=228), TEAE was 88.6%, TRAE was 64.5%, Grade 3 TRAE was 12.7%, the incidence of drug-related SAEs was 11%, causing study withdrawal of TRAE of 6.6%, and TRAE was 0. TRAEs at 5% of all subjects and Grade 3 TRAEs in 2 subjects are summarized below:

	Total (N=228)		6mg/kg (N=141)		450mg (N=50)		10mg/kg (N=18)	
	任何级别 n (%)	3/4级 n (%)	任何级别 n (%)	3/4级 n (%)	任何级别 n (%)	3/4级 n (%)	任何级别 n (%)	3/4级 n (%)
至少发生一次TRAE	147 (64.5)	29 (12.7)	86 (61.0)	11 (7.8)	33 (66.0)	11 (22.0)	0	0
皮疹	32 (14.0)	0	18 (12.8)	0	7(14.0)	0	4 (22.2)	0
发热	19 (8.3)	1 (0.4)	11 (7.8)	0	4(8.0)	0	3 (16.7%)	1 (5.6%)
恶心	19 (8.3)	0	11 (7.8)	0	4 (8.0)	0	2 (11.1%)	0
瘙痒	19 (8.3)	0	9 (6.4)	0	6 (12.0)	0	3 (16.7%)	0
ALT升高	18 (7.9)	1 (0.4)	11 (7.8)	1 (0.7)	4 (8.0)	0	1(5.6)	0
输液相关反应	17 (7.5)	6 (2.6)	8 (5.7)	2 (1.4)	4 (8.0)	3 (6.0)	2 (11.1%)	0
AST升高	17 (7.5)	2 (0.9)	10 (7.1)	1 (0.7)	5(10.0)	0	0	0
腹泻	13 (5.7)	0	8 (5.7)	0	2(4.0)	0	1(5.6)	0
白细胞计数降低	12 (5.3)	0	12 (8.5)	0	0	0	0	0
甲状腺功能亢进症	8 (3.5)	2 (0.9)	4 (2.8)	1 (0.7)	0	0	2 (11.1)	1 (5.6)
心肌炎	3 (1.3)	2 (0.9)	2 (1.4)	1 (0.7)	1 (2.0)	1 (2.0)	0	0
高血压	2 (0.9)	2 (0.9)	1 (0.7)	1 (0.7)	1 (2.0)	1 (2.0)	0	0

The results preliminarily showed that AK 104 had a good safety profile and tolerability, as well as antitumor activity

1.2 Type of study (necessary)

This study is an interventional study, and all the drugs used in the study are already marketed. The target population is the second-line resistant NPC population, and there is no standard treatment plan in the diagnosis and treatment guidelines and principles. By exploring effective treatment options in such a patient population. There is clear preliminary study information on the efficacy and safety of any of the individual drugs used in this study protocol. This study is a single-arm exploratory study.

1.3 Study rationale (must)

NPC is dominated by poorly differentiated and undifferentiated carcinoma, with more than half of the patients with advanced disease at initial diagnosis, and about 10% of patients with distant metastasis. According to global cancer statistics in 2012, the age-standardized incidence (ASR) was 6.4 per 100000 and 2.4 per 100000, respectively. In China, there are 60,000 new cases of nasopharyngeal cancer and 34,000 deaths each year. Therefore, nasopharyngeal cancer is a serious disease that endangers human health.

The traditional treatment of NPC includes surgical treatment, radiotherapy and chemotherapy. Radiation therapy has always been the main treatment method because of its deep anatomical site, complex anatomical structure that limit the surgical approach, and its sensitive to radiation. Studies have shown that with intensity-modulated conformate radiotherapy (IMRT) combined with chemotherapy, the 5-year local recurrence-free rate is estimated to be 90%, but the 5-year overall survival rate is only about 80%, and distant metastasis has become the main cause of treatment failure.

The treatment of advanced or recurrent nasopharyngeal carcinoma is mainly platinum-containing systemic chemotherapy, and the standard treatment regimen for locally advanced nasopharyngeal carcinoma is cisplatin concurrent chemoradiation. Synchronous chemoradiotherapy is important in improving the treatment results of local advanced NPC, but concurrent chemoradiotherapy often leads to complications such as xerostomia, trismus, and secondary tumors, which seriously reduces the quality of life of patients. Therefore, the study of novel therapies that can both improve patient disease-free survival and reduce treatment-related complications is of great clinical value. And the emerging immunotherapy provides more treatment options for NPC patients.

According to the report, NPC is closely associated with EB virus infection, and the tumor has high expression of PDL 1, suggesting that PDI blockade is an ideal treatment option for NPC. PD-1 is a negative immunomodulator molecule that mediates tumor immunosuppression in the local tumor microenvironment. The KEYNOTE-028 phase Ib study (NCT 02054806) evaluated the clinical efficacy of the immune checkpoint blockade agent pembrolizumab in the treatment of recurrent / metastatic NPC. Twenty-seven patients with recurrent / metastatic NPC with positive PD-L1 expression receiving 10mg / kg pembrolizumab once every 2 weeks achieved an ORR of 25.9% by investigator assessment, a median response duration of 17.1 months, and one additional unconfirmed partial response. Five of the confirmed partial responses (26.3%) in 19 subjects assessed by the Independent Imaging Evaluation Committee (IRRC). Pembrolizum ab The median overall survival for the

treatment of recurrent / metastatic NPC was 16.5 months, and the overall 1-year survival rate was 63%. In some other cytotoxic and noncytotoxic drug studies, overall 1-year survival is reported at around 45%.

Another phase II study (NCT02339558) evaluated the clinical efficacy of the immune checkpoint blocker nivolumab in the treatment of recurrent / metastatic NPC.44 patients with recurrent / metastatic NPC treated with 3mg / kg nivolum ab every 2 weeks achieved ORR of 20.5% by investigator assessment, median remission continuation of 9.3 months, median overall survival of 17.1 months and overall 1-year survival rate of 59%. ORR reached 33% in 18 PD-L1 positive patients; in 23 PDL 1 negative cases. This shows that the application of PD-1 inhibitors in NPC patients has a solid theoretical basis and sufficient practical basis as a support. However, with the gradual and widespread application of PD-1 inhibitors in clinical practice, PD-1 inhibitor resistance has also become another therapeutic challenge.

