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Phase II study of KN046 in patients with thymic carcinoma who failed immune checkpoint inhibitors

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WHOLE BLOOD SAMPLES WILL BE STORED IN -80 C WITHIN 16 HOURS TO PRESERVE NUCLEIC ACID QUALITY. FORMALIN-FIXED PARAFFIN-EMBEDDED (FFPE) UNSTAINED SECTIONS WILL BE STORED IN +4 C AND FFPE BLOCKS WILL BE STORED AT ROOM TEMPERATURE. 58

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Statement of Compliance

(1) The trial will be carried out in accordance with International Conference on Harmonization Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

Confidentiality Statement

This document is confidential and is to be distributed for review only to investigators, potential investigators, consultants, study staff, and applicable independent ethics committees or institutional review boards. The contents of this document shall not be disclosed to others without written authorization from WCM.

List of Abbreviations

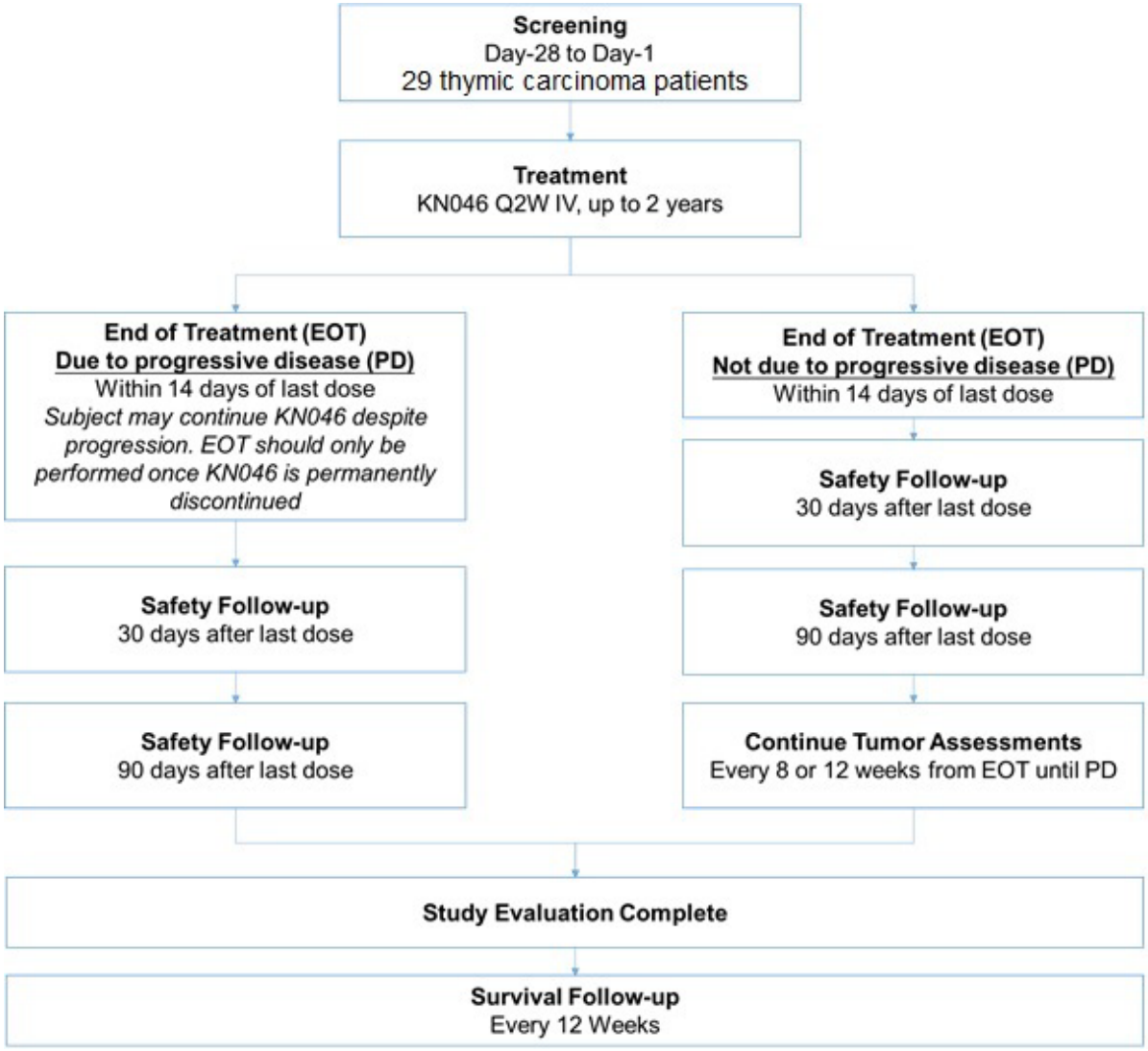
All abbreviations used throughout the protocol must be defined. Add additional abbreviations specific to protocol.

AE	Adverse Event
CFR	Code of Federal Regulations
CRF	Case Report Form
CTSC	Clinical Translational Science Center
DSMB	Data Safety Monitoring Board
DSMP	Data Safety Monitoring Plan
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act of 1996
HRBFA	Human Research Billing Analysis Form
HUD	Humanitarian Use Device
ICF	Informed Consent Form
IDE	Investigational Device Exemption
IND	Investigational New Drug
IRB	Institutional Review Board
PHI	Protected Health Information
PI	Principal Investigator
REDCap	Research Electronic Data Capture
SAE	Serious Adverse Event
SUSAR	Suspected Unexpected Serious Adverse Reaction
UIRTSO	Unanticipated Problem Involving Risks to Subjects or Others
WCM	Weill Cornell Medicine

1. Protocol Summary

Full Title:	Phase II study of KN046 in patients with thymic carcinoma who failed immune checkpoint inhibitors
Short Title:	KN046 in thymic cancer with prior IO
Clinical Phase:	II
Principal Investigator:	Giuseppe Giaccone, MD PhD
Study Description:	This study will assess the safety and efficacy of KN046 in patients with advanced thymic carcinoma who progressed after prior treatment with immune checkpoint inhibitors
Sample Size:	N= 29
Enrollment:	This study will enroll 29 patients
Study Population:	These are patients with advanced thymic carcinoma who have had progression after treatment with chemotherapy and an immune checkpoint inhibitor. They have no prior or current history of autoimmune disorders.
Enrollment Period:	24 months
Study Design:	Open-label, single arm, single center non-randomized Phase II study to investigate the efficacy and safety of KN046 in patients with advanced thymic carcinoma who have progressed on prior immune checkpoint inhibitor therapy. Subjects will be treated with KN046 5 mg/kg q2wk
Description of Sites/ Facilities Enrolling Participants:	Weill Cornell Medicine/New York Presbyterian Hospital
Study Duration:	7/2024
Participant Duration:	24 months
Study Agent/Device Name	KN046
Intervention Description:	KN046 will be given intravenously at 5 mg/kg every 2 weeks. A cycle is defined as 2 treatments (28 days). Treatment will be until progression or excessive toxicity for up to 2 years.
Primary Objective:	To evaluate the anti-tumor activity of KN046 in subjects with thymic carcinoma as measured by overall response rate
Secondary Objectives:	To assess the safety and tolerability of KN046
Exploratory Objectives:	To explore the association of biomarkers (including, but not limited to, PD-L1 expression, tumor immune microenvironment determined by multiplex IHC, tumor mutational burden (TMB), T-cell inflamed gene expression profile (GEP)) and clinical efficacy parameters To characterize the safety laboratory results (AChR autoantibody and CPK) and the occurrence of adverse events of interest
Endpoints:	Response rate, progression-free survival, overall survival

1.1 Schema


Screening
Day-28 to Day-1
29 thymic carcinoma patients
Treatment
KN046 Q2W IV, up to 2 years
End of Treatment (EOT)
Due to progressive disease (PD)
Within 14 days of last dose
Subject may continue KN046 despite progression. EOT should only be performed once KN046 is permanently discontinued
Safety Follow-up
30 days after last dose
Safety Follow-up
90 days after last dose
End of Treatment (EOT)
Not due to progressive disease (PD)
Within 14 days of last dose
Safety Follow-up
30 days after last dose
Safety Follow-up
90 days after last dose
Continue Tumor Assessments
Every 8 or 12 weeks from EOT until PD
Study Evaluation Complete
Survival Follow-up
Every 12 Weeks

1.2 Study Objectives

1.2.1 Primary Objectives

- To evaluate the anti-tumor activity of KN046 in subjects with thymic carcinoma as measured by overall response rate

1.2.2 Secondary Objectives

- To assess the safety and tolerability of KN046 in thymic carcinoma

1.2.3 Exploratory Objectives

- To explore the association of biomarkers (including, but not limited to, PD-L1 expression, tumor immune microenvironment determined by multiplex IHC, tumor mutational burden (TMB), T-cell inflamed gene expression profile (GEP)) and clinical efficacy parameters
- To characterize the safety laboratory results (AChR and MusK autoantibody and CPK) and the occurrence of adverse events of interest

2. Background

2.1 Thymic carcinomas

Thymic epithelial tumors (TETs) are rare tumors of the thymic gland. Surveillance, Epidemiology, and End Results (SEER) and the EURopean CAncer REgistry (EUROCARE-5) data suggests that 1.5 malignant thymic tumors occur for every 1,000,000 person-years, with approximately 400-600 new cases each year in the United States. Thymic malignancies are generally divided into thymomas (WHOA A-B) and thymic carcinomas (WHO C) (for review, see (1, 2)). Amongst these subtypes, thymic carcinomas are the most aggressive histological type of TETs, are rare, and are associated with a particularly poor prognosis. Thymic carcinoma accounts for approximately 10-15% of all TETs. Survival depends on stage at presentation and completeness of resection. They are often not operable with development of distant metastases. In addition, thymic carcinomas are also more resistant to chemotherapy than thymomas. Subsequently, patients with thymic carcinomas have inferior survival with a 5-year survival rate of about 40%.

An interesting phenomenon that differs between thymomas and thymic carcinomas is that autoimmune syndromes are almost exclusively seen in thymomas but are only infrequently seen in thymic carcinomas (3-6). Myasthenia gravis is most commonly seen (30-40%) in thymomas. The majority of patients with thymomas had at least one autoantibody present even if not associated to any autoimmune syndrome whereas, in contrast, only 1 of 4 patients with thymic carcinomas had autoantibodies detectable in the blood (7). In patients treated with cixutumumab (anti-IGF1R), 9 of 37 patients with thymoma developed an autoimmune syndrome while there were none in 12 patients with thymic carcinomas (4). Furthermore, patients with autoimmune syndromes had worse survival (4). Patient selection based on histology is important.

Standard of care systemic therapy for patients with advanced thymic epithelial tumors is chemotherapy. The classic regimens used include PAC (cisplatin, doxorubicin, cyclophosphamide) and carboplatin/paclitaxel (8-10). However, chemotherapy induces responses in <50% of patients with thymic carcinomas.

The Principal Investigator has conducted several phase II studies in patients with TETS over the years and more recently with the use of targeted agents (4, 9, 11-13). Amongst the treatment options listed in the NCCN guidelines after chemotherapy has failed, immune checkpoint inhibitor pembrolizumab and anti-angiogenesis agent sunitinib are particularly promising, with response rates in the range of 20-25% in patients (12, 13). Another angiogenesis inhibitor, lenvatinib, has also demonstrated marked efficacy in a phase II study performed in Japan (14). Durable responses from pembrolizumab has been demonstrated in his previous study (3.2 years median; Giaccone G et al. WCLC 2019)(12).

Thymic carcinomas are the most frequently mutated tumors among TETs. There have been p53 mutations found in 26% of 47 cases analyzed using next generation sequencing (15). Frequency of somatic mutations however is very low in TETs in general. A high tumor mutational burden (TMB) may also make tumors more sensitive to immune checkpoint blockade (16, 17). Tumor cell PD-L1 expression and TMB are established biomarkers of response to immune checkpoint inhibitors. PD-L1 activates the inhibitor signaling pathway on anti-tumor T cells by binding to PD-1, and its expression level influences the activity of anti-PD-1 and anti-PD-L1 immune checkpoint inhibitors. TMB reflects the number of non-synonymous single nucleotide variants in a tumor, which affects the odds of generating antigens that can trigger an antitumor immune response. Higher TMB is associated with improved survival in patients receiving immunotherapy independent of cancer type (18). Robust anti-tumor immune response requires pre-existing presence of tumor-infiltrating lymphocytes (TILs). Therefore, the density of TILs also correlates with patients' response to immunotherapy (19). PD-L1 is commonly expressed in TETs, with 36-100% of tumor cells in thymic carcinoma expressing PD-L1 (20, 21). These results provide a rationale for using PD-1/PD-L1 inhibitors to treat TETs.

Pembrolizumab in pretreated patients with thymic carcinomas resulted in an overall response rate of 22.5%, with median PFS of 4.2 months, and a marked correlation between high PD-L1 expression and better response (12). Nevertheless, pembrolizumab has been associated with a significant increase in immune-related adverse events (irAEs) in 15% (6 of 40) of patients with thymic carcinoma, even after selection for no prior history of an autoimmune disorder (12). Similar response rates (19.2%) and similar incidence of irAEs (15.4%) were observed in a Korean Phase II trial that also used pembrolizumab in 33 patients with TETs, of which 26 had thymic carcinomas (22). Other immune checkpoint inhibitors that have been tested in thymic carcinomas include immune checkpoint PD-L1 inhibitor avelumab (23) and another PD-1 inhibitor nivolumab (24). High PD-L1 expression appears to be associated with a greater likelihood of response and a subset of patients achieve durable responses. Although the responses obtained in my phase II study with pembrolizumab were durable, no patient appeared to be cured, as all patients who responded eventually progressed.

Cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) antibodies are active in melanoma, and have some more limited activity also in lung cancer. In melanoma, combinations of CTLA-4 and PD-1 inhibitors have produced better results than either drug alone, albeit at the cost of more toxicity [3]. However, they cause occurrence of autoimmune disorders in a significant number of patients, higher than with programmed death receptor (PD-1) or programmed death ligand 1 (PD-L1) inhibitors.

There is an urgent need to develop active and well tolerated treatments for patients with advanced thymic carcinoma who have progressed on prior treatment regimens. Combination studies with alternative agents are warranted, with careful patient selection based on tumor biomarkers (e.g. PD-L1 expression in the tumor) or risk of autoimmune disorders in order to minimize toxicity.

2.2 KN046

Recently molecules that combine PD-1 and CTLA-4 moieties have been developed. KN046 is a novel bispecific antibody that can simultaneously bind to both PD-L1 and CTLA-4. KN046 is a dual blocker of both PD-L1 pathway and CTLA-4 pathway with a mechanism of action (MOA) that is the same as the combination therapy with anti-PD-L1 and anti-CTLA-4 agent. It blocks both the PD-1/PD-L1 interaction and CTLA-4 interaction with the costimulatory molecules CD80/CD86, to promote T cell activation. KN046 is genetically engineered and recombinantly expressed in CHO cells. KN046 has a wild type IgG1 Fc portion that maintains Fc-mediated effector functions, antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC).

KN046 is believed to be less toxic with an assumption that the whole molecule can actively target tumor tissue via a much higher affinity of the anti-PD-L1 portion and a weaker affinity for anti-CTLA4. From phase I studies of this molecule, the incidence of irAEs does not appear to be similar to CTLA-4 antibodies, but more similar to PD1 antibodies. Thus, KN046 is believed to have strong potency to activate the immune system and with lower toxicity, which may provide a strategic advantage over the combination of two single agents.

2.3 Rationale

Thymic carcinoma is sensitive to pembrolizumab, however pembrolizumab is not curative and most patients recur. A multicenter study of KN046 is planned by the company in patients with advanced thymic carcinoma who have not received immune checkpoint inhibitors. This study will provide safety and activity data in that population. The present study will test KN046 in patients with advanced thymic carcinoma who failed treatment with immune checkpoint inhibitors.

2.3.1. Rationale for study population

This study will recruit subjects who have histologically proven thymic carcinoma.

The subjects should have inoperable or metastatic disease and have failed at least one prior line of systemic therapy including prior immune checkpoint inhibitor immunotherapy. Platinum-based chemotherapy, especially cisplatin-based chemotherapy is the preferred first line treatment yielding reasonably high response rates. For patients who have failed first line platinum-based chemotherapy, there is no standard of care and often anti-angiogenesis agents or immune checkpoint inhibitors are used as alternative treatment options. After progression on immune checkpoint inhibitor therapy, there is no standard of care and patients need promising candidates for investigational therapies.

This study will exclude subjects who have history of tumor associated autoimmune diseases with the exception of hypothyroidism stable on hormone replacement or Sjogren's syndrome. In early clinical studies from immune checkpoint inhibitors, high rate of immune-related adverse events, mainly Myasthenia gravis and myositis, have been observed mainly in thymoma patients. In Phase I KN046-AUS-001 study, 4 subjects with thymic epithelial tumors were enrolled. Out of 4 patients with TETs, 3 experienced a major response. However, one patient with thymoma with previous diagnosis of ocular myasthenia gravis, developed severe myasthenia symptoms that required hospitalization. This

indicates a safety profile from KN046 that is in line with other I-O. Therefore, subjects with thymomas will be excluded. Also, subjects with history or baseline positive antiacetylcholine receptor (AChR) autoantibody and anti-MuSK autoantibody will be excluded.

2.3.2. Rationale for KN046

KN046 is currently being investigated in the following clinical trials:

- Trial KN046-AUS-001 is "a first-in-human, open-label, multicenter, dose-escalation phase I study to evaluate safety, tolerability, pharmacokinetics, and immunogenicity of KN046 in subjects with advanced solid tumors". This trial is mainly enrolling subjects from Australia.
- Trial KN046-CHN-001 is "A phase Ia/Ib study to evaluate safety, tolerability, pharmacokinetics/pharmacodynamics and anti-tumor activity of KN046 in subjects with advanced solid tumors and hematology malignancies". This trial is enrolling subjects from mainland China.
- Trial KN046-201 is "A phase II study to evaluate the efficacy, safety and tolerability of KN046 in subjects with advanced unresectable or metastatic non-small cell lung cancer who fail platinum-based chemotherapy".
- Trial KN046-202 is "A phase II study to evaluate the efficacy, safety and tolerability of KN046 in combination with standard-of-care chemotherapy as the first line treatment for subjects with advanced unresectable or metastatic non-small cell lung cancer".
- Trial KN046-203 is "A phase II study to evaluate the efficacy, safety and tolerability of KN046 as a monotherapy or in combination with standard-of-care chemotherapy for the treatment of subjects with advanced unresectable or metastatic triple-negative breast cancer".
- Trial KN046-204 is "A phase II study to evaluate the efficacy, safety and tolerability of KN046 as a monotherapy as a late line treatment for subjects with locally advanced unresectable or metastatic esophageal squamous cell carcinoma".

2.3.2.1 Phase I data from trial KN046-AUS-001

A Phase I, open-label, multiple-ascending dose-escalation and expansion Trial KN046-AUS-001 is currently ongoing to evaluate the maximum tolerated dose (MTD), recommended phase 2 doses (RP2Ds), biological effective dose (BED), the safety, tolerability and pharmacokinetics (PK) of intravenously administered KN046 in subjects with metastatic or locally advanced solid tumors.

Trial KN046-AUS-001 consists of a dose escalation phase (3+3 design) followed by an expansion phase. The dose escalation phase was designed to provide safety and tolerability, as well as PK data for KN046 at sequential doses ranging from 0.3 to 10.0 mg/kg in subjects with advanced malignancies, for which there are no established standard treatments. As of 20-Jan-2020, enrollment has been completed and 54 subjects have been treated with KN046.

The dose escalation (3 + 3 design) phase included a total of 13 subjects and was performed at the following dose levels:

- Dose level 1: 0.3 mg/kg (Cohort 1), 1 subject treated
- Dose level 2: 1.0 mg/kg (Cohort 2), 3 subjects treated
- Dose level 3: 3.0 mg/kg (Cohort 3), 3 subjects treated

- Dose level 4: 5.0 mg/kg (Cohort 4), 6 subjects treated
- Dose level 5: 10.0 mg/kg (Cohort 5), 3 subjects treated

The 3 + 3 dose escalation algorithm to determine the MTD/RP2Ds/BED is complete and doses of 3.0 and 5.0 mg/kg once every 2 weeks was determined for the tumor treatment expansion cohorts on the basis of safety, PK, preliminary efficacy and ex vivo pharmacodynamics observations.

