CLINICAL STUDY PROTOCOL

Protocol Title:	A Phase 2 Study to Assess the Safety and Efficacy of HBI-8000 in Combination with Pembrolizumab for Advanced or Metastatic Non-Small Cell Lung Cancer (NSCLC)
Protocol Number:	HBI-8000-305
Study Phase:	2
Sponsor Name/Address:	HUYABIO International, LLC 12531 High Bluff Drive, Suite 138 San Diego, CA 92130 USA
IND Number:	[redacted]
Version:	Original Protocol, Version 1.0
Date of Protocol:	27 September 2021
Medical Monitor:	[redacted]

CONFIDENTIAL

The concepts and information contained in this document or generated during the study are considered proprietary and may not be disclosed in whole or in part without the express written consent of HUYABIO International, LLC and constitute Confidential Information under the Confidential Disclosure Agreement (CDA) between the parties.

The study will be conducted according to the International Council for Harmonisation (ICH) harmonised tripartite guideline E6 (R2): Good Clinical Practice (GCP), including the archiving of essential documents.

STATEMENT OF COMPLIANCE

The study will be conducted in compliance with this clinical study protocol, Good Clinical Practice (GCP) as outlined by International Council for Harmonisation (ICH) E6 (R2), and all applicable local regulations including US Code of Federal Regulations [CFR] Title 21 and with the ethical principles laid down in the Declaration of Helsinki. Enrollment at the clinical study site may not begin prior to receiving Institutional Review Board (IRB) approval of this protocol, the Investigator's Brochure (IB), and all patient facing materials (e.g., all advertising materials or materials given to the subject during the study).

Any amendments to the protocol and changes to the consent document must also be approved by the IRB before implementation of that amendment.

The Principal Investigator will ensure that changes to the study plan as defined by this protocol will not be made without prior agreement from the Sponsor and documented approval from the IRB of record, unless such a change is necessary to eliminate an immediate hazard to the study subjects.

SPONSOR'S APPROVAL

PROTOCOL TITLE: A Phase 2 Study to Assess the Safety and Efficacy of HBI-8000 in Combination with Pembrolizumab for Advanced or Metastatic Non-Small Cell Lung Cancer (NSCLC)

PROTOCOL NO: HBI-8000-305

[redacted]

INVESTIGATOR AGREEMENT

PROTOCOL TITLE: A Phase 2 Study to Assess the Safety and Efficacy of HBI-8000 in Combination with Pembrolizumab for Advanced or Metastatic Non-Small Cell Lung Cancer (NSCLC)

PROTOCOL NO: HBI-8000-305

I have read this protocol and agree to conduct this study in accordance with ethical principles as outlined in the International Council for Harmonisation (ICH) guidelines on Good Clinical Practice, and the US Code of Federal Regulations (CFR Title 21), any applicable laws and requirements and any additional conditions mandated by the US Food and Drug Administration and/or Institutional Review Board (IRB).

I acknowledge that I am responsible for the overall study conduct and I agree to personally conduct or supervise the described clinical study.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of HUYABIO International, LLC.

Instructions to the Investigator: Please SIGN and DATE this signature page. PRINT your name, title, and the name of the center in which the study will be conducted. Return the signed copy to Sponsor/Contract Research Organization (CRO).

I have read this protocol in its entirety and agree to conduct the study accordingly:

Signature of Investigator: _____ Date: _____
(DDMMMYYYY)

Printed Name: _____

Investigator Title: _____

Name/Address of Study Site: _____

_____

_____

STUDY SYNOPSIS

Name of Sponsor/ Company:	HUYABIO International, LLC
Name of Finished Product:	HBI-8000 (tucidinostat)
Name of Active Ingredient:	*N*-(2-amino-4-fluorophenyl)-4-{[(2E)-3-(pyridin-3-yl)prop-2-enamido]methyl} benzamide
Title of Study:	A Phase 2 Study to Assess the Safety and Efficacy of HBI-8000 in Combination with Pembrolizumab for Advanced or Metastatic Non-Small Cell Lung Cancer (NSCLC)
Protocol No:	HBI-8000-305
Lead Investigator:	Lyudmila Bazhenova, MD
Indication	Advanced or Metastatic NSCLC
Study Population	Subjects ≥18 years of age with advanced or metastatic NSCLC who have not received immune checkpoint inhibitor for their disease but have programmed death ligand 1 (PD-L1) expression Tumor Proportion Score (TPS): ≥1%.
Study center(s):	Multicenter study (US): 6-10
Study duration:	Approximately 38 months (including follow-up) The study will include a screening period (up to 28 days), up to 24 months of treatment of HBI-8000 with pembrolizumab, up to 1 month post-treatment follow-up for safety, and up to 12 months after the last dose of HBI-8000 for survival follow-up by telephone calls/e-mails.
Phase	2
Study Treatment	HBI-8000 tablets 30 mg/dose, orally twice a week An HBI-8000 treatment cycle consists of twice a week dosing over 21 consecutive days. Pembrolizumab will be administered at 400 mg every 6 weeks or 200 mg every 3 weeks according to Prescribing Information and institutional practice. Treatment will continue until disease progression or unacceptable toxicity occurs. Should toxicity be deemed not related to pembrolizumab but HBI-8000, subject may continue to receive pembrolizumab under standard of care. Should toxicities be deemed related to pembrolizumab, the subject may continue receiving HBI-8000 at the discretion of Investigator.
Objectives:	Primary: • To evaluate the efficacy of HBI-8000 in combination with a standard dose and regimen of pembrolizumab as a first line checkpoint inhibitor therapy for advanced or metastatic NSCLC, as measured by Objective Response Rate (ORR) according to the Response Evaluation Criteria in Solid Tumors (RECIST) criteria version 1.1 [Eisenhauer 2009]. Secondary: • To evaluate the safety and tolerability of HBI-8000 in combination with a standard dose and regimen of pembrolizumab • To explore the additional efficacy parameters for HBI-8000 in combination with a standard dose and regimen of pembrolizumab as measured by Disease Control Rate (DCR), Duration of Response (DoR), and Progression-Free Survival (PFS)

Study design	This is a multicenter, open label, Phase 2 study of HBI-8000 in combination with a U.S. Food and Drug Administration (FDA) approved dose of pembrolizumab as a first line checkpoint inhibitor therapy for advanced or metastatic NSCLC where subjects must have programmed death ligand 1 (PD-L1) expression Tumor Proportion Score (TPS) ≥1%.
Planned number of subjects:	20 to 24 subjects are planned for the study.
Diagnosis and main criteria for inclusion:	Inclusion Criteria Subjects may be entered in the study only if they meet all the following criteria: 1. Adults at least 18 years of age. 2. Eastern Cooperative Oncology Group (ECOG) performance status ≤2. 3. Histopathologically confirmed diagnosis of NSCLC PD-L1 expression TPS ≥1% as determined by an FDA-approved test. 4. Have at least one measurable target lesion as defined by RECIST v.1.1. 5. Have not received immune checkpoint inhibitor therapy or more than one regimen of chemotherapy for advanced or metastatic disease. Subjects who have previously received immune checkpoint inhibitor therapy in the adjuvant or neoadjuvant setting may be allowed if disease progression occurred >6 months after the last dose and no clinically significant immune related toxicities leading to treatment discontinuation were observed. 6. Prior adjuvant or neoadjuvant systemic therapy with chemotherapy, EGFR or ALK mutation directed therapy must have been completed >4 weeks before Cycle 1 Day 1 (C1D1) dosing and recovered from all treatment related toxicity. 7. Any prior palliative radiotherapy or minor surgery must be completed at least 2 weeks and 1 week respectively before C1D1 dosing and recovered from all treatment related toxicities. 8. Adequate major organ functions at baseline as evidenced by laboratory findings within 14 days prior to C1D1 study drug administration as defined below: a. White blood cells (WBC) ≥3000/μL, neutrophils ≥1500/μL, platelets ≥100×10^3/μL, hemoglobin ≥9.0 g/dL, independent of transfusion. b. Serum creatinine ≤1.5 mg/dL, normal electrolytes, phosphorus, and calcium. c. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤3 × upper limit of normal (ULN), alkaline phosphatase ≤2.5 × ULN unless bone metastases present, bilirubin ≤1.5 × ULN (unless known Gilbert's disease where it must be ≤3 × ULN) and serum albumin ≥3.0 g/dL. d. Thyroid stimulating hormone (TSH) within normal limits. 9. Life expectancy ≥12 weeks. 10. A negative serum pregnancy test at baseline for women of childbearing potential (WOCBP). 11. Women of childbearing potential. (WOCBP), non-surgically sterile or premenopausal female capable of becoming pregnant and men (due to potential risk of drug exposure through the ejaculate) must agree to use an acceptable method of contraception while enrolled on this study, and for a period of 5 months following the last dose of treatment. Acceptable methods of birth control in this trial include 2 highly effective methods of birth control (as determined by the Investigator; one of the methods must be a barrier technique) or abstinence. 12. Have the ability to understand and the willingness to sign a written informed consent document. Exclusion Criteria Subjects who fulfill any of the following criteria at screening will not be eligible for admission into the study: 1. History of Grade ≥3 hypersensitivity reactions to monoclonal antibodies.

	2. History of a cardiovascular illness including: QT interval corrected by heart rate using Fridericia's correction formula (QTcF) >450 ms in male or >470 ms in female, congenital long QT syndrome, congestive heart failure (New York Heart Association Grade III or IV) (Appendix 2); unstable angina or myocardial infarction within the previous 6 months; or symptomatic cardiac arrhythmia despite medical management. 3. Uncontrolled hypertension, systolic blood pressure (SBP) >160 mmHg or diastolic blood pressure (DBP) >100 mmHg. 4. Central nervous system metastasis or leptomeningeal disease except when treatment for brain metastasis is completed >14 days prior to C1D1 and stable for ≥4 weeks on <10 mg daily prednisone or equivalent. 5. History of hemorrhagic diarrhea, inflammatory bowel disease, active uncontrolled peptic ulcer disease or bowel resection that affects absorption of orally administered drugs. 6. Recurrent pleural effusion requiring repetitive palliative thoracentesis within 3 months prior to study entry, except for subjects with a pleurex port. 7. Active, known, or suspected autoimmune disease, or history of immune-mediated toxicity leading to treatment discontinuation, except for type I diabetes mellitus, hypothyroidism only requiring hormone replacement or skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic therapy. 8. Active pneumonitis, history of non-infectious pneumonitis that required treatment with steroids, or history of interstitial lung disease. 9. Active uncontrolled bacterial, viral, or fungal infection requiring systemic therapy. 10. Known history of testing positive for human immunodeficiency virus (HIV), known acquired immunodeficiency syndrome (AIDS). 11. Active hepatitis B (hepatitis B surface antigen [HBVsAg] positive), or hepatitis C (HCV antibody test or serum hepatitis C ribonucleic acid [RNA] positive). 12. Received approved live vaccines within 30 days of planned C1D1. Inactivated viral vaccines or vaccines based on subviral component are allowed; however intranasal influenza vaccines (e.g., Flu-Mist) are not allowed. COVID-19 vaccination should be administered >7 days before C1D1. 13. Any condition requiring chronic systemic treatment with either corticosteroids (>10 mg daily prednisone equivalents) or other immunosuppressive medications, or steroids use within 14 days of study drug administration. Inhaled or topical steroids are permitted. 14. Use of other investigational agent (drug not marketed for any indication) within 28 days or at least 5 half-lives (whichever is shorter) before study drug administration. 15. Pregnant or breast-feeding women. 16. Second malignancy unless in remission for 2 years; subjects with non-melanomatous skin cancer, carcinoma in situ of the cervix treated with curative intent, or curatively treated prostate cancer with prostate-specific antigen (PSA) <2.0 ng/mL can be included. 17. Underlying medical conditions that, in the Investigator's opinion, will make the administration of study drug hazardous or obscure the interpretation of toxicity determination or adverse events. 18. Unwilling or unable to comply with procedures required in this protocol.

Criteria for evaluation:

Safety Endpoints:

Adverse events (AEs) reported by the subjects or observed during physical examination, vital signs assessment, electrocardiograms (ECGs) will be recorded by severity according to NCI CTCAE v5.0 and association with HBI-8000 and pembrolizumab will be assessed. Laboratory test results will be recorded and assessed against normal ranges. ECOG performance status will be monitored.

Efficacy Endpoints:

Target lesion(s) and non-target lesion(s) will be assessed by imaging studies at screening (baseline assessment), in the last week of Cycle 2 including C3D1, and then every 6 weeks (±3 days) thereafter. Tumor assessments will follow guidelines specified in RECIST criteria v1.1.

- ORR (complete response [CR]+partial response [PR])
- DCR (CR+PR+Stable disease [SD])
- DoR (Duration of response)
- PFS (Progression-Free Survival)

After the discontinuation of HBI-8000 treatment, subjects without disease progression will be followed for progression with imaging of measurable disease every 12 (±1) weeks until progression, initiation of another anti-cancer treatment, or referral to hospice whichever occurs first. Survival follow-up will be performed every 12 (±1) weeks by telephone contact or e-mail for up to 12 months after the last dose of HBI-8000.

Statistical methods:

General:

Statistical analyses will be performed using SAS® v9.4 or higher (SAS Institute, Cary NC, US). Statistical analyses of safety, tolerability and efficacy endpoints will be primarily descriptive in nature. Continuous variables will be summarized using descriptive statistics (n, mean, standard deviation, median, minimum, and maximum). Categorical variables will be summarized with the number and percentage (n, %) of subjects within each category. Time to event variables (i.e., PFS, DoR) will be analyzed using the Kaplan-Meier method. Where confidence limits are appropriate, the confidence level will be 95% (two sided), unless otherwise stated.
All subjects in the safety population (who received any amount of HBI-8000) will be included in the final summaries and listings of the safety data.

Sample Size Estimation:

Approximately 20 to 24 subjects are planned to be enrolled to characterize safety and allow for preliminary evaluation of efficacy endpoints in the specific patient population of interest.

Interim Analysis:

There will be no interim analysis for this Phase 2 study.