Resistance to tumor PD-1 inhibitors became the biggest obstacle to the clinical application of anti-PD-1 / anti-PD-L1. So far, because of the clinical unpredictability of anti-PD-1 / anti-PD-L1 and the non-reproducible resistance in the laboratory. In the context of widespread clinical and extensive use of anti-PD-1 / anti-PD-L1 worldwide, tens of thousands of tumor patients develop PD-1 inhibitor resistance. Therefore, improving the mechanism of drug resistance of PD-1 inhibitors inducing tumor drug resistance is imminent and crucial. The solution of this problem greatly helps to clarify how to develop new treatments or use combination therapies to eliminate PD-1 inhibitor resistance.

Little research has been done on the biological mechanisms of resistance to tumor PD-1 inhibitors. Most previous studies have shown that the high expression of PD-L1 on the surface of DCs can inhibit the T cell immune response through the PD-1 / PD-L1 pathway.

CD28 and CTLA-4, PD-1 are receptors expressed by T cells. During T cell activation, CD28 plays the "refueling" role, CTLA-4 plays the "front brake" role, and PD-1 plays the "rear brake" role. Upon recognition of the antigen peptide / major histocompatibility complex (MHC) by the T cell receptor (TCR), the binding of CD80

or CD86 to CD28 generates a costimulatory signal that promotes T cell activation. After T-cell activation, the co-inhibitory receptor CTLA-4 was upregulated, along with the expression of other inhibitory receptors on the T-cell surface, including PD-1. CTLA-4 binds more strongly to CD80 than CD28, thus resulting in CD80 endocytosis and downregulation of both antigen presentation capacity and T cell activity. Thus triggering PD-1 inhibitor resistance. Meanwhile, the researchers found that the combination of PD-1 / PD-L1 antibody and anti-CTLA-4 antibody (Ipilimumab and Opdivo-IO regimen) had significantly enhanced tumor-infiltrating T cell function on day 25 than mice treated with anti-CTLA-4 alone or PD-L1 antibody alone or control. The combination of PD-1 antibody and CTLA-4 antibody can be considered to avoid the dark side of PD-1 antibody to some extent, effectively reducing the occurrence of tumor resistance to PD-1 inhibitors. PD-1 and CTLA-4 complement each other and do not repeat in regulating immune responses, based on their mechanisms preventing T cell depletion and promoting T cell activation, respectively. When the PD-1 pathway initially occurs at the tumor locus, CTLA-4 modulation of T cells suppresses activation and spread that occurs at the site of antigen presentation in the lymphoid region, yet this distribution of CTLA-4 and PD-1 is far from unique. Target the two pathways may require additional activity or synergistic activity (Pardoll, 2012), and combination therapy are more effective than monotherapy.

Therefore, this study aimed to evaluate the efficacy and safety of cadradinilizumab combination chemotherapy in patients with PD-1 inhibitor-resistant NPC and to determine its PK and immunogenicity characteristics to provide evidence for subsequent studies.

1.4 Risk / benefit assessment (must)

1.4.1 Known potential risks

The irAE is defined as an AE associated with drug exposure, consistent with an immune-mediated mechanism of action, and without a clear alternative etiology. Based on the mechanism of action of AK 104 targeting PD-1 and CTLA-4 leading to T cell activation and proliferation, it is possible that irAE could be observed during the conduct of this study. The underlying irAE may be similar to the adverse events

seen with anti-PD-1 / L1 drugs, including immune-mediated colitis, dermatitis, pneumonia, hepatitis, encephalitis, nephritis, and endocrine disorders.

Based on the severity of toxicity occurring in treatment according to NCI CTCAE 5.0 grade, AK 104 treatment adjustments will be performed to manage potential irAEs.

- The maximum interval allowing an AK 104 pause is 12 weeks. If not returning to AK 104 within 12 weeks, the subject permanently discontinued AK 104 and, if applicable, considered systemic corticosteroids (such as prednisone or intravenous equivalent) for persistent low grade or severe (grade 3) events.
- If symptoms recur or worsen during the glucocorticoid reduction, the dose was increased until the symptoms stabilized or improved, and then gradually rereduced at a slower rate.
- For events that do not respond to systemic corticosteroids, more potent immunosuppressive agents (e. g. infliximab, maccohenyl esters, etc.) should be considered after discussion with the medical monitor.
- For multiple low-grade AEs (no treatment termination is required separately), AK 104 will be terminated at the discretion.
- After discontinuation of study drug for Grade 3 or 4 events, if the subject responded well and the toxicity resolved rapidly, AK 104 could be resumed after discussion with the medical monitor.
- For abnormal laboratory findings, suspension or permanent termination should be determined based on concomitant clinical symptoms / signs and the clinical judgment of the investigator.

1.4.2 Known potential benefits

As a population resistant to PD-1 inhibitors, only chemotherapy is used clinically, and the effective rate is less than 20%. If combined with A K104 and chemotherapy, patients are highly likely to obtain the most effective treatment from this combination treatment.

1.4.3 discuss

Two phase Ib / II clinical studies. One was to evaluate the safety, tolerability, PK profile, immunogenicity, pharmacodynamics, and antitumor activity of AK 104 alone in advanced solid tumors and AK 104 in combination with oxaliplatin and capecitabine (mXELOX) in the first-line treatment of locally advanced or metastatic gastric adenocarcinoma or gastric esophageal adenocarcinoma. In terms of efficacy, as of April 30,2020, the ORR and 63.6% in 44 subjects with standard treatment failure. In the cohort of AK 104 combined with mXELOX for advanced gastric cancer or gastroesophageal adenocarcinoma, of 19 evaluable subjects, 2 CR, 11 PR, 5 SD, ORR reached 68.4% and 9 DCR reached 94.7%.

Tumor PD-1 inhibitor resistance is increasingly emerging in a large number of NPC patients. Regarding the biological mechanism of resistance to tumor PD-1 inhibitors associated with the upregulation of CTLA-4 expression. CTLA-4 binds more strongly to CD80 than CD28, thus resulting in CD80 endocytosis and downregulation of both antigen presentation capacity and T cell activity. Thus triggering PD-1 inhibitor resistance. Meanwhile, the researchers found that the combination of PD-1 / PD-L1 antibody and anti-CTLA-4 antibody (Ipilimumab and Opdivo-IO regimen) resulted in better tumor control in mice treated with anti-CTLA-4 alone or with PD-L1 antibody alone or control. The combination of PD-1 antibody and CTLA-4 antibody can be considered to avoid the dark side of PD-1 antibody to some extent, effectively reducing the occurrence of tumor resistance to PD-1 inhibitors. AK 104 is able to bind both programmed cell death receptor-1 (PD-1) and cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) and block the interaction of PD-1 / programmed cell death ligand-1 (PD-L1), PD-1 / PD-L2, CTLA-4 / B7.1, and CTLA-4 / B7.2.