As of 20-Jan-2020, the dose expansion phase included a total of 14 subjects at 3.0 mg/kg dose level and 24 subjects at 5.0 mg/kg dose level.

- Expansion cohort 1: 3 mg/kg, 14 subjects treated
- Expansion cohort 2: 5 mg/kg, 24 subjects treated

2.3.2.1.1 Safety results of KN046-AUS-001

As of January 20, 2020, a total of 54 subjects were included in the safety data analysis, including 16 and 37 subjects enrolled in the dose escalation and dose expansion, respectively. Median duration of therapy was 11 weeks (range: 2 to 67). In total 13.0% patients discontinued KN046 treatment due to adverse events.

Four DLT events were observed in three subjects, including (i) one subject with grade 3 treatment-related hepatic function abnormalities without bilirubin increase from the 5.0 mg/kg Q2W cohort; and (ii) one subject with grade 3 pruritic erythematous rash, and one subject with grade 3 aspartate aminotransferase increase accompanied by grade 3 arthritis from the 10.0 mg/kg Q2W cohort. The relevant subjects recovered within three weeks. Maximum tolerated dose (MTD) has been declared at 5 mg/kg Q2W.

As of the Data Cut-off Date, 41 (75.9%) out of the 54 subjects had experienced treatment-related adverse events (TRAE) of all grades, and 20 (37.0%) subjects had experienced treatment-related adverse events at grade 3 or higher levels. 14 (25.9%) subjects had experienced treatment-related SAEs and 26 (48.1%) subjects had experienced irAEs, 13 (24.1%) of which were grade 3 or higher levels. The most frequent TRAEs included arthralgia (16.7%), fatigue (14.8%), infusion-related reaction (14.8%), diarrhea (11.1%) and pruritus (11.1%). Skin and subcutaneous tissue disorders and musculoskeletal and connective tissue disorders were the most frequent irAEs. The TRAE and irAEs were not found to occur in a dose-dependent manner up to 5 mg/kg Q2W, and neither the number nor severity of TRAE or irAEs was exacerbated due to dose escalation at the RP2D or lower levels.

4 subjects with thymic neoplasms were enrolled in KN046-AUS-001. 2 out 4 patients are still under treatment (340+ and 240+ days). 1 patient (BOR SD) had spinal injury and off treatment due to this treatment unrelated AE. The patient had been on treatment for 146 days before KN046 withdrawal. One patient had baseline ocular MG as paraneoplastic disease to underlying advanced thymoma and enrolled (the patient did not undergo thymectomy). After 8 KN046 doses (Q2W), the patient developed ocular symptoms and then generalized symptoms requiring intensive care. The investigator considered this SAE as disease related due to rapid elevation of anti-acetylcholine receptor levels indicating antibody mediated rather T cell mediated which was thought to be unusual as a checkpoint inhibitor related toxicity. Imaging at that time showed slow and steady increase (having 13% increase in target lesion from baseline) and lack of other organ specific immune related adverse events. The

patient was withdrawn from KN046 treatment and developed partial response thereafter. This SAE was completely recovered.

Table 2-1 Subject disposition for Trial KN046-AUS-001 (Safety Population)

	0.3 mg/kg Q2W (N = 1)	1.0 mg/kg Q2W (N = 3)	3.0 mg/kg Q2W (N = 17)	5.0 mg/kg Q2W (N = 30)	10.0 mg/kg Q2W (N = 3)	Total (N = 54)
Subjects enrolled	1 (100%)	3 (100%)	17 (100%)	30 (100%)	3 (100%)	54 (100%)
Subjects dosed	1 (100%)	3 (100%)	17 (100%)	30 (100%)	3 (100%)	54 (100%)
Treatment ongoing at data cut-off	0	0	1 (5.9%)	7 (23.3%)	0	8 (14.8%)
Treatment termination	1 (100%)	3 (100%)	15 (88.2%)	22 (73.3%)	3 (100%)	44 (81.5%)
Confirmed disease progression	1 (100%)	2 (66.7%)	10 (58.8%)	12 (40.0%)	1 (33.3%)	26 (48.1%)
Intercurrent illness that prevents further administration of treatment	0	0	0	1 (3.3%)	0	1 (1.9%)
Unacceptable adverse experiences	0	1 (33.3%)	0	5 (16.7%)	1 (33.3%)	7 (13.0%)
Subject withdraws consent	0	0	1 (5.9%)	1 (3.3%)	1 (33.3%)	3 (5.6%)
If in the opinion of the Investigator, a change or discontinuation of therapy would be in the best interest of the subject	0	0	3 (17.6%)	2 (6.7%)	0	5 (9.3%)
Death	0	0	1 (5.9%)	0	0	1 (1.9%)
Other	0	0	0	1 (3.3%)	0	1 (1.9%)

Note: 1. Percentages are based on the number of subjects of each dose level in the evaluable analysis set.
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Table 2-2 Safety summary for Trial KN046-CHN-001 (Safety Population)

	0.3 mg/kg Q2W (N = 1)	1.0 mg/kg Q2W (N = 3)	3.0 mg/kg Q2W (N = 17)	5.0 mg/kg Q2W (N = 30)	10 mg/kg Q2W (N = 3)	Total (N = 54)
Number of TEAE	5	35	153	271	34	498
Subjects with at least 1 TEAE	1 (100%)	3 (100%)	17 (100%)	28 (93.3%)	3 (100%)	52 (96.3%)
Related to KN046	1 (100%)	2 (66.7%)	13 (76.5%)	22 (73.3%)	3 (100%)	41 (75.9%)
Subjects with at least 1 CTCAE Grade ≥ 3 TEAE	0	2 (66.7%)	11 (64.7%)	19 (63.3%)	3 (100%)	35 (64.8%)
Related to KN046	0	2 (66.7%)	4 (23.5%)	11 (36.7%)	3 (100%)	20 (37.0%)
Subjects with at least 1 DLT Event	0	0	0	1 (3.3%)	2 (66.7%)	3 (5.6%)
Subjects with at least 1 irAE	0	2 (66.7%)	9 (52.9%)	12 (40.0%)	3 (100%)	26 (48.1%)
Subjects with at least 1 CTCAE Grade ≥ 3 irAE	0	1 (33.3%)	3 (17.6%)	6 (20.0%)	3 (100%)	13 (24.1%)
Subjects with at least 1 Infusion Reaction	0	1 (33.3%)	3 (17.6%)	4 (13.3%)	0	8 (14.8%)
Subjects with at least 1 CTCAE Grade ≥ 3 Infusion Reaction	0	0	0	0	0	0
Subjects with at least 1 Treatment-emergent SAE	0	1 (33.3%)	9 (52.9%)	14 (46.7%)	2 (66.7%)	26 (48.1%)
Related to KN046	0	1 (33.3%)	4 (23.5%)	7 (23.3%)	2 (66.7%)	14 (25.9%)
Subjects with at least 1 CTCAE Grade ≥ 3 Treatment-emergent SAE	0	1 (33.3%)	7 (41.2%)	12 (40.0%)	1 (33.3%)	21 (38.9%)
Related to KN046	0	0	3 (17.6%)	6 (20.0%)	1 (33.3%)	10 (18.5%)
Subjects with at least 1 TEAE Leading to Drug Withdrawn	0	1 (33.3%)	1 (5.9%)	7 (23.3%)	1 (33.3%)	10 (18.5%)
Related to KN046	0	1 (33.3%)	1 (5.9%)	4 (13.3%)	1 (33.3%)	7 (13.0%)
Subjects with TEAE Leading to Death	0	0	0	2 (6.7%)	0	2 (3.7%)
Related to KN046	0	0	0	0	0	0

Note: 1. Percentages are based on the number of subjects of each dose level in the safety analysis set. 2. MedDRA 22.0 3. CTCAE 4.03

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Table 2-3 Treatment related TEAEs (TRAEs) for Trial KN046-AUS-001 (Safety Population)

	0.3 mg/kg Q2W (N = 1)		1.0 mg/kg Q2W (N = 3)		3.0 mg/kg Q2W (N = 17)		5.0 mg/kg Q2W (N = 30)		10.0 mg/kg Q2W (N = 3)		Total (N = 54)	
Preferred Term	All grades	Grade≥3	All grades	Grade≥3	All grades	Grade≥3	All grades	Grade≥3	All grades	Grade≥3	All grades	Grade≥3
Subjects with at least 1 KN046 related TEAE	1 (100%)	0	2 (66.7%)	2 (66.7%)	13 (76.5%)	4 (23.5%)	22 (73.3%)	11 (36.7%)	3 (100%)	3 (100%)	41 (75.9%)	20 (37.0%)
Arthralgia	0	0	1 (33.3%)	0	4 (23.5%)	0	4 (13.3%)	1 (3.3%)	0	0	9 (16.7%)	1 (1.9%)
Fatigue	0	0	0	0	0	0	7 (23.3%)	0	1 (33.3%)	1 (33.3%)	8 (14.8%)	1 (1.9%)
Infusion related reaction	0	0	0	0	4 (23.5%)	0	4 (13.3%)	1 (3.3%)	0	0	8 (14.8%)	1 (1.9%)
Diarrhea	0	0	0	0	2 (11.8%)	0	2 (6.7%)	0	2 (66.7%)	0	6 (11.1%)	0
Pruritus	0	0	0	0	3 (17.6%)	1 (5.9%)	3 (10.0%)	0	0	0	6 (11.1%)	1 (1.9%)
Alanine aminotransferase increased	0	0	0	0	1 (5.9%)	0	1 (3.3%)	1 (3.3%)	2 (66.7%)	0	4 (7.4%)	1 (1.9%)
Flushing	0	0	0	0	1 (5.9%)	0	3 (10.0%)	1 (3.3%)	0	0	4 (7.4%)	1 (1.9%)
Nausea	0	0	1 (33.3%)	0	1 (5.9%)	0	1 (3.3%)	1 (3.3%)	1 (33.3%)	0	4 (7.4%)	1 (1.9%)
Pyrexia	0	0	1 (33.3%)	0	0	0	2 (6.7%)	0	1 (33.3%)	0	4 (7.4%)	0
Aspartate aminotransferase increased	0	0	0	0	0	0	1 (3.3%)	0	2 (66.7%)	1 (33.3%)	3 (5.6%)	1 (1.9%)
Hyperthyroidism	0	0	1 (33.3%)	0	1 (5.9%)	0	1 (3.3%)	0	0	0	3 (5.6%)	0
Myalgia	0	0	0	0	1 (5.9%)	0	2 (6.7%)	0	0	0	3 (5.6%)	0
Rash	0	0	0	0	0	0	3 (10.0%)	0	0	0	3 (5.6%)	0
Transaminases increased	0	0	0	0	1 (5.9%)	0	2 (6.7%)	0	0	0	3 (5.6%)	0
Abdominal pain	0	0	0	0	0	0	1 (3.3%)	0	1 (33.3%)	0	2 (3.7%)	0

Note: 1. Percentages are based on the number of subjects of each dose level in the safety analysis set. 2. MedDRA 22.0 3. CTCAE 4.03

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Table 2-4 Immune-related AEs for Trial KN046-AUS-001 (Safety Population)

	0.3 mg/kg Q2W (N = 1)		1.0 mg/kg Q2W (N = 3)		3.0 mg/kg Q2W (N = 17)		5.0 mg/kg Q2W (N = 30)		10.0 mg/kg Q2W (N = 3)		Total (N = 54)	
Preferred Term	All grades	Grade≥3	All grades	Grade≥3	All grades	Grade≥3	All grades	Grade≥3	All grades	Grade≥3	All grades	Grade≥3
Subjects with at least 1 irAE	0	0	2 (66.7%)	1 (33.3%)	9 (52.9%)	3 (17.6%)	12 (40.0%)	6 (20.0%)	3 (100%)	3 (100%)	26 (48.1%)	13 (24.1%)
Arthralgia	0	0	1 (33.3%)	0	2 (11.8%)	0	2 (6.7%)	1 (3.3%)	0	0	5 (9.3%)	1 (1.9%)
Infusion related reaction	0	0	0	0	3 (17.6%)	0	2 (6.7%)	0	0	0	5 (9.3%)	0
Pruritus	0	0	0	0	3 (17.6%)	0	1 (3.3%)	0	0	0	4 (7.4%)	0
Transaminases increased	0	0	0	0	1 (5.9%)	0	3 (10.0%)	0	0	0	4 (7.4%)	0
Alanine aminotransferase increased	0	0	0	0	0	0	1 (3.3%)	1 (3.3%)	1 (33.3%)	0	2 (3.7%)	1 (1.9%)
Aspartate aminotransferase increased	0	0	0	0	0	0	1 (3.3%)	0	1 (33.3%)	0	2 (3.7%)	0
Autoimmune arthritis	0	0	0	0	1 (5.9%)	1 (5.9%)	1 (3.3%)	0	0	0	2 (3.7%)	1 (1.9%)
Autoimmune myositis	0	0	0	0	0	0	2 (6.7%)	2 (6.7%)	0	0	2 (3.7%)	2 (3.7%)
Diarrhea	0	0	0	0	2 (11.8%)	0	0	0	0	0	2 (3.7%)	0
Hepatic function abnormal	0	0	1 (33.3%)	1 (33.3%)	0	0	1 (3.3%)	1 (3.3%)	0	0	2 (3.7%)	2 (3.7%)
Hepatitis	0	0	0	0	1 (5.9%)	0	1 (3.3%)	0	0	0	2 (3.7%)	0
Hyperthyroidism	0	0	1 (33.3%)	0	1 (5.9%)	0	0	0	0	0	2 (3.7%)	0
Myalgia	0	0	0	0	1 (5.9%)	0	1 (3.3%)	0	0	0	2 (3.7%)	0
Myositis	0	0	0	0	0	0	1 (3.3%)	0	1 (33.3%)	0	2 (3.7%)	0

Note: 1. Percentages are based on the number of subjects of each dose level in the safety analysis set.□ 2. MedDRA 22.0□ 3. CTCAE 4.03

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2.3.2.1.2 Efficacy results of KN046-AUS-001

All subjects enrolled in this study had previously failed standard-of-care treatments. As of the Data Cut-off Date, there were 35 evaluable subjects. The efficacy results showed that among the 35 evaluable subjects, the ORR (defined as the proportion of subjects with a BOR of confirmed or unconfirmed CR or PR), was 16.7% (95% CI 7.0, 31.4). At recommended Phase 2 dose levels (3 mg/kg Q2W and 5 mg/kg Q2W), the ORR was 15.4% (95% CI: 1.9, 45.4) and 20.8% (95% CI: 7.1, 42.2), respectively.

4 subjects with thymic neoplasms were enrolled in KN046-AUS-001 (stage IV thymoma 2; thymic carcinoma 2). 3 subjects obtained complete response (n = 1) or partial response (n = 2). 1 thymoma patient obtained stable disease. KN046 showed preliminary efficacy in this study population.

Table 2-5 Efficacy Summary for Trial KN046-AUS-001 (Efficacy Population)

	0.3 mg/kg Q2W (N = 1)	1.0 mg/kg Q2W (N = 3)	3.0 mg/kg Q2W (N = 13)	5.0 mg/kg Q2W (N = 24)	10.0 mg/kg Q2W (N = 1)	Total (N = 42)
Best Overall Response						
Complete Response (CR)	0	0	1 (7.7%)	0	0	1 (2.4%)
Partial Response (PR)	0	0	0	2 (8.3%)	0	2 (4.8%)
Unconfirmed Complete Response (uCR)	0	0	0	0	0	0
Unconfirmed Partial Response (uPR)	0	0	1 (7.7%)	3 (12.5%)	0	4 (9.5%)
Stable Disease (SD)	0	1 (33.3%)	2 (15.4%)	12 (50.0%)	0	15 (35.7%)
Progressive Disease (PD)	1 (100%)	2 (66.7%)	9 (69.2%)	7 (29.2%)	1 (100%)	20 (47.6%)
Objective Response Rate (ORR)	0	0	2 (15.4%)	5 (20.8%)	0	7 (16.7%)
95% CI	0.0%, 97.5%	0.0%, 70.8%	1.9%, 45.4%	7.1%, 42.2%	0.0%, 97.5%	7.0%, 31.4%
Disease Control Rate (DCR)	0	1 (33.3%)	4 (30.8%)	17 (70.8%)	0	22 (52.4%)
95% CI	0.0%, 97.5%	0.8%, 90.6%	9.1%, 61.4%	48.9%, 87.4%	0.0%, 97.5%	36.4%, 68.0%

Note: 1. Percentages are based on the number of subjects of each dose level in the evaluable analysis set.
2. ORR=CR+PR+uCR+uPR.
3. DCR=CR+PR+uCR+uPR+SD.
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2.3.1.1.3 Pharmacokinetic results of KN046-AUS-001

Trial KN046-AUS-001 was performed in Australia and enrolled mainly Caucasian patients. The table below displays the main PK parameters that were evaluated after the first dose in Trial KN046-AUS-001. After a single dose, the terminal half-life does not appear to be dose-dependent and ranges from 100.8 to 181.8 hours across dose ranges of 3.0 to 10 mg/kg. Formal dose proportionality has not been performed. From exploratory analysis, it appears that both C_{max} and AUC_{inf} increase with increasing dose across the dose range of 0.3 to 10.0 mg/kg.

Table 2-6 Summary of Pharmacokinetic Parameters on Cycle 1 Day 1 (KN046-AUS-001)

PK parameters	0.3 mg/kg Q2W (N=1)	1.0 mg/kg Q2W (N=3)	3.0 mg/kg Q2W (N=17)	5.0 mg/kg Q2W (N=16)	10.0 mg/kg Q2W (N=2)
AUC_{inf} (ng*h/mL)					
Mean (SD)	505552	2463669 (712624.2)	8520038.8 (2472946.6)	13675607 (3908026.9)	17917942 (3326685.7)
Median	505552	2540594	7956885	13712441	17917942
Geometric Mean	505552	2390699.1	8198420.7	13141043	17762861

PK parameters	0.3 mg/kg Q2W (N=1)	1.0 mg/kg Q2W (N=3)	3.0 mg/kg Q2W (N=17)	5.0 mg/kg Q2W (N=16)	10.0 mg/kg Q2W (N=2)
C_{max} (ng/mL)					
Mean (SD)	6446	25586.7 (10153.2)	96308.8 (96041.7)	119118.7 (41359.7)	148228 (48202.1)
Median	6446	25292	71716	105547	148228
Geometric Mean	6446	24183.6	79423.8	113315.1	144256.1
Terminal $T_{1/2}$ (h)					
Mean (SD)	59	100.8 (19.9)	165.5 (45.1)	181.8 (52.5)	170.5 (0.7)
Median	59	98	164	183.5	170.5
Geometric Mean	59	99.5	159.1	172.7	170.5
CL (mL/h)					
Mean (SD)	35.6	30.0 (1.7)	28.6 (7.2)	26.3 (6.2)	31.0 (5.4)
Median	35.6	30.3	27.7	25.9	31.0
Geometric Mean	35.6	29.9	27.8	25.6	30.7

2.3.2.2. Phase I data from trial KN046-CHN-001

KN046-CHN-001 is a Phase Ia/Ib, open-label, multiple-ascending dose-escalation and expansion trial currently ongoing to evaluate the MTD, RP2Ds, the safety, tolerability, PK, pharmacodynamics (PD) and immunogenicity of KN046 in subjects with metastatic or locally advanced solid tumors. Trial KN046-CHN-001 plans to recruit over 300 subjects.

Trial KN046-CHN-001 consists of a dose escalation and expansion phase (mTPI-2 design) [25] followed by a cohort expansion phase in multiple solid tumor indications. The dose escalation and expansion phase was designed to provide safety and tolerability, as well as PK and PD data for KN046 at sequential doses ranging from 1.0 to 5.0 mg/kg in subjects with advanced malignancies, for which there are no established standard treatments.