Schedule of Events (Dosing and Assessments)

Table 1: Schedule of Dosing and Assessments

Visit	Screening	BL	Cycle 1	Cycle 2	Cycle 3	Cycle 4	≥Cycle 5	EoT Visit[b]	Survival F/U
Study Day	−28 to −1	−14 to −1	1	1 (±3d) [a]	1 (±3d)	1 (±3d)	1 (±3d)	30 days post dose [b] (±3d)	Every 12 Weeks (±1 week)
Informed consent [c]	X								
Inclusion/Exclusion Criteria	X	X							
Medical History, Baseline Signs and Symptoms, Cancer Diagnosis, and Treatment History [d]	X								
Demographics, height	X								
Vital signs [e]	X	X	X	X	X	X	X	X	
Physical exam, weight, ECOG Performance Status	X	X [f]	X	X	X	X	X	X	
ECG [g]		X						X	
Brain MRI [h]	X								
PD-L1 expression TPS [i]	X								
Hematology [j]		X	X	X	X	X	X	X	
Coagulation (PT/INR, aPTT)		X						X	
Serum chemistry [k] and LDH		X	X	X	X	X	X	X	
Urinalysis [l]		X						X	
Pregnancy test [m]		X						X	
Hepatitis B and C panel [n]	X								
HBI-8000 PO BIW [o]			X						
Pembrolizumab 200 mg infusion [p]			X	X	X	X	X		
OR Pembrolizumab 400 mg infusion [p]			X		X		X		
Tumor assessment [q]	X				Day 1 of Cycle 3, 5, 7, etc. (every 6 weeks ± 3 days)				
Adverse events [r] and SAE [r]			Continuous Assessment					X	
Concomitant medication	X	X	Continuous Assessment					X	
Treatment Compliance			X	X	X	X	X	X	

Visit	Screening	BL	Cycle 1	Cycle 2	Cycle 3	Cycle 4	≥Cycle 5	EoT Visit[b]	Survival F/U
Study Day	−28 to −1	−14 to −1	1	1 (±3d) [a]	1 (±3d)	1 (±3d)	1 (±3d)	30 days post dose [b] (±3d)	Every 12 Weeks (±1 week)
Survival [s] and Tumor Assessment F/U [t]									X

Abbreviations: ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BIW = twice weekly; BL = baseline; BUN = blood urea nitrogen; CT = computed tomography; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic Case Report Form; EoT = end of treatment; F/U = follow-up; HBsAg = hepatitis B surface antigen; INR = international normalized ratio; LDH = lactate dehydrogenase; MRI = magnetic resonance imaging; PO = by mouth; PD = progressive disease; PT = prothrombin time; TSH = thyroid stimulating hormone; T4 = thyroxine

a. All visits and assessments from Cycle 2 onwards may be performed ± 3 days from the date of the projected visit.
b. End-of-Treatment Safety Follow-Up visit, performed 30 ± 3 days after the last day of HBI-8000 administration, or before the initiation of new cancer treatment, whichever is earlier.
c. Informed consent must be obtained prior to initiation of any study-specific procedures.
d. Cancer diagnosis must include known mutation status for BRAF V600, EGFR, and ALK.
e. Temperature, heart rate, diastolic and systolic blood pressure after subject is in a supine position for at least 5 minutes.
f. Complete physical exam at baseline. Symptom directed physical exam for screening and all other cycles.
g. Standard 12-lead ECG will be done using local standard procedures at Baseline and at End of Treatment Safety Follow-Up visits.
h. MRI performed per institutional guidelines and practice, and if clinically indicated for subjects with documented brain metastasis.
i. Historical data may be used to assess for eligibility. If historical data is not available, tumor tissue will be analyzed locally by an FDA-approved test to yield PD-L1 status prior to enrollment.
j. Hematology panel to include hemoglobin, hematocrit, red blood cell count, white blood cell count, differential, platelet count.
k. Chemistry panel to include BUN, creatinine, AST, ALT, LDH, total bilirubin (including direct fraction if total bilirubin abnormal), lipase, amylase, TSH, T4 free (direct), total protein, albumin, uric acid, alkaline phosphatase, sodium, potassium, calcium, magnesium, phosphorus, and glucose.
l. Urinalysis: dipstick followed by microscopic examination, if abnormal results.
m. For women of childbearing potential (including those with tubal ligation): Serum pregnancy test at baseline (within 14 days of starting treatment) and at the end of treatment.
n. Hepatitis B and Hepatitis C testing to include HBsAg, anti-HCV antibodies.
o. HBI-8000 should be administered twice a week approximately 30 minutes after a meal.
p. Pembrolizumab 400 mg every 6 weeks or 200 mg every 3 weeks on Day of 1 of each Cycle should be administered as intravenous (IV) infusion over 30 minutes and in accordance with the manufacturer package insert and institutional practice.
q. Tumor assessment of all lesions by radiographic or other modality (CT, MRI). Tumor assessments to be performed at Screening, and Day 1 of Cycles 3, 5, 7, etc. every 6 weeks (± 3 days) thereafter until PD.
r. Following the subject's written consent to participate in the study, all SAEs whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. Subjects with HBI-8000-related AEs of Grade ≥2 observed at the EoT visit should be followed-up and assessed monthly until the AEs have resolved to Grade ≤1 or are determined to be chronic or subject receives other anti-cancer therapy.
s. Subject survival data will be collected by telephone contact or e-mail every 12 (±1) weeks after End-of-Treatment visit for up to 12 months after the last dose of HBI-8000 or until death.
t. After discontinuation of HBI-8000 treatment, subjects without disease progression will be followed for progression with imaging of measurable disease every 12 (±1) weeks until progression, initiation of another anti-cancer treatment, or referral.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ADL	Activities of daily living
AE	Adverse event
AESI	Adverse event of special interest
ALK	Anaplastic lymphoma kinase
ALT	Alanine aminotransferase
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
ATC	Anatomical therapeutic chemical classification system
ATL	Adult T-cell leukemia/lymphoma
AUC	Area under the curve
BIW	Twice a week
BRAF	B-Raf proto-oncogene, serine/threonine kinase gene
BUN	Blood urea nitrogen
C1D1	Cycle 1 Day 1
CFR	Code of Federal Regulations
COVID-19	Coronavirus disease 2019
CPI	Checkpoint inhibitor
CR	Complete response
CRO	Contract research organization
CT	Computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTL	Cytotoxic T lymphocyte
CYP	Cytochrome P450
DBP	Diastolic blood pressure
DCR	Disease control rate
DNA	Deoxyribonucleic acid
DoR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group

Abbreviation	Definition
eCRF	Electronic Case Report Form
EDC	Electronic data capture
EGFR	Epidermal growth factor receptor
EoT	End-of-treatment
ESF	Eligibility Screening Form
FAS	Full analysis set
FDA	Food and Drug Administration (US)
GCP	Good clinical practice
G-CSF	Granulocyte-colony stimulating factor
HBVsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HDAC	Histone deacetylase
HDACi	Histone deacetylase inhibitor
HDPE	High-density polyethylene
HEENT	Head, eye, ear, nose, and throat
HIV	Human immunodeficiency virus
HR	Hazard ratio
HUYABIO	HUYABIO International LLC
IC_{50}	50% inhibitory concentration
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IgG	Immunoglobulin G
INR	International normalized ratio
IP	Investigational Product
irAE	Immune-related Adverse Event
IRB	Institutional Review Board
IV	Intravenous
LAR	Legally authorized representative
LDH	Lactate dehydrogenase

Abbreviation	Definition
MDSC	Myeloid-derived suppressor cells
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
NCI	National Cancer Institute
NE	Not evaluable
NK	Natural killer
NSCLC	Non-small cell lung cancer
ORR	Objective Response Rate
OS	Overall survival
PD	Progressive disease
PD-1	Programmed cell death protein 1
PD-L1	Programmed death-ligand 1
PFS	Progression-Free Survival
PPS	Per-Protocol Set
PR	Partial response
PSA	Prostate specific antigen
PSRMC	Product Safety and Risk Management Committee
PT	Prothrombin time
PTCL	Peripheral T-cell lymphoma
Q2W	Every two weeks
QTc	QT interval corrected by heart rate
QTcF	QT interval corrected by heart rate using Fridericia's correction formula
RBC	Red blood cell
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RENCA	Renal adenocarcinoma
RNA	Ribonucleic acid
ROS	c-ros oncogene
RP2D	Recommended Phase 2 dose

Abbreviation	Definition
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure
SD	Stable disease
SOP	Standard operating procedure
STD	Sum of target lesion(s) diameter(s)
SUSAR	Suspected unexpected serious adverse drug reaction
T4	Thyroxine
TEAE	Treatment-emergent adverse event
TIW	Three times a week
T_{Reg}	Regulatory T-cell
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
US	United States (of America)
USP	United States Pharmacopeia
USPI	US package insert
WBC	White blood cell
WHO	World Health Organization
WHO DDE	World Health Organization drug dictionary enhanced

1 BACKGROUND

1.1 Introduction

HBI-8000 (chidamide, tucidinostat) is an orally bioavailable inhibitor, selective for cancer-associated histone deacetylase (HDAC) isoenzymes 1, 2, 3, and 10. By affecting the acetylation of histones and non-histones in cancerous and immune cells, it regulates the gene expression epigenetically without changing the DNA sequence and modulates immune functions and malignant phenotypes. Selective HDAC inhibitors (HDACi) such as HBI-8000 have been shown to alter the expression of genes which are aberrant, silenced or overexpressed in cancer cells. HUYABIO International, LLC (HUYABIO) is developing HBI-8000 as a monotherapy for the treatment of hematological malignancies and in combinations for the treatment of solid tumors such as melanoma, breast, kidney, and lung cancers. Combination regimens of HDACi with other cancer drugs have shown synergistic effects both in pre-clinical and clinical studies. At the same time, these combinations have enhanced the efficacy, reduced the toxicity and tumor resistance to therapy [Hontecillas-Prieto 2020].

Programmed cell death protein (PD-1) and its ligands (PD-1/PD-L1 axis) play a fundamental role in the evasion of tumor cells from antitumor immunity. The safety and efficacy of HBI-8000 in combination with nivolumab, an inhibitor to PD-1/PD-L1 axis, has been evaluated in a Phase 1b/2 study (HBI-8000-302) in patients with advanced melanoma, renal cell carcinoma (RCC) and non-small cell lung cancer (NSCLC). Interim results from the Phase 1b part of the study established that HBI-8000, 30 mg twice weekly in combination with the standard dose of nivolumab was well tolerated. The tolerability was further confirmed in the expanded cohorts in Phase 2. Efficacy signals were also observed throughout this study, including patients with NSCLC regardless of their prior exposure to immune checkpoint inhibitor(s).

The hypothesis is that HBI-8000, combined with approved immune checkpoint inhibitors can improve the antitumor immune response in cancer patients, possibly by enhancing tumor immunogenicity and inflammatory response in tumor microenvironment. In the present study, the safety and efficacy of HBI-8000 in combination with KEYTRUDA® (pembrolizumab) in advanced and metastatic NSCLC will be explored. Efficacy will be assessed based on objective response rate (ORR), progression-free survival (PFS), and duration of response (DoR).

1.1.1 Non-Small Cell Lung Cancer (NSCLC)

Immune checkpoint therapy in Non-Small Cell Lung Cancer (NSCLC)

According to American Cancer Society Facts and Figures 2021, there will be approximately 235,760 new cases of lung cancer, resulting in 131,880 deaths in the United States (US) [SEER 2021]. Despite reductions in the incidence of lung cancer over the past 20 years, lung cancer remains the 2nd most common cancer (12.4%) in both men and women in the US, and the leading cause of cancer death (21.7%). Despite progress in treatment, the relative survival rate of lung cancer was 21.7% from 2011-2017 [SEER 2021].

Historically, platinum containing chemotherapy has been the mainstay of systemic therapy for NSCLC. With the discovery of tyrosine kinase inhibitors targeting specific aberrant gene expressions in NSCLC, such as epidermal growth factor receptor (EGFR), the anaplastic lymphoma kinase (ALK) and the c-ros oncogene (ROS) receptor tyrosine kinase, small molecule

non-cytotoxic therapies targeting these genes (erlotinib, gefitinib, and afatinib and osimertinib in EGFR mutations and crizotinib, ceritinib, alectinib and brigatinib in ALK and ROS mutated NSCLC) were integrated into NSCLC management more recently.

The activities of immune checkpoint inhibitors in NSCLC were observed in clinical studies of pembrolizumab and nivolumab.

Nivolumab, a human immunoglobulin G4 (IgG4) anti-PD-1, was the first drug approved as second line therapy for advanced NSCLC in 2015. The results from CheckMate 017 study showed nivolumab significantly improved OS, PFS and ORR over the standard therapy of docetaxel in NSCLC with squamous histology and the clinical benefits were independent of PD-L1 expression [Brahmer 2015]. The safety profiles were acceptable with 7% treatment-related AEs of Grade 3 or 4 in nivolumab group of 7% as compared with 55% of those in the docetaxel group. The clinical benefit of nivolumab in non-squamous NSCLC, was evaluated in CheckMate 057 study. Although in this study, nivolumab did not extend PFS, it improved OS and ORR regardless of the level of PD-L1 tumor membrane expression levels. Grade 3 to 5 treatment-related adverse events were reported in 10% of nivolumab and 54% of docetaxel-treated patients [Borghaei 2015]. Results of both studies were updated subsequently [Horn 2017]. The 2-year OS rate was 23% in nivolumab group comparing to 8% docetaxel group in squamous and 29% versus 16% in non-squamous NSCLC. The relative reductions in the risk of death with nivolumab versus docetaxel remained similar to those reported in the primary analyses. Durable responses were observed with nivolumab; 10 (37%) of 27 confirmed responders with squamous NSCLC and 19 (34%) of 56 with nonsquamous NSCLC had ongoing responses after 2 years' minimum follow-up. No patient in either docetaxel group had an ongoing response. In the pooled analysis, the relative reduction in the risk of death with nivolumab versus docetaxel was 28% (hazard ratio (HR), 0.72; 95% CI, 0.62 to 0.84), and rates of treatment-related adverse events were lower with nivolumab than with docetaxel (any grade, 68% v 88%; grade 3 to 4, 10% v 55%). Both studies demonstrated clinical benefit of nivolumab across tumor histology and all levels of PD-L1 expression.