Therefore, this study aimed to evaluate the efficacy and safety of cadradinilizumab combination chemotherapy in patients with PD-1 inhibitor-resistant NPC and to determine its PK and immunogenicity characteristics to provide evidence for subsequent studies.

2. Study objective / endpoint (necessary, flexible withholding according to project characteristics)

2.1., for the purpose of the study

2.1.1 Main study objectives

To evaluate the safety and efficacy of carbenilizumab plus chemotherapy (platinum-based) second-line treatment of PD-1 inhibitor-resistant NPC based on RECIST v l.1 Objective response rate (ORR) and PFS as assessed.

2.1.2 Secondary study objectives

· To evaluate DoR, DCR, TTR, TTP, and OS in PD-1 inhibitor-resistant NPC with capradilimumab plus chemotherapy (platinum-based).

· To evaluate the pharmacokinetics of carradilizumab plus chemotherapy (Pharmacokinet ics, PK).

· To assess the immunogenicity of caldradilizumab in combination with chemotherapy.

· To evaluate the correlation of PD-Ll expression with efficacy in immunohistochemical detection of tumor samples.

· To evaluate the association of EB virus (EBY) DNA copy number in blood and antitumor activity of caadilimumab in subjects with advanced NPC.

· To assess health-related quality of life (HRQoL) in subjects treated with carradiniilizumab plus chemotherapy

2.2 Study Endpoints

2.2.1 Primary Study Endpoints

· Safety:, incidence and severity of adverse events (AEs), clinically significant abnormal laboratory findings.

· Based on the following data in RECIST v i. The ORR as assessed by the I.

· Based on the following data in RECIST v i. I of the assessed PFS.

2.2.2 Secondary Study Endpoints

- According to the RECIST vi. The DoR, DCR, TTR, TTP, and OS as assessed by I.
- PK characteristics: including serum concentrations of cadadilimumab at different time points after cadilimumab administration.
- Immunogenicity assessment: Number and percentage of subjects presenting with detectable antimicrobial antibodies (ADA).
- To evaluate the correlation of PD-Ll expression with efficacy in immunohistochemical detection of tumor samples.
- To evaluate the association of EB virus (EBY) DNA copy number in blood and antitumor activity of caadilimumab in subjects with advanced NPC.
- Health-related Quality of Life Assessment HRQoL-as measured using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTCQLQ-C30) and EORTCQLQ-H & N35.

3. research design

3.1 Overall design (must)

This study is a Phase II clinical study of carradilimumab (AK 104) plus chemotherapy for PD-1 inhibitor-resistant nasopharyngeal cancer to evaluate the safety and efficacy of carradilimumab plus chemotherapy as second-line and above treatment for PD-1 inhibitor-resistant nasopharyngeal cancer. This study is a single-arm, phase II clinical study with approximately 30 PD-1 inhibitor-resistant NPC subjects scheduled to be enrolled. PD-Ll CPS (<50% vs> 50%, subjects whose PDLl expression was not evaluated were classified as <50%) were used as the stratification factor. The study will have a safe lead-in period of approximately 6 PD-1 inhibitor-resistant subjects, and the investigator will conduct an preliminary safety assessment. If the safety and tolerance are good and initial efficacy signals are observed, the extended enrollment phase will enter. Efficacy analysis will be performed for approximately 15 subjects. If 6 of the 15 subjects are not tolerated,

subject enrollment may be stopped after the investigator discussion. After poor safety, the investigator decided to revise or stop the study. For 4-6 cycles, the use of calduilizumab until the investigator determines that there is no clinical benefit (based on the comprehensive judgment of RECISTv1.1 imaging assessment and clinical symptoms), toxicity intolerance, completion of 24 months of treatment, or satisfaction of other criteria for treatment termination in the regimen, whichever occurs first.

- Subject treatment protocol:
- Carradilizumab (200 mg, administered on day 1 of each cycle, Q3W until no longer had clinical benefit) + platinum was based chemotherapy, 1 treatment cycle every 3 weeks (21 days).

3.2 Sample size (necessary)

Thirty subjects are planned to be enrolled in this study

4. Study population (necessary)

Patients with nasopharyngeal carcinoma who had received a previous PD-1 inhibitor-containing regimen, presented with disease progression and no indication for radical local treatment

4.1 Diagnostic criteria (if any)

Histologically or cytologically confirmed nasopharyngeal carcinoma.

4.2 Inclusion criteria (must)

Subjects must meet all of the following inclusion criteria to be enrolled in the study:
Voluntary signed the written ICF.

1) Age was over 18 and 75 at the time of enrollment, acceptable for both men and women.
2) The Eastern Cooperative Oncology (ECOG) physical performance score was 0 or 1.
3) Expected survival is greater than 3 months.
4) Histologically or cytologically confirmed nasopharyngeal carcinoma.
5) The subject had previously failed treatment with PD-1 inhibitor and had no indication for radical local treatment.

6) According to the efficacy evaluation criteria of solid tumors RECIST v l. And l with at least one measurable lesion.