As of January 20, 2020, the dose escalation and dose expansion phase (Phase Ia) included a total of 88 subjects and was performed at the following dose levels:

- Dose level 1: 1.0 mg/kg Q2W (Cohort 1), 1 subject treated
- Dose level 2: 3.0 mg/kg Q2W (Cohort 2), 30 subjects treated;
- Dose level 3: 5.0 mg/kg Q2W (Cohort 3), 45 subjects treated; 30 subjects planned
- Dose level 4: 5.0 mg/kg Q3W (Cohort 4a), 6 subjects treated
- Dose level 4: 300 mg Q3W (Cohort 4b), 6 subjects treated

In the cohort expansion phase (Phase Ib and Ic), a total of 4 cohorts are planned to assess the efficacy, safety and predictive biomarker of KN046 in the following tumor types:

- ≥Second line treatment of unresectable/metastatic melanoma

- ≥Third line treatment of unresectable/metastatic NPC
- Second line treatment of unresectable/metastatic UC
- Second line treatment of ED-SCLC

Importantly, availability of tumor tissue is required to participate in the dose and cohort expansion phases of this trial. The objectives of these treatment expansion cohorts are to:

- Establish the clinical activity of KN046 as a monotherapy in each indication.
- Confirm the safety profile observed during the dose escalation phase.
- Explore the potential correlation between biomarker (TMB, GEP, and a pattern of expression of PD-L1 at the surface of the tumor cells or at the surface of infiltrating immune cells) and clinical activity for the purpose of developing a companion diagnostic specific to each of these tumors.

In order to detect signals of clinical activity and to provide additional safety, PK, PD, and biomarker information, and to guide further clinical evaluation of KN046, further expansion in biomarker enriched population in Trial KN046-CHN-001 are planned as follows:

- Biomarker positive (DDR, TMB) UC
- Biomarker positive (TMB, TMB/GEP) ED-SCLC

Primary objective for escalation cohort is to assess the DLTs of KN046 in Chinese subjects and expansion cohorts is to assess the best overall response (BOR) and duration of response (DOR) according to RECIST 1.1 per IRC assessment.

Recommended phase 2 doses (RP2Ds) have been determined as 3 and 5 mg/kg Q2W. As of January 20, 2020, a total of 88 subjects had received KN046 either in the dose escalation or in the dose expansion phase (1, 30, 45, 6 and 6 subjects received 1.0 mg/kg Q2W, 3.0 mg/kg Q2W, 5.0 mg/kg Q2W, 5.0 mg/kg Q3W and 300 mg, respectively).

2.3.2.2.1. Safety results of Phase I KN046-CHN-001

As of January 20, 2020, 88 subjects enrolled in the dose escalation study, including 13 and 65 subjects enrolled in Phase Ia dose escalation and dose expansion stages, respectively. 88 subjects were included in the safety data analysis. Median duration of therapy was 12 weeks (range: 2 to 54). The median relative dose intensity of KN046 was 100% (range: 99.5% to 100%). In total 5.7% patients discontinued KN046 treatment due to adverse event. The results have exhibited favorable safety profile of our KN046 and the safety results showed no significant differences from the KN046-AUS-001 trial.

No subjects experienced DLTs during dose escalation phase. MTD was not reached at 5.0 mg/kg. 5.0 mg/kg Q2W was determined to be the RP2D.

As of January 20,2020, 74 (84.1%) out of the 88 subjects had experienced treatment-related adverse events of all grades and nine (10.2%) subjects had experienced treatment- related adverse events at grade 3 or higher levels. The most frequently observed TRAEs was rash reported in 30 subjects (34.1%), followed by pruritus in 28 subjects (31.8%), alanine aminotransferase increased (ALT) in 17 subjects

(19.3%), fatigue in 15 subjects (17.0%), infusion related reaction in 15 subjects (17.0%), aspartate aminotransferase (AST) increased in 12 subjects (13.6%), pyrexia in 11 subjects (12.5%) and arthralgia in 9 subjects (102%). 9 of the 88 subjects (10.2%) experienced at least one ≥Grade 3 TRAEs. These included event terms of infusion related reaction (4 subjects; 4.5%), AST increased (3 subjects; 3.4%), rash (2 subjects; 2.3%), ALT increased (1 subject; 1.1%), anemia (1 subject; 1.1%), hyponatremia (1 subject; 1.1%) and transaminase increase (1 subject; 1.1%). No Grade 5 TRAEs were observed. Four (4.5%) subjects experienced treatment-related SAE. The event terms of the treatment-related serious TEAEs included infusion related reaction (2 subjects; 2.3%), ALT increased (1 subject; 1.1%), AST increased (1 subject; 1.1%), pneumonitis (1 subject; 1.1%), rash (1 subject; 1.1%) and transaminases increased (1 subject; 1.1%). 40 (45.5%) subjects had experienced irAEs, Four (4.5%) were grade 3. The event terms of these irAEs include rash (2 subjects; 2.3%), ALT increased (1 subject; 1.1%), AST increased (1 subject; 1.1%), pneumonitis (1 subject; 1.1%) and transaminase increased (1 subject; 1.1%). None irAE led to death. Similar to the results of the KN046-AUS-001 trial, neither the treatment-related TEAEs nor the irAEs in the dose escalation study of the KN046-CHN-001 trial were found to occur in a dose-dependent manner.

Overall, the TEAE profile was similar across different dose cohorts and the incidences of TEAEs by TEAE category did not increase with increasing dose.

Table 2-7 Subject disposition for Trial KN046-CHN-001 (Safety Population)

Subject disposition	1.0 mg/kg Q2W (n = 1)	3.0 mg/kg Q2W (n = 30)	5.0 mg/kg Q2W (n = 45)	5.0 mg/kg Q3W (n = 6)	300 mg (n = 6)	Total (N = 88)
Subjects remaining on treatment (%)	0	8 (26.7%)	22 (48.9%)	2 (33.3%)	1 (16.7%)	33 (37.5%)
Discontinued, n (%)	1 (100%)	22 (73.3%)	23 (51.1%)	4 (66.7%)	5 (83.3%)	55 (62.5%
Disease progression	1 (100%)	17 (56.7%)	14 (31.1%)	2 (33.3%)	2 (33.3%)	36 (40.9%)
Adverse events	0	2 (6.7%)	3 (6.7%)	0	0	5 (5.7%)
Death	0	0	0	1 (16.7%) [1]	2 (33.3%) [2]	3 (3.4%)
Lost to follow-up	0	1 (3.3%)	1 (2.2%)	0	0	2 (2.3%)
Other reasons [3]	0	2 (6.7%)	5 (11.1%)	1 (16.7%)	1 (16.7%)	9 (10.2%)

1 Death from disease progression
2 One subject died from Acute Respiratory Distress Syndrome; For another subjects, the investigator was not be able to determine the reason for the death
3 Other reasons including eight patients discontinued due to clinical deterioration, one patent discontinued due to investigator determined no longer clinical benefit.

Source: Table 1 Dated 20200213

Table 2-8 Safety summary for Trial KN046-CHN-001 (Safety Population)

CTCAE version 5.0	1.0 mg/kg Q2W (N = 1)	3.0 mg/kg Q2W (N = 30)	5.0 mg/kg Q2W (N = 45)	5.0 mg/kg Q3W (N = 6)	300 mg Q3W (N = 6)	Total (N = 88)
Subjects with at least 1 TEAE	1 (100%)	30 (100%)	44 (97.8%)	6 (100%)	6 (100%)	87 (98.9%)
Related to KN046	1 (100%)	27 (90.0%)	36 (80.0%)	6 (100%)	4 (66.7%)	74 (84.1%)
Subjects with at least 1 CTCAE Grade ≥ 3 TEAE	1 (100%)	14 (46.7%)	9 (20.0%)	2 (33.3%)	4 (66.7%)	30 (34.1%)
Related to KN046	0	6 (20.0%)	2 (4.4%)	1 (16.7%)	0	9 (10.2%)
Subjects with at least 1 IRR	0	7 (23.3%)	6 (13.3%)	2 (33.3%)	0	15 (17.0%)
Subjects with at least 1 irAE	0	20 (66.7%)	15 (33.3%)	5 (83.3%)	0	40 (45.5%)
Subjects with at least 1 CTCAE Grade ≥ 3 irAE	0	4 (13.3%)	0	0	0	4 (4.5%)
Subjects with at least 1 SAE during treatment [2]	1 (100%)	9 (30.0%)	4 (8.9%)	1 (16.7%)	4 (66.7%)	19 (21.6%)
Related to KN046 [3]	0	4 (13.3%)	0	0	0	4 (4.5%)
Subjects with at least 1 TEAE Leading to Drug Withdrawn	0	2 (6.7%)	5 (11.1%)	1 (16.7%)	2 (33.3%)	10 (11.4%)
Related to KN046	0	2 (6.7%)	3 (6.7%)	0	0	5 (5.7%)

CTCAE version 5.0	1.0 mg/kg Q2W (N = 1)	3.0 mg/kg Q2W (N = 30)	5.0 mg/kg Q2W (N = 45)	5.0 mg/kg Q3W (N = 6)	300 mg Q3W (N = 6)	Total (N = 88)
Subjects with at least 1 TEAE Leading to Death	1 (100%)	0	1 (2.2%)	0	3 (50.0%)	5 (5.7%)
Related to KN046	0	0	0	0	0	0

TEAE = treatment emergent adverse event; CTCAE = common terminology criteria for adverse event; IRR = infusion related adverse event; irAE = immune-related adverse event; SAE = serious adverse event.
1 19 subjects experienced 24 SAEs, including Death (2, 2.3%), Infection (2, 2.3%), Infusion related reaction (2, 2.3%), Pneumonitis (2, 2.3%), Acute respiratory distress syndrome (1, 1.1%), Alanine aminotransferase increased (1, 1.1%), Aspartate aminotransferase increased (1, 1.1%), Bone pain (1, 1.1%), Brain edema (1, 1.1%), Cardiac arrest (1, 1.1%), Dysphagia (1, 1.1%), Hemoptysis (1, 1.1%), Hemorrhoidal hemorrhage (1, 1.1%), Hepatic failure (1, 1.1%), Hyponatremia (1, 1.1%), Pleural effusion (1, 1.1%), Pyrexia (1, 1.1%), Rash (1, 1.1%), Tachypnoea (1, 1.1%) and Transaminases increased (1, 1.1%).
2 Four subjects experienced seven treatment-related SAEs, including Infusion related reaction (2, 2.3%), Alanine aminotransferase increased (1, 1.1%), Aspartate aminotransferase increased (1, 1.1%), Pneumonitis (1, 1.1%), Rash (1, 1.1%) and Transaminases increased (1, 1.1%).
Source: Table 5.1 Dated 20200213

Table 2-9 Treatment related TEAEs (TRAEs) for Trial KN046-CHN-001 (all grades with a frequency ≥10%, or any ≥grade 3) (Safety Population)

Preferred Term	1.0 mg/kg Q2W		3.0 mg/kg Q2W		5.0 mg/kg Q2W		5.0 mg/kg Q3W		300 mg Q3W		Total	
	Grade ≥ 3 (N = 1)	Total (N = 1)	Grade ≥ 3 (N = 30)	Total (N = 30)	Grade ≥ 3 (N = 45)	Total (N = 45)	Grade ≥ 3 (N = 6)	Total (N = 6)	Grade ≥ 3 (N = 6)	Total (N = 6)	Grade ≥ 3 (N = 88)	Total (N = 88)
Subjects with at least 1 KN046 related TEAE	0	1 (100%)	6 (20.0%)	27 (90.0%)	2 (4.4%)	36 (80.0%)	1 (16.7%)	6 (100%)	0	4 (66.7%)	9 (10.2%)	74 (84.1%)
Rash	0	0	2 (6.7%)	14 (46.7%)	0	13 (28.9%)	0	3 (50.0%)	0	0	2 (2.3%)	30 (34.1%)
Pruritus	0	0	0	10 (33.3%)	0	14 (31.1%)	0	3 (50.0%)	0	1 (16.7%)	0	28 (31.8%)
Alanine aminotransferase increased	0	0	1 (3.3%)	9 (30.0%)	0	6 (13.3%)	0	1 (16.7%)	0	1 (16.7%)	1 (1.1%)	17 (19.3%)
Fatigue	0	0	0	8 (26.7%)	0	4 (8.9%)	0	3 (50.0%)	0	0	0	15 (17.0%)
Infusion related reaction	0	0	3 (10.0%)	7 (23.3%)	1 (2.2%)	6 (13.3%)	0	2 (33.3%)	0	0	4 (4.5%)	15 (17.0%)
Aspartate aminotransferase increased	0	0	1 (3.3%)	6 (20.0%)	1 (2.2%)	3 (6.7%)	1 (16.7%)	2 (33.3%)	0	1 (16.7%)	3 (3.4%)	12 (13.6%)
Pyrexia	0	0	0	4 (13.3%)	0	7 (15.6%)	0	0	0	0	0	11 (12.5%)
Arthralgia	0	0	0	5 (16.7%)	0	4 (8.9%)	0	0	0	0	0	9 (10.2%)
Anemia	0	0	1 (3.3%)	2 (6.7%)	0	0	0	0	0	0	1 (1.1%)	2 (2.3%)
Hyponatremia	0	0	1 (3.3%)	2 (6.7%)	0	0	0	0	0	0	1 (1.1%)	2 (2.3%)
Transaminases increased	0	0	1 (3.3%)	1 (3.3%)	0	0	0	0	0	0	1 (1.1%)	1 (1.1%)

Source: Table 5.5 Dated 20200213

Table 2-10 Immune-related AEs for Trial KN046-CHN-001 (Safety Population)

	1.0 mg/kg Q2W		3.0 mg/kg Q2W		5.0 mg/kg Q2W		5.0 mg/kg Q3W		300 mg Q3W		Total	
Preferred Term	Grade ≥ 3 (N = 1)	Total (N = 1)	Grade ≥ 3 (N = 30)	Total (N = 30)	Grade ≥ 3 (N = 45)	Total (N = 45)	Grade ≥ 3 (N = 6)	Total (N = 6)	Grade ≥ 3 (N = 6)	Total (N = 6)	Grade ≥ 3 (N = 88)	(N = 88)
Subjects with at least 1 immune related AE	0	0	4 (13.3%)	20 (66.7%)	0	15 (33.3%)	0	5 (83.3%)	0	0	4 (4.5%)	40 (45.5%)
Rash	0	0	2 (6.7%)	12 (40.0%)	0	10 (22.2%)	0	3 (50.0%)	0	0	2 (2.3%)	25 (28.4%)
Pruritus	0	0	0	9 (30.0%)	0	11 (24.4%)	0	3 (50.0%)	0	0	0	23 (26.1%)
Arthralgia	0	0	0	3 (10.0%)	0	2 (4.4%)	0	0	0	0	0	5 (5.7%)
Fatigue	0	0	0	3 (10.0%)	0	0	0	2 (33.3%)	0	0	0	5 (5.7%)
Alanine aminotransferase increased	0	0	1 (3.3%)	2 (6.7%)	0	0	0	0	0	0	1 (1.1%)	2 (2.3%)
Aspartate aminotransferase increased	0	0	1 (3.3%)	2 (6.7%)	0	0	0	0	0	0	1 (1.1%)	2 (2.3%)
Pneumonitis	0	0	1 (3.3%)	2 (6.7%)	0	0	0	0	0	0	1 (1.1%)	2 (2.3%)
Transaminases increased	0	0	1 (3.3%)	1 (3.3%)	0	0	0	0	0	0	1 (1.1%)	1 (1.1%)

Source: Table 5.11 Dated 20200213

2.3.2.2.2 Efficacy results of Phase I KN046-CHN-001

In general, the subjects enrolled in the KN046-CHN-001 trial had previously failed standard-of-care treatments, including subjects who failed prior immune checkpoint inhibitors. As of January 20, 2020, there were 75 evaluable subjects. The efficacy analysis showed that, among the 75 evaluable subjects, nine had confirmed PRs and 27 had SD. 29 of the evaluable subjects remained on the study treatment as of 20-Jan-2020. ORR is 12.0% (95% CI: 5.6, 21.6) in the overall population and 12.5% (95% CI: 2.5, 31.2) in subjects who have failed prior immune checkpoint inhibitors.

As of January 20, 2020, median progression free survival (PFS) was 2.66 (95% CI: 1.3, 5.5) months. Median overall survival (OS) was not reached. PFS rates for 3, 6 and 9 Months were 40.5 (95% CI: 28.2,52.4), 32.1 (95% CI: 19.8,45.1) and 27.5 (95% CI: 14.9,41.8), respectively. OS rates for 6 and 9 months were 74.3 (95% CI: 61.4,83.5) and 65.2 (95% CI: 47.4,78.2), respectively.

In subjects with prior immune checkpoint inhibitor treatments, median progression free survival was 2.69 (95% CI: 1.3,5.5) months. Median overall survival was not reached. PFS rates for 3 and 6 Months were 41.0% (95% CI: 18.5, 62.5) and 21.9% (95% CI: 4.6, 47.3). OS rates for 6 and 9 months were 88% (95% CI: 57.2, 97.1) and 58.7% (95% CI: 8.3, 89.2), respectively.

Table 2-2 Efficacy Summary for Trial KN046-CHN-001 (Efficacy Population)

	1.0 mg/kg Q2W (N = 1)	3.0 mg/kg Q2W (N = 29)	5.0 mg/kg Q2W (N = 36)	5.0 mg/kg Q3W (N = 6)	300 mg Q3W (N = 3)	Total (N = 75)
Best overall response						
Complete response (CR)	0	0	0	0	0	0
Partial response (PR)	0	7 (24.1%)	1 (2.8%)	0	0	8 (10.7%)
Unconfirmed CR (uCR)	0	0	0	0	0	0
Unconfirmed PR (uPR)	0	0	1 (2.8%)	0	0	1 (1.3%)
Stable disease (SD)	0	6 (20.7%)	15 (41.7%)	4 (66.7%)	2 (66.7%)	27 (36.0%)
Progressive disease (PD)	1 (100%)	14 (48.3%)	19 (52.8%)	2 (33.3%)	1 (33.3%)	37 (49.3%)
Not evaluable (NE)	0	2 (6.9%)	0	0	0	2 (2.7%)
Objective response (ORR)	0	7 (24.1%)	2 (5.6%)	0	0	9 (12.0%)
95% CI		10.298, 43.5	0.680, 18.66			5.637, 21.56

Note: ORR=CR+PR+uCR+uPR; DCR=CR+PR+uCR+uPR+SD≥37 days

Table 2-3 Efficacy Summary for Trial KN046-CHN-001 in Subjects Who Failed Prior Immune Checkpoint Inhibitor (Efficacy Population)

	3.0 mg/kg Q2W (N = 3)	5.0 mg/kg Q2W (N = 17)	5.0 mg/kg Q3W (N = 4)	300 mg Q3W (N = 1)	Total (N = 25)
Best overall response	0	0	0	0	0
Complete response (CR)	0	0	0	0	0
Partial response (PR)	1 (33.3%)	1 (5.9%)	0	0	2 (8.0%)
Unconfirmed CR (uCR)	0	0	0	0	0
Unconfirmed PR (uPR)	0	1 (5.9%)	0	0	1 (4.0%)
Stable disease (SD)	1 (33.3%)	6 (35.3%)	3 (75.0%)	0	10 (40.0%)
Progressive disease (PD)	1 (33.3%)	9 (52.9%)	1 (25.0%)	1 (100%)	12 (48.0%)
Not evaluable (NE)	2 (6.9%)	0	0	0	0

	3.0 mg/kg Q2W (N = 3)	5.0 mg/kg Q2W (N = 17)	5.0 mg/kg Q3W (N = 4)	300 mg Q3W (N = 1)	Total (N = 25)
	0	0	0	0	0
Objective response (ORR)	1 (33.3%)	2 (11.8%)	0	0	3 (12.0%)
95% CI	0.840, 90.570	1.458, 36.441	0	0	2.547, 31.219

Note: ORR=CR+PR+uCR+uPR; DCR=CR+PR+uCR+uPR+SD≥37 days

2.3.1.2.3 Pharmacokinetic results of KN046-CHN-001

Trial KN046-CHN-001 was performed in China and enrolled all Chinese subjects. The below table displays the main PK parameters that were evaluated after the first dose in Trial KN046-CHN-001. The preliminary concentrations obtained over time and the clearance during the first dosing interval were similar in Chinese and Caucasian patients. After single dose, both C_{max} and AUC_{inf} increase with increasing dose across the dose range of 1.0 to 5.0 mg/kg drug exposure. Terminal half-life does not appear to be dose-dependent and ranges from 137 to 157.4 hours across dose range of 1.0 to 5 mg/kg.