Pembrolizumab is a humanized IgG4 anti-PD-1. Various dosing regimens of pembrolizumab were evaluated in the Phase 1b study KEYNOTE 001 in 101 patients with treatment-naïve NSCLC. The most common treatment related AEs were fatigue (27.7%), followed by pruritus (14.9%), hypothyroidism (13.9%), rash (13.9%), arthralgia (11.9%), and nausea (11.9%). However, Grade 3/4 treatment-related AEs occurred in 12% subjects [Hui 2017]. The immune-mediated AEs, regardless of attribution to treatment as reported by investigators, were observed in 22% of patients, with hypothyroidism being most common in 15% of patients. All were of grade 1 or 2 severity, except for 1 case each of grade 3 pneumonitis, hypophysitis, colitis, and dermatitis, manageable with steroids and supportive care. There were no treatment-related deaths. Efficacy was apparent in all treatment regiments and was more prominent in tumors with higher PD-L1 expression.

KEYNOTE 010, a phase 2/3 study, further evaluated the efficacy and safety of pembrolizumab at 2 and 10 mg/kg given every 3 weeks (Q3W) in previously treated NSCLC. This study demonstrated superior overall survival (OS) over standard-of-care docetaxel treatment in patients with previously treated, PD-L1-positive NSCLC [Herbst 2016]. Improvement of PFS and ORR over docetaxel were also evident in all patients with positive PD-L1 expression status assessed by an immunohistochemical assay reported as tumor proportion score (TPS) ≥1% of either

archival or newly biopsied tumor specimens [Herbst 2019]. (The overall safety profile of this combination was well tolerated, consistent with findings from KEYNOTE 001 study. Similarly, in the KEYNOTE-042 study, patients with NSCLC (squamous and non-squamous) had better outcomes when treated with pembrolizumab alone than chemotherapy (paclitaxel/carboplatin or pemetrexed/carboplatin). Survival in the pembrolizumab arm was superior at all levels of PD-L1 expression. Higher PD-L1 expression resulted in greater improvement. For patients with tumor TPS ≥50%, median OS was 20.0 months (95% CI 15·4–24·9) for the pembrolizumab group vs. 12.2 months (10·4–14·2) for the chemotherapy group (HR=0.69; 95% CI: 0.56, 0.85; p=0.0003); for TPS of ≥20%, median OS was 17.7 (15·3–22·1) for the pembrolizumab group vs. 13 months (11·6–15·3) for chemotherapy group (HR=0.77; 95% CI: 0.64, 0.92; p=0.0020); and for TPS >1%, median OS was 16.7 months (13·9–19·7) for the pembrolizumab group vs. 12.1 months (11·3–13·3) for chemotherapy group (HR=0.81; 95% CI: 0.71, 0.93; p=0.0018). Treatment-related adverse events of grade 3 or worse occurred in 113 (18%) of 636 treated patients in the pembrolizumab group and in 252 (41%) of 615 in the chemotherapy group and led to death in 13 (2%) and 14 (2%) patients, respectively [Mok 2019].

Pembrolizumab was also evaluated in combination with chemotherapy. In the first-line setting of advanced NSCLC, results from KEYNOTE-189 study showed superiority of pembrolizumab/chemotherapy over chemotherapy alone in PFS and ORR in all PD-L1 expressing disease. The estimated rate of overall survival at 12 months was 69.2% (95% CI, 64.1 to 73.8) in the pembrolizumab-combination group versus 49.4% (95% CI, 42.1 to 56.2) in the placebo combination group (HR for death, 0.49; 95% CI, 0.38 to 0.64; P <0.001). Median progression-free survival was 8.8 months (95% CI, 7.6 to 9.2) in the pembrolizumab-combination group and 4.9 months (95% CI, 4.7 to 5.5) in the placebo-combination group (HR for disease progression or death, 0.52; 95% CI, 0.43 to 0.64; P <0.001). Adverse events of grade 3 or higher occurred in 67.2% of the patients in the pembrolizumab-combination group and in 65.8% of those in the placebo-combination group. The improvement of PFS was more prominent among patients whose tumors had TPS ≥50% (HR=0.42) than TPS 1% - 49% (HR=0.55) Incidence of grade 3-5 adverse events was similar in the pembrolizumab-combination (71.9%) and placebo-combination (66.8%) groups [Gandhi 2018; Gadgeel 2020].

Thus, pembrolizumab became the first FDA approved checkpoint inhibitor for first-line treatment of patients with metastatic NSCLC whose tumors express PD-L1 as determined by an FDA-approved test, with expansion of indication for second-line treatment of lung cancer to include all patients with PD-L1 expressing NSCLC. This approval was based on results of two randomized, open-label, active-controlled trials that demonstrated statistically significant improvements in PFS and OS for patients randomized to pembrolizumab compared with chemotherapy. Shortly after, pembrolizumab was approved for first-line treatment of patients with stage III NSCLC who are not candidates for surgical resection or definitive chemoradiation or metastatic NSCLC based on KEYNOTE-042.

1.1.2 Rationale for HBI-8000 and immune checkpoint combination

Inhibition of different subtypes of HDAC could have distinct effects on regulatory T cell (T_{REG}) activity [Wang 2009; Beier 2012; Pili 2012; Shen 2012]. Furthermore, a recent publication demonstrated the newly discovered role of HDAC2 in the nuclear translocation of PD-L1 that regulates the immune-response gene expression [Gao 2020]. This observation is consistent with

the notion that inhibition of HDAC2-dependent acetylation of intracellular transport system could enhance the therapeutic effect of immune checkpoint inhibitors commonly used in clinics.

Recent reports suggest that HDACi has a significant effect on the expression of immune checkpoint co-inhibitory and co-stimulatory molecules. Additionally, HDACi may affect immunogenicity, antigen-presenting cells and T cell priming, regulatory T cells, myeloid-derived suppressor cells (MDSCs), and effector cell functions. For example, HDAC inhibition has been shown to upregulate PD-1 ligand in melanoma and thereby augmenting immunotherapy with PD-1 blockade [Woods 2015]. Class I HDAC inhibitors upregulate the expression of PD-L1 and to a lesser extent PD-L2 in human and murine melanoma cell lines and in tumor tissue from cancer patients. The upregulation of PD-ligands was durable and lasted beyond 96 hours. These results suggest that combination of Class I HDAC inhibitors, such as HBI-8000, may have additive or synergistic activity in combination with PD-1 blockade antibodies.

The direct evidence supporting the synergy of HBI-8000 with immune checkpoint inhibitors was observed in animal models. Gene expression analysis of the treated MC38 tumors revealed significant changes in mRNA expression of immune checkpoints, with enhanced dendritic cell and antigen-presenting cell functions, and modulation of MHC class I and II molecules. These findings suggest that HBI-8000 mediates epigenetic modifications in the tumor microenvironment, leading to improved efficacy of immune checkpoint inhibitors, and provide strong rationale for combination therapies with immune checkpoint inhibitors and HBI-8000 in the clinical setting.

1.1.3 HBI-8000 (tucidinostat)

HBI-8000 (tucidinostat, chidamide), *N*-(2-amino-4-fluorophenyl)-4-{[(2E)-3-(pyridine-3-yl)prop-2-enamido]methyl} benzamide, is a member of the benzamide class of HDACi designed to bind and prevent access to the catalytic pocket primarily of Class I HDACs [Pan 2014]. HUYABIO initiated clinical development of this compound in 2012 in the United States (US) and 2014 in Japan. The Ministry of Health, Labor and Welfare (MHLW) in Japan approved tucidinostat 10 mg tablet for treatment of relapsed or refractory adult T-cell leukemia/lymphoma (ATLL) in June 2021 and a new drug application for relapsed and refractory peripheral T-cell lymphoma (PTCL) is under regulatory review. Worldwide, in addition to the Phase 1b/2 study (HBI-8000-302), a phase 3 study (HBI-8000-303) in metastatic melanoma has been initiated to evaluate the efficacy of HBI-8000 in combination with nivolumab. In China, this compound (tucidinostat) was developed by Shenzhen Chipscreen Biosciences Co., Ltd. (Chipscreen). It was approved by China Food and Drug Administration (CFDA) in December 2014 for the treatment of relapsed or refractory PTCL, and for hormone receptor-positive advanced breast cancer in combination with aromatase inhibitor in Nov 2019. As of December 2020, approximately 26,000 cancer patients were treated with this drug in China under the brand name of Epidaza®.

HBI-8000 is an orally bioavailable, low-nanomolar inhibitor of cancer-associated HDAC enzymes with favorable pharmacology and tolerability profiles relative to existing benzamide and non-benzamide HDAC inhibitors. Please refer to the Investigator's Brochure for further information on HBI-8000.

The structural formula for HBI-8000 is shown in Figure 1.

Further information on HBI-8000 may be found in the Investigator's Brochure.

1.1.3.1 HBI-8000 (tucidinostat) and Preclinical Pharmacology

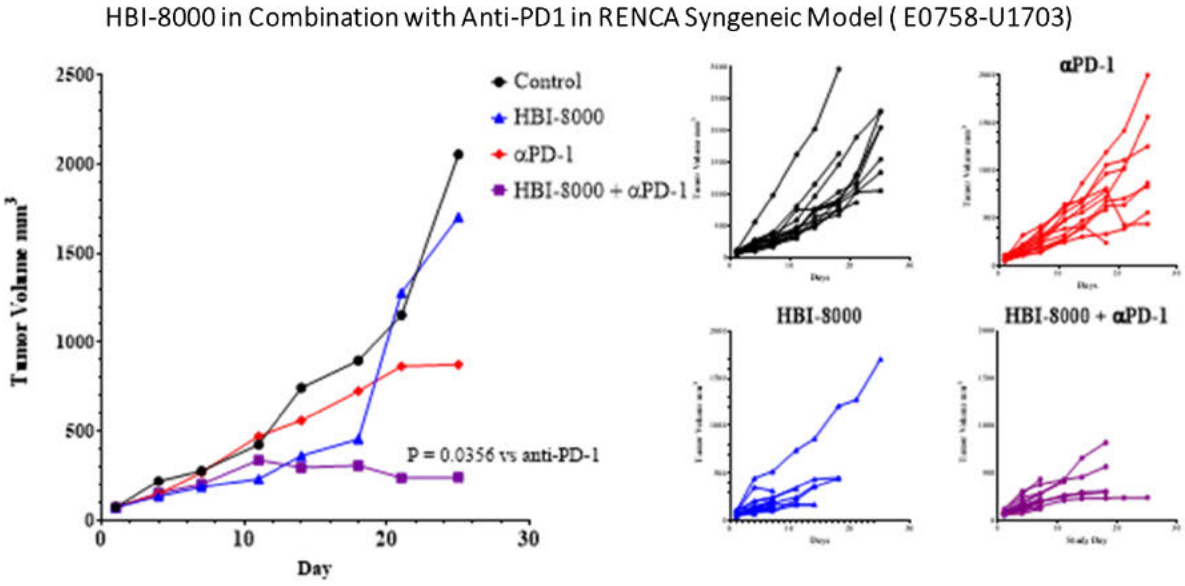
HBI-8000 inhibits several cancer-associated Class I (HDAC 1, 2, 3) and one Class IIb (HDAC10) HDACs in the nanomolar range and stimulates accumulation of acetylated histones H3 and H4 in tumor cells [Ning 2012]. In vitro, HBI-8000 inhibits the growth of a variety of tumor cell lines, with 50% inhibitory concentrations (IC_{50}) in the single-digit micromolar range. HBI-8000 is non-toxic to non-transformed cells (IC_{50} ≥100 micromolar) [Ning 2012]. In vivo, HBI-8000 has demonstrated direct dose-dependent anti-tumor activity in human xenograft models [Ning 2012].

Preclinical studies [Barrero 2017] have demonstrated several positive effects on antitumor immunity, including: re-priming (reactivating) the immune response to the tumor, enhancing the activity of immune cytotoxic T lymphocytes (CTL) and natural killer (NK) cells, and blocking the immune suppressive activity of certain regulatory T cells (T_{REG}) and MDSCs present in the tumor environment. HBI-8000 displayed direct activity on tumor cells, overcoming their resistance to immune cell killing, i.e., apoptosis.

HBI-8000 was active in vivo as a single agent in several tumor models, including the following: A549 human lung carcinoma, MCF-7 human breast carcinoma, EMT-6 mouse breast carcinoma, Mouse Lewis lung carcinoma, HCT-8 human colorectal carcinoma, BEL-7402 human liver carcinoma. HBI-8000 was administered orally 5, 10, 20, or 28 times per 28 days, at doses ranging from 12.5 to 50 mg/kg (Study CXHL0502435). Tumor growth inhibition of 25% to 84% was observed in all models, without gross body weight loss [Ning 2012]. These results were consistent with the in vitro potency seen in the NCI-60 screening assay.

HBI-8000 has also demonstrated activity in several preclinical tumors (MC38, RENCA, A20) and in combination with anti-PD1, a checkpoint inhibitor. As the results in Figure 2 illustrate, in syngeneic mice bearing renal adenocarcinoma (RENCA) tumors, treatment with HBI-8000 plus anti-PD1 significantly inhibited tumor growth compared with single agent therapy (Study E0758-U1703).

Figure 2: RENCA Renal Adenocarcinoma Cell Line Treated with HBI-8000 and Anti-PD1



1.1.3.2 Clinical Studies

HUYABIO has conducted several clinical studies (Table 2) using HBI-8000 (tucidinostat) as a mono- and combination therapy. Tucidinostat has been administered to more than 26000 cancer patients in U.S., Japan, South Korea and China. Its safety profile has been well established. Additional information on HBI-8000 clinical studies can be found in the Investigator's Brochure.