4.3 Exclusion criteria (must)

- Declaration that all baseline subjects meeting any of the exclusion criteria will be excluded from the study

1) Other than NPC, the subject had any other malignancy within 2 years prior to enrollment. Subjects who have been cured by local treatment of other tumors, such as basal or cutaneous squamous cell carcinoma, superficial bladder cancer, cervix or breast in situ carcinoma, are not excluded.
2) Attreatment the investigational drug within 4 weeks prior to the first study administration.
3) Having active autoimmune diseases requiring systemic therapy over the past two years (e. g. use of modifying medication, corticosteroids, immunosuppressive therapy), alternative therapy (e. g., thyroxine, insulin, or physiological corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a systemic therapy.
4) History of immunodeficiency; test positive for HIV antibodies; ongoing use of systemic corticosteroids or other immunosuppressants.
5) Active TB should be excluded in subjects with suspected active TB (TB).
6) Known history of allogeneic organ transplantation and allogeneic HSCT.
7) For subjects with untreated active hepatitis B (HBsAg positive with HBV-DNA over 1 000 copies / ml (200 IU / ml) or above the lower limit of testing, whichever higher), anti-hepatitis B treatment was required during study treatment; subjects with active hepatitis C (HCV antibody positive and HCV-RNA levels above the lower limit of testing).
8) Major surgery or severe trauma within 30 days prior to the first dose, or a major surgical planner within 30 days after the first dose (at the discretion of the investigator); a minor local procedure (excluding transperipheral venous

puncture central venous catheterization) within 3 days prior to the first dose.

9) The presence of CNS metastases.

10) Current uncontrolled concurrent conditions, including but not limited to symptomatic congestive heart failure (grade 2 or above under the New York Heart Association functional classification), unstable angina, acute myocardial ischemia, poorly controlled arrhythmia, decompensated cirrhosis, nephrotic syndrome, uncontrolled metabolic disorders, severe active peptic ulcer disease or gastritis, or psychiatric / social conditions that may limit study requirements or affect the subject's ability to provide written informed consent.

11) There was a past history of myocarditis, cardiomyopathy, and malignant arrhythmia. Unstable angina, congestive heart failure, or vascular disease (such as aortic aneurysm or peripheral venous thrombosis requiring surgical repair) within 2 months before the first dose, Or other cardiac lesions that may affect the safety evaluation of the study drug (e. g. poorly controlled arrhythmias, Myocardial infarction or ischemia); presence of esophageal-gastric varices within 6 months before the first dose, Severe ulcer, The wound has not healed, gastric-intestinal perforation, abdominal pain, Gastrointestinal obstruction, History of intra-abdominal abscess or acute gastrointestinal bleeding; any arterial thromboembolic event within 6 months prior to the first dose, NC I CTCAE 5.0 grade 3 and above, Transient cerebral ischemic attack, cerebrovascular accident, Hypertensive crisis or hypertensive encephalopathy; acute exacerbation of chronic obstructive pulmonary disease within 1 month before the first dose; current presence of hypertension with SBP> 160mmHg or DBP <100mmHg after oral antihypertensive medication.

12) History of severe bleeding tendency or coagulation opathy; blood symptoms of significant clinical significance within 1 month before the first dose, including but not limited to gastrointestinal bleeding, hemoptysis, screening imaging showing tumor wrapping around important blood vessels or significant necrosis and emptiness, and the investigator believes that participation in the study may

cause bleeding risk;

13) No response of prior anti-tumor therapy, defined as not returning to Grade 0 of NC l CTCAE 5.0 or 1, or the level specified in the inclusion / exclusion criteria, except for sequelae of alopecia, neurotoxicity associated with prior lead therapy. Subjects with irreversible toxicity not expected to worsen after study drug administration (e. g. hearing loss) may be included in the study after consultation with the medical monitor. Long-term toxicity from radiotherapy, subjects not recoverable as judged by the investigator may be included in the study after consultation with the medical monitor.

14) Live vaccination was administered within 30 days before the first dose, or was planned to be administered during the study period.

15) Known allergy to any component of any study drug; known history of severe hypersensitivity to other monoclonal antibodies.

16) Known history of mental illness, substance abuse, alcohol abuse, or drug use.

17) Pregnant or lactating women.

18) Prior or current presence of any disease, treatment, laboratory abnormalities that may confuse the findings, affect the subject's full participation, or participation in the study may not be in the subject's best interest at the time.

19) Local or systemic disease due to nonmalignancy, or disease or symptoms secondary to tumor, and can lead to higher medical risk and / or uncertainty in survival evaluation, such as leukemic response (white cell count> 20 X 109 / L or malmalignant manifestations (such as known weight loss of more than 10% in the 3 months prior to screening).

4.4 Subject Exit Criteria (if any)

① Treatment failure as specified in the protocol occurs.

② Unacceptable treatment toxicity occurs.

③ Diseases that may significantly affect clinical status assessment or require interruption of treatment.

④ Patients may withdraw from this study at any time and for any reason.

Withdrawal procedure: Patients should be asked about the reason for their withdrawal and any adverse events occurring and, if possible, should be observed and evaluated by the investigator. Serious or unexpected adverse reactions should be followed-up. Once the patient withdraws or discontinues the trial, the investigator should try to obtain information about the patient. The investigator should do his best to complete the final evaluation and record their efforts. The results of these evaluations and observations, together with the description of the reasons for patient withdrawal, must be recorded in the original data. The primary reasons for withdrawal or discontinuation must be documented in the case report form (CRF) and the relevant follow-up study steps (discharge visit) completed whenever possible.

5. appraise

5.1 Primary and secondary endpoints / outcome evaluation

Main end point

· The ORR was based on the RECIST 1.1 assessment.

· The PFS based on the RECIST 1.1 assessment.

Secondary end point

· According to the RECIST vi. The DoR, DCR, TTR, TTP, and OS as assessed by I.

· PK characteristics: including serum concentrations of cadadilimumab at different time points after cadilimumab administration.

· Immunogenicity assessment: Number and percentage of subjects presenting with detectable antimicrobial antibodies (ADA).

· To assess the correlation of PD-L1 expression with efficacy in tumor samples by immunohistochemical detection.

· To evaluate the association of EB virus (EBY) DNA copy number in blood and antitumor activity of caadilimumab in subjects with advanced NPC.

Health-related Quality of Life Assessment HRQoL-as measured using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTCQLQ-C30) and EORTCQLQ-H & N35.

5.2 Safety evaluation (necessary)

Safety:, incidence and severity of adverse events (AEs), clinically significant abnormal laboratory findings.

6. Adverse events and serious adverse events (must)

All treated patient (APaT) population was used for the safety data analysis for this study. All treated patient populations included all patients receiving at least 1 dose of study medication.

6.1 Adverse events

Definition: Any adverse medical event between the entry of the patient and the last follow-up, whether causally related to the trial drug.

Adverse events were truthfully recorded during the trial, including the time, severity, duration, measures taken and outcome of the adverse events.