Table 2-13 Summary of Pharmacokinetic Parameters on Cycle 1 Day 1 (KN046-CHN-001)

PK parameters	1.0 mg/kg Q2W (N=1)	3.0 mg/kg Q2W (N=31)	5.0 mg/kg Q2W (N=18)	5.0 mg/kg Q3W (N=5)	300 mg Q3W (N=5)
AUC_{inf} (ng*h/mL)					
Mean (SD)	1994829	7165351.4 (2866653)	11603361 (3370238)	11526905 (3835867.7)	9247562 (2197379.8)
Median	1994829	6711248	11093661	10746387	8502697
Geometric Mean	1994829	6739073.5	11173134	11013834	9052837.2
C_{max} (ng/mL)					
Mean (SD)	21935	66129.2 (12840.6)	95843.4 (16776.7)	89608.6 (17786.3)	96594.2 (19378.1)
Median	21935	65613	95070	91703	88301
Geometric Mean	21935	64916.7	94434.4	88093.5	95082.8
Terminal $T_{1/2}$ (h)					
Mean (SD)	111	144.4 (70.2)	157.4 (58.5)	137 (91.0)	141.6 (60.9)
Median	111	138	160.5	173	132
Geometric Mean	111	126.4	143.5	106.3	131.8
CL (mL/h)					
Mean (SD)	27.4	28.0 (9.4)	28.4 (9.3)	24.8 (5.2)	33.8 (7.2)
Median	27.4	23.8	25.45	26.8	35.3
Geometric Mean	27.4	26.6	27.1	24.3	33.2

2.4 Risk/Benefit Assessment

The risk-benefit relationship has been carefully considered in the planning of the trial. Based on the clinical data available to date, the conduct of the trial is considered justifiable using the dose established in Trials KN046-AUS-001 and KN046-CHN-001.

2.4.1 Known Potential Risks

The important identified and potential risks with KN046 have been determined based on observations in preclinical toxicity or clinical studies; risks reported with other immune checkpoint inhibitors (anti-PD-1 and anti-PD-L1) and CTLA-4 antibodies; as well as risks generally associated with monoclonal antibodies (mAbs).

Important identified risks:

- Immune-related adverse events (excluding hypersensitivity reaction);
- Infusion related reactions;
- Systemic hypersensitivity reactions.

Important potential risks:

- Immunogenicity (anti-KN046 antibody formation);
- Embryo fetal toxicity

2.4.1.1 Immune-related adverse events

Investigators should be extremely vigilant and be ready to intervene early in the management of irAEs, as the onset of symptoms of irAEs from KN046 treatment (eg, hepatitis) may be subtle. Immune-related AEs have been reported with KN046 and with other anti-PD-1, anti-PD-L1 and anti-CTLA4 antibodies; these are considered consistent with the mechanism of action of immune checkpoint inhibitors.

An immune-related AE can occur shortly after the first dose or several months after the last dose of treatment. All AEs of unknown etiology associated with drug exposure should be evaluated for a possible immune etiology. Efforts should be made to rule out autoimmunity, infection, neoplastic, metabolic disorder, toxin or other etiologic causes prior to classifying an AE as an irAE.

Management guidelines to irAE are provided. Exclusion criteria E09, E10 and E11 will be applied to exclude susceptible subjects. During the study, routine hematologic, chemistry (including creatine phosphokinase) and immune safety assays (including AChR autoantibody and anti-MuSK autoantibody if clinically indicated) are performed at baseline, during the treatment phase and 30- and 90-day safety follow-up. Vital signs and physical examinations are closely monitored according to the study protocol.

From Phase I data of KN046-AUS-001, the most frequent treatment-related adverse events included arthralgia (16.7%), fatigue (14.8%), infusion-related reaction (14.8%), diarrhea (11.1%) and pruritus (11.1%). Skin and subcutaneous tissue disorders and musculoskeletal and connective tissue disorders were the most frequent irAEs. The TRAE and irAEs were not found to occur in a dose-dependent manner up to 5 mg/kg

Q2W, and neither the number nor severity of TRAE or irAEs was exacerbated due to dose escalation at the RP2D or lower levels.

In Phase I data of KN046-CHN-001, the most frequently observed TRAEs was rash reported in 30 subjects (34.1%), followed by pruritus in 28 subjects (31.8%), alanine aminotransferase increased (ALT) in 17 subjects (19.3%), fatigue in 15 subjects (17.0%), infusion related reaction in 15 subjects (17.0%), aspartate aminotransferase (AST) increased in 12 subjects (13.6%), pyrexia in 11 subjects (12.5%) and arthralgia in 9 subjects (102%). 9 of the 88 subjects (10.2%) experienced at least one ≥Grade 3 TRAEs. Similar to the results of the KN046-AUS-001 trial, neither the treatment-related adverse events nor the irAEs in the dose escalation study of the KN046-CHN-001 trial were found to occur in a dose-dependent manner.

Management of irAEs include withholding KN046 until resolution of toxicity to Grade 1 or less. If toxicity is Grade 3 or more, steroids may be used. Further details for management can be found in Section Appendix A.

2.4.1.2. Infusion-related reaction and systemic hypersensitivity reaction

There is no general consensus on the definition of infusion-related reaction. Though technically infusion reactions might be due to hypersensitivity or immune-related reaction, the mechanism of action that leads to such reactions is often not known. For the purpose of this protocol, it is reaction suspected to be related to the infusion of drug, but not classified as immune-related reaction or systemic reaction.

Infusion-related reactions and systemic hypersensitivity reactions are known to occur with protein therapeutic infusions and have been observed in KN046 clinical studies. Acute infusion reactions are defined as any AEs that occur during the infusion or within 2 hours after the infusion is completed. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. As with other protein therapeutics, hypersensitivity reactions usually develop immediately or within a few hours of infusion. However, it might occur weeks later as in serum sickness, a type III hypersensitivity, resulting from high titer of anti-drug antibody. The time of onset of serum sickness is typically 1~2 weeks after commencement of antibody infusion.

Suggested management guidelines to infusion related reactions and hypersensitivity reactions are provided in Section 7.5.1 and Appendix A. Exclusion criterion E15 will be applied to exclude susceptible subjects.

During KN046 treatment, emergency equipment and medication for the treatment of these potential adverse events must be available for immediate use. After completion of KN046 infusion, subjects should be observed for at least 2 hours before being discharged. Grade 2 or greater infusion-related reactions are considered AE of interest and must be reported within 24 hours of identification by the investigator.

2.4.1.3. Other potential risks

KN046 has wide type Fc and maintains antibody-dependent cell-mediated cytotoxicity (ADCC) effect. There is a potential risk of tumor lysis syndrome. Monitoring includes chemistry and hematology assessments.

In addition, women with childbearing potential should apply highly effective method of contraception (with a failure rate of less than 1.0% per year) from first study treatment to 24 weeks after completion of the trial treatment. Investigator must notify the Sponsor / designee in an expedited manner of any pregnancy using the Pregnancy Report Form which should be transmitted according to the same process for SAE reporting.

2.4.2 Known Potential Benefits

KN046 is a bispecific antibody immune checkpoint inhibitor simultaneously targeting two clinically validated immune checkpoints, PD-L1 and CTLA-4, representing a next generation immune-oncology blockbuster drug. In Phase I clinical trials in Australia and China, among all subjects receiving KN046 at 5 mg/kg Q2W (RP2D), the DCR was 77.8% and 69.2% respectively and 10 (55.6%) and 4 (30.8%) subjects had target lesion shrinkage, respectively. These subjects have generally failed at least first-line standard of care. The results from the Phase I clinical trials have shown a favorable safety profile, and early efficacy signals in solid tumors such as nasopharyngeal carcinoma, especially in subjects with high PD-L1 expression.

2.4.3 Assessment of Potential Risks and Benefits

Given the promising antitumor effects of dual blockades from PD-1/PD-L1 and CTLA4 and comprehensive risk management measures applied, the current trial is justified and the benefit of treatment with KN046 in the targeted trial population is considered outweigh the potential risk. This clinical trial will be conducted in compliance with the clinical trial protocol, international conference on harmonization (ICH), good clinical practice (GCP), and the applicable regulatory requirements.

2.5 Correlative Studies Background

Correlative studies analyzing blood, archival tumor, and new tumor biopsies (in patients who develop irAEs) will help identify biomarkers to prognosticate response, toxicity, and correlate outcomes. To validate toxicity markers, we will obtain baseline neutrophil-to-lymphocyte ratio (NLR), absolute lymphocyte count (ALC), inflammatory cytokines (IL-6, IL-10, IFN-γ, TNFα, etc), and Myasthenia gravis autoantibodies. ALC >2000 (26) and NLR <3 (27) correlate with increased risk of irAEs. Inflammatory cytokines help calculate CYTOX score, which predicts early risk of severe irAEs in melanoma patients (28). ctDNA will assessed at baseline, best response and progression. For archival tumors, GEP, RNAseq and WES results will be correlated with clinical outcome and treatment response. We will perform immunohistochemistry for T cells (CD3, CD4, CD8, FoxP3), DC (CD11c), macrophages (CD68), and PD-L1 expression. When feasible, fresh tissue will be used to establish organoids and patient-derived xenograft models for drug testing. TCR sequencing will be performed on tumor, serial blood samples and non-lesional/lesional tissue biopsies in patients who develop irAEs.

Archival tissue or a new biopsy will be used to perform immunohistochemistry for PD-L1 staining. PD-L1 expression and response to treatment will be correlated.

Whenever feasible fresh tissue will be obtained to establish new organoids or cell lines. Cells will be characterized with several immunohistochemistry markers and a genetic level.

Tumor tissues (either fresh and paraffin embedded) will be submitted to Next-Generation sequencing for a selected number of genes. Correlation between number and type of mutations and response to treatment will be studied. Results obtained in new biopsies will be compared to those obtained before systemic treatment, since potentially this could increase or change the mutational spectrum of the tumor.

In patients where a new biopsy will be available, PD-L1 expression will be performed and compared to the archival material, since potentially exposure to systemic treatment might change the expression of this immune checkpoint.

- Correlation between PD-L1 expression in thymic carcinomas and response to KN046 therapy
- Correlation between the type/number of genetic mutations of thymic carcinomas and PD-L1 expression as well as response to KN046
- The impact of genetic heterogeneity of thymic carcinomas on the response to KN046.

3. Study Design

3.1 Overall Design

This is a Phase II, open-label, single-center, single arm study in subjects with advanced thymic carcinoma after failure of platinum-based combination chemotherapy. Subjects should have documented progressive disease after a platinum-based combination chemotherapy and an immune checkpoint inhibitor (PD-1 or PD-L1 antibodies). Subjects will be treated with KN046 at 5 mg/kg Q2W.

For individual subjects, the study begins with a screening period to assess eligibility up to and including 28 days prior to the first dose of KN046.

The treatment period begins on Day 1 of Cycle 1. All subjects will be treated with KN046 at 5 mg/kg Q2W intravenously until progressive disease according to RECIST 1.1, unacceptable toxicity, completion of 2 years of KN046 treatment, start of a new anti-cancer therapy, death, lost follow-up or withdrawal of informed consent, whichever comes first. After completion of 2 years of KN046 treatment, if investigator considers that subject continuing KN046 treatment will obtain clinical benefit, KN046 will be administered on a compassionate basis under the treating physician's responsibility. Treatment of KN046 beyond initial investigator evaluated progression (either clinical or imaging progression per RECIST 1.1 criteria) is allowed if the subject has an investigator assessed clinically stable status and is tolerating the treatment that meets the "Criteria for Continuation of Treatment Beyond Progression". Rechallenge with KN046 will be allowed if a patient responded and stopped the treatment for reasons other than progression while on treatment or toxicity.

Tumor evaluation will be performed at baseline, every 8 weeks in the first 12 months and every 12 weeks thereafter. Tumor evaluation will continue until confirmed progressive disease per RECIST 1.1, starting new anti-cancer therapy, withdrawal of informed consent, or subject's death, whichever comes first. Once objective response is observed, response should be confirmed by a second scan at approximately 8 weeks apart (no earlier than 4 weeks and no later than 8 weeks).

Clinical and laboratory assessments will be performed as described in Section 6.

After the last dose of KN046, subject will be asked to have an end-of-treatment (EOT) visit, a 30-day safety follow up visit, a 90-day safety follow up visit and overall survival follow up. EOT visit must be performed as soon as possible and within 14 days of last dose of KN046. Subjects who do not have progressive disease after EOT visit will continue tumor assessment until progressive disease, start of a new anti-cancer therapy, subject withdrawal of informed consent or death, whichever comes first. Subjects will be contacted every 12 weeks to obtain information pertaining to survival status until death, lost to follow-up, withdrawal of consent to survival follow-up or the end of study.

3.2 Scientific Rationale for Study Design

This is an open-label, single arm, single center non-randomized Phase II study to investigate the efficacy and safety of KN046 in patients with advanced thymic carcinoma who have progressed on prior immune checkpoint inhibitor therapy.

3.3 Justification for Dose

Target engagement pharmacodynamics (PD) of KN046 were assayed using the interleukin-2 (IL-2) stimulation ratio in peripheral blood samples drawn from cancer patients at baseline, pre-dose and 24, 168 and 336 hours post-dose of Cycle 1 Day 1, pre-dose of Cycle 3 Day 1 and 30-day safety follow-up (Trial KN046-CHN-001). No IL-2 release from lymphocytes with activated PD-1 pathway. Staphylococcal Enterotoxin B causes release, further enhanced by KN046 effect on PD-1/PD-L1.

Pharmacodynamic response was best described by an Imax inhibition model with an IC_{50} of 138 ng/mL and maximum inhibition of 1 (fixed). IC_{95} for target engagement is estimated at 2629 ng/mL.

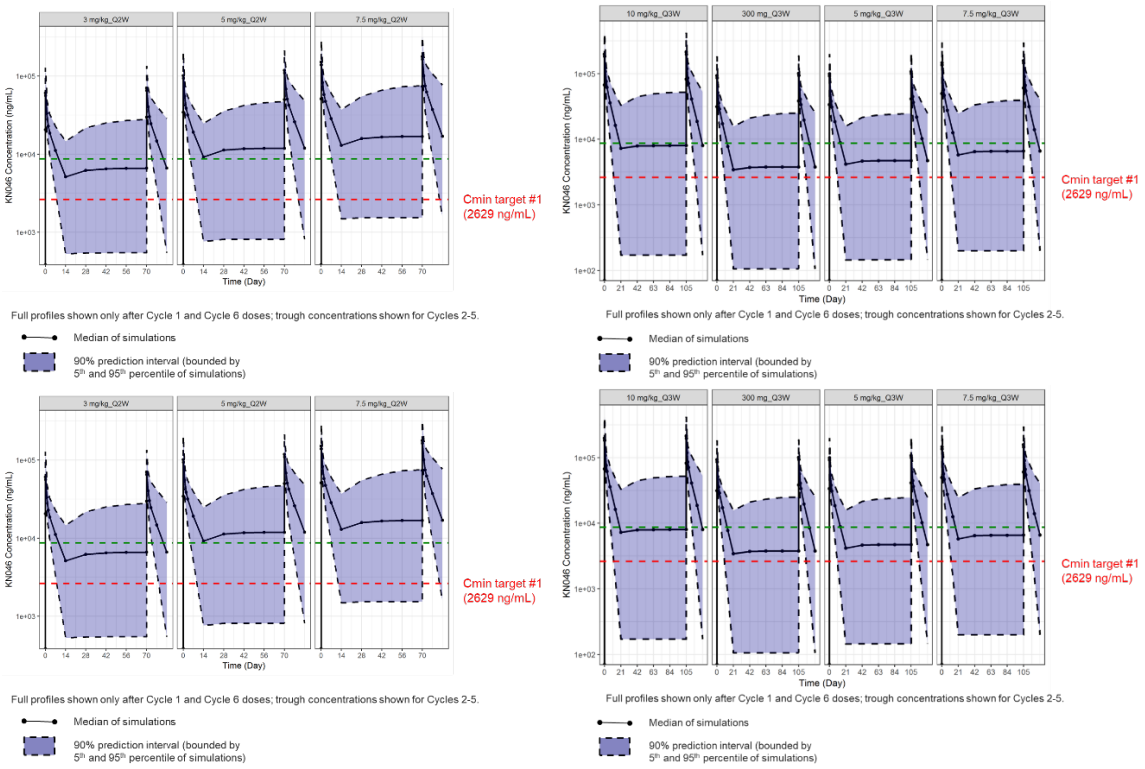
Population PK model was built based on available human PK data. Simulation was performed. 5 mg/kg every 2 weeks was needed to reach 85% probability of 95% target engagement.

No apparent relationship between dose and safety parameters in terms of TRAE and irAE has been observed between 3 and 5 mg/kg dose levels. MTD has been declared at 5 mg/kg Q2W for monotherapy.

An exploratory analysis has been performed to investigate the relationship between PK parameters (C_{min1} and $C_{avg,ss}$) to tumor shrinkage (ORR and sum of longitudinal diameter (SLD)) based on efficacy data from Phase I trials (KN046-AUS-001, KN046-CHN-001). Weak correlation has been observed in terms of $C_{avg,ss}$ (calculated by AUC_{inf}/tau) and SLD. Preliminary analysis indicated that higher exposure may be associated with better anti-tumor activity.

Figure 3-1 Simulation of KN046 Q2W and Q3W schedules

KN046 Q2W schedule **KN046 Q3W schedule**

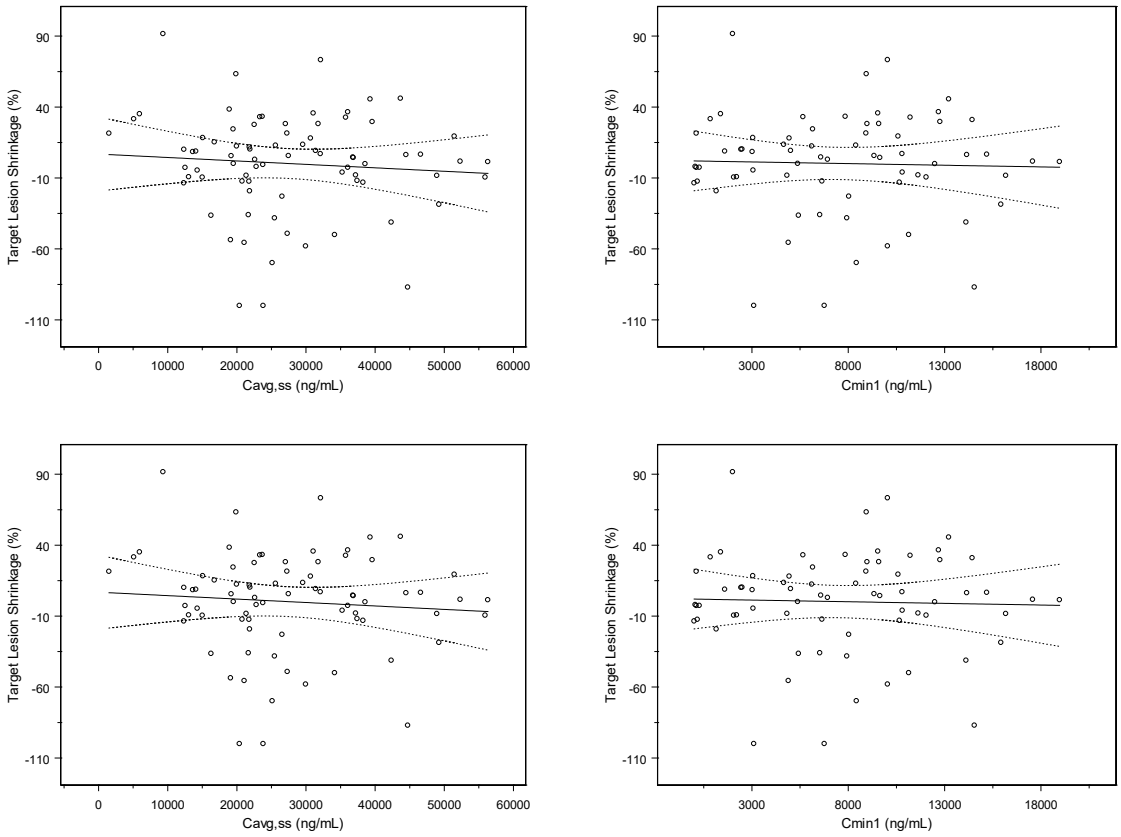


- **Percentage of subjects attaining 95% target engagement**

Regimen	Cycle 1 Dose C_{min} Target (2629 ng/mL)	Cycle 6 Dose C_{min} Target (2629 ng/mL)
3 mg/kg Q2W	73.5	76.0
5 mg/kg Q2W	85.1	86.2
7.5 mg/kg Q2W	88.7	89.0
5 mg/kg Q3W	62.3	63.5
300 mg Q3W	58.6	60.2

Figure 3-2 Exploratory exposure-efficacy analysis including subjects with prior immune checkpoint inhibitor treatment

$C_{average,ss}$ vs target lesion shrinkage **C_{min1} vs target lesion shrinkage**



3.4 End of Study Definition

A participant is considered to have completed the study if he or she has completed all phases of the study including the last visit or the last scheduled procedure shown in the **Schedule of Assessments (SoA), Section 6.1**. The end of the study is defined as completion of the last visit or procedure shown in the SoA in the trial globally. Subjects continuing to derive benefit from trial treatment at the end of the study in the opinion of the investigator will be able to continue receiving trial treatment on a separate protocol. The Sponsor may terminate the study early.