Table 2: Clinical Studies Conducted with HBI-8000

Study ID	HBI-8000 Dose	Disease	N	Phase (Status)	Treatment	Countries
HBI-8000-210	40 mg BIW	Relapsed or refractory ATL	23	Phase 2b (Completed)	Monotherapy	Japan
HBI-8000-203	40 mg BIW	Relapsed or refractory PTCL	56	Phase 2b (Ongoing)	Monotherapy	Japan South Korea
HBI-8000-302	Phase 1b: 20, 30, 40 mg BIW Phase 2: 30 mg BIW	RCC, NSCLC, melanoma Melanoma, NSCLC	16 73	Phase 1b (Completed) Phase 2 ongoing	Combination with nivolumab	US

Study ID	HBI-8000 Dose	Disease	N	Phase (Status)	Treatment	Countries
HBI-8000-101	5-60 mg TIW	Advanced Solid Tumors	25	Phase 1 (Completed)	Monotherapy	US
HBI-8000-201	30 or 40 mg BIW	Non-Hodgkin's Lymphoma	14	Phase 1 (Completed)	Monotherapy	Japan
HBI-8000-304	20 mg single dose	Normal volunteers	16	Phase 1 (Completed)	Food effect/drug-drug interaction	US

Abbreviations: ATL = adult T-cell leukemia/lymphoma; BIW = twice weekly; NSCLC = non-small cell lung cancer; PTCL = peripheral T-cell lymphoma; RCC = renal cell carcinoma; US = United States.

1.1.3.3 HBI-8000 Safety Profile

As a monotherapy, the main safety findings for HBI-8000 are myelosuppression (thrombocytopenia, neutropenia, leukopenia, and anemia) observed in heavily pre-treated relapsed and refractory T-cell lymphoma patients. Additional toxicities included gastrointestinal symptoms, fatigue and asymptomatic laboratory abnormalities. Toxicities were generally mild and manageable with supportive care, dose reductions, interruption, or delays.

In clinical studies, treatment with HBI-8000 has been associated with exposure-related myelosuppression, categorized as important identified risk and includes thrombocytopenia, anemia, and neutropenia or lymphopenia. These myelosuppression related toxicities were more severe in patients with relapsed and refractory hematological malignancies than in patients with solid tumors. In general, the hematologic AEs are manageable with supportive care such as hematological growth factor administration, dosing interruption and dose reduction. Other important identified risks are pneumonitis, interstitial lung disease, and interstitial pneumonia.

In the HBI-8000-302 study, the safety of HBI-8000 administered in combination with standard dose immune checkpoint inhibitor (CPI), nivolumab, has been evaluated in 89 patients total including 49 with melanoma, 29 with NSCLC and 11 with renal cell carcinoma. The most common AEs of all grades associated with HBI-8000 were fatigue (59.6%), thrombocytopenia (49.4%), nausea (48.3%), diarrhea (47.2%), anemia (42.7%), dyspnea (37.1%), peripheral edema (33.7%), anorexia (32.6%), neutropenia (31.5%) and leukopenia (31.6%). The most reported Grade 3 or higher adverse events were lymphopenia, neutropenia, hypophosphatemia, fatigue, anemia and diarrhea. Only 3 subjects had transaminase elevation were reported as Grade 3. The safety profiles so far have been consistent with those observed in HBI-8000 monotherapy, although the hematological toxicities were less severe and less frequent, as expected with solid tumor patient population. There has been no evidence of increased risk for immune-related toxicity over those expected with nivolumab treatment alone.

Arrhythmia including QTc prolongation may occur and are categorized as important potential risk. However, recently, a QT interval corrected by heart rate (QTc) HBI-8000-302

QTc-sub-study with time-matched PK was completed to evaluate the potential for QTc prolongation. There was no evidence of QTc prolongation when HBI-8000 was administered in a dose range of 20 to 40 mg BIW. Other important potential risks that may occur are electrolyte abnormality (hyponatremia and hypokalemia) and hypersensitivity.

1.1.3.4 Overall Safety Risk Assessment

In clinical studies, treatment with HBI-8000 has been associated with exposure-related myelosuppression, including thrombocytopenia, anemia, and neutropenia or leukopenia. These myelosuppression related toxicities were more severe (grade 3 or 4) in patients with relapsed and refractory hematological malignancies who have been treated with high dose cytotoxic chemotherapy, than in patients with solid tumors. In general, the hematologic AEs are manageable with supportive care such as hematological growth factor administration, dosing interruption and dose reduction.

When HBI-8000 was administered concurrently with CPI (nivolumab) in patients with solid tumor, the combination was well tolerated, with toxicity profiles consistent with either agent alone, without apparent exacerbation of known toxicities or new toxicity, manageable with standard supportive therapy established for either agent.

1.1.3.5 Overall Risk/Benefit Assessment

In general, HBI-8000 in combination with immune CPI, nivolumab. is well tolerated by cancer patients. Evidence of enhanced efficacy was observed, compared to CPI single agent, with durability of response, Therefore, the potential clinical benefit appears to outweigh the potential risks from combining HBI-8000 with the standard of care of pembrolizumab.

1.1.4 Rationale for Statistical Design

This open label Phase 2 study is designed to characterize safety and allow for preliminary evaluation of efficacy endpoints in the specific patient population of interest. With a sample size of 20 to 24 subjects the probability that an adverse event with at least a 10% incidence will be detected in at least one subject is high (87.8% to 92.0%) (Table 4). Obtaining this information will help in planning for future immuno-oncology studies.

1.1.5 HBI-8000 Dose Selection and Justification for Combination with Pembrolizumab

The safety of HBI-8000 in combination with immune checkpoint inhibitor has been evaluated with the standard dose of nivolumab. In study HBI-8000-302 (Phase 1b), patients received HBI-8000 tablets, 20, 30, or 40 mg BIW, with the standard IV dose of nivolumab at 240 mg every two weeks (Q2W) until maximum tolerated dose (MTD) was achieved and the frequency and severity of toxicities of this combination were evaluated.

A total of 15 patients evaluable for dose-limiting toxicity (DLT) were enrolled. At 40 mg BIW, DLTs were observed: Grade 3 headache in one melanoma patient and Grade 3 fatigue in one RCC patient. Following the 3 + 3 design, an additional 3 patients were evaluated at the 30-mg dose level, in whom no DLT was observed. The recommended phase 2 dose (RP2D) selected for cohort expansion portion of this study was 30 mg BIW.

Overall, in Study HBI-8000-302 the safety of HBI-8000 administered in combination with standard dose immune CPI, nivolumab, has been evaluated in over 89 patients with melanoma, NSCLC and renal cell carcinoma. The most common AEs of all grades associated with HBI-8000 were fatigue, thrombocytopenia, anemia, diarrhea, nausea and anorexia. However, only neutropenia, thrombocytopenia, hypophosphatemia, fatigue, and less frequently, nausea, anorexia, diarrhea, and transaminase elevation were reported as Grade 3, lymphopenia was reported as Grade 4. Thus, the collective data investigating dose and schedule of HBI-8000 as related to safety, QTc prolongation, tolerability, PK, and related efficacy have established the 30 mg twice weekly to be appropriate when used in combination with nivolumab, and likely other immune checkpoint inhibitors, at approved dosing and regimen. (See Investigator's Brochure for more information.)

This phase 2 study will evaluate HBI-8000 30 mg administered twice weekly in pembrolizumab combination, with appropriate dose modification guidelines.

2 OBJECTIVES

2.1 Primary Objectives

The primary objective of the study is:

- To evaluate the efficacy of HBI-8000 in combination with a standard dose and regimen of pembrolizumab as a first line checkpoint inhibitor therapy for advanced or metastatic NSCLC, as measured by Objective Response Rate (ORR) according to RECIST criteria version 1.1 [Eisenhauer 2009].

2.2 Secondary Objectives

The secondary objectives of the study are:

- To evaluate the safety and tolerability of HBI-8000 in combination with a standard dose and regimen of pembrolizumab
- To explore the additional efficacy parameters for HBI-8000 in combination with a standard dose and regimen of pembrolizumab as measured by Disease Control Rate (DCR), Duration of Response (DoR), and Progression-Free Survival (PFS)

2.3 Criteria for Evaluation

2.3.1 Safety Endpoints

Adverse events reported by the subjects or observed during physical examination, vital signs assessment, electrocardiograms (ECGs) will be recorded by severity according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5.0, and association with HBI-8000 and pembrolizumab will be assessed. Laboratory test results will be recorded and assessed against normal ranges. ECOG performance scores, as applicable, will be monitored.

2.3.2 Efficacy Endpoints

Target lesion(s) and non-target lesion(s) will be assessed by imaging studies at screening (baseline assessment), in the last week of Cycle 2 including C3D1, and then every 6 weeks (±3 days) thereafter. Tumor assessments will follow guidelines specified in RECIST criteria v1.1.

- ORR (complete response [CR]+partial response [PR])
- DCR (CR+PR+Stable disease [SD])
- DoR
- PFS

After the discontinuation of HBI-8000 treatment, subjects without disease progression will be followed for progression with imaging of measurable disease every 12 (±1) weeks until progression, initiation of another anti-cancer treatment, or referral to hospice whichever occurs first. Survival follow-up will be performed every 12 (±1) weeks by telephone contact or e-mail for up to 12 months after the last dose of HBI-8000.

3 STUDY DESIGN

3.1 Overall Design

This is a multicenter, open label, non-randomized, Phase 2 study of HBI-8000 in combination with a Food and Drug Administration (FDA) approved dose of pembrolizumab as the first checkpoint inhibitor therapy for advanced or metastatic NSCLC where subjects have programmed death ligand 1 (PD-L1) expression Tumor Proportion Score (TPS) ≥1%. Prior to enrollment, the PD-L1 expression status must be available. Historical data may be used to assess for eligibility. If historical data is not available, tumor tissue will be analyzed locally by an FDA-approved test to yield PD-L1 status prior to enrollment.

The dose of HBI-8000 is 30 mg twice weekly. Pembrolizumab is administered according to prescribing information.

The study will include a screening period of up to 28 days before the first dose of HBI-8000. Study Treatment may be with or without pembrolizumab. HBI-8000 and pembrolizumab will continue up to 24 months. HBI-8000 will continue until disease progression, unacceptable toxicity related to HBI-8000 ensues or withdrawal of informed consent to receive HBI-8000.

The Treatment Phase allows for up to 24 months of treatment (cycles are 21 days), providing the subject does not experience disease progression or unacceptable toxicity. An End of Treatment safety visit will be performed 30 (±3) days after last dosing of HBI-8000. If HBI-8000 is discontinued due to unacceptable toxicities related to HBI-8000, pembrolizumab may continue as single agent under standard of care. Subjects will be followed for up to 12 months after the last dose of HBI-8000 for disease status, including initiating a new cancer treatment and experiencing disease progression, death, or becoming lost to follow-up or consent withdrawal.

3.1.1 Expected Duration of Subject Participation

Subject participation duration from screening through end of treatment visit is approximately up to 38 months, including:

Screening period:	Up to 28 days
Treatment period:	Until radiographic disease progression per RECIST v1.1 (assessed by the Investigator), unacceptable toxicity, or other reasons for discontinuation with a maximum treatment duration of 24 months, unless there is an agreement between the Sponsor and the Investigator to allow HBI-8000 beyond 24 months.
Short-term Follow up/ End of treatment (EoT) period	Up to 30 days (±3 days) after the last dose HBI-8000. This will be defined as EoT.
Long-term Follow-up period:	Every 12 weeks (3 months) up to a maximum of 12 months after the last dose of HBI-8000.

3.1.2 Tumor Status and Survival Follow-Up

Subjects without disease progression who completed up to 24 months of treatment or discontinued from HBI-8000 due to reasons other than PD are followed with imaging studies every 12 (±1) weeks until progression is documented, another anti-cancer treatment is initiated, or referral to hospice, whichever occurs first.

All subjects will be contacted approximately every 12 (±1) weeks by telephone contact or e-mail for survival follow-up for up to 12 months after the last dose of HBI-8000.

3.1.3 Study Population

Approximately 20-24 subjects with advanced or metastatic non-small cell lung cancer will be enrolled at approximately 6-10 investigational sites in the United States. Subjects that have signed an informed consent but did not receive HBI-8000 may be considered for this study provided they are re-consented and undergo screening procedures specified in the protocol.

Under no circumstances will subjects who enroll in this study and have completed treatment as specified, be permitted to enroll for a second time.

3.2 Justification for Dose

The Sponsor plans to evaluate HBI-8000 at 30 mg orally twice a week (BIW) in combination with pembrolizumab administered intravenously at 400 mg every 6 weeks or 200 mg every 3 weeks in the present study (HBI-8000-305). This dosing regimen was selected based on clinical observations related to safety, tolerability, PK, and efficacy from previously conducted Phase 1b/2 study (HBI-8000-302).

3.3 End of Treatment Definition

The end of treatment is defined as the date of the last dose of HBI-8000 taken by the subject.

3.4 End of Study Definition

The study completes when all subjects have experienced progressive disease or 12 months after the last dose of HBI-8000 administration, whichever comes first. All subjects will be followed until death, lost to follow-up, withdrawn consent from study participation entirely, or study terminated by Sponsor.

4 STUDY POPULATION

4.1 Inclusion Criteria

Subjects may be entered in the study only if they meet all of the following criteria:

1. Adults at least 18 years of age.
2. Eastern Cooperative Oncology Group (ECOG) performance status ≤2.
3. Histopathologically confirmed diagnosis of NSCLC PD-L1 expression TPS ≥1% as determined by an FDA-approved test.
4. Have at least one measurable target lesion as defined by RECIST v.1.1.
5. Have not received immune checkpoint inhibitor therapy or more than one regimen of chemotherapy for advanced or metastatic disease. Subjects who have previously received immune checkpoint inhibitor therapy in the adjuvant or neoadjuvant setting may be allowed if disease progression occurred >6 months after the last dose and no clinically significant immune related toxicities leading to treatment discontinuation were observed.
6. Prior adjuvant or neoadjuvant systemic therapy with chemotherapy, EGFR or ALK mutation directed therapy must have been completed >4 weeks before Cycle 1 Day 1 (C1D1) dosing and recovered from all treatment related toxicity.
7. Any prior palliative radiotherapy or minor surgery must be completed at least 2 weeks and 1 week respectively before C1D1 dosing and recovered from all treatment related toxicities.
8. Adequate major organ functions at baseline as evidenced by laboratory findings within 14 days prior to C1D1 study drug administration as defined below:
    a. White blood cells (WBC) ≥3000/μL, neutrophils ≥1500/μL, platelets ≥100×10^3/μL, hemoglobin ≥9.0 g/dL, independent of transfusion.
    b. Serum creatinine ≤1.5 mg/dL, normal electrolytes, phosphorus, and calcium,
    c. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤3 × upper limit of normal (ULN), alkaline phosphatase ≤2.5 × ULN unless bone metastases present, bilirubin ≤1.5 × ULN (unless known Gilbert's disease where it must be ≤3 × ULN) and serum albumin ≥3.0 g/dL.
    d. Thyroid stimulating hormone (TSH) within normal limits.
9. Life expectancy ≥12 weeks.
10. A negative serum pregnancy test at baseline for women of childbearing potential (WOCBP).