The severity criteria for adverse events: according to the WHO evaluation criteria for adverse drug reactions (Annex 4). The adverse reactions listed in the table are indicated in the following case:

- Mild: it does not affect the normal function of the subject.
- Moderate: to affect the normal function of the subjects to some extent.
- Severe severity: obviously affecting the normal function of the subjects.

Criteria for determining the relationship between adverse events and trial drug:

The Investigator should assess the possible association between the adverse event and the trial drug according to the following criteria:

Positive concern: the timing of the reaction, the timing of the known type of response of the test drug, improvement after withdrawal, and repeated administration reappeared.

Related to: the timing of the reaction, the known type of response to the trial drug, and the patient's clinical status or other treatments.

Probably unrelated: the timing of the reaction does not match the chronological order of the medication, the response is not quite within the known

type of response given by the trial drug, or because of the patient's clinical status or other treatments.

No: The time of the response does not conform to the chronological order of the medication, the response has the response type known to the non-trial drug, the patient's clinical status or other treatment methods may also produce the response, the improvement of the disease state or the elimination of other treatment methods, and the reuse of other treatment methods.

It cannot be determined that there is no clear relationship between the time of the reaction and the chronological order of the medication, the response is similar to the known type of response of the test drug, and other drugs used may also cause the same response.

6.2 Serious Adverse Events

6.2.1 Determination of serious adverse events

- □ die
- □ Life is in danger
- □ Leading to a prolonged hospitalization or hospital stay
- □ Permanent or severely disabling condition
- □ Lead to congenital malformations, defects

6.2.2 Any serious adverse reaction occurring during the clinical trial or within 30 days of the last treatment, whether it is related to the drug, should be immediately and orally reported to the study director, the Ethics Committee and the sponsor within 24 hours.

6.2.3 The investigator should follow up for serious adverse reactions until the symptoms disappear or the condition is stable.

7. Statistical analysis and statistical methods (necessary)

7.1, and the analysis set

7.1.1, and the enrollment analysis set

The enrollment analysis set included all subjects who signed the ICF into the study.

7.1.2 Full Analysis set

The full Analysis set (FAS) included all subjects who had received at least one dose of study drug and had measurable lesions at baseline (as defined by RECIST v1.1).

7.1.3 Safety Analysis Set

The Safety Analysis Set (SS) includes all subjects who have received at least one study medication. Analysis was performed based on the treatment that the subject actually received.

7.1.4 Pharmacokinetic analysis set

Pharmacoanalysis Set (PKS): Subjects who had received at least 1 study drug and had at least 1 effective postdose plasma concentration data.

7.1.5 Immunogenicity analysis set

The immunogenicity analysis set included all subjects who were randomized and used at least one study drug, pre-medication and at least one post-medication immunogenicity assessment data.

8. Medical treatment and protection of the subjects (necessary)

8.1 Assessment of risk in the study and risk management measures and plan (necessary)

In order to better protect the safety and interests of the subjects, the protocol of the trial is strictly followed and the quality of the trial data is ensured. The test site must be equipped with necessary medical rescue equipment, first-aid drugs and emergency measures. When necessary, an emergency medical emergency team shall be set up to deal with emergency medical events and accidental disasters in

accordance with relevant standard operating procedures. Closely observe possible adverse events, especially non-expected adverse events, timely analysis and communication, and record adverse events. Establish linkage procedures with the hospital intensive care unit for subject transfer and care. Establish communication and communication between researchers and laboratories and cooperative units to ensure timely communication and treatment of possible adverse events.

8.2 Infusion reaction

Subjects will be monitored for signs and symptoms of infusion reactions (e. g., fever and / or chills, flushing and / or pruritus, changes in heart rate and blood pressure, dyspnea or chest discomfort, rash, etc.) and systemic allergic reactions (e. g., generalized urticaria, angioedema, asthma, hypotension, tachycardia).

In this study, to avoid confounding the potential safety signals regarding the assessment of the infusion response:

1) Primary prophylaxis is not allowed for infusion reactions (in subjects without infusion events).

2) The investigator may decide regarding appropriate secondary prevention (that is, preventing reactions related to infusion after the initial episode):

- An acetaminophen / paracetamol and / or antihistamide (e. g. diphenhydramine) may be administered approximately 30 minutes before the start of a subsequent infusion, and / or glucocorticoids or equivalent drugs according to the diagnostic routine at each center.
- Non-sedating antihistamines (e. g. cetirizine) may be considered for subjects with repeated infusion reactions.
- If the symptoms persist, the corticostertherapy should be considered.
- According to the routine of each center, the investigator may at his discretion decide whether to administer piperidine / morphine sulfate and promethazine or the equivalent prior to the start of the subsequent infusion.

Readministration of pretreated agents may be required during the infusion; therefore, this should be considered in determining the dose of pretreated agents. Any

significant reactions and use requirements related to corticosteroids must be discussed with the medical monitor.

In the event of a level 2 infusion reaction, the infusion rate of AK 104 can be reduced by 50% or interrupt the infusion until the event resolves (up to 6 hours) and restart the infusion at 50% of the initial infusion rate after event resolution until the infusion is completed. Once the infusion rate of AK 104 is reduced by 50% or the infusion is interrupted due to the infusion reaction, all subsequent infusion must be continued at the reduced infusion rate. If the subject has a second level 2 infusion reaction at a slower infusion rate, the infusion should be stopped. If the subject has a grade 3 or 4 infusion reaction at any time, the AK 104 treatment must be stopped.

If severe hypersensitivity (grade CTCAE 3 or 4) is observed during the infusion, the infusion will be stopped immediately and no further AK 104 treatment will be given. Supportive treatment is provided according to the standard medical practice. If subjects develop symptoms or signs of systemic anaphylaxis or type 1 hypersensitivity during AK 104 administration, they will be treated with appropriate drugs and medical devices that will always be available at all sites. Glucocorticoids, epinephrine, allergic drugs (antihistamines) or equivalent should be readily available. The subject should be informed to report to the investigator on any delayed response.

Guidelines for toxicity management of AK 104 treatment related to infusion reactions are shown in the table below. In case of multiple low-grade AEs (permanent AK 104 treatment is not required separately), the permanent AK 104 treatment will be determined at the discretion of the investigator.