3.4.1. Premature Termination of the Trial

The whole study may be discontinued prematurely in the event of any of the following:

- New information leading to unfavorable risk-benefit judgement of the study drug;
- Sponsor's decision that continuation of the study is not justifiable for medical or ethical reasons;
- Poor enrollment of subjects making completion of the study within an acceptable time frame unlikely;
- Discontinuation of development of the Sponsor's study drug or discontinuation of the development of the defined indication.

The study can be terminated at any time for any reasons by Alphamab Oncology. Should premature termination of the study or the cohort of certain subtype occur, the subject should be seen as soon as possible and the same assessments as required for a prematurely withdrawn subject should be performed as described in Section **Error! Reference source not found.**. The investigator may be informed of additional procedures to be followed for the purpose of the protection of the subject's interest.

Health authorities and independent ethnic committee (IECs)/institutional review boards (IRBs) will be informed about the discontinuation of the study in accordance with applicable regulations. The study may also be terminated or suspended upon request of the health authorities.

4. Subject Selection

4.1 Study Population

Subjects with a diagnosis of advanced thymic carcinoma who meet the inclusion and exclusion criteria will be eligible for participation in this study.

4.2 Inclusion Criteria

1. Signed informed consent form;
2. Male or female, 18 years of age or older; willing and able to complete all required procedures of study;
3. Pathologically confirmed diagnosis of thymic carcinoma; a tumor sample is required for confirmation of pathological diagnosis and further studies on the tumor tissue (see correlative science Section 9)
4. Inoperable or metastatic disease;
5. Progressive disease documented in the last 6 months
6. Has failed platinum-based chemotherapy, with progression either during or after treatment
7. Had failed at least one regimen of systemic therapy containing immune checkpoint blockade therapy targeting PD-1, PD-L1, or CTLA-4 for locally advanced unresectable or metastatic disease. Subjects should have documented progressive disease while or after an immune checkpoint therapy. If subjects discontinued therapy due to reasons other than progressive disease, subjects should have completed at least 2 cycles of immune checkpoint therapy
8. Baseline measurable disease according to RECIST 1.1. Target lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions;
9. ECOG performance status of 0 or 1;
10. Adequate organ function assessed within 7 days prior to first trial treatment:
    - Hematological function
        i. ANC≥1.5 x 10^9/L;
        ii. Hemoglobin≥9 g/dL;
        iii. Platelets≥100 x 10^9/L;

- Renal function
    i. Calculated creatinine clearance≥60 mL/min (Cockcroft-Gault method);
- Hepatic function
    i. Total bilirubin≤1.5 x ULN (or 2.5 x ULN for documented Gilberts' syndrome);
    ii. ALT/AST≤3.0 x ULN (or 5.0 x ULN for documented liver metastasis);
- INR or aPTT ≤1.5 x ULN;

11. Have a life expectancy of at least 3 months;
12. If female of childbearing potential, have a negative serum pregnancy test within 7 days prior to first trial treatment;
13. If female of childbearing potential or a male subject with a partner with childbearing potential, be willing to use a highly effective method of contraception (with a failure rate of less than 1.0% per year) from first study treatment to 24 weeks after completion of the trial treatment.

4.3 Exclusion Criteria

1. Thymomas, thymolipoma, germ cell tumors, teratomas, seminomas;
2. Leptomeningeal metastasis or untreated active CNS metastasis or leptomeningeal metastasis. Subjects with CNS metastasis may be eligible provided they are treated and clinically stable for at least 4 weeks and have no evidence of new or enlarging brain metastases and also are off steroids 7 days prior to first trial treatment;
3. Is currently participating and receiving an investigational drug or has participated in a study of an investigational drug within 4 weeks or within 5 times of half-life (no less than 2 weeks), whichever is shorter, prior to the first dose of trial treatment;
4. Major surgery for any reason, except diagnostic biopsy, within 4 weeks of the first administration of trial treatment and/or if the subject has not fully recovered from the surgery within 4 weeks of the first administration of trial treatment;
5. Radiation within 4 weeks prior to the first administration of trial treatment; palliative radiation will be allowed if more than 2 weeks before start of KN046 treatment
6. Subjects receiving immunosuppressive agents (such as systemic steroids); topical use of steroids and steroid inhalers are allowed. Replacement therapy because of adrenal insufficiency is also allowed
7. Vaccination within 28 days of the first administration of trial treatment, except for administration of inactivated vaccines (e.g., inactivated influenza vaccines);
8. Has interstitial lung disease, or a history of pneumonitis that required oral or intravenous glucocorticoids to assist with management;
9. History or current active autoimmune disease that might deteriorate when receiving an immunostimulatory agent, including but not limited to:
    - Myasthenia gravis (MG), Good syndromes, ISAACS syndromes, polymyositis, myocarditis, neuromuscular syndrome (myotonic dystrophy myositis, Eaton-Lambert syndrome), blood disorders (red cell aplasia, hypogammaglobulinemia, T-

cell deficiency syndrome, erythrocytosis, pancytopenia, megakaryocytopenia, T-cell lymphocytosis, pernicious anemia), systemic lupus erythematosus, sarcoidosis, scleroderma, Crohn's disease, inflammatory bowel disease, Wegener syndrome (granulomatosis with polyangitis, Grave's disease, rheumatoid arthritis, hypophysitis, uveitis), autoimmune hepatitis, systemic sclerosis (for example scleroderma), Hashimoto thyroiditis (with the exception as stated below), hyperparathyroidism, stiff-person syndrome, Addison disease, panhypopituitarism, autoimmune vasculitis, autoimmune neuropathy (Guillain-Barre syndrome) etc. NOTE: Subjects with Type I diabetes, vitiligo, psoriasis, hypo- or hyperthyroid disease, Sjögren syndrome not requiring immunosuppressive treatment are eligible. Subjects requiring hormone replacement with corticosteroids are eligible if the steroids are administered only for the purpose of hormonal replacement and at doses ≤10 mg or equivalent prednisone per day. Administration of steroids for other conditions through a route known to result in a minimal systemic exposure (topical, intranasal, intra-ocular, or inhalation) are acceptable;

10. Previous malignant disease other than the target malignancy to be investigated in this study with the exception of adequately treated non-melanomatous cancers of the skin, in situ carcinoma of the prostate/cervical/breast cancer, or other malignancy treated at least 5 years previously with surgery and/or curative radiotherapy, and there is no evidence of recurrence since that time;
11. History of uncontrolled intercurrent illness including but not limited to:
    - Active HBV or HCV infection;
    - If HBsAg and HCV antibody positive, HBV DNA and HCV RNA assay should be performed. Subjects may be eligible if HBV DNA ≤ 500 UI/ml (or 2000 copies/ml) or HCV RNA negative.
    - Known HIV infection or known history of acquired immune deficiency syndrome (AIDS);
    - Active tuberculosis infection;
    - Active infection within 2 weeks prior to the first dose of trial treatment that require the use of systemic antibiotics;
    - Hypertension uncontrolled by standard therapies (not stabilized to 150/90 mmHg);
    - Clinically significant (that is, active) cardiovascular disease: cerebral vascular accident/stroke (< 6 months prior to enrolment), myocardial infarction (< 6 months prior to enrolment), unstable angina pectoris, congestive heart failure (New York Heart Association Classification Class II-IV) or serious cardiac arrhythmia requiring medication (including corrected QT interval prolongation of > 470 msec calculated according to Fridericia and/or pacemaker or prior diagnosis of congenital long QT syndrome;
12. Persisting toxicity related to prior therapy (including any prior investigational therapy) of CTCAE ≥ grade 2 (NCI-CTCAE v5.0) or related toxicity not recovery to baseline, with the exception of alopecia of any grade;

13. Prior allo-HSCT or solid organ transplant;
14. Known severe hypersensitivity reactions to antibody drug (≥ grade 3 NCI-CTCAE v5.0), any history of anaphylaxis, uncontrolled asthma (that is, 3 or more features of partially controlled asthma), or any history of severe drug hypersensitivity (for example immune mediated liver toxicity, immune mediated thrombocytopenia or anemia);
15. Is pregnant or breastfeeding;
16. Other medical conditions that at the discretion of investigator interfere with the requirements of the trial in terms of safety or efficacy evaluation, or treatment compliance. These include but are not limited to psychiatric or substance abuse disorder, moderate to large pleural fluid/cardiac effusion/ascites, or recurrent/refractory pleural fluid/cardiac effusion/ascites.
17. Subjects with history or baseline positive antiacetylcholine receptor (AChR) autoantibody and anti-MuSK autoantibody
18. Subjects who developed grade 3 or above immune related AE which could not be managed by steroid or immune suppressant will be excluded

4.4 Lifestyle Considerations

Not applicable

4.5 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals may be rescreened if they meet the eligibility criteria for participation in this trial after they had failed screening before. Rescreened participants should be assigned the same participant number as for the initial screening.

4.6 Strategies for Recruitment and Retention

Subjects will be identified and approached by treating medical oncologists or radiation oncologists in the outpatient clinic. The trial may also be discussed with patients who are admitted to the hospital.

The trial will be listed on the Joint Clinical Trials Office (JCTO) public website and will also be discussed at local professional meetings such as the NY Lung Cancer Learning Center conferences, in order to help generate referrals.

Subjects will not be compensated for taking part in this trial.

5. Registration Procedures

5.1 Subject Registration

Subjects will be registered within the WRG-CT as per the standard operating procedure for Subject Registration.

6. Study Procedures

6.1 Schedule of Assessments

A complete Schedule of Assessments is provided in **Error! Reference source not found.**. Prior to performing any trial assessments not part of the subject's routine medical care, the investigator will ensure that the subject or the subject's legal representative has provided written informed consent.

Table 4. Schedule of Assessments														
Assessment	**Screening**	**Treatment Period**									**End of Treatment (EOT)**	**30-day Safety Follow-up**	**90-day Safety Follow-up**	**Survival Follow-up**
Visit	Screening	C1D1	C1D15	C2D1	C2D15	C3D1	C3D15	C4D1	C4D15	CXD1 and D15	EOT	30-day FU	90-day FU	Every 12 weeks
Day (d)	(-28~-1)	1(±3d)	1(±3d)	1(±3d)	1(±3d)	1(±3d)	1(±3d)	1(±3d)	1(±3d)	1(±3d)	(within 7 days after determination of treatment discontinuation)	30 days after last dose of trial treatment (±7 d)	90 days after last dose of trial treatment (±14 d)	Every 12 weeks after last dose of trial treatment (±14 d)
General procedure														
Informed consent [1]	X													
Inclusion / exclusion criteria	X													
Demography and history of alcohol and tobacco use [2]	X													
Medical history [3]	X													
Oncology history [4]	X													
Prior and concomitant medications and procedures [5]	X	X									X	X	(X)	(X)
New anti-cancer therapy											X	X	X	X
Overall survival														X
Clinical examination and test														
AE [6]	X	X									X	X	X	X
Full physical examination [7]	X	X	X	X	X	X	X	X	X	X	X			
Height (in cm)	X													
Body weight (to the nearest 0.1 kilogram [kg]) [14]	X	X	X	X	X	X	X	X	X	X	X	X	X	
Vital signs [9, 14]	X	X	X	X	X	X	X	X	X	X	X	X	X	
12-lead ECG [10]	X	Clinically indicated									X			
ECOG performance status	X	X	X	X	X	X	X	X	X	X	X	X	X	
Cardiac Ultrasonography	X			X	X	X								
Local laboratory test / evaluation														

Immunoglobulin	X													
CPK	X	(X)	X	X	X	X	X	X	X	X				
Hematology test (including reticulocyte) [11, 14]	X [8]	(X)	X	X	X	X	X	X	X	X	X	(X) [15]	(X) [15]	
Coagulation test (aPTT, PT, INR)	X [8]	Clinically indicated												
Serum chemistry [12, 14]	X [8]	(X)	X	X	X	X	X	X	X	X	X	(X) [15]	(X) [15]	
Urinalysis [13]	X [8]	Clinically indicated									X	(X) [15]	(X) [15]	
Serum beta-HCG (if applicable) [16]	(X) [8]										(X)			
T3, FT3, FT4 and TSH	X	(X)				X				X[23, 24]				
Troponin	X	X		X		X		X		X[23]				
Urine beta-HCG (if applicable)[16]		(every 12 weeks; or as clinically indicated)												
FSH (if applicable)[22]	X													
HBV, HCV, HIV [17]	X													
ANA, ENA[25]	X													
CRP, IL-6	X	As clinically indicated (IRR, suspected cytokine release syndrome or serum sickness)												
Anti-AChR autoantibody	X													
Anti-MuSK autoantibody	X													
Lymphocytic analysis (B cell count)	X													
Correlative studies														
Multiplex cytokine/chemokine assay for calculation of CYTOX score (as defined by Section 9.1.1)	X	As clinically indicated (IRR, suspected cytokine release syndrome or serum sickness)												
ctDNA[26]	X	To occur at time of best response and at tumor progression												
Tumor tissue[18]	X	On-treatment tissue-targeted biopsy if tissue-specific irAE occurs												
TCR sequencing	X	On blood and tissue if tissue-specific irAE occurs												
Peripheral blood for WES	X													
Tumor evaluation														

CT C/A/P[19]	X	To occur every 2 cycles for the first year, then every 4 cycles for the second year									(X)	(X)	(X)	(X)
PET/CT[19]	X	To occur at best response, and as clinically indicated												
Brain CT/MRI [20]	X	(clinically indicated)												
RECIST 1.1	X	Every 8 weeks												
Investigational drug														
KN046 administration [21]		X	X	X	X	X	X	X	X	X				

(X) Does not need to be repeated if done within 7 days of C1D1

1 Informed consent should be obtained before any trial related procedure and treatment;

2 Demographic data include date of birth, sex, race and ethnicity;

3 Medical history includes past and concurrent nonmalignant diseases and treatment, past and concurrent malignant diseases and treatment;

4 Oncology history includes detailed history of the target indication of this study including histopathological diagnosis, grading and staging in accordance to Masaoka staging; all therapy used for prior treatment of the tumor (including surgery, radiotherapy, chemotherapy, and immunotherapy); any other conditions that were treated with chemotherapy, radiation therapy, or immunotherapy; current cancer signs and symptoms, and AEs effects from current and/or previous anticancer treatments; and current cancer disease status;

5 All medications (including herbal medications) taken and procedures performed within 28 days prior to first trial treatment should be recorded; radiation therapy should be recorded;

6 All AEs will be collected from time of signature of inform consent through 30 days following the last dose of study drug or the date of subject initiates new anticancer therapy, whichever is earlier. All SAE and treatment related adverse event will be collected from the time of informed consent through 90 days following the last dose of study drug. However, if an investigator learns of any SAE, after 90-day safety follow-up period, and she/he considers there is a reasonable possibility that the event is related to the study drug, the investigator should report to sponsor. All AEs and SAEs should be proactively followed up for each patient, adverse events should be followed to resolution or stabilization at a level acceptable to the investigator.

7 Full physical examination includes an examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, and a basic nervous system evaluation;

8 Examination or test results should be obtained within 7 days prior to first trial treatment;

9 Vital signs include temperature, respiration rate, pulse rate and blood pressure;

10 12-lead ECG will be performed in the supine position after the subject has been breathing quietly for 5 minutes; The ECG results will be used to evaluate heart rate, atrial-ventricular conduction, QR and QT intervals, and possible arrhythmias. Interpretation of the ECG trace must be made by a qualified physician and documented on the ECG eCRF. Each ECG trace should be labeled with the Study Number, Subject Identifier Number, and date, and kept in the source documents at the site;

11 Hematology test includes absolute lymphocyte count, absolute neutrophil count, hematocrit, hemoglobin, platelet count, red blood cells, white blood cells and differential count, red blood cell morphology, reticulocytes, mean corpuscular hemoglobin, mean corpuscular volume, mean corpuscular hemoglobin concentration;

12 Serum chemistry test includes albumin, alkaline phosphatase, alanine aminotransferase, amylase, aspartate aminotransferase, gamma-glutamyl transferase, blood urea nitrogen/total urea, calcium, chloride, creatine kinase, creatinine, glucose, lactate dehydrogenase, lipase, phosphorus/phosphates, magnesium, potassium, sodium, troponin, total bilirubin, total protein;

13 Urinalysis includes bilirubin, blood, glucose, ketones, pH, protein, specific gravity, and color and appearance. If urinalysis is positive for protein, segments and 24-hour urine protein exam should be performed;

14 Examination or test results should be obtained before each trial treatment;

15 Only be performed when clinically significant abnormal findings are found at EOT visit;

16 For women of child bearing potential, a serum pregnant test should be performed within 7 days prior to the first dose of trial treatment. Subsequently, urine beta-HCG test will be monitored every 12 weeks or as clinically indicated. Female subjects who are not considered to be of childbearing potential (for example, age-related natural [spontaneous] amenorrhea ≥ 12 consecutive months and increased FSH > 40 mIU/mL), or who are surgically sterile or are sexually inactive, are exempt from pregnancy testing;

17 HBV, HCV and HIV tests include HBsAg, HCV and anti-HIV1/2. If HBsAg is positive, HBsAb, HBeAb, HBeAg, HBcAb and HBV DNA should be measured to exclude active HBV infection as clinically indicated; HCV RNA should be tested to exclude active HCV infection If anti-HCV is positive;

18 A tumor biopsy should be collected at Screening unless tissue (blocks or slides) from an archival specimen (biopsy or surgery) is available. 10 slides required. On-treatment biopsies would be obtained at time of irAE development if it occurs

19 Tumor assessment will be performed using PET/CT at baseline, at time of best response, and when clinically indicated. CT scans of chest, abdomen and pelvis (Chest CT and MRI of Abdomen and Pelvis also acceptable) are also required at baseline, every 2 cycles (8 weeks) for the first year, then every 4 cycles (16 weeks) for the second year. Screening tumor assessment should be performed within 28 days of first trial treatment in order to document baseline status of tumor disease using RECIST 1.1 target and non-target lesions. During treatment period, the tumor assessment visit time window is ±7 days. CT or MRI scan (if MRI is used, CT of chest is mandatory) should always be used in the same modality as the screening period. If a tumor response is documented during the study, confirmation of the response should be performed according to RECIST 1.1, preferably at the regularly scheduled 8-week assessment interval, but no sooner than 4 weeks and no later than 8 weeks after the initial documentation of CR or PR. Confirmation of PR/CR can be done at an assessment later than the next assessment after the initial documentation of PR/CR. If disease progression is documented, confirmation of PD is required, preferably at 8-week assessment interval (but no sooner than 4 weeks and no later than 8 weeks). Tumor assessment will continue until confirmed disease progression per RECIST 1.1, start of new anti-cancer therapy, or withdrawal of informed consent, whichever comes first. If treatment discontinuation is due to reasons other than RECIST 1.1 defined progressive disease, tumor assessment should continue until RECIST 1.1 defined progressive disease, start of new anti-cancer therapy, or withdrawal of informed consent, whichever comes first;

20 Brain CT/MRI scan (either, with contrast preferred) is required at screening if not performed within the previous 42 days prior to first trial treatment. During treatment period, brain CT/MRI scan should be done if clinically indicated by development of new specific symptoms;

21 Each KN046 will be administered intravenously over at least 90 minutes (90-120 minutes). After the completion of KN046 infusion, subject should be observed at site for at least 2 hours.