11. Females of childbearing potential (non-surgically sterile or premenopausal female capable of becoming pregnant) and all males (due to potential risk of drug exposure through the ejaculate) must agree to use an acceptable method of contraception while enrolled on this study and for 5 months after the last dose of study drug. Acceptable methods of birth control in this trial include 2 highly effective methods of birth control (as determined by the Investigator; one of the methods must be a barrier technique) or abstinence.
12. Have the ability to understand and the willingness to sign a written informed consent document.

4.2 Exclusion Criteria

Subjects who fulfill **any** of the following criteria at screening will **not** be eligible for admission into the study:

1. History of Grade ≥3 or above hypersensitivity reactions to monoclonal antibodies.
2. History of a cardiovascular illness including: QT interval corrected by heart rate using Fridericia's correction formula (QTcF) >450 ms in male or >470 ms in female, congenital long QT syndrome, congestive heart failure (New York Heart Association Grade III or IV) (Appendix 2); unstable angina or myocardial infarction within the previous 6 months; or symptomatic cardiac arrhythmia despite medical management.
3. Uncontrolled hypertension, systolic blood pressure (SBP) >160 mmHg or diastolic blood pressure (DBP) >100 mmHg.
4. Central nervous system metastasis or leptomeningeal disease except when treatment of brain metastasis is completed >14 days prior to C1D1 and stable for ≥4 weeks on <10 mg daily prednisone or equivalent.
5. History of hemorrhagic diarrhea, inflammatory bowel disease, active uncontrolled peptic ulcer disease or bowel resection that affects absorption of orally administered drugs.
6. Recurrent pleural effusion requiring repetitive palliative thoracentesis within 3 months prior to study entry, except for subjects with a pleurex port.
7. Active, known, or suspected autoimmune disease, or history of immune-mediated toxicity leading to treatment discontinuation, except for type I diabetes mellitus, hypothyroidism only requiring hormone replacement or skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic therapy.
8. Active pneumonitis, history of non-infectious pneumonitis that required treatment with steroids, or history of interstitial lung disease.
9. Active uncontrolled bacterial, viral, or fungal infection requiring systemic therapy.
10. Known history of testing positive for human immunodeficiency virus (HIV), known acquired immunodeficiency syndrome (AIDS).
11. Active hepatitis B (serum hepatitis B surface antigen [HBVsAg] positive), or hepatitis C (HCV antibody test or serum hepatitis C ribonucleic acid [RNA] positive).
12. Received approved live vaccines within 30 days of planned C1D1. Inactivated viral vaccines or vaccines based on subviral component are allowed; however intranasal influenza vaccines (e.g. Flu-Mist) are not allowed. COVID-19 vaccination should be administered >7 days before C1D1.

13. Any condition requiring chronic systemic treatment with either corticosteroids (>10 mg daily prednisone equivalents) or other immunosuppressive medications, or steroids use within 14 days of study drug administration. Inhaled or topical steroids are permitted.
14. Use of other investigational agent (drug not marketed for any indication) within 28 days or at least 5 half-lives (whichever is shorter) before study drug administration.
15. Pregnant or breast-feeding women.
16. Second malignancy unless in remission for 2 years; subjects with non-melanomatous skin cancer, carcinoma in situ of the cervix treated with curative intent, or curatively treated prostate cancer with prostate-specific antigen (PSA) <2.0 ng/mL can be included.
17. Underlying medical conditions that, in the Investigator's opinion, will make the administration of study drug hazardous or obscure the interpretation of toxicity determination or adverse events.
18. Unwilling or unable to comply with procedures required in this protocol.

4.3 Subject Registration

4.3.1 Subject Registration

Based on medical history, potentially eligible subjects will be identified. After obtaining informed consent, the screening procedures will be performed. Once a subject's eligibility has been confirmed, a 4-digit subject number will be assigned. The first 2 digits are the site number (provided by the Sponsor or CRO to investigational sites). The following 2 digits are a sequential number within an investigational site. An Eligibility Screening Form (ESF) provided by the Sponsor or CRO documenting the Investigator's assessment of each screened subject with regard to the protocol's inclusion and exclusion criteria is to be completed, submitted for review and approval by the Sponsor or Sponsor representative and kept at the investigational site

4.3.2 Blinding

This is an open-label study; no blinding procedures will be performed.

4.4 Withdrawal Criteria

4.4.1 Subject Withdrawal from the Study

Subjects may withdraw from the study at any time for any reason. The Investigator should try to ascertain the reason for withdrawal as completely as possible. The Investigator may also decide to discontinue a subject from the study. HBI-8000 may be discontinued, and the subject withdrawn from the study under the following circumstances:

- Unacceptable toxicity (AE)
- Progression of the disease under study
- Decision by the Investigator or subject to permanently discontinue HBI-8000
- Intercurrent illness that would, in the judgment of the Investigator, affect clinical assessments, patient safety, or follow-up to a significant degree
- Significant protocol deviations that jeopardize the usefulness of the data

- Subject noncompliance, examples include omitting >1/3 of protocol specified dose over 6 consecutive weeks, not adhering scheduled safety assessments, etc.
- Subject is beginning another anti-cancer treatment
- Subject becomes pregnant
- Subject request to withdraw informed consent
- Death

All subjects who withdraw from HBI-8000 must complete an EoT safety follow-up visit, to be performed 30 (± 3) days after the last dose of HBI-8000, or before initiation of new cancer treatment, whichever is earlier. After HBI-8000 is discontinued, the subjects should be followed for disease progression (if not already recorded) and survival. Only subjects who have withdrawn from study participation entirely, including the period after HBI-8000 is discontinued, will not be followed. In other words, a subject may withdraw consent for treatment but still allow follow-up, in which case he/she should be followed for safety, survival, and disease status.

4.4.2 Lost to Follow-up

All reasonable efforts must be made to locate subjects to determine and report their ongoing status. Lost to follow-up is defined by the inability to reach the subject after a minimum of three documented phone calls, faxes, or emails as well as lack of response by subject to one registered mail letter. All attempts should be documented in the subject's medical records. If it is determined that the subject has died, the site will use permissible local methods to obtain the date and cause of death.

4.5 Discontinuation of Investigational Product and Participant Withdrawal

Subjects discontinued from HBI-8000 for toxicity in the absence of disease progression may continue to receive pembrolizumab under standard of care and be followed for disease response as long as consent to study participation remains effective. Similarly, if pembrolizumab administration is discontinued due to unacceptable toxicities (other than immune-mediated reactions) associated with pembrolizumab, the subject may continue to receive HBI-8000, at the Investigator's discretion in consultation with Sponsor Medical Monitor and be followed for disease response as long as consent to study participation remains effective. When both HBI-8000 and pembrolizumab have been discontinued and disease has not progressed, the subject will continue to be followed for disease status in the Follow-up Phase until evidence of progression.

5 STUDY TREATMENT

5.1 Investigational Product(s) Administered

Table 3: Investigational Products

Investigational Product	Dosage Form and Strength	[redacted]
HBI-8000	Immediate-release, 10 mg film coated tablet	[redacted]
KEYTRUDA®(pembrolizumab)	100 mg/4 mL (25 mg/mL) single-dose vial	[redacted]

5.1.1 HBI-8000 Information

The HBI-8000 Drug Product is formulated as a coated tablet containing 10 mg of HBI-8000, [redacted]

The drug substance, drug product intermediate (dispersion), and film coated tablets are manufactured in the US.

5.1.2 Pembrolizumab Information

Pembrolizumab is a humanized monoclonal IgG4 kappa antibody supplied as a sterile, preservative-free, clear to slightly opalescent, colorless to slightly yellow solution in a single-dose vial for intravenous use. [redacted]

The vial should be visually inspected for particulate matter and discoloration prior to administration. The solution is clear to slightly opalescent, colorless to slightly yellow. Discard the vial if visible particles are observed.

5.2 Clinical Supplies Storage and Accountability

5.2.1 Clinical Materials

HBI-8000 Investigational Product tablets are supplied as film coated tablets in a high-density polyethylene (HDPE) bottle containing 26 tablets, a 1-gram silica gel desiccant cannister and a polyester coil for moisture protection. Bottles will be labeled in accordance with GCP, US FDA requirements under Code of Federal Regulations (CFR) 21.201.

5.2.2 Investigational Product Storage

HBI-8000 Investigational Product: The storage and distribution condition is 15° to 30° Celsius (59°F to 86° Fahrenheit).

HBI-8000 must be stored out of the reach of children and in original container with tightly closed cap to protect from moisture.

Pembrolizumab: Must be stored under refrigeration at 2 to 8°Celsius (36 to 46°Fahrenheit), protected from light by storing it in the original package until time of use. It must not be frozen or shaken.

Pembrolizumab does not contain a preservative. Diluted pembrolizumab from the 100 mg/4 mL vial should be stored either:

- At room temperature for no more than 6 hours from the time of dilution. This includes room temperature storage of the diluted solution, and the duration of infusion.
- Or, under refrigeration at 2°C to 8°C (36°F to 46°F) for no more than 96 hours from the time of dilution. If refrigerated, allow the diluted solution to come to room temperature prior to administration. Do not shake.

Discard diluted pembrolizumab after 6 hours at room temperature or after 96 hours under refrigeration.

Do not freeze.

5.2.3 Investigational Product Accountability

The Investigator, or his/her designee, must maintain a complete and accurate record of the receipt and distribution of all study medication using the Drug Accountability Form provided by the CRO, or local site equivalent.

All study medication must be accounted for at the termination of the study, and a written explanation provided for any discrepancies. The study monitor will conduct a final drug reconciliation for all subjects. All records of HBI-8000 administration, accountability records, and disposition records will be examined and reconciled by the study monitor. All unused, partially used, and expired study medication and packaging materials are to be inventoried and returned to depot or destroyed as per the sites' Standard Operating Procedure (SOP). The timing of the returns will be coordinated with the study monitor. The Investigator is not permitted to destroy unused clinical drug supplies or packaging materials unless authorized by HUYABIO or Sponsor representative.

5.3 Investigational Product Compliance

The prescribed dosage, timing, and mode of administration may not be changed. Any departures from the intended regimen must be recorded in the eCRFs. Treatment compliance will be monitored by drug accountability as well as the subject's medical record and eCRF.

Study subjects will be provided with a drug diary to record times of administration, AEs, and missed doses. Study subjects will be instructed to bring the drug diary and study drug bottles (including empty bottles) to each study visit for reconciliation.

At each visit, prior to dispensing HBI-8000, previously dispensed HBI-8000 will be reviewed by the Investigator or designee and compliance assessed. Subjects exhibiting poor compliance as assessed by tablet counts should be counseled on the importance of good compliance to the study dosing regimen.

5.4 Concomitant Therapy

All concomitant medications, defined as medications other than study medications, which are taken at baseline and throughout HBI-8000 treatment phase by the study subjects must be recorded on the eCRF.

Palliative radiation therapy (limited-field) is permitted only for pain control to sites of bone disease present at baseline. The Sponsor Medical Monitor must be consulted prior to initiating any radiotherapy.

5.4.1 Prohibited Medications and Therapy

Concomitant administration of the following types of drugs and procedures is not allowed:

- Recently completed drug-drug interaction study showed a mild (approximately 40%) increase of AUC of HBI-8000 when itraconazole, a strong CYP3A4, was administered concurrently. The use of potent CYP3A4 inducers or inhibitors (Appendix 3) should be avoided.
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, seasonal flu (that contain a live virus), H1N1 flu, rabies, BCG, and typhoid vaccine.
- Surgery for tumor control or symptoms management is not permitted during the study.
- Concomitant administration of anti-tumor treatment other than the Study Treatment, or procedures that could interfere with the evaluation of safety or anti-tumor effect of Study Treatment, is prohibited during the study.

5.4.2 Supportive Care and Other Medications

Systemic use of corticosteroids at doses ≤10 mg/day of prednisolone, or converted equivalent dose, is permitted during the study. Brief use of higher dose of prednisone or its equivalent is also permitted to manage immune related toxicities as indicated. Supportive care to mitigate toxicities such as anti-emetics for nausea, and granulocyte-colony stimulating factor (G-CSF) for neutropenia are also allowed.

Palliative and supportive care is permitted during the course of the trial for underlying medical conditions and management of symptoms.

Palliative radiation therapy (limited field) is permitted only for pain control if considered medically necessary by the treating physician as long as the lesion is NOT a RECIST 1.1 defined target lesion and is NOT administered for tumor control. Study treatment should be held during the course of palliative radiotherapy and should be resumed no earlier than the next scheduled administration of study treatment. The specifics of the radiation treatment, including the location,

will be recorded. The Sponsor Medical Monitor must be consulted prior to initiating any radiation therapy.

In order to provide optimal patient care, and to account for individual medical conditions, the Investigator may apply discretion to prescribe supportive care (e.g., acetaminophen, diphenhydramine, antimicrobials) according to local institutional guidelines. After the first cycle, pre-medication for anticipated adverse events may also be provided, according to local institutional guidelines.

Subjects must be instructed to first consult with their study doctor before taking any additional medications (including over-the-counter or prescription medications and supplements including those prescribed/recommended by other physicians/dentists) during the study.

5.4.3 Restricted Medications

- Antiarrhythmic drugs such as amiodarone, disopyramide, procainamide, etc., and other drugs known to prolong the QT interval such as clarithromycin, moxifloxacin, bepridil, etc., may increase QT interval prolongation, and their coadministration should therefore be avoided. If such a drug is going to be co-administered, the patient's condition should be monitored closely.
- Bisphosphonates and/or RANKL inhibitor therapies used to prevent bone resorption, cannot be initiated after informed consent has been signed. These therapies may be continued IF treatment with an agent from one of these two classes was initiated PRIOR to signing informed consent.
- COVID-19 vaccination should be administered >7 days before Cycle 1 Day 1.