Table 1 Treatment adjustments for infusion response symptoms caused by AK 104

NCI-CTCAE grade	**Regarding the treatment adjustment for AK 104**
Level 1 mild Minor, temporary reaction; no infusion	Reduce the AK 104 infusion rate by 50% and closely monitor any deterioration. The total infusion time of AK 104 should not

interruption; no treatment.	exceed 120 minutes.
Level 2 moderate Treatment or infusion interruption is required, but symptomatic treatment (such as antihistamines, NSAID, corticosteroids, intravenous infusion), rapid effect; preventive administration of <24 hours.	Interrupt the AK104 infusion. The infusion was restarted at 50% of the previous infusion rate at times when the infusion response had subsided or the severity had dropped to at least level 1, and any deterioration was monitored closely. If the subject has a second level 2 infusion reaction at a slower infusion rate, the infusion should be discontinued and the subject must be withdrawn from AK 104 treatment.
Grade 3 or 4 is serious or life-threatening Grade 3: delay in symptom relief (e. g. symptomatic treatment and / or infusion interruption, lack of rapid response); relapse after symptom improvement; sequelae requiring hospitalization. Grade 4: life-threatening; requiring urgent treatment.	The AK 104 infusion was stopped immediately, and the subject's infusion tube was disconnected. Subjects must immediately withdraw from AK 104 treatment and must not receive any further AK 104 treatment.

8.3 Complications of infection

Bacterial, mold, tuberculosis virus infection and some special microorganisms of each system.

Countermeasures: Most of the above situations can be alleviated by themselves or improved after symptomatic treatment, and in rare cases, they may be life-threatening; the prevention measures include eliminating contraindications, strictly following the treatment procedures and specifications, strictly monitoring the subjects, and treating the symptoms according to the doctor.

8.4 **Immune-related adverse events (irAE)**

The irAE is defined as an AE associated with drug exposure, consistent with an immune-mediated mechanism of action, and without a clear alternative etiology. Based on the mechanism of action of AK 104 targeting PD-1 and CTLA-4 leading to T cell activation and proliferation, it is possible that irAE could be observed during the conduct of this study. The underlying irAE may be similar to the adverse events seen with anti-PD-1 / L1 drugs, including immune-mediated colitis, dermatitis, pneumonia, hepatitis, encephalitis, nephritis, and endocrine disorders. Subjects should be monitored for the signs and symptoms of an irAE. In the absence of other alternative causes (e. g., infection or PD), immune-related causes associated with signs or symptoms of colitis, dermatitis, pneumonia, hepatitis, encephalitis, nephritis, and endocrine disorders should be considered.

Based on the severity of toxicity occurring in treatment according to NCI CTCAE 5.0 grade, AK 104 treatment adjustments will be performed to manage potential irAEs.

- The maximum interval allowing an AK 104 pause is 12 weeks. If they could not return to the reuse of AK 104 within 12 weeks, the subject permanently discontinued AK 104 and entered the follow-up phase. Except: AK 104 was suspended for more than 12 weeks or AK 104 for more than 12 weeks due to AEs that may be unrelated or unrelated to AK 104. In this case, a discussion with the medical monitor is needed to decide whether the AK 104 treatment can be continued.

Generally, it is recommended to manage irAEs according to the following principles. Subjects should be comprehensively evaluated, excluding any other alternative etiology (e. g. disease progression, concomitant medication, infection, etc.). Serological, immunological, and histological (biopsy) data should be used to support the diagnosis of irAE, as appropriate.

- If applicable, systemic corticosteroids (e. g., prednisone or intravenous equivalent) should be considered for persistent low-grade or severe (grade 3) events.

- If symptoms recur or worsen during the glucocorticoid reduction, the dose was increased until the symptoms stabilized or improved, and then gradually rereduced at a slower rate.
- For events that do not respond to systemic corticosteroids, more potent immunosuppressive agents (e. g. infliximab, maccohenyl esters, etc.) should be considered after discussion with the medical monitor.
- Termination of study drug treatment is not mandatory for grade 3 or 4 inflammatory reactions (e. g., sites of metastatic disease, lymph nodes).
- Doctors in other fields (such as cardiology or autoimmune diseases) should be arranged to make appropriate treatment decisions.
- For multiple low-grade AEs (no treatment termination is required separately), AK 104 will be terminated at the discretion.
- After discontinuation of study drug for Grade 3 or 4 events, if the subject responded well and the toxicity resolved rapidly, AK 104 could be resumed after discussion with the medical monitor.
- For abnormal laboratory findings, suspension or permanent termination should be determined based on concomitant clinical symptoms / signs and the clinical judgment of the investigator.

AK 104 dose adjustment and toxicity management principles for immune-related AEs are shown in the following table for irAEs or when specific toxicities exist, refer to the management of immune-related adverse events in patients treated with immune checkpoint inhibitors: Clinical Practice Guidelines of the American Society for Clinical Oncology (Brahmer et al., 2018) processing. Guidelines for the diagnostic assessment of immune-related adverse events are detailed in the appendix.

Table 2: The recommended principles for dose adjustment and toxicity management of AK 104 immune-related AEs

Immune-related AEs	**Toxicity level**	**Measures taken against AK 104**	**Management of irAE (corticosteroids and other treatments)**	**Monitoring and follow-up**

pneumonia	Level 2	Suspension of medication	Corticosteroid hormone (initial dose of 1-2mg / kg prednisone or equivalent), then tapered thereafter	The subject was monitored for the symptoms and signs of pneumonia Subjects with suspected pneumonia by imaging evaluation and were started on corticosteroid hormone therapy Prophylactic use of antibiotics to prevent opportunistic infections
	Grade 3 – 4, or recurrent grade 2	Permanent withdrawal of drugs		
Diarrhea / enteritis	Level 2-3	Suspension of medication	Corticosteroid hormone (initial dose of 1-2mg / kg prednisone or equivalent), then tapered thereafter	Participants were monitored for symptoms and signs of gastroenteritis (diarrhea, abdominal pain, hematology, blood, stool, with or without fever) or bowel perforation (peritoneal irritation or intestinal obstruction) Subjects with grade 2 diarrhea and suspected enteritis should consider consulting a gastroenterologist for endoscopy to exclude enteritis
	Level 4	Permanent withdrawal of drugs		
AST/ALT	Level 2	Suspension of	Corticosteroid (initial	Monitor liver