22 If necessary to confirm postmenopausal status

23 Day 1 of each cycle only

24 To occur on Day 1 of odd Cycles only

25 If ANA or ENA positive, rheumatologic workup indicated.

26 Will only repeat ctDNA if genetic alteration detected at baseline.

6.1.1 Screening Visit (*28 days before start of treatment*)

During the Screening period and before any trial-related investigations and assessments are started, subjects will be asked to sign the informed consent form (ICF). The Screening procedures and Baseline assessments will be completed within 28 days of signing the ICF before first trial treatment.

The subjects' information that will be documented during Screening includes the demographic information (date of birth, sex, race and ethnicity) and the complete medical history (oncology history, previous and ongoing medications, prior surgery, radiation and medication therapies, and baseline medical condition etc). The AE reporting period for safety surveillance and a concomitant medication recording period begins when the subject first signs an informed consent.

During Screening, subjects will undergo a complete physical examination, vital signs, recording height and body weight, 12-lead ECG, and a determination of the ECOG performance status.

During Screening, pathology reports will be reviewed to confirm diagnosis.

The Screening laboratory examination includes hematology, coagulation, serum chemistry, anti-AChR autoantibody, anti-MuSK autoantibody, immunoglobulin, urinalysis, troponin, B cell count, neutrophil count, lymphocyte count, Cardiac ultrasonography, total T3, free T3, free T4 and TSH will also be assessed at Screening for all subjects. Viral tests for HBV, HCV and HIV should be performed at Screening.

During Screening, a serum beta-human chorionic gonadotropin pregnancy test will be performed for females of childbearing potential. Females who are postmenopausal or who have undergone hysterectomy or bilateral oophorectomy are exempt from pregnancy testing. If necessary to confirm postmenopausal status, FSH will be drawn at Screening.

During Screening, the tumor evaluation will be performed using CT scan or MRI or any other established methods. A brain CT/MRI scan is required at Screening if not performed within 42 days prior to first trial treatment.

Failure to establish subject eligibility due to laboratory parameters is allowed to be re-tested following consultation with the Medical Monitor.

6.1.2 Treatment Phase

The Treatment period begins on Cycle 1 Day 1 with the first administration of KN046 and will continue until 2 years have passed or until confirmed disease progression per RECIST 1.1, significant clinical deterioration (clinical progression), unacceptable toxicity, or any criterion for withdrawal from the investigational medicinal product. A subject may remain on KN046 beyond disease progression per RECIST 1.1 if their ECOG performance status remains stable, no new symptoms or worsening of existing symptoms and if in the opinion of the investigator the subject will benefit from continued treatment. For subjects that continue KN046 treatment beyond progression, treatment should be stopped immediately if the subject no longer tolerates KN046 or if therapeutic failure occurs.

Subjects will be asked to visit the study site every 2 weeks during the Treatment Period. A time window of up to 3 days before or after the scheduled visit day (+/-3 days) will be permitted for all study procedures except for body weight, which should be measured on the day prior to, or the day of, administration of KN046. In addition, the tumor evaluation has a tumor assessment

window of up to 7 days before or after the scheduled visit day (+/- 7 days) throughout the Treatment phase.

6.1.2.1 Day 1 of each Cycle (unless otherwise noted in the SOA)

- Concomitant medications and procedures
- Adverse Event Assessment
- Full physical exam
- Body Weight
- Tumor Imaging (if applicable)
- Vital Signs
- 12-lead ECG (if clinically indicated)
- ECOG Performance Status
- CBC, metabolic panel, CPK, troponin
- Coagulation tests (if clinically indicated)
- Urinalysis (as defined in SOA)
- T3, FT3, FT4, TSH (as defined in SOA)
- CRP, IL-6 (as clinically indicated)
- Anti-AChR Autoantibody, Anti-MuSK autoantibody (as clinically indicated)
- For C2D1 and C3D1 only: Cardiac Ultrasonography
- Tumor Imaging (to occur every 8 weeks)
- Brain CT/MRI (as clinically indicated)

6.1.2.2 Day 15 of each Cycle

- Concomitant medications and procedures
- Adverse Event Assessment
- Full physical exam
- Body Weight
- Tumor Imaging (if applicable)
- Vital Signs
- ECOG Performance Status
- CBC, metabolic panel, CPK, troponin
- Coagulation tests (if clinically indicated)
- Urinalysis (as defined in SOA)
- T3, FT3, FT4, TSH (as defined in SOA)
- CRP, IL-6 (as clinically indicated)
- Brain CT/MRI (as clinically indicated)
- For C2D15 only: Cardiac Ultrasonography

6.1.3 End of Treatment

- Concomitant medications and procedures
- Adverse Event Assessment
- Physical exam
- Body Weight
- Vital Signs

- 12-lead ECG
- ECOG Performance Status
- CBC, metabolic panel
- Urinalysis (as defined in SOA)
- T3, FT3, FT4, TSH (as defined in SOA)
- Tumor Imaging

6.1.4 Safety Follow Up Phase

- Concomitant medications and procedures
- New anti-cancer therapy Assessment
- Adverse Event assessment
- Full physical exam
- Body Weight
- Vital Signs
- ECOG Performance Status
- CBC, metabolic panel
- Coagulation tests (if clinically indicated)
- Urinalysis (as defined in SOA)
- T3, FT3, FT4, TSH (as defined in SOA)
- Tumor Imaging (to occur every 8 weeks)

6.1.5 Survival Follow Up Phase

- Concomitant medications and procedures
- New anti-cancer therapy Assessment
- Adverse Event assessment
- Full physical exam
- Body Weight
- Vital Signs
- ECOG Performance Status
- CBC, metabolic panel
- Coagulation tests (if clinically indicated)
- Urinalysis (as defined in SOA)
- T3, FT3, FT4, TSH (as defined in SOA)
- Tumor Imaging (to occur every 8 weeks)

7. Study Intervention

7.1 Study Intervention/Device Description

KN046 is the investigational medicinal product of this study.

KN046 is a sterile, clear and colorless to light yellow solution intended for IV administration. It is presented as a 40 mg/1.6 mL/vial in a single use glass vial closed with a rubber stopper and sealed with an aluminum polypropylene flip-off seal.

7.2 Dilution and Dosing

Subjects in this trial will receive IV infusion of KN046 over at least 90 minutes (90~120 minutes) once every 2 weeks.

The volume of KN046 solution will be calculated based on the body weight of the subject determined the day prior to, or on the day of each drug administration. For a 70 kg subject who is enrolled and planned to receive 5 mg/kg treatment, the dose of KN046 is 350 mg, and the volume of solution is 350 mg/40 mg x 1.6 mL = 14 mL. The dilution needs to be done aseptically by transferring 14 mL of 40 mg/ 1.6 mL KN046 from 9 vials into 186 mL of sterile 5% dextrose in water to have a final concentration of KN046 for infusion at 1~5 mg/mL. The diluted KN046 solution should be mixed gently and thoroughly before application by intravenous infusion, with an adequate normal saline flush at the end of the infusion.

Visual inspection of the diluted solution and the vials for particulate matter and discoloration prior to infusion will be conducted. The infusion duration should be no less than 90 minutes. KN046 should be administered under the supervision of physician or other study personnel experienced in the use of IV agents. Do not administer study drug as an IV push or bolus injection.

For the detailed process of the dilution and infusion, please refer to the Pharmacy Manual.

Every subject will receive KN046 at protocol scheduled dose and regimen until confirmed disease progression per RECIST 1.1 criteria, significant clinical deterioration (clinical progression), unacceptable toxicity, start of new anti-cancer therapy, withdrawal of informed consent, or until protocol-defined criteria for withdrawal from KN046 or the study are met. Dose modifications of KN046 is discussed in Section 7.3.

After initial determination of disease progression per RECIST 1.1, if patient is clinically stable, a subsequent assessment should be performed preferably 4~8 weeks (but not later) after initial documentation of progressive disease (PD) to determine whether there has been a decrease in the tumor size, or continued PD (Confirmed Progression).

The decision to continue treatment beyond progression should be discussed with the Principal Investigator and Treating physician and documented in the study records.

7.3 Dose modifications

KN046 will be withheld for ≥ Grade 3 drug-related toxicity, including laboratory abnormalities with the exception of laboratory abnormalities that are not clinically significant or that do not meet the criteria of adverse event, and severe or life-threatening AEs (i.e. anemia grade 3, lymphocytopenia grade 3-4, hypercholesterolemia grade 3-4, hypertriglyceridemia grade 3-4).

If a dose of KN046 is withheld due to toxicity, subjects may resume dosing with KN046 when toxicity has improved to ≤ Grade 1.

In case toxicity does not resolve to Grade 0-1 within 12 weeks after last infusion, trial treatment will be discontinued. With the agreement between investigator and Sponsor Medical Monitor, subjects with a laboratory adverse event at Grade 2 after 12 weeks may continue treatment only if asymptomatic and controlled, for example, hypothyroidism or Type I diabetes controlled by replacement treatments.

Subjects who require corticosteroids to manage drug-related adverse events must be at an equivalent dose of ≤ 10 mg per day of prednisone to resume dosing with KN046. In case of an inability to reduce the corticosteroid dose for managing a drug-related adverse event to the equivalent of ≤ 10 mg prednisone per day within 12 weeks of last KN046 dose, patient will go off treatment.

For a subject who experiences a recurrence of the same serious adverse event at the same grade or greater after rechallenge of KN046, study medication will be discontinued.

In addition, if any of below drug-related adverse events occur, KN046 treatment will be permanently discontinued:

- ≥ Grade 3 immune related pneumonitis;
- Recurrence of ≥ Grade 2 immune related pneumonitis lasting ≥ 4 weeks after appropriate medical interventions;
- ≥ Grade 2 immune related CNS toxicities lasting ≥ 4 weeks after appropriate medical interventions;
- ≥ Grade 3 immune related colitis;
- ≥ Grade 3 uveitis or optic neuritis;
- ≥ Grade 3 immune related hepatitis with ALT/AST > 8 x ULN OR TBIL > 3 x ULN;
- ≥ Grade 3 immune related nephritis or renal dysfunction.
- ≥ Grade 2 myocarditis
- ≥ Grade 2 myositis

Table 7-1 Guideline on KN046 dose modification

Toxicity	**Grade**	**Withheld treatment**	**Resume treatment**	**Dose / schedule for resuming treatment**	**Discontinuation of treatment**
Hematological toxicity	1, 2	No	Not applicable	Not applicable	Not applicable
	3 (except for isolate event of grade 3 neutropenia)	Yes			

Toxicity	Grade	Withheld treatment	Resume treatment	Dose / schedule for resuming treatment	Discontinuation of treatment
	4	Yes	Toxicity resolves to ≤Grade 1 or baseline within 12 weeks of last KN046 dose	Resume at planned dose and increase the dose interval by 1 week at each occurrence	Permanent discontinuation if toxicity does not resolve to ≤Grade 1 or baseline within 12 weeks of last KN046 infusion
Non-hematological toxicity with the exception for alopecia of any Grade and Grade 2 fatigue which will be treated as Grade 1 adverse reaction (with the exception of those reported in 7.3)	1	No	Not applicable	Not applicable	Not applicable
	2	Yes	Toxicity resolves to ≤Grade 1 or baseline within 4 weeks of last KN046 dose	Resume at planned dose and dose interval	Permanent discontinuation if toxicity does not resolve to ≤Grade 1 or baseline within 12 weeks of last KN046 infusion
			Toxicity resolves to ≤Grade 1 or baseline beyond 4 weeks and within 12 weeks of last KN046 dose	Resume at planned dose and increase the dose interval by 1 week at each occurrence	
	3, 4	Yes	Toxicity resolves to ≤Grade 1 or baseline within 12 weeks of last KN046 dose	Resume at planned dose and increase the dose interval by 1 week at each occurrence	Permanent discontinuation if toxicity does not resolve to ≤Grade 1 or baseline within 12 weeks of last KN046 infusion; Permanent discontinuation should also be considered for any life-threatening or severe adverse reactions
Note: if increased Grade 3 or 4 CPK occurs, myocardial enzymes (CPK, CK, Tn1, TnT) should also be measured. KN046 will be permanently discontinued in case of elevation on treatment-related myocardial enzymes					

Infusion related reactions, hypersensitivity reactions, and immune related adverse event should be handled according to the guidelines provided in Sections 7.5.1 and Appendix A, respectively.

7.4. Concurrent medications and therapies

7.4.1 Permitted medications and procedures

Any medications considered necessary for subjects' welfare and will not interfere with KN046 may be given at the investigator's discretion. Other drugs to be used for prophylaxis, treatment of anaphylactic reactions, infusion-related reactions, severe hypersensitivity reaction are described in Sections 7.5.1. The investigator will record all concomitant medications taken by the subject from 28 days prior to first trial treatment, during the study till 90 days after last KN046 dose.

7.4.2 Prohibited medications and procedures

The following treatments must not be administered during the study:

- Anticancer treatment other than the investigational drug (for example, cytoreductive therapy, radiotherapy, immunotherapies, or cytokine therapy);
- Concurrent systemic therapy with steroids or other immunosuppressive agents with the exception of the treatment of irAEs, prophylactic use to prevent allergic reactions to the contrast for imaging evaluation, for the prevention of acute infusion-related reactions, or administration of steroids for hormone replacement at doses ≤10 mg or equivalent of prednisone per day. Steroids with no or minimal systemic effect (topical, intranasal, intra-ocular, or inhalation) are allowed;
- Immunosuppressive drugs with the exception for the treatment of irAEs;
- Other investigational drug;
- Major surgery;

If the administration of a nonpermitted concomitant drug becomes necessary during the study, the subject will be withdrawn from treatment with KN046.

7.5. Special precautions

As a routine precaution, subjects enrolled in this study must be observed for 2 hours after the completion of infusion of KN046 in an area with resuscitation equipment and emergency agents. At all times during study drug administration, immediate emergency treatment of an infusion-related reaction or a severe hypersensitivity reaction according to institutional standards must be assured, for instance, dexamethasone 10 mg and epinephrine in a 1:1000 dilution or equivalents should always be available along with equipment for assisted ventilation.

Infusion of KN046 will be stopped in case of ≥Grade 3 hypersensitivity or anaphylactic reaction. The treatment recommendations for infusion-related reactions, severe hypersensitivity reactions according to the NCI are outlined in Sections 7.5.1. All infusion-related reactions occurring during the infusion of KN046 or within 2 hours after completion of the administration of KN046 should be reported as AE of interest (See Section 13).

Investigators should monitor subjects closely for potential irAE, which may manifest at the earliest after the first dose of treatment. Such events may consist of autoimmune hepatitis, diarrhea and colitis, arthritis, persistent rash, glomerulonephritis, cardiomyopathy or inflammatory eye conditions etc. Details for irAE management please refer to Section Appendix A.

7.5.1 Infusion-related reactions and hypersensitivity reactions

Infusion-related reactions could manifest as fever, chills, rigors, diaphoresis or headache. Hypersensitivity reactions could manifest as impaired airway, decreased oxygen saturation (<93%), confusion, lethargy, hypotension, pale or clammy skin and cyanosis.

Management of infusion-related reactions and hypersensitivity caused by KN046 is provided in below

table.

If a hypersensitivity reaction occurs, the subject must be treated according to the best available medical practice. A complete guideline for the emergency treatment of anaphylactic reactions according to the Working Group of the Resuscitation Council (United Kingdom) can be found at https://www.resus.org.uk/pages/reaction.pdf (refer to: Emergency Treatment of Anaphylactic Reactions: Guidelines for Healthcare Providers, 2008). Subjects should be instructed to report any delayed reactions to the Investigator immediately.

If severe immediate systemic hypersensitivity occurs, the subject should be placed on a monitor immediately and receive epinephrine and corticosteroid infusion as appropriate. The intensive care unit should be alerted for possible transfer if required.

If the subject is suspected to have systemic hypersensitivity reaction, the investigator is advised to collect plasma histamine, C-reactive protein (CRP) and the presence of drug-specific immunoglobulin E within 30 minutes of system onset, and urinary methyl histamine within 24 hours of onset of symptoms, as well as unplanned ADA and PK samples. For subjects with chest pain, ECG, myocardial enzymes (CPK, CK, Tn1, TnT) and BNP are recommended within 30 minutes of the onset of symptoms.

If investigator determines that the benefit of the continued administration outweighs the risk, the KN046 treatment is allowed to continue and the prophylactic medical must be administered 30-45 minutes prior to the administration of all subsequent dosing cycles. Examples of prophylactic dosing regimens are: diphenhydramine 25~50 mg IV, cimetidine 300 mg IV and acetaminophen 650 mg po.

If the subject's hypersensitivity reaction includes bronchospasm or dyspnea, montelukast 10 mg PO is recommended as part of a prophylactic regimen. Investigators can use medical judgment to determine whether steroids need to be added to a preventive regimen. Encourage discussion with immunologists to determine treatment options.

Table 7-2 Guideline on management of infusion-related reactions and systemic hypersensitivity reactions

NCI-CTCAE Grade	**Treatment Modification for KN046**
Grade 1 – mild Mild transient reaction; infusion interruption not indicated; intervention not indicated.	Decrease the KN046 infusion rate by 50% and monitor closely for any worsening.
Grade 2 – moderate Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, i.v. fluids); prophylactic medications indicated for □ 24 hours.	Stop KN046 infusion. Resume infusion at 50% of previous rate once infusion-related reaction has resolved or decreased to at least Grade 1 in severity, and monitor closely for any worsening. **Once the KN046 infusion rate has been decreased by 50% due to an infusion-related reaction, it must remain decreased for all subsequent infusions. At next cycle, a premedication regimen of diphenhydramine 25~50 mg IV, cimetidine 300 mg IV and acetaminophen 650 mg po is mandatory 30 to 60**

NCI-CTCAE Grade	Treatment Modification for KN046
	minutes prior to each dose of KN046). If subject developed symptomatic bronchospasm, premedication with montelukast (10 mg PO) is mandatory as part of premedication regimen mentioned above. At the discretion of investigator, premedication of corticosteroid can also be considered. If a subject has a recurrence of ≥grade 2 infusion related reactions despite the premedications as well as decreased infusion rate, the subject should be withdrawn from KN046 treatment. **It's also suggested to the investigator discuss with the allergist locally.**
Grade 3 or Grade 4 – severe or life-threatening Grade 3: Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae. **Grade 4**: Life-threatening consequences; urgent intervention indicated.	Stop the KN046 infusion immediately and disconnect infusion tubing from the subject. Subjects have to be withdrawn permanently from KN046.
Note: once the subject develops infusion related reactions, additional appropriate medical therapy may include but is not limited to: IV fluids, antihistamines, NSAIDS, acetaminophen and narcotics. Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g. from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next cycle.	

i.v.=intravenous, NCI-CTCAE=National Cancer Institute-Common Terminology Criteria for Adverse Event, NSAIDs=nonsteroidal anti-inflammatory drugs.

7.6 Packaging and labeling of the investigational medicinal product

The Sponsor's Clinical Trial Supply Chain department will supply the investigational medicinal product, KN046.

Packaging and labeling of KN046 will be in accordance with applicable regulatory requirements and Good Manufacturing Practice guidelines. KN046 will be packed in boxes containing a suitable number of vials. The information on the KN046 will be in accordance with approved submission documents. KN046 will be shipped in transport cool container (2°C to 8°C), according to the storage and shipping conditions. Shipments will be monitored with temperature control devices.