5.5 Food Effects

The study evaluating the effect of food on oral bioavailability of HBI-8000 has shown comparable drug exposure of HBI-8000 tablets when taken under fasting or fed conditions. In this study, HBI-8000 should be taken approximately 30 minutes after a meal.

Due to potential food-drug interactions, grapefruit, grapefruit juice, Seville oranges, and any products that contain Seville oranges or grapefruit should be avoided within 7 days prior to C1D1 through 7 days after the last dose of HBI-8000.

5.6 Dose Modification

5.6.1 HBI-8000 Administration

Subjects will take 30 mg of Study Treatment orally approximately 30 minutes after a meal, beginning on Day 1 and continue every 3 to 4 days on the BIW schedule without interruption (e.g., Monday and Thursday, or Monday and Friday repeating every week).

5.6.1.1 HBI-8000 Dose Reduction

Once HBI-8000 dose is reduced, it will not be increased. This dose reduction guideline applies to the entire study duration.

If a subject experiences any of the toxicities described below, the dose of HBI-8000 will be reduced. One dose reduction (30 mg to 20 mg) is allowed for non-hematological toxicities, and two dose reductions (30 mg to 20 mg and 20 mg to 10 mg) are allowed for hematological toxicities. Dose reduction for other toxicities not described below may be possible after approval from the sponsor.

A. Hepatic Non-Hematologic Toxicity

- Isolated Grade 4 AST/ALT
- Isolated Grade 3 AST/ALT that fails to return to Grade 1 or less within 5 days
- Isolated total bilirubin ≥Grade 3
- AST or ALT >3 × ULN AND concurrent total bilirubin >2 × ULN

B. Non-Hepatic Non-Hematological Toxicity

Any Grade 3 or greater non-hepatic non-hematologic toxicity except for the following:

- Grade 3 electrolyte abnormalities that are not complicated by associated clinical adverse experiences, last less than 48 hours and either resolve spontaneously or respond to conventional medical intervention.
- Grade 3 nausea or vomiting that lasts less than 48 hours, and either resolves spontaneously or responds to conventional medical intervention.
- Isolated Grade 3 elevation of amylase or lipase not associated with clinical or radiographic evidence of pancreatitis.
- Isolated Grade 3 fever that lasts ≤3 days and is not associated with hemodynamic compromise (i.e., hypotension, clinical or laboratory evidence of impaired end-organ perfusion).

C. Immune-related AEs (irAE)

- Any Grade 2 or greater eye pain or reduction in visual acuity that does not respond to topical therapy and does not improve to Grade 1 severity within 2 weeks of the initiation of topical therapy or any Grade 2 or greater eye pain or reduction in visual acuity that requires systemic treatment.
- Any other Grade 3 or greater irAE

  If pembrolizumab is withheld or permanently discontinued due to an immune-mediated reaction, HBI-8000 should be withheld or permanently discontinued, respectively.

D. Hematologic Toxicity

- Grade 4 neutropenia ≥7 days in duration
- Grade 4 thrombocytopenia, or any Grade 3 thrombocytopenia associated with clinically significant bleeding

- Grade ≥3 febrile neutropenia
- Grade ≥3 hemolysis

HBI-8000 treatment will resume at a reduced dose only after toxicity has returned to Grade ≤1 within 14 days from the occurrence of the toxicity. For neutropenia, the use of G-CSF should be considered. If the same toxicity recurs despite allowed dose reduction(s), HBI-8000 will be discontinued. If toxicity is not related to pembrolizumab, at Investigator's discretion a subject may continue to receive pembrolizumab while remaining in study Follow-Up.

5.6.1.2 HBI-8000 Dose Delay Independent of Pembrolizumab Administration

At the Investigator's discretion, the dose of HBI-8000 may also be delayed for up to 14 days from the scheduled time of dosing, for any toxicity possibly or probably related to HBI-8000 that does not meet toxicity criteria described in Section 5.6.1.1. In the event of Grade 3 uncomplicated thrombocytopenia or neutropenia HBI-8000 dosing should be held until recovery to Grade ≤1 before resuming again. Supportive care with hematological growth factors may be prescribed at the discretion of the Investigator.

Dosing may be interrupted to assess or treat intercurrent illnesses. The Sponsor's representative should be notified of any treatment interruption. In the event of interruption of >14 days, resumption of dosing should be discussed with Sponsor to assess potential benefit for continuation of HBI-8000.

5.6.2 Pembrolizumab Administration

Pembrolizumab will be administered by intravenous infusion in accordance with KEYTRUDA® Prescribing Information (Package Insert and institutional practice either as 200 mg on Day 1 of every cycle or 400 mg on Day 1 of every other cycle (Cycle 1, 3, 5, etc.). If administration of HBI-8000 is delayed or interrupted due to an AE not attributed to pembrolizumab, administration of pembrolizumab will not be affected.

To manage infusion reactions, pembrolizumab will be administered only at sites that are fully equipped to handle infusion reactions, and with study personnel that are properly trained.

5.6.2.1.1 Pembrolizumab Dose Modifications

Dose modifications for pembrolizumab should be followed according to the most recent approved label for KEYTRUDA®; therefore, withhold or permanently discontinue pembrolizumab for adverse events as outlined in the KEYTRUDA US package insert (USPI) as per its use in non-small cell lung cancer.

In the event that pembrolizumab is discontinued (for reasons other than immune-mediated reactions), HBI-8000 may be continued until one of the conditions for HBI-8000 discontinuation is met at the Investigator's discretion in consultation with Sponsor Medical Monitor.

5.6.2.1.2 Pembrolizumab Dose Delay Independent of HBI-8000 Administration

Investigators should withhold a dose as described in the KEYTRUDA USPI (Recommended treatment modifications) until it is reduced to a Grade 1 or resolved. Once resolved, the dose may be reinstated. For subjects who were treated with steroids for irAE, steroids need to be tapered to

a dose 10 mg or less of prednisone or equivalent over at least 1 month before resuming pembrolizumab. The administration of HBI-8000 may continue as scheduled during pembrolizumab dosing interruption.

5.6.2.1.3 Infusion-Related Reactions

Pembrolizumab can cause severe infusion-related reactions. For severe and life-threatening infusion reactions, pembrolizumab should be discontinued; for mild or moderate infusion reactions the infusion should be interrupted, or the rate of infusion slowed. Immediate access to an Intensive Care Unit or equivalent environment and resuscitation equipment and appropriate medical therapy (including epinephrine, corticosteroids, IV antihistamines, bronchodilators, and oxygen) must be available to treat infusion-related reactions.

All Grade 3 or 4 infusion reactions should be reported within 24 hours to HUYABIO Medical Monitor and reported as a serious adverse event (SAE) if criteria are met. Infusion reactions should be graded according to NCI-CTCAE guidelines.

5.6.2.1.4 Severe Hypersensitivity Reactions

If a hypersensitivity reaction occurs, the subject must be treated according to the best available medical care. Subjects should be instructed to report any delayed reactions to the Investigator immediately based on the appropriate complete guideline for emergency treatment of anaphylactic reactions.

Corticosteroids can be administered intravenously. The subject should be placed on a monitor immediately and the Intensive Care Unit must be alerted for possible transfer if needed. Investigators should withhold a dose as described in the KEYTRUDA® USPI (Dose Modifications).

6 STUDY ASSESSMENTS AND PROCEDURES

The procedures and assessments to be performed during each period of the study are outlined in the Schedule of Dosing and Assessments (Table 1) and described in the following section.

6.1 Study Visits and List of Procedures

6.1.1 Screening Assessments (within 28 days prior to start of treatment)

Written informed consent for participation in the study must be obtained before performing any study-specific screening tests or evaluations. Informed Consent Forms (ICFs) for all subjects screened will be maintained at the study site.

Screening assessments will be performed within 28 days prior to Day 1. Results of standard of care tests or examinations performed prior to obtaining informed consent and within 28 days prior to Day 1 may be used (and do not need to be repeated during screening unless they do not meet the criteria defined in the protocol).

The following will be collected or performed between Day -28 and Day -1:

- Written informed consent

- Inclusion/exclusion criteria review for confirmation of eligibility
- Medical history, concomitant medications, baseline signs and symptoms, demographics, and height
- HBsAg and anti-HCV serology tests
- Cancer diagnosis history including histological diagnosis, PD-L1 expression, known mutation status for B-Raf proto-oncogene serine/threonine kinase gene (BRAF) V600, EGFR, and ALK and treatment history
- Brain magnetic resonance imaging (MRI) if clinically indicated, and radiographic tumor assessment. If a subject has metal implants, a computerized tomography (CT) scan should be used instead of an MRI.

6.1.2 Baseline Assessments (within 14 days prior to start of treatment)

Baseline assessments may be completed within 14 days before C1D1. If there is any history or findings suggestive of significant heart disease, a cardiology consultation should be obtained. Women of childbearing potential must have a negative serum pregnancy test at baseline within 14 days of start of treatment per the Schedule of Dosing and Assessments (Table 1).

Baseline assessments include a complete physical examination, vital signs, ECOG performance status, weight, concomitant medications, laboratory tests (hematology, chemistry, coagulation and urinalysis), serum pregnancy test (if applicable), and ECG.

All screening and baseline assessments must be completed and reviewed to confirm that subjects meet all eligibility criteria. Subject registration and ESF approval will be obtained in accordance with Section 4.3.

6.1.3 Treatment Phase Assessments

Cycle 1 Day 1: physical exam, vital signs, ECOG performance status, weight, concomitant medications, and laboratory assessments will be performed according to the Schedule of Dosing and Assessments (Table 1).

All visits and assessments from Cycle 2, Day 1 onwards may be performed ±3 days from the date of the projected visit date. First assessment of tumor response will be scheduled on C3D1 and every 6 weeks (±3 days) thereafter, or sooner if a subject develops clinical signs and symptoms of disease progression, until disease progression or end of study treatment.

6.1.4 End of Treatment (EoT) Safety Visit Assessments

The EoT safety follow-up visit will be conducted 30 (±3) days following the last dose of HBI-8000, or before the initiation of new cancer treatment, whichever is earlier. Assessments will include a physical examination, vital signs, ECOG performance status, weight, concomitant medications, laboratory tests (hematology, chemistry, coagulation and urinalysis), serum pregnancy test (if applicable), ECG, and assessment of any ongoing adverse events.

Subjects with HBI-8000-related AEs of Grade ≥2 observed at the EoT visit should be followed-up and assessed monthly until the AEs have resolved to Grade ≤1 or are determined to be chronic or subject receives other anti-cancer therapy.

Any pregnancies while on this study or within 28 days of the last dose of HBI-8000 will be followed up, with female subject's permission, until the birth of the baby (Refer to Section 6.2.2.4.8).

6.1.5 Tumor Status and Survival Follow-up

After the discontinuation of treatment (HBI-8000), subjects without disease progression will be followed for tumor status with imaging studies of target lesions every 12 (±1) weeks until progression, initiation of another anti-cancer treatment, or referral to hospice. Subjects will be contacted every 12 weeks (±1) weeks for survival follow-up, until death or end of the study.

6.2 Study Procedures Details

6.2.1 Efficacy Assessments

The following evaluations will be performed throughout the course of the study:

- Tumor response assessments by physical examination and tumor imaging by CT or magnetic resonance imaging (MRI) according to RECIST v1.1: CT scans are the required modality for measurable disease unless a subject has a clinical condition, e.g. severe contrast allergy, when CT without contrast may be used per institution guidelines. The same scanning modality and the same technique must be used to measure each identified and reported lesion at baseline and throughout the study for a given subject.
- Brain magnetic resonance imaging (MRI) if clinically indicated, and radiographic tumor assessment. If a subject has metal implants, a computerized tomography (CT) scan should be used instead of an MRI.

6.2.1.1 Tumor Response Criteria

All measurable disease (target lesions and non-target lesions) must be documented at screening and reassessed at each subsequent tumor evaluation. Reassessment will be done by imaging studies according to RECIST Guidelines version 1.1 (Appendix 4), along with physical examinations and other methods as needed. At the Investigator's discretion, CT scans may be repeated at any time if PD is suspected.

Tumor response will be evaluated by the Investigator using the RECIST 1.1 criteria [Eisenhauer 2009] (Appendix 4) and recorded in the appropriate eCRFs. Tumor response will also be assessed centrally.

Taking into consideration possible pseudo progression, the subject may continue study treatment until the next imaging evaluation to assess tumor response according to irRECIST critieria. The same scanning modality should be used at baseline and throughout treatment for each subject.

Subjects with isolated CNS progression, but responsive/stable extracranial disease, may remain on the study protocol after consultation with Sponsor Medical Monitor.

6.2.1.1.1 Immune-related RECIST (irRECIST)

Immunotherapeutic agents may produce anti-tumor effects by potentiating endogenous cancer-specific immune responses. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents and can manifest a clinical response after an initial increase in tumor burden or even the appearance of new lesions.

Conventional RECIST 1.1 may thus not provide a complete response assessment of immunotherapeutic agents. To account for the unique tumor response characteristics seen with treatment with immunotherapy, irRECIST 1.1 has been adapted from conventional RECIST [Nishino 2013] (Appendix 4).

Assessment of potential tumor progression is the responsibility of the Investigator. The Investigator will determine the date of progression and report it in the appropriate eCRF.

6.2.1.1.2 Survival Follow-up

Post-treatment tumor status in subjects whose disease has not progressed, and survival follow-up will be conducted until study completion. Subjects for whom disease progression has not been observed will have assessments of tumor status every 12 weeks (±1 week) until a date of disease progression is obtained, initiation of another anti-cancer treatment, or referral to hospice. Survival will be followed approximately every 12 (±1) weeks by telephone contact or e-mail for up to 12 months after the last dose of HBI-8000.