Elevated or with an elevated bilirubin		medication	dose 0.5-1mg / kg prednisone or equivalent), tapered	function (weekly or more frequently until liver enzymes return to baseline or remain stable)
	Level 3	Suspend or permanently	Corticosteroid hormone (initial dose of 1-2mg / kg prednisone or equivalent), then tapered thereafter	
	Level 4	Permanent withdrawal of drugs	Corticosteroid hormone (initial dose of 1-2mg / kg prednisone or equivalent), then tapered thereafter	
Type 1 diabetes mellitus (T1DM) or hyperglycemia	New T1DM or hyperglycemia (related to cell failure)	Suspension of medication	T1DM subjects were started on insulin replacement therapy and hyperglycemic subjects were started on antidiabetic agents	The subject was monitored for blood glucose, or other symptoms and signs of diabetes
hypophysitis	Level 2	Suspension of medication	Use of corticosteroid hormones and, if clinically indicated, initiate hormone replacement therapy	Monitor for symptoms and signs of hypophysitis (including pituitary and adrenal dysfunction)
	Level 3-4	Suspend or permanently		
hyperthyrea	Level 2	cont.rem	Treatment with nonselective receptor blockers (e. g. propranolol) or thioamide (if appropriate)	Monitor for the symptoms and signs of thyroid disease
	Level 3-4	Suspend or permanently		
hypothyrea	Level 2-4	cont.rem	Thyroid hormone replacement therapy was initiated based on standard therapy (e. g. L Thyroxine or triiodothyronine)	Monitor for the symptoms and signs of thyroid disease

Nephritis and renal insufficiency	Level 2	Suspension of medication	Corticosteroid hormone (initial dose of 1-2mg / kg prednisone or equivalent), then tapered thereafter	Monitor for changes in renal function
	Level 3-4	Permanent withdrawal of drugs		
carditis	Level 1	Suspension of medication	Corticosteroid hormones were used based on the type and severity of the AE	Ensure adequate evaluation to confirm the cause and or to exclude other causes
	Level 2	Suspend or permanently		
	Level 3-4	Permanent withdrawal of drugs		
All of the other irAEs	Level 2, that could not be tolerated or persisted	Suspension of medication	Corticosteroid hormones were used based on the type and severity of the AE	Ensure adequate evaluation to confirm the cause and or to exclude other causes
	Level 3	AEs based on type of AE suspension or permanent withdrawal include but are not limited to Guillain-Barre syndrome, encephalitis, etc		
	Grade 4 or recurrent grade 3	Permanent withdrawal of drugs		
1. Suspension or permanent withdrawal will be decided after discussion between the investigator and the medical supervisor pay attention to:				

When the AE returns to grade 0-1 or baseline, corticosteroid hormones began to be gradually reduced for more than 4 weeks;

For AK 104 suspension: restart AK 104 if the AE returns to Grade 0-1 or baseline with corticosteroid tapering (10mg prednisone or equivalent dose) and if the AE does not resolve within 12 weeks after the last dose or 12 weeks;

For severe and life-threatening irAEs, intravenous corticosteroids and sequential oral hormone therapy should be started, and if corticosteroids are not effective, other immunosuppressants should be considered;

For subjects with grade 3-4 immune-related endocrine disorders requiring AK 104 suspension, allow medication to resume when the AE returns to level 2 and is controlled by hormone replacement therapy or achieves metabolic stability (e. g., T1DM).

Where the above principles are inconsistent with the toxicity management guidelines related to other immune checkpoint inhibitors or the local standard clinical practice, the investigator organizes the meeting to discuss the corresponding toxicity management.

8.5 Non-immune-related adverse events

AK 104-associated AE should often be attributed to an immune-mediated mechanism, namely irAE. For AK 104-related grade 3 or above non-immune-related AEs assessed by the investigator, AK 104 administration may be suspended and treated clinically. When the adverse event is relieved or improved, the medication may be continued according to the judgment of the investigator. No dose interruption may be required for AEs specifically unrelated to AK 104 or for laboratory abnormalities that are not clinically significant. All toxicities were graded according to NCI CTCAE 5.0. Non-immune-related reactions were handled according to the diagnostic routine of each study center.

9. Supporting documents and precautions

9.1 Informed Consent Process (if any)

Prior to subject participation, the investigator has the responsibility to fully explain the study purpose, methods, expected benefits and potential hazards to the subject for further voluntary written consent from the subject or his legal representative (if permitted by local regulations). Legal representative refers to the individual or institution who has obtained the authorization of the subject or the

authorization of the law. The informed consent form should be written in the native language of the potential subject population.

The investigator should follow the relevant regulatory requirements, GCP and the ethical principles derived from the Declaration of Helsinki. IEC / IRB approval should be obtained before the informed consent form and its revision are provided to potential subjects. The investigator should ensure that each subject was informed that they could voluntarily terminate the study at any time and that each subject had the opportunity to ask questions and time to think about the information obtained.

Informed consent form should be obtained before the subject participates in the study and documented in the site. The ICF shall be signed by the subject or his legal representative (if permitted by local regulations) and the name and date by the investigator. The original signed ICF should be kept at the study site and provided with a copy of the signed consent form by the subject or their legal representative. The date of giving the informed consent should be recorded in the medical record and the case report form.

If the subject or his legal representative (if permitted by local regulations) is not reading, a fair witness should be present throughout the informed consent discussion. The witness should sign the ICF after the subject or his legal representative agrees the subject to participate in the study and sign the ICF (if possible). Signing the ICF indicates that the witness confirmed that the information in the ICF and any other written information had been fully explained to the subject or his legal representative, that they had clearly understood this information, and that the subject or his legal representative agreed to sign the written informed consent.

The informed consent form approved by the IRB / IEC should describe any incentives for the subjects to participate in the study.