7.7 Preparation, handling and storage of the investigational medicinal product

KN046 drug product must be diluted with sterile 5% dextrose in water supplied in an infusion bag. Detailed information on preparation of the dilutions and subsequent administration will be provided in the Manual of Preparation.

The study drug must be stored at 2°C to 8°C until use, with a temperature log maintained daily. The

study drug must be stored carefully and safely from other drugs that can only be accessed by investigators and authorized site personnel.

7.8 Investigational medicinal product accountability

The Investigator is responsible for ensuring accountability for KN046, including reconciliation of drugs and maintenance of drug records.

Upon receipt of study drugs, the Investigator (or designee) will check for accurate delivery and acknowledge receipt by signing (or initialing) and dating the documentation provided by the Sponsor and returning it to the Sponsor. A copy will be retained for the Investigator Site File.

Dispensing of study drugs will be carefully recorded on the appropriate drug accountability forms provided by the Sponsor and an accurate accounting will be available for verification by the Clinical Research Associate (CRA) (or equivalent) at each monitoring visit.

Study drug accountability records will include:

- Confirmation of study drug delivery to the study site;
- The inventory at the site of study drug provided by the Sponsor and prepared at the site;
- The use of each dose of study drug by each subject;
- Destruction of unused study drug;
- Dates, quantities, batch number, expiry dates and formulation, as well as the subjects' Study Identifier Numbers.

The investigator should maintain records that adequately document:

- That the subjects were provided the doses specified by the Clinical Trial Protocol / Amendment(s);
- That all study drug provided by the Sponsor was fully reconciled.

Unused study drug must not be discarded or used for any purpose other than this study. Any study drug that has been dispensed to a subject must not be re-dispensed to a different subject. The CRA will periodically collect the study drug accountability forms and will check all returns (both unused and used containers) before authorizing their destruction by the site.

At the conclusion or termination of this study, site personnel and the CRA will conduct a final product supply inventory on the Drug Accountability Forms and all unused containers will be destroyed. Instructions for destruction of study drug will be provided to the site. The CRA will be supplied with a copy of the Drug Accountability Forms for filing. This documentation must contain a record of clinical supplies used, unused and destroyed, and shall include information on:

- All administered units;
- All unused units;
- All destroyed units (during the study);
- All destroyed units at the end of the study;
- Date(s) of destruction(s);
- Name and signature of the Investigator/pharmacist.

In addition, it must be ensured at each study site that the study drug **MUST NOT BE** used:

- After the expiry date;
- After the retest date, unless the study drug is reanalyzed and its retest date extended.

This is to be closely monitored by the CRA.

7.9 Assessment of investigational medicinal product compliance

In this study, subjects will receive the KN046 at the study site. Well trained medical staff will monitor and perform administration of KN046. Details of each administration of KN046 including the date, time, and dose will be recorded on the eCRF. The Investigator will make sure that the information entered onto the eCRF regarding administration is accurate for each subject. Any reason for noncompliance should be documented.

Noncompliance is defined as a subject missing > 3 cycles or 12 weeks of KN046 for nonmedical reasons. Should these situations occur, the subject should be withdrawn from KN046 treatment (See Section **Error! Reference source not found.**).

7.10 Duration of Follow Up

Subjects will be followed for 2 years after removal from study or until death, whichever occurs first. Subjects removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

7.11. Measures to Minimize Bias: Randomization and Blinding

This is an open-label trial. There is no blinding.

8. Study Intervention Discontinuation and Participant Discontinuation/Withdrawal

Participants are free to withdraw from participation in the study at any time.

8.1 Criteria for subject withdrawal

A subject must be withdrawn from KN046 in the event of any of the following:

- Confirmed PD per RECIST 1.1 and the investigator consider that continuing KN046 treatment will not benefit (note: subject receiving KN046 may continue past the initial determination of PD if the subject meets the criteria of clinically stable);
- Significant clinical deterioration (clinical progression) is defined as new symptoms that are deemed by the investigator to be clinically significant or significant worsening of existing symptoms;
- Therapeutic failure requiring urgent additional anticancer drug;
- Unacceptable toxicity (if a subject does not occur RECIST 1.1 defined confirmed PD, the subject will be asked to continue tumor assessment until RECIST 1.1 defined PD is confirmed);
- Occurrence of pregnancy;
- Use of a nonpermitted concomitant drug as defined in Section 7.4.2 where the predefined consequence is withdrawal from KN046;

- Withdrawal of the subject's consent to continue KN046 (if a subject withdraws consent, the subject will be asked to continue tumor assessments if RECIST 1.1 defined confirmed PD does not occur);

- Noncompliance.

- Withdrawal of the subject's consent. If the subject withdraws consent, it must be clearly stated if the subject is also withdrawing their consent from the post-treatment follow-up assessments;

- Participation in any other therapeutic study during the Treatment Phase of this study; however, subjects will continue to be followed for new anticancer therapy and for survival;

- Lost to follow-up.

In case of withdrawal from the study, the assessment schedule for end-of-treatment visit should be performed if possible and focus on the most relevant assessments. Subjects will be asked to continue safety and long-term follow-up, which includes the collection of data on survival and subsequent anticancer therapy.

The investigator must determine the primary reason for the subject's withdrawal as completely and accurately as possible. The reason for participant discontinuation or withdrawal from the study will be recorded in the medical record and RedCap.

8.2 Lost to Follow Up

A participant will be considered lost to follow-up if he or she fails to return for 3 scheduled visits and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study. If treatment cannot be resumed within 12 weeks from last administration, patient will go off treatment.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

9. Correlative/Special Studies

Correlative studies analyzing blood, archival tumor tissue, and new tumor biopsies will run concurrently with the study. We will investigate biomarkers to prognosticate response and immune related side effects. All findings will be correlated with patient outcomes.

We will assess gene expression and immune cell infiltrates at baseline. In case of severe autoimmune disorders after initiation of KN046 treatment, tissue-directed biopsies and blood will

be drawn for TCR sequencing and to assess circulating levels of cytokines. The primary hypothesis will be that treatment will reduce systemic levels of cytokines associated with a suppressive myeloid environment in patients who develop irAEs. To that end, we will quantify pre and on treatment levels of the following cytokines: IL-8, IL-6, and IL-1 all of which have been associated with a non-permissive tumor microenvironment. As a secondary hypothesis, we will test whether levels of pro-inflammatory cytokines are increased in a compensatory manner – those studies will focus on IFN-γ, IL-12 and IL-2.

9.1. Laboratory Correlative Studies

Correlative laboratory studies will be collected, sent, and stored to the PI's laboratory, located on 1300 York Avenue, 6th floor Room A601, New York, NY 10065.

9.1.1 Laboratory Correlative Study

We will obtain baseline neutrophil-to-lymphocyte ratio (NLR) and absolute lymphocyte counts (ALC) since ALC >2000 (26) and NLR <3 (27) have been shown to be correlated with an increased risk of irAEs. Levels of multiple cytokines and chemokines reflecting inflammatory immune responses (IL-6, IL-10, IFN-γ, CXCL10/11, TNFα, CCL2, CCL5, etc.) will be measured using human cytokine array (HD71; Eve Technologies). A CYTOX score was identified in melanoma patients, which predicts early risk of severe irAEs (28). We will use these laboratory results to validate CYTOX as a biomarker for toxicity in patients on immune checkpoint blockade.

Circulating tumor DNA will be sequentially assessed at baseline, at time of best response and at tumor progression. Autoantibodies against Acetylcholine Receptor, striated muscle (anti-SM) and muscle-specific kinase (MUSK) will be assessed at baseline. Patients with elevated autoantibodies at baseline will be excluded. Blood samples for TCR sequencing will be collected at baseline and if irAE occurs.

9.1.1.1 Collection of Specimen(s)

Serial blood samples will be collected for serum and peripheral blood mononuclear cells (PBMC) at baseline and during treatment. Timepoints will be at baseline, after 2 cycles, and at occurrence of irAE (if any).

9.1.1.2 Handling of Specimen(s)

Whole blood samples will be stored in -80 C within 16 hours to preserve nucleic acid quality. Formalin-fixed paraffin-embedded (FFPE) unstained sections will be stored in +4 C and FFPE blocks will be stored at room temperature.

9.2. Special Studies

9.2.1 Special Correlative Studies

We hypothesize that additional mutations may appear after chemotherapy that could potentially lead to PD-L1 upregulation in thymic carcinomas and therefore induce sensitivity to PD-1 antibody therapy. Thus we plan to explore whether specific genetic mutations and the number of mutations are associated with PD-L1 expression in thymic carcinomas and patients' response to KN046 therapy (targeting CTLA-4 and PD-L1). Attempts will be made to obtain tumor material before enrolling onto this study. Samples (fresh or FFPE samples) collected post chemotherapy and their normal blood pairs as well as 10 fresh or archived FFPE tumor materials derived from the same patients before systemic chemotherapy will be sequenced using NEXTGEN technology focusing on all the identified recurrent mutations in thymic carcinomas [33; 38], published cancer driver genes

[39] and COSMIC cancer gene census (http://cancer.sanger.ac.uk/cosmic/census). Comparative sequencing analysis of the tumor/blood pairs allows us to identify specific somatic mutations and the number of somatic mutations in a given tumor. Moreover, comparative analysis of tumor samples from the same patient before and after systemic treatment can uncover whether the tumor may acquire additional mutations after chemotherapy. The data will be employed to evaluate the correlation between the type/number of mutations and PD-L1 expression in the tumors and patients' response to PD-1 antibody therapy.

9.2.1.1 Assessment

For archival tumor specimens, gene expression profiling (GEP) by Nanostring (12), RNAseq and Whole Exome Sequencing (WES) will be performed and results will be correlated with clinical outcome and response to therapy. We will obtain normal peripheral blood as a control for WES. Tumor specimens will also be evaluated for tumor-infiltrating lymphocyte (TIL) infiltration. The main immune cell subsets will be quantified by immunohistochemical analysis for markers of T cells (CD3, CD4, CD8, FoxP30), DC (CD11c) and macrophages (CD68), and for expression of PD-L1.

9.2.1.2 Method of Assessment

Whenever feasible, fresh tissue will be obtained to establish organoids(29, 30). If sufficient tumor material is available, attempts will also be made to develop patient-derived xenograft (PDX) models. Both organoids and PDX tumors will be characterized with several immunohistochemistry markers and by sequencing as described above. Organoids will be subjected to in vitro drug testing using a robotic platform that is available in our cancer center through the Weill Cornell Medicine Englander Institute for Precision Medicine. PDX models will be subjected to in vivo drug testing. TCR sequencing will be performed on tumor, sequential blood samples and non-lesional/lesional tissue biopsies in patients who develop autoimmune disorders, using the Adaptive platform (12).

9.2.1.3 Timing of Assessment

On-treatment biopsies would be obtained at time of irAE development if it occurs.

10. Measurement of Effect

10.1 Response Criteria

RECIST v1.1 will be applied by the site as the primary measure of tumor assessment and response and as the basis for protocol guidelines related to disease status (e.g., discontinuation of study treatment).

Radiological scans of all suspected sites of disease will be performed utilizing the same method and technique throughout the study. Target lesions should demonstrate the patient's baseline tumor burden and will be selected based on size (i.e., lesions with the longest diameter), and suitability for accurate repeat assessment.

The following should be performed:

- PET-CT scans are required for all patients at Screening, at the time of best response, and as clinically indicated
- Chest, abdomen, and pelvis CT (Chest CT and Abdomen/Pelvis MRI acceptable) are required for all patients every 2 cycles for the first year and then every 4 cycles for the second year.

Additional imaging evaluations may be performed at any time if there is symptomatic evidence suggesting the possibility of disease progression based on clinical symptoms or physical examination.

10.2 Duration of response

Among subjects with a confirmed response (PR or CR) per RECIST 1.1, duration of response (DOR) is defined as the time from first documented response (PR or CR) to the date of first documented disease progression or death due to underlying cancer. DOR will be listed by subject and described using Kaplan-Meier curves and relevant statistics if appropriate.

10.3 Progression-Free Survival

PFS is defined as the duration of time from start of treatment to time of progression.

10.4 Other Response Parameters

None

11. Data Reporting / Regulatory Considerations

11.1 Data Collection

The data collection plan for this study is to utilize REDCap to capture all treatment, toxicity, efficacy, and adverse event data for all enrolled subjects.

11.1.1 REDCap

REDCap (Research Electronic Data Capture) is a free data management software system that is fully supported by the Weill-Cornell Medical Center CTSC. It is a tool for the creation of customized, secure data management systems that include Web-based data-entry forms, reporting tools, and a full array of security features including user and group based privileges, authentication using institution LDAP system, with a full audit trail of data manipulation and export procedures. REDCap is maintained on CTSC-owned servers that are backed up nightly and support encrypted (SSL-based) connections. Nationally, the software is developed, enhanced and supported through a multi-institutional consortium led by the Vanderbilt University CTSA.

11.2 Regulatory Considerations

11.2.1 Institutional Review Board/Ethics Committee Approval

As required by local regulations, the Investigator will ensure all legal aspects are covered, and approval of the appropriate regulatory bodies obtained, before study initiation.

Before initiation of the study at each study center, the protocol, the ICF, other written material given to the patients, and any other relevant study documentation will be submitted to the appropriate Ethics Committee. Written approval of the study and all relevant study information must be obtained before the study center can be initiated or the IP is released to the Investigator. Any necessary extensions or renewals of IRB approval must be obtained for changes to the study,

such as amendments to the protocol, the ICF, or other study documentation. The written approval of the IRB together with the approved ICF must be filed in the study files.

The Investigator will report promptly to the IRB any new information that may adversely affect the safety of the patients or the conduct of the study. The Investigator will submit written summaries of the study status to the IRB as required. On completion of the study, the IRB will be notified that the study has ended.

All agreed protocol amendments will be clearly recorded on a protocol amendment form and will be signed and dated by the original protocol approving signatories. All protocol amendments will be submitted to the relevant institutional IRB for approval before implementation, as required by local regulations. The only exception will be when the amendment is necessary to eliminate an immediate hazard to the trial participants. In this case, the necessary action will be taken first, with the relevant protocol amendment following shortly thereafter.

Once protocol amendments or consent form modifications are implemented at the lead site, Weill Cornell Medicine, updated documents will be provided to participating sites, as applicable. Weill Cornell Medicine must approve all consent form changes prior to local IRB submission.

Relevant study documentation will be submitted to the regulatory authorities of the participating countries, according to local/national requirements, for review and approval before the beginning of the study. On completion of the study, the regulatory authorities will be notified that the study has ended.

11.2.2 Ethical Conduct of the Study

The Investigators and all parties involved should conduct this study in adherence to the ethical principles based on the Declaration of Helsinki, GCP, ICH guidelines and the applicable national and local laws and regulatory requirements.

This study will be conducted under a protocol reviewed and approved by the applicable ethics committees and investigations will be undertaken by scientifically and medically qualified persons, where the benefits of the study are in proportion to the risks.

11.2.3 Informed Consent

The investigator or qualified designee must obtain documented consent according to ICH-GCP and local regulations, as applicable, from each potential subject or each subject's legally authorized representative prior to participating in the research study. Subjects who agree to participate will sign the approved informed consent form and will be provided a copy of the signed document.

The initial ICF, any subsequent revised written ICF and any written information provided to the subject must approved by IRB prior to use. The ICF will adhere to IRB requirements, applicable laws and regulations.

11.2.4 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the Sponsor-Investigator of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to http://www.clinicaltrials.gov. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial site contact information.

11.2.5 Record Retention

Essential documents are those documents that individually and collectively permit evaluation of the study and quality of the data produced. After completion of the study, all documents and data relating to the study will be kept in an orderly manner by the Investigator in a secure study file. Essential documents should be retained for 2 years after the final marketing approval in an ICH region or for at least 2 years since the discontinuation of clinical development of the IP. In addition, all subjects medical records and other source documentation will be kept for the maximum time permitted by the hospital, institution, or medical practice.

12. Statistical Considerations

12.1 Study Design/Endpoints

This is an open-label, single arm, single center non-randomized Phase II study to investigate the efficacy and safety of KN046 in patients with advanced thymic carcinoma who have progressed on prior immune checkpoint inhibitor therapy. Subjects will be treated with KN046 5 mg/kg q2wk.

A Simon's two-stage design will be used. Under the optimum design criterion, a sample size of 29 is required to test a null hypothesis of H_o: $\pi \leq 0.05$ versus an alternative hypothesis of H_1: $\pi \geq 0.2$ with a one-sided significance level of 0.047 and 80.11% power, where π is the true proportion of successes. This design results in an expected sample size of 17.624 and a probability of early termination of 0.599. If the number of responses is less than or equal to 0 out of 10 subjects in the first stage then the trial will be stopped. If the trial proceeds to the second stage, 29 subjects in total will be studied. If 3 or less responses are observed, then KN046 is rejected.

12.2 Sample Size/Accrual Rate

29 subjects are anticipated to be enrolled in this protocol.
A Simon's two-stage design will be used. Under the optimum design criterion, a sample size of 29 is required to test a null hypothesis of H_o: $\pi \leq 0.05$ versus an alternative hypothesis of H_1: $\pi \geq 0.2$ with a one-sided significance level of 0.047 and 80.11% power, where π is the true proportion of successes. This design results in an expected sample size of 17.624 and a probability of early termination of 0.599. If the number of responses is less than or equal to 0 out of 10 subjects in the first stage then the trial will be stopped. If the trial proceeds to the second stage, 29 subjects in total will be studied. If 3 or less responses are observed, then KN046 is rejected. A total sample size of 29 subjects are planned.

12.3 Stratification Factors
None

12.4 Analysis of Endpoints

12.4.1 Analysis of Primary Endpoints

Primary endpoint: Response rate. Responses will be assessed according to RECIST 1.1.

For ORR analysis, 95% confidence interval (CI) will be calculated using the Clopper Pearson method.

12.4.2 Analysis of Secondary Endpoints

Secondary endpoints: duration of response, PFS, OS, safety and tolerability.
Safety will be assessed by monitoring all adverse events, including serious adverse events, immune-related adverse events (irAEs), infusion reactions, regular monitoring of bloodwork (including CPK and troponin levels), vital signs, EKGs, and echocardiograms. Kaplan–Meier estimator will be used to estimate PFS and OS.

Safety and tolerability analysis will be performed on SS. The safety endpoints will be tabulated using descriptive statistics.

The extent of exposure to KN046 will be characterized by duration (weeks), number of administrations, cumulative dose (mg/kg), dose intensity (mg/kg/week), relative dose intensity (actual dose given/planned dose), number of dose reductions, and number of dose delays.

Safety assessments will be based on review of the incidence of AEs, adverse drug reactions (ADRs), and changes in vital signs, ECGs, body weight, and laboratory values (hematology and serum chemistry).

For a single proportion, such as PFS rate, and OS rate, 95% CIs will be calculated using the Clopper Pearson method. For time to event variable, for example DOR, PFS and OS analysis, the Kaplan-Meier method will be used to estimate parameters (including the median with corresponding 2-sided 95% CIs). The PFS and OS rates will be estimated with corresponding 95% CIs at appropriate time points, e.g., at 6 and 12 months.

12.4.3. Exploratory Endpoints
(1) Determine the association of PD-L1 expression in tumor samples and treatment response
(2) Perform RNAseq and whole exome sequencing (WES), and determine the association of the molecular profile with treatment response,
(3) Identify and validate blood and tumor biomarkers that are associated with efficacy-related endpoints or toxicity,
(4) Develop organoids and PDX models whenever feasible, in order to functionally characterize the tumor of origin and perform drug testing

12.4.4 Analysis Population

Efficacy Analysis Set (EAS): all subjects who are centrally confirmed diagnosis of thymic carcinoma and received at least 1 trial treatment. EAS will be used for efficacy analysis.
Safety set (SS): all subjects who receive at least one dose of trial treatment and have at least one valid post-baseline safety assessment. The statement that a patient has no AE (on the Adverse Event eCRF) continues a valid safety assessment.
Per-protocol set (PPS): consist of a subset of subjects who are compliant with requirements of the Clinical Trial Protocol (CTP). The PPS will include subjects who have an adequate tumor assessment at baseline, a follow-up tumor assessment >6 weeks after starting treatment, and no major protocol deviations

12.5 Interim Analysis

Response will be assessed in the first 10 patients and the study will be continued if responses are seen, or discontinued if no responses are seen.

12.6 Reporting and Exclusions

12.6.1 Evaluation of Toxicity

All subjects will be evaluable for toxicity from the time of their first treatment with KN046.

12.6.2 Evaluation of Response

All subjects included in the study will be assessed for response to treatment if they have received at least *one* treatment. The response rate will be estimated as a binomial proportion with 95% exact Clopper-Pearson confidence interval using exact binomial calculation

13. Adverse Event Reporting Requirements

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The investigator will be required to provide appropriate information concerning any findings that suggest significant hazards, contraindications, side effects, or precautions pertinent to the safe use of the drug or device under investigation. Safety will be monitored by evaluation of adverse events reported by subjects or observed by investigators or research staff, as well as by other investigations such as clinical laboratory tests, x-rays, electrocardiographs, etc.

13.1 Adverse Event Definition

An adverse event (also referred to as an adverse experience) can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, and does not imply any judgment about causality. An adverse event can arise with any use of the drug (e.g., off-label use, use in combination with another drug) and with any route of administration, formulation, or dose, including an overdose.

13.1.1 Investigational Agent or Device Risks (Expected Adverse Events)

Expected adverse events to monitor for include infusion-related adverse events, hypersensitivity reactions and immune-related adverse events.

13.1.2 Adverse Event Characteristics and Related Attributions

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov).

- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.
  - Unlikely – The AE *is doubtfully related* to the study treatment.
  - Unrelated – The AE *is clearly NOT related* to the study treatment.

13.1.3 Recording of Adverse Events

All adverse events will be recorded on a subject specific AE log. The AE log will be maintained by the research staff and kept in the subject's research chart.

13.1.4 Reporting of AE to WCM IRB

All AEs occurring on this study will be reported to the IRB according to the IRB policy, which can be accessed via the following link: http://researchintegrity.weill.cornell.edu/forms_and_policies/forms/Immediate_Reporting_Policy.pdf.

13.1.6 Events of Special Interest

See section 2.4.1

13.1.7 Reporting of Pregnancy

If, following initiation of the study drug, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of study exposure, including during at least 24 weeks after product administration, the investigator must immediately notify the Sponsor Medical Monitor/designee of this event and complete and forward a Pregnancy Reporting Form to sponsor within 24 hours of awareness of the event and in accordance with SAE reporting procedures. In the event of a pregnancy in a subject occurring during the course of the study, the subject must be discontinued from KN046 administration immediately.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on the Pregnancy Reporting Form.

Any pregnancy that occurs in a female partner of a male study participant should be reported to Alphamab. Information on this pregnancy will be collected on the Pregnancy Reporting Form.

Any abnormal outcome must be reported in an expedited manner, while normal outcomes must be reported within 45 days from delivery

13.2 Definition of SAE

SAEs include death, life threatening adverse experiences, hospitalization or prolongation of hospitalization, disability or incapacitation, overdose, congenital anomalies and any other serious events that may jeopardize the subject or require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or research subject and may require medical or surgical intervention to prevent one of the outcomes listed as serious

13.2.1 Reporting of SAE to IRB

All SAEs occurring on this study will be reported to the IRB according to the IRB policy, which can be accessed via the following link: http://researchintegrity.weill.cornell.edu/forms_and_policies/forms/Immediate_Reporting_Policy.pdf.

13.2.2 Reporting of SAE to FDA

The Principal Investigator must report any suspected adverse reaction or adverse reaction to study treatment that is both serious and unexpected. Unexpected fatal or life-threatening suspected adverse reactions represent especially important safety information and must be reported to FDA as soon as possible but no later than 7 calendar days following the Principal Investigator's initial receipt of the information.

CDER INDs:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of *Biological* Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

13.2.3 Reporting of SAE to Jiansu

Institution will send Jiansu copies of any and all serious adverse event reports filed with the FDA or other applicable regulatory authorities, as well as copies of any correspondence with the FDA or other applicable regulatory authorities, regarding any

and all serious adverse events, irrespective of association with the Study Drug(s) in the course of the Clinical Trial, within 7 business days of such report or correspondence being sent to the FDA or other applicable regulatory authorities.

13.3 AE/SAE Follow Up

All SAEs and AEs reported during this study will be followed until resolution or until the investigator confirms that the AE/SAE has stabilized and no more follow-up is required. This requirement indicates that follow-up may be required for some events after the subject discontinues participation from the study.

14. Data and Safety Monitoring Plan (DSMP)

- The WCM DSMB will monitor all aspects of the safety of this trial.
- All applicable adverse events will be captured and reported to the DSMB. Efficacy data in this trial are the biological and imaging endpoints will be batched and not processed until the end of the trial so they will not be reported in real time to the DSMB.
- The study will be submitted to the DSMB for review every 4 months.

15. Stopping Rules

- If severe autoimmune disorders markedly exceed the expected 15%, the study will be terminated. If in the first 10 patients accrued in the stage I of the study, 4 or more patients develop severe autoimmune disorders, accrual to the study will be stopped and an assessment of safety will be performed with the Sponsor.
- Treatment stopping rules for an individual patient include:
    - Disease progression,
    - Significant study intervention non-compliance
    - Pregnancy
    - Intercurrent illness that prevents further administration of treatment,
    - Unacceptable adverse event(s),
    - Patient decides to withdraw from the study, or
    - General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator
    - Participant lost to follow-up after several attempts to contact subject to schedule study visit.

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16. Appendix A: Guidelines on the management of immune related adverse events

Only the general principles of treatment for relatively common immune-related adverse events are listed below. Other immune-related toxicities, including rare but severe immune-related toxicity treatments (such as immune-related ocular toxicity and central nervous system toxicity) can be found in ESMO (31) and NCCN (32). Subjects who have been treated for more than 3 weeks with steroids recommend the use of drugs such as sulfamethoxazole/trimethoprim to prevent opportunistic infections such as pneumocystis.

Table 06-1 Management of immune related pneumonitis

CTCAE v5.0 Grade	KN046 Dosing Management	Action and Guidelines	Diagnostic Consideration
Grade 1 Asymptomatic. Radiographic changes only presenting as ground glass change, non-specific interstitial pneumonia	• Consider delay KN046 treatment	• Monitor symptoms and signs every 2~3 days • Radiologic findings should be followed on serial imaging studies at least every 3 weeks • Consider pulmonary consultation. Perform bronchoscopy if clinically indicated	All attempts should be made to rule out other causes such as metastatic disease, bacterial (eg, Legionella, Mycoplasma) or viral infection
Grade 2 Mild/moderate new symptoms of dyspnea, cough, chest pain	• Withhold KN046 • Treatment with KN046 may be resumed if the event improves to ≤Grade 1 within 12 weeks and corticosteroids have been reduced to the equivalent of methylprednisolone 10 mg/day orally or less • Discontinue KN046 if upon rechallenge the patient develops a second episode of ≥Grade 2 pneumonia • Discontinue KN046 if Grade 2 pneumonia lasting for ≥4 weeks despite appropriate medical intervention	• Rule out other causes such as infectious diseases • Consider pulmonary function tests • Consider pulmonary consultation. Perform bronchoscopy and biopsy/bronchoalveolar lavage (BAL) if clinically indicated • Start empirical antibiotics treatment if suspicion of infection (fever, CRP increased, neutrophil counts increased) • Consider hospitalization and monitor signs and symptoms every day • If no evidence of infection or no improvement in signs and symptoms with antibiotics after 48 hours, add in prednisolone 1 mg/kg/day (or equivalent) orally with prolonged	

CTCAE v5.0 Grade	KN046 Dosing Management	Action and Guidelines	Diagnostic Consideration
		taper lasting for at least 4 weeks	
Grade 3-4 Severe new symptoms; new/worsening hypoxia; life threatening; difficulty in breathing; acute respiratory distress syndrome (ARDS)	• Discontinue KN046	• Perform pulmonary function tests • Pulmonary consultation. Recommend to perform bronchoscopy and biopsy/bronchoalveolar lavage (BAL) • Treat with intravenous (IV) methylprednisolone 2~4 mg/kg/day (or equivalent). When symptoms improve to Grade 1 or less, a high-dose oral steroid (eg, prednisone 1~2 mg/kg/day or equivalent) taper should be started and continued over no less than 4 weeks • If IV steroids followed by high-dose oral steroids does not reduce initial symptoms within 48~72 hours, treat with infliximab at 5 mg/kg once every 2 weeks. Discontinue infliximab upon symptom relief and initiate a prolonged steroid taper over 6~8 weeks. If symptoms worsen during steroid reduction, initiate a retapering of steroid starting at a higher dose of 80 or 100 mg followed by a more prolonged taper with or without administration of infliximab. Addition of mycophenolate mofetil to replace infliximab could	

CTCAE v5.0 Grade	KN046 Dosing Management	Action and Guidelines	Diagnostic Consideration
		be considered if the subject has liver injury • Add prophylactic antibiotics for preventing opportunistic infections	

Table 0-2 Management of immune related colitis

CTCAE v5.0 Grade	KN046 Dosing Management	Action and Guidelines	Diagnostic Consideration
Grade 1 < 4 liquid stools per day over baseline	• No change in KN046 dose	• For diarrhea, treat symptomatically (loperamide, oral hydration, electrolyte substitution, ADA colitis diet and avoid high fiber high lactose diet) • Grade 1 diarrhea that persist for > 1 week should be treated with the addition of oral diphenoxylate hydrochloride and atropine sulfate four times daily and budesonide 9 mg daily • Grade 1 diarrhea that persist for > 2 weeks should consider to add treatment with prednisolone 0.5~1 mg/kg (non-enteric coated) • If diarrhea persists, endoscopy is recommended	All attempts should be made to rule out other causes such as metastatic disease, bacterial or parasitic infection, viral gastroenteritis, or the first manifestation of an inflammatory bowel disease by examination for stool leukocytes, stool cultures, and a Clostridium difficile titer
Grade 2 4~6 liquid stools per day over baseline, or abdominal pain, or blood in stool or nausea or nocturnal episodes	• Withhold KN046 till ≤ Grade 1	• Consultation with gastroenterologist and endoscopy is recommended to confirm or rule out colitis for Grade 2 diarrhea that persists > 1 week or Grade 1~2	

CTCAE v5.0 Grade	KN046 Dosing Management	Action and Guidelines	Diagnostic Consideration
		diarrhea with rectal bleeding • Grade 2 diarrhea should be treated with the addition of oral diphenoxylate hydrochloride and atropine sulfate four times daily and budesonide 9 mg daily • Grade 2 diarrhea that persists > 1 week or Grade 2 diarrhea with diffuse ulceration and bleeding seen on endoscopy is recommended to add oral prednisolone 0.5~1 mg/kg (or equivalent) with prolonged taper lasting for at least 4 weeks prednisolone. Diffuse ulceration and bleeding seen on endoscopy represents an increased risk for the development of bowel perforation and indicates longer taper of steroid	
Grade 3-4 ≥7 liquid stools per day or life-threatening	• Withhold KN046 • KN046 will be permanently discontinued if ≥Grade 3 colitis is confirmed • Discontinue KN046 if unable to reduce corticosteroid dose to < 10 mg per day prednisone or equivalent within 12 weeks of toxicity	• Require hospitalization • Endoscopy is recommended to confirm or rule out colitis • Grade 3-4 colitis • Systemic corticosteroids should be initiated at a dose of 1~2 mg/kg/day of prednisone or equivalent. When symptoms improve to Grade 1 or less, corticosteroid taper should be started and continued over at least 4 weeks • Grade 3-4 diarrhea	

CTCAE v5.0 Grade	KN046 Dosing Management	Action and Guidelines	Diagnostic Consideration
		• Rule out bowel perforation. Imaging with plain films or computed tomography (CT) can be useful • Consider consultation with gastroenterologist and confirmation biopsy with endoscopy • Treat with intravenous (IV) steroids (methylprednisolone 125 mg) followed by high-dose oral steroids (prednisone 1~2 mg/kg once per day or equivalent). When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Taper over 6~8 weeks in patients with diffuse and severe ulceration and/or bleeding • If IV steroids followed by high-dose oral steroids does not reduce initial symptoms within 48~72 hours, consider treatment with infliximab upon symptom relief and initiate a prolonged steroid taper over 6~8 weeks. If symptoms worsen during steroid reduction, initiate a retapering of steroids starting at a higher dose of	

CTCAE v5.0 Grade	KN046 Dosing Management	Action and Guidelines	Diagnostic Consideration
		80 or 100 mg followed by a more prolonged taper with or without administration of infliximab. **Caution:** infliximab is contradicted in patients with bowel perforation or sepsis • If symptoms persist despite the above treatment, a surgical consult should be obtained	

Table 16-3 Management of immune related endocrinopathies

CTCAE v5.0 Grade	KN046 Dosing Management	Action and Guidelines	Diagnostic Consideration
Grade 1-2 • Hyperthyroidism • Hypothyroidism • Thyroid disorder • Thyroiditis	• No change in KN046 dose	• Monitor thyroid function or other hormone level tests and serum chemistries more frequently (every 3~6 weeks) until returned to baseline values or clinically stable • Replacement of thyroid hormone or thyroid suppression therapy as clinically indicated	All attempts should be made to rule out other causes such as brain metastases, sepsis, and/or severe infection
Grade 3-4 • Hyperthyroidism • Hypothyroidism • Thyroid disorder • Thyroiditis	• Withhold KN046 treatment until on stable replacement dose as determined by resolution of symptoms and normalization of hormone levels	• Consider endocrine consultation • Replacement of thyroid hormone or thyroid suppression therapy as clinically indicated	
Grade 1-4 • Adrenal insufficiency • Hypophysitis • Hypopituitarism • Pan-hypopituitarism	• Withhold KN046 treatment until on stable replacement dose as determined by resolution of symptoms and normalization of hormone levels	• Consider endocrine consultation • Thyroid hormone and/or steroid replacement therapy to manage adrenal insufficiency • If Grade 1~2 hypophysitis is considered, pituitary gland imaging should be considered (magnetic resonance imaging [MRIs] with gadolinium and selective cuts of the pituitary can show enlargement or heterogeneity and confirm the diagnosis) • If adrenal crisis occurs (Grade 3~4 hypophysitis with clinically significant adrenal insufficiency and hypotension, dehydration, and	

		electrolyte abnormalities, such as hyponatremia and hyperkalemia), it requires hospitalization and intravenous methylprednisolone should be initiated	

Table 0 Management of immune related hepatitis

CTCAE v5.0 Grade	**KN046 Dosing Management**	**Action and Guidelines**	**Diagnostic Consideration**
Grade 1 • ALT or AST>1-3 x ULN • Subjects with baseline ALT or AST increased, toxicity Grading worsened for ≤1	• No change in KN046 dose	• Weekly monitor liver function tests	All attempts should be made to rule out other causes such as medications (eg, statins, antibiotics), alcohol history, viral infections (eg, anti-HAV/HBV/HCV antibody, HEV PCR), other liver diseases (eg, anti-ANA / SMA / LKM / SLA / LP / LCI, iron studies) or metastasis / clot
Grade 2 • ALT or AST 3-5 x ULN • Subjects with baseline ALT or AST increased, toxicity Grading worsened for ≤1 and ≤5 x ULN	• Withhold KN046	• Monitor liver function tests every 3 days • If no improvement in liver function tests, treat with oral steroids (prednisolone 1 mg/kg/ day)	
Grade 3-4 • ALT or AST >5 x ULN • With or without total bilirubin increased > 3x ULN	• Discontinue KN046	• Liver biopsy to establish etiology of hepatic injury, if necessary • Treat with high-dose IV prednisolone 2 mg/kg/day or equivalent for 24~48 hours. When symptoms improve to Grade 1 or less, a steroid taper with oral prednisone at 1~2 mg/kg/day (or equivalent) should be started and continue over no less than 4 weeks	

		• If serum transaminase levels do not decrease 48 hours after initiation of systemic steroids, oral mycophenolate mofetil 500 mg every 12 hours may be given. **Caution:** infliximab is not recommended due to its potential for hepatotoxicity • Several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased	

Table 16-5 Management of immune related skin toxicity

CTCAE v5.0 Grade	**KN046 Dosing Management**	**Action and Guidelines**	**Diagnostic Consideration**

Grade 1-2
• Skin rash, with or without symptoms, <30% body surface area (BSA)
	• No change in KN046 dose	• Symptomatic treatment
		  • Topical corticosteroids, eg betamethasone 0.1% cream or hydrocortisone 1%)
		  • Urea-containing creams in combination with oral antipruritics (eg, diphenhydramine HCl or hydroxyzine HCl)
		• At investigator's discretion, treatment with oral steroids for Grade 2 events
		• Treat as Grade 3 skin toxicity if Grade 2 skin toxicity accompanies apparent clinical signs and symptoms
			All attempts should be made to rule out other causes such as metastatic disease, infection or allergic dermatitis

Grade 3 • Rash covers >30% BSA or Grade 2 with substantial symptoms	• Withhold KN046 treatment	• Dermatology consultation. Consider biopsy to confirm diagnosis • Recommend oral steroids treatment, starting with prednisone 1 mg/kg/day or equivalent. When	

		symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks	
Grade 4 • Skin sloughing >30% BSA with associated symptoms (eg, erythema, purpura, epidermal detachment)	• Discontinue KN046	• Dermatology consultation. Consider biopsy and clinical dermatology photograph • Initiate steroids at methylprednisolone 1~2 mg/kg/day or equivalent. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks	

Table 16-6 Management of immune related nephritis

CTCAE v5.0 Grade	KN046 Dosing Management	Action and Guidelines	Diagnostic Consideration
Grade 1 • Creatinine 1.5 x baseline or > ULN~1.5 x ULN	• No change in KN046 dose • Withhold KN046 if event does not improve with symptomatic treatment	• Symptomatic treatment • Monitor creatinine weekly; resume routine creatinine monitoring per protocol when it returns to baseline	All attempts should be made to rule out other causes such as obstructive uropathy, progression of disease, or injury to other medications
Grade 2 • Creatinine > 1.5~3 x baseline or > 1.5~3 x ULN	• Withhold KN046 treatment • Discontinue KN046 treatment if elevations persists > 7 days or worsen after appropriate medical interventions	• Renal consultation. Consider ultrasound and/or biopsy as appropriate • Treat with systemic corticosteroids at a dose of prednisolone 1~2 mg/kg/day or equivalent. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks • If elevations persist > 7 days or worsen, treat as Grade 3 or 4	
Grade 3-4 • Creatinine > 3 x baseline or >3 x ULN	• Discontinue KN046	• Renal consultation. Consider ultrasound and/or biopsy as appropriate • Monitor creatinine daily • Treat with systemic corticosteroids at a dose of prednisolone 1~2 mg/kg/day or equivalent. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks	

Table 0 Management of immune related myocarditis

CTCAE v5.0 Grade	KN046 Dosing Management	Action and Guidelines	Diagnostic Consideration

Grade 1
• Abnormal in cardiac tests (eg, myocardial enzymes, ECG)
	• Discontinue KN046	• Cardiology consultation
		• Exam ECG, troponin, BNP, cardiac ultrasound and chest X-ray
		• Immediately initiate high-dose steroid treatment
		  • Prednisolone 1~2 mg/kg/day or equivalent
		  • Increase steroid dose (eg, methylprednisolone 1 g/day) and add in infliximab, mycophenolate mofetil or anti-thymocyte globulin if symptoms do not promptly respond to steroids
		• Treat cardiovascular symptoms according to ACC/AHA guidelines
		• Subjects with troponin or conduction abnormalities requires to be treated within cardiac ICU
			All attempts should be made to rule out myocardial infarction, viral myocarditis, infectious heart valve disease etc

Grade 2 • Abnormal in cardiac tests with mild symptoms			
Grade 3-4 • Moderate to severe cardiac dysfunction requiring intravenous treatment or life-threatening			