6.2.2 Safety Assessments

The following safety evaluations will be performed at screening and various time points throughout the course of the study (treatment phase, post-treatment, etc., refer to Table 1):

- Medical history
- Physical examinations
- Evaluation of adverse events (AEs)
- ECOG performance status
- Vital signs
- Electrocardiogram (ECG)
- Clinical Safety Laboratory tests: complete blood count (CBC) and serum chemistry, Thyroid function (Baseline, Day 1 of each Cycle throughout study and EoT Safety Follow-Up Visit) , hepatitis B and C panel (Screening), urinalysis (Baseline and EoT Safety Follow-up Visit), serum pregnancy test (at Baseline and during study when clinically indicated, if applicable)
- Coagulation tests to include PT/INR, aPTT (at Baseline, at EoT Safety Follow-Up Visit, and during the study when clinically indicated)

Treatment-emergent adverse events reported by the subjects or observed during physical examination, vital sign assessment, ECGs and/or review of laboratory test results will be assessed according to NCI CTCAE v.5.0 (CTCAE home page: http://evs.nci.nih.gov/ftp1/CTCAE/About.html) and recorded by severity grades and association

with HBI-8000 and pembrolizumab. Results of clinical laboratory tests, vital signs, physical findings, ECGs and ECOG performance status will be monitored and recorded.

6.2.2.1 Vital Signs, ECG, Physical Examinations, and ECOG Assessments

Vital sign measurements will include temperature, heart rate, systolic blood pressure (SBP) and diastolic blood pressure (DBP) in a supine position. Vital sign measurements should be performed prior to the ECG and after the subject has been supine for at least 5 minutes.

Physical examinations will include the evaluation of head, eye, ear, nose, and throat (HEENT), cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, and neurological systems. Changes from baseline abnormalities should be recorded at each subsequent physical examination. New or worsened abnormalities should be recorded as adverse events if appropriate.

ECOG Performance Status will be used to assess subjects' performance status. Refer to Appendix 1. for definitions of ECOG performance score.

6.2.2.2 Clinical Laboratory Assessments

Hematology testing will include the following parameters: hemoglobin, hematocrit, red blood cell (RBC) count, WBC count with differential, and platelet count.

Coagulation will include the following parameters: prothrombin time (PT), activated partial thromboplastin time (aPTT), and International Normalized Ratio (INR).

Serum chemistry testing will include the following parameters: blood urea nitrogen (BUN), creatinine, AST, ALT, lactate dehydrogenase (LDH), total bilirubin (including direct fraction if total bilirubin is abnormal), lipase, amylase, thyroid stimulating hormone (TSH), free thyroxine (T4) (direct), total protein, albumin, uric acid, alkaline phosphatase, sodium, potassium, calcium, magnesium, phosphorus and glucose.

Urinalysis will be performed using a dipstick method followed by microscopic examination in the event of abnormal dipstick results.

Pregnancy test: All women of childbearing potential (including those who have had a tubal ligation) will have a serum pregnancy test at baseline and at the EoT Safety Follow-up visit.

Adverse Events and Serious Adverse Events: All abnormal laboratory results must be reviewed by the Investigator and evaluated. All clinically significant results will be documented as adverse events. Clinically significant is defined as an abnormal laboratory value that meets the following criteria:

- Requires additional tests, medication and/or interventions to follow or treat the event
- Results in subject discontinuation
- Results in an SAE
- Manifests clinically
- Changes the treatment regimen of the subject
- New onset of any ≥grade 3 event (regardless of relationship to study drug or outcome of the event)

6.2.2.3 PD-L1 Testing

The PD-L1 status will be determined by PD-L1 IHC 22C3 pharmDx test (Dako North America, Inc) approved by FDA in 2015, performed at local diagnostic laboratory.

PD-L1 IHC 22C3 pharmDx is indicated as an aid in identifying NSCLC patients for treatment with KEYTRUDA® (pembrolizumab). [redacted]

6.2.2.4 Adverse Events

An adverse event (AE) is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may not be considered related to the medical treatment or procedure. Assessment of the occurrence of an AE will be based on changes in the subject's physical examination, ECG, clinically significant laboratory results, and/or signs and symptoms. An AE also includes any newly occurring event or previous condition that has increased in severity or frequency after the subject received the first dose of Study Treatment.

Adverse events will be monitored until they are resolved and/or deemed stable, as in the case of an event that is related to a chronic condition or intercurrent illness. Medical care will be provided, as defined in the informed consent, for any AE related to study participation.

6.2.2.4.1 Serious Adverse Events

A serious adverse event (SAE) is any untoward medical occurrence, regardless of its relationship to Study Treatment, that meets any of the following criteria:

- Results in death
- Is life-threatening (i.e., the subject is at a risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Requires in patient hospitalization or prolongation of existing hospitalization; hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the subject was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study. (Please read the **NOTE** below)
- Results in persistent or significant disability/incapacity
- Is a congenital abnormality/birth defect
- Is an important medical event, defined as a medical event that may not be immediately life-threatening or result in death or hospitalization, but based upon appropriate medical

and scientific judgment, may jeopardize the subject or may require intervention (e.g., medical or surgical) to prevent one of the other serious outcomes listed in the definition of an SAE. Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.

It is common that several other AEs are observed when the SAE qualifying event occurs. Not all observed AEs are SAEs. Efforts must be made to identify the chief event(s) leading to the SAE qualifying event, e.g., hospitalization.

Suspected transmission of an infectious agent (e.g., pathogenic or nonpathogenic) via the study drug is an SAE.

Any component of a study endpoint that is considered related to study therapy (e.g., death is an endpoint) if death occurred due to anaphylaxis, anaphylaxis must be reported.

Although pregnancy and overdose are not always serious by regulatory definition, these events must be reported on a Pregnancy Surveillance form and an AE/SAE form respectively in the eCRF within 24 hours of Investigator awareness of the overdose, regardless of association with an AE.

Pregnancies of study subject or partner of study subject receiving Study Treatment currently or within 28 days of last dose, regardless of outcome.

If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should include the same Investigator term(s) initially reported, change in event terms should be accompanied by proper documentation of the rationale for the event term change.). Multiple signs, symptoms and manifestation of disease entity should be subsumed under umbrella diagnosis rather than reporting the signs and the symptoms of the diagnosis.

If an ongoing SAE changes in its intensity or relationship to Study Treatment or if new information becomes available, a follow-up SAE report should be sent within 24 hours to the Sponsor (or designee) using the same procedure used for transmitting the initial SAE report.

All SAEs should be followed to resolution or stabilization

NOTE: The following hospitalizations are not considered SAEs in sponsored clinical studies:

- A <24-hour visit to the emergency room or other hospital department, that does not result in admission (unless considered to be an important medical event or an event that is life threatening)
- Elective surgery planned prior to signing ICF
- Admissions as per protocol for a planned medical/surgical procedure
- Routine health assessment requiring admission for pretreatment assessment/trending of health status (e.g., routine colonoscopy)
- Medical/surgical admission for a purpose other than remedying ill state of health and was planned prior to entry into the study. Appropriate documentation is required in all these cases.

- Admission for a life circumstance that has no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative)
- Admission for progressive disease (PD)

6.2.2.4.2 Intensity of Adverse Events

The intensity of adverse events will be graded according to the NCI-CTCAE scale:

- **Grade 1: Mild**; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- **Grade 2: Moderate**; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (ADL). Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
- **Grade 3: Severe or medically significant**, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL. Self-care ADL refers to bathing, dressing and undressing, feeding oneself, using the toilet, taking medications, and not being bedridden.
- **Grade 4: Life-threatening consequences**; urgent intervention indicated.
- **Grade 5: Death** (at least possibly) related to the AE.

6.2.2.4.3 Causal Relationship Assessment

The relationship of an AE to the HBI-8000 and pembrolizumab is to be graded by the Investigator as follows:

Definite:

- Distinct temporal relationship with the Study Treatment
- Stops/improves when the Study Treatment has been stopped
- Can reasonably be explained by known characteristics of the Study Treatment

Probable:

- Reasonable temporal sequence from the Study Treatment administration
- Stops/improves when the Study Treatment has been stopped
- Event cannot easily be explained by subject's clinical state or other factors

Possible:

- Reasonable temporal relationship with the Study Treatment
- Event could have been produced by the subject's clinical state or other factors

Unlikely:

- Poor temporal relationship to the Study Treatment

- Subject's clinical state is likely to have an association with the effect

Unrelated:

- Definitely not associated with the Study Treatment administered

Events that are assessed as "definite", "probable" and "possible" in relation to HBI-8000 or pembrolizumab are regarded as AEs that cannot be denied a causal relationship to the Study Treatment and will be handled as "related to HBI-8000 or pembrolizumab" respectively for reporting purposes. Events that are assessed as "unlikely" or "unrelated" to HBI-8000 or pembrolizumab will be handled as "not related to HBI-8000 or pembrolizumab" respectively for reporting purposes.

6.2.2.4.4 Reporting of Adverse Events

All treatment-emergent adverse events (TEAEs) reported by the subjects, observed during physical examination, vital sign assessment, ECGs and/or review of laboratory test results will be assessed according to NCI CTCAE v.5.0 (CTCAE home page:

http://evs.nci.nih.gov/ftp1/CTCAE/About.html

and recorded by severity grades and association with HBI-8000 and pembrolizumab in the eCRF. The reporting of TEAEs should begin at initiation of Study Treatment. Baseline signs and symptoms should also be collected from screening to establish a baseline status for the subjects and will be documented as part of the subject's medical history. The Investigator should complete all the details requested including dates of onset, severity, action taken, outcome, relationship to HBI-8000 or pembrolizumab. Each event should be recorded separately.

Disease progression, signs, symptoms and manifestations of disease progression should not be recorded as an AE. Diagnostic and therapeutic noninvasive and invasive procedures, such as surgery, will not be reported as an AE, but the procedure and/or therapeutic treatment should be recorded on the appropriate eCRF. The medical condition for which the procedure was performed must also be reported.

6.2.2.4.5 Time Period and Frequency for Collecting and Reporting of Serious Adverse Events and Pregnancy Information

Following the subject's written consent to participate in the study, all SAEs whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. An SAE report should be completed for any event where doubt exists regarding its seriousness.

If the Investigator believes that an SAE is not related to study drug but is potentially related to the conditions of the study (such as withdrawal of previous therapy or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE Report Form.

All SAEs must be reported to the Sponsor (or designee) within 24 hours of awareness of the event. All available SAE data, irrespective of the extent of available AE information, must also be recorded in the eCRF within 24 hours of Investigator awareness of the event. In case the eCRF cannot be used by the Investigator to generate the SAE/Pregnancy form, a paper SAE/Pregnancy form will be used and submitted to the Sponsor (or designee). Once the eCRF limitation is

resolved, the Investigator must, as soon as possible, enter all the information from the paper report into the eCRF.

This timeframe also applies to additional new information (i.e., follow-up) on previously forwarded SAE reports. For all SAEs, the Investigator is obligated to pursue and provide information to the Sponsor (or designee). In addition, an Investigator may be requested by the Sponsor (or designee) to obtain specific additional follow-up information in an expedited fashion. In general, this will include a description of the AE in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications and illnesses must be provided. In the case of death, a summary of available autopsy findings must be submitted as soon as possible to the Sponsor (or designee). All SAEs requiring expedited regulatory reporting will be evaluated, summarized, and reported to Investigators.

Investigators will be notified by the Sponsor (or designee) of all SAEs that require prompt submission to their IRB or IEC. Investigators should provide written documentation of IRB/IEC notification for each report to the Sponsor (or designee). The Sponsor (or designee) will ensure that all SAEs are reported to the appropriate regulatory authorities.

6.2.2.4.6 Follow-Up of Adverse Events

Subjects should be asked to specifically describe any signs, symptoms, or AEs (regardless of relationship to Study Treatment) they may notice prior to the start of the study or thereafter. At a minimum, subjects should be asked to report any changes at each visit to the study center. Conditions that the subject experienced prior to informed consent should be recorded in the medical history section of the eCRF.

AEs, Grade 2 and above, considered to be at least possibly related to the Study Treatment must be followed up after the EoT assessment until the events have resolved, returned to the baseline level, are judged by the Investigator to be stable, or no longer require follow up provided the subject is withdrawn from the study due to initiation of new therapy or consent withdrawal for further follow-up. AEs that are assessed by the Investigator as unrelated to Study Treatment will be followed only to the EoT visit. The outcome of any AEs which do not resolve will be recorded as “ongoing” on the eCRF.

Serious adverse events (SAE) and adverse events of speciaal interest (AESI), namely immune-related toxicities, will be collected for up to 90 days following cessation of treatment or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier.

6.2.2.4.7 Clinical Laboratory Evaluations

Clinical laboratory tests will be reviewed for results of potential clinical significance at all time points throughout the study. The Investigator will evaluate any change in laboratory values. If the Investigator determines a laboratory abnormality to be clinically significant, it is considered a laboratory AE; however, if the abnormal laboratory value is consistent with a current diagnosis, it may be documented accordingly.

Abnormal laboratory test values that are not considered clinically significant by the Investigator will be recorded only on the laboratory section of the eCRF and not in the AE section. However,

abnormal laboratory test results that require Study Treatment modification or other treatment or considered clinically significant by the Investigator are to be recorded in the AE section of the eCRF in addition to the laboratory section. Abnormal laboratory results that meet the definition of an SAE should also be reported on an AE/SAE form. Relationship (i.e., reasonable causal relationship) to HBI-8000 or pembrolizumab and the countermeasures taken will be noted on the eCRF.

6.2.2.4.8 Pregnancy

If a pregnancy is reported during active treatment of HBI-8000 until EoT, the Investigator must inform the Sponsor within 24 hours of learning of the pregnancy. Protocol-required procedures for study discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy. Other appropriate pregnancy follow-up procedures should be considered if indicated.

6.2.2.4.9 Overdose

Overdose is defined as administration to the subject of a dose of test article that exceeds by more than 50 mg/dose or 100 mg/week for HBI-8000, and any dose above the approved 400 mg every 6 weeks or 200 mg every 3 weeks for pembrolizumab. In the case that the overdose did not result in an AE, the Investigator should report this as “overdose, no AE” on the AE/SAE form and specify the intended amount, as well as the actual amount, of drug administered.

All occurrences of overdose must be reported as an AE.

6.2.2.4.10 Deaths

All adverse events leading to death that occur during the protocol-specified adverse event reporting period, regardless of relationship to Study Treatment, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (or designee).

6.2.2.4.11 Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, electrocardiogram, or any other potential safety assessment required or not required by protocol should also be recorded as a nonserious or serious AE, as appropriate, and reported accordingly.

6.3 Safety Monitoring Plan

Safety oversight is provided by the Sponsor’s internal, Product Safety and Risk Management Committee (PSRMC) that will monitor the study safety data on a periodic basis (frequency of the meeting established by the committee) throughout the study, including review of AEs, adverse events of special interest (AESI) and SAEs.

All enrolled subjects will be evaluated clinically and with clinical laboratory tests during their participation in this study per Schedule of Dosing and Assessments (Table 1) and as clinically indicated.

Safety evaluations will consist of medical interviews, recording of AEs, physical examinations, and laboratory measurements (hematology, chemistry, virology, and urinalysis).

Subjects will be evaluated for AEs (all grades according to the NCI CTCAE version 5.0), SAEs, and any AEs requiring IP interruption or permanent discontinuation. Subjects who, at time of

progression, have an ongoing AE leading to IP permanent discontinuation will be followed until the event resolves, the Investigator assesses the event as stable, or if the subject is lost to follow-up.

7 STATISTICAL CONSIDERATIONS

Statistical analyses will be performed using SAS® v9.4 or higher (SAS Institute, Cary NC, US). Continuous variables will be summarized using descriptive statistics (n, mean, standard deviation, median, minimum, and maximum). Categorical variables will be summarized showing the number and percentage (n, %) of subjects at each category. Time to event variables (i.e., PFS, DoR) will be analyzed using the Kaplan-Meier method. Where confidence limits are appropriate, the confidence level will be 95% (two-sided), unless otherwise stated. Individual data (including relevant derived variables) will be presented by parameter in listings. Results of statistical analyses, descriptive summary statistics and supportive listings will also be presented.

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a Statistical Analysis Plan (SAP), which will be finalized and approved before database lock and maintained by the Sponsor. The SAP may modify the plans outlined in the protocol; however, any major modifications will also be reflected in a protocol amendment.

7.1 Sample Size Determination

Approximately 20 to 24 subjects are planned to be enrolled to characterize safety and allow for preliminary evaluation of efficacy endpoints in the specific patient population of interest. With a sample size of 20 to 24 subjects the probability that an adverse event with at least a 10% incidence will be detected in at least one subject is high (87.8% to 92.0%) (Table 4). Obtaining this information will help in planning for future immuno-oncology studies.

Table 4: Probability of Detecting AEs that Occur at Various Frequencies

True Frequency of AE	Probability of Detecting at Least 1 AE in 20 Subjects (%)	Probability of Detecting at Least 1 AE in 24 Subjects (%)
1%	18.2	21.4
5%	64.2	70.8
10%	87.8	92.0
15%	96.1	98.0
20%	98.9	99.5
25%	99.7	99.9
30%	>99.9	>99.9

7.2 Populations for Analyses

The following analysis sets are defined in the study for analyses of safety, efficacy, and pharmacodynamics endpoints.

Safety Set: Safety set consists of all enrolled subjects who received at least one dose (any amount) of Study Treatment (HBI-8000).

All safety analyses will be based on Safety Set.

Full Analysis Set (FAS): Full analysis set for efficacy consists of all subjects meeting eligibility criteria who receive at least one dose of HBI-8000 in combination with standard of care pembrolizumab, have at least one post-baseline assessment of efficacy, with or without imaging study.

Per-Protocol Set (PPS): Per-protocol set for efficacy consists of subjects meeting all eligibility criteria, having received at least 9 doses (75% of 2 cycles) of HBI-8000, with at least 1 imaging study to evaluate disease status after completing 6 weeks (2 cycles) of treatment.

Efficacy endpoints will be analyzed in both FAS and PPS.

7.3 Subject Disposition

The disposition of subjects will be tabulated for all enrolled subjects. Subjects who discontinue treatment or discontinued from the study will also be summarized and further broken down by reason for discontinuation.

7.4 Pretreatment Characteristics

Demographic and baseline characteristics will be summarized with descriptive statistics.

7.4.1 Medical History

Medical histories will be coded using MedDRA (Medical Dictionary for Regulatory Activities) version 22.0 or current classification system and summarized by system organ class (SOC) and preferred term (PT) for the subjects in the safety set. For each SOC and PT, subjects with multiple events will be counted only once.

7.4.2 Exposure to Study Medications

Exposure parameters to HBI-8000 and pembrolizumab will include:

- Duration of treatment of HBI-8000.
- Number of pembrolizumab administrations and dose per administration.
- Cumulative doses of HBI-8000 and pembrolizumab administered.
- Compliance to HBI-8000 administration
- Relative dose intensity (RDI) of HBI-8000 administered.

A detailed description of calculations of each of the above parameters will be provided in the SAP.

7.5 Statistical Analyses

7.5.1 Efficacy Analyses

Efficacy analyses will be performed on FAS and PPS. ORR will be estimated based on the proportion of subjects whose best overall response is CR or PR. Disease response will be assessed using RECIST v1.1 as the primary methodology and iRECIST will be used to exclude pseudo-progression when suspected. The estimate of the ORR will be accompanied by a 2-sided

95% exact binomial confidence interval (CI). DCR (CR+PR+SD) will be analyzed similarly. DOR and PFS will be summarized descriptively using Kaplan-Meier methods. The final SAP will provide more details on these analyses.

The efficacy endpoints are the following:

- **Objective Response Rate (ORR),** defined as the percent of subjects with CR or PR according to RECIST 1.1 and irRECIST criteria, relative to the efficacy population. Subjects who do not have an on-study assessment due to safety issues will be included as non-responders.
- **Disease Control Rate (DCR),** defined as the percent of subjects with CR, PR or SD according to RECIST 1.1 and iRECIST criteria, relative to the efficacy population.
- **Duration of Response (DoR),** defined as the time from documentation of tumor response to disease progression.
- **Progression-Free Survival (PFS),** defined as the time from the start of treatment (Day 1 Cycle 1) until objective tumor progression or death.

The EoT Safety Follow-up visit is scheduled 30 ± 3 days after the last dosing of the HBI-8000 or before the initiation of new cancer treatment, whichever is earlier.

Response rate endpoints (ORR, DCR) will be summarized by number and percentage of subjects meeting the definition of ORR and DCR along with the corresponding exact 95% CI based on binomial distribution.

Time-to-event endpoints (DoR, and PFS) will be summarized by Kaplan-Meier methods (median, 95% CI, number of events, number censored, and Kaplan-Meier figures).

7.5.2 Safety Analyses

The assessment of safety will include general safety information such as adverse events, vital signs, laboratory tests (hematology, biochemistry, coagulation, urinalysis), concomitant medications, and 12-lead ECGs.

All safety analyses will be conducted using the Safety Population. Descriptive statistics will be used to summarize safety data.

7.5.2.1 Adverse Events

Adverse events will be coded using the MedDRA classification system version 24.0 or higher. The severity of the events will be graded by the Investigator according to the NCI CTCAE version 5.0 or higher.

All adverse events (AEs) will be summarized, and emphasis will be placed on treatment-emergent adverse events (TEAEs). An AE will be considered treatment-emergent if it occurs or worsens in severity from pre-treatment state on or after the first dose date of any study treatment through 30 days after the last dose of any study treatment. All AEs will be listed.

An overall summary of AE will be provided by the frequency and percentage of subjects experiencing an AEs by MedDRA systems organ class (SOC) and preferred term (PT). TEAEs will be summarized by the frequency and percentage of subjects experiencing TEAEs SOC and

PT, and by worst NCI CTCAE severity grade. Summaries will also be provided for treatment related TEAEs, namely, those judged by the Investigator to be at least possibly related to study drug treatment.

Adverse events resulting in discontinuation from treatment or withdrawal from the study, Grade 3 or higher, serious adverse events, and deaths on-study will be tabulated.

All AEs noted during the study will be listed per subject, detailing reported term, system organ class, preferred term, start date, stop date, severity, relationship to each Treatment, TEAE flag, and outcome.

7.5.2.2 Laboratory Tests

Laboratory data will be summarized for the observed values at each scheduled assessment, together with the corresponding changes from baseline (the value obtained prior to dosing on Day 1 of Cycle 1) using descriptive statistics.

For those analytes that are gradable with CTCAE version 5.0 severity criteria, will be summarized by shift tables showing shifts from Baseline grade (i.e., grade prior to dosing on Day 1 of Cycle 1) and maximum severity grade on treatment.

Laboratory values outside the normal range will be flagged in the data listings.

7.5.2.3 Vital Signs and Physical Examination

Vital signs data will be summarized by the observed valued at each scheduled assessment, together with the corresponding changes from baseline using descriptive statistics.

Physical examination findings will be presented in data listings.

7.5.2.4 Concomitant Medications

All documented and reported concomitant medications will be coded using the World Health Organization Drug Dictionary Enhanced (WHO DDE) version March 2021 or higher and classified by the Anatomical Therapeutic Chemical (ATC) classification system and preferred drug name (often the generic drug name).

7.5.3 Interim Analyses

No interim analyses are planned for this study.

7.5.4 Guidance to Address a Pandemic or Other Global Health Emergencies and Potential Impact on the Clinical Study

In the occurrence of a global health emergency affecting the conduct of the ongoing study, such as the coronavirus disease 2019 (COVID-19) pandemic, study conduct may be adjusted due to subjects being in self-isolation/quarantine, limited access to public places (including hospitals) due to the risk of spreading infections, and health care professionals being committed to critical tasks.

Adjustments to this protocol may be made as described below, in line with global regulatory authorities guidance in order to ensure the safety of study subjects, maintain compliance with GCP, and minimize the risks to study integrity during the COVID-19 pandemic [FDA September 2020]. Other countries may issue their own guidance requiring country specific recommendations to be followed.

Informed Consent

If written consent by the study subject is not possible (for example because of physical isolation due to COVID-19 or other global health emergencies), consent could be given orally by the study subject and documented according to current regulatory guidance and IRB requirements.

Study subjects or the subject's legally authorized representative (LAR) and the Investigator/designee (person obtaining consent) could sign and date separate ICFs.

In case a written informed consent cannot be obtained at the clinical site, electronic informed consent can be obtained remotely. Alternatively, the consent form may be sent to the subject/LAR by facsimile, or e-mail, and the consent interview may then be conducted by telephone/telemedicine when the subject or subject's legally authorized representative can read the consent form during the discussion. If facsimile or email is not possible, the subject or subject's legally authorized representative will be requested to sign and date a blank piece of paper with a written statement affirming that subject agrees to participate in the study and documented according to the current regulatory guidance and IRB approval.

If re-consent is necessary for the implementation of **new urgent changes in study conduct** (mainly expected for reasons related to global health emergencies or important safety issues for other studies), alternative ways of obtaining consent may include contacting the study subject via phone or video-calls and obtaining oral consents, to be documented in the study subjects' medical records, supplemented with e-mail confirmation.

The informed consent procedure is to remain compliant with the study protocol as well as local regulatory requirements. All relevant records should be archived in the Investigator's site master file. A correctly signed and dated ICF should be obtained from the study subjects later, as soon as possible.

Study Visits and Procedures

COVID-19 screening procedures that may be mandated by the health care system in which a clinical study is being conducted do not need to be reported as an amendment to the protocol even if done during clinical study visits. The Investigator in consultation with the Sponsor will decide if it is in the best interest of COVID-positive subjects to remain in the study.

In the case of missed visits due to global health emergencies (or other health pandemic) related reasons:

The site should make every effort to contact the study subject to confirm and document the reason for the missed visit, and at a minimum evaluate AEs/SAEs, and concomitant medications in order to assess subject safety.

8 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

8.1 Data Collection and Management

8.1.1 Electronic Case Report Forms

Electronic Data Capture (EDC) will be used for this study, meaning that all eCRF data will be entered in electronic forms at the study center. Data collection will be completed by authorized study center staff designated by the Investigator. Appropriate training and security measures will be completed with the Investigator and all authorized study center staff prior to the study being initiated and any data being entered into the system for any study subjects.

All data must be entered in English. The eCRFs should always reflect the latest observations on the subjects participating in the study. Therefore, the eCRFs are to be completed as soon as possible during or after the subject's visit. To avoid inter-observer variability, every effort should be made to ensure that the same individual who made the initial baseline determinations completes all efficacy and safety evaluations. The Investigator must verify that all data entries in the eCRFs are accurate and correct. If some assessments are not done, or if certain information is not available or not applicable or unknown, the Investigator should indicate this in the eCRF. The Investigator will be required to electronically sign off on the clinical data.

8.1.2 Source Documentation

The eCRF is essentially considered a data entry form and should not constitute the original (or source) medical records unless otherwise specified. Source documents are all documents used by the Investigator or hospital that relate to the subject's medical history, that verify the existence of the subject, the inclusion and exclusion criteria and all records covering the subject's participation in the study. They include laboratory notes, electrocardiogram (ECG) results, memoranda, pharmacy dispensing records, subject files, etc.

The Investigator is responsible for maintaining source documents containing data that is attributable, legible, contemporaneous, original, accurate, complete, consistent, enduring, and available. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (e.g., via an audit trail). Source documents are to be made available for inspection by the study monitor at each monitoring visit. The Investigator must submit a completed eCRF for each subject who is enrolled, regardless of duration. All supportive documentation submitted with the eCRF, such as laboratory or hospital records, should be clearly identified with the study and subject number. Any personal information, including subject name, should be removed or redacted (deidentified) to preserve individual confidentiality.

8.1.3 Data Management/Coding

Data generated within this clinical study will be handled according to the relevant SOPs of the Data Management and Biostatistics departments of the Sponsor and CRO, where applicable.

Adverse events and medical history will be coded using the most current version of MedDRA. Concomitant medications will be coded using WHO Drug Dictionary Enhanced (WHO DDE).

8.2 Quality Control and Quality Assurance

According to the Guidelines of Good Clinical Practice (GCP) (CPMP/ICH/135/95), the Sponsor is responsible for implementing and maintaining quality assurance and quality control systems with written SOPs.

Quality control will be applied to each stage of data handling.

The following steps will be taken to ensure the accuracy, consistency, completeness, reliability, and integrity of the data:

- Investigator meeting(s)
- Site initiation visit
- Early center visits post-enrollment
- Routine center monitoring
- Ongoing center communication and training
- Data management quality control checks
- Continuous data acquisition and cleaning
- Internal review of data
- Quality control check of the final clinical study report
- Investigator verification by electronically signing the eCRF
- In addition, the Sponsor or Sponsor representative(s) may conduct