9.2 Privacy protection (must)

In clinical trials and collection and processing of patient personal data, strictly abide by the clinical trial privacy protection procedures, data protection legislation and ethical standards, implement the safeguard procedures to protect the subject's personal data, to prevent loss or theft, unauthorized access, improper use, copying,

transmission or tampering, modification, retention or damage. During centralized screening, independent space is needed to conduct separate informed consent after group knowledge, to ensure that subjects can ask questions and get answers without concern. The physical examination as well as the electrocardiogram requires independent space to avoid exposing the subject's body parts. In the process of clinical trial, various forms, such as physical examination records, electrocardiogram records, PK blood collection records, local laboratory sample collection records, drug distribution forms, etc., should be distinguished by the unique number conforming to the project requirements in the clinical trial, and no personal information of the subjects, such as name, gender, etc. After the bedside card is numbered instead of name, the subject wears a chest plate, mark the item number, subject number, and identify with the chest plate during operation. When sent to external institutions and departments (such as the third-party testing platform), the sample is identified with the only code that cannot reflect the subject's personal information. Quality control checks shall be performed for all documents before sending email, transmitting data or entering them into the system. Keep the password and permission for access to the clinical trial system, such as browsing the electronic medical record system and laboratory sheet, etc., only by qualified staff. In case of any privacy disclosure, timely correct and strengthen management and take preventive measures to prevent such situation from happening again. Any documents and data reflecting the personal information of subjects in a relatively fixed position, and timely sorting and archive, only authorized personnel can write or browse, not in large areas or open area, unauthorized personnel can not access to any medical records related to the study, for blinded studies, unblinded personnel can not access to any subject's medical records. The research data should be kept in the archives room and managed by special personnel. The archived documents should be locked in time. Only those with authority can borrow them, and lend and return them need to be registered. When the results are published, report with the group synthesis data rather than the individual data of the subject. When describing the special situation of the individual, there is no personal information that can identify the subject, and it can be coded instead.

9.3 Quality Control and Quality Assurance (must)

The investigator / site is required to open direct access to the source data / documents allowing study related monitoring, audit, IRB / IEC review and regulatory audit. Direct access includes permits for examination, analysis, validation, and replication of any records and reports critical to the evaluation of clinical studies.

9.4 Data processing and record keeping (must)

9.4.1 Data collection and management

9.4.1.1 Data acquisition

All data collected during the study will be recorded in the subject's individual-specific case report form. The designated person will provide the case report form and instructions for completing the case report form, and any modifications will be automatically recorded through the Audit Traces function of the EDC system.

The case report form should be kept up to date to help the monitor review subject status throughout the study. The case report form should be filled in as soon as possible after the follow-up, and questions should be answered as soon as possible. The case report form should be completed, reviewed as soon as the last subject follow up and signed by the investigator.

Each subject who has signed the ICF and has passed all the screening steps must have a completed case report form. If the subject is not treated, the cause must be recorded in the case report form.

All external data (e. g. data generated from the central laboratory, PK process, PD process) are integrated with the subject's case report form data based on the data management plan.

Subject number and the date of study participation should be recorded by the investigator in the subject's medical / study file along with the study code. The investigator should also record the following information in the medical / study files: written and verbal confirmation of informed consent, subject clinical status, date of each study follow-up, administration date of study medication, concomitant

medication, copies of all relevant reports and laboratory test results, comments on the results, and any AEs mentioned.

The investigator signed the name and date at the designated location of the case report form via the electronic signature function of the EDC system. These signatures indicate that the investigator has checked or reviewed the data, data queries and site notification, and agreed to the form.

All information and other materials used by subjects and researchers must be in clear and understandable vocabulary and language.

9.4.1.2 Data management

To ensure the quality of clinical data for all subjects and sites, subject data will be reviewed for clinical data management. When checking the case report form data electronically and manually, and electronically using the internal programmed data rules electronically, edit the checks and questions established for data entry in the EDC system. Post-entry verification was performed as described in the Data Management Plan. The doubt arising by the rules and raised by the auditor will arise within the EDC application. This review process will check the consistency, omissions and any apparent differences in subject data. In addition, data compliance with the protocol and the GCP will be reviewed. To address all issues arising during the clinical data management review, case sheet questions will be addressed and resolved within the EDC application.

Data obtained from external (e. g. central laboratory) will be consistent with the clinical database. Serious adverse events in the clinical database will be consistent with the safety database.

All AEs were encoded using MedDRA. Concomitant medications and previous oncology treatments selected per the World Health Organization Drug Dictionary (WHO-DD) reference catalogue are also documented in the Case Report Form.

9.4.2 Study data retained

The investigator will keep a signed list of appropriately qualified persons with research responsibilities. All persons authorized to enter or modify to the case report form are included in the signature list.

Source documents refer to the original documents, data and records from which the subject's case report form data are obtained. These documents include, but are not limited to, hospital records, clinical and outpatient medical records, laboratory testing and pharmacy records, diaries, microfilms, X-rays, and letters. It is the responsibility of the investigator and investigator to maintain a complete central documentation archiving system (trial master document) for all study related (critical) documents for ready inspection by representatives of the appropriate regulatory authorities. Key documents include:

Subject file, containing the completed CRF informed consent form and a copy of the supporting source document (if available). For studies using EDC, at the end of the study, a PDF file (portable document format) was generated for each subject's data (case report form, doubt), kept in the trial master file.

Study documents, containing copies of the protocol and all amendments, investigator's manual, and relevant critical documents required before the start of the clinical study.

Records related to study medication, including site receipt, accountability notes, final reconciliation and correspondence.

In addition, all the original documents supporting the entries in the case report form must be retained and easily accessible. All key documents will be maintained by the research institution until at least 5 years or more after completion of the study (if specified in other applicable regulations or requirements). No study documents will be destroyed until written consent between the investigators.

9.5 Conflict of interest statement (must)

See the Interest and Conflict Statement document

10. References (must)

- Mojgan Ahmadzadeh, Laura A Johnson, Bianca Heemskerk, John R Wunderlich, Mark E Dudley, Donald E White, Steven A Rosenberg.Tumor antigen-specific CD8 T cells infiltrating the tumor

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- Philipp Holliger, Peter J Hudson.Engineered antibody fragments and the rise of single domains.Nat Biotechnol.2005 Sep;23(9):1126-36. doi: 10.1038/nbt1142.
- Michael A Curran, Welby Montalvo, Hideo Yagita, James P Allison.PD-1 and CTLA-4 combination blockade expands infiltrating T cells and reduces regulatory T and myeloid cells within B16 melanoma tumors.Proc Natl Acad Sci U S A.2010 Mar 2;107(9):4275-80. doi: 10.1073/pnas.0915174107. Epub 2010 Feb 16.
- Drew M.Pardoll.The blockade of immune checkpoints in cancer immunotherapy.Nature Reviews Cancer volume 12, pages252–264 (2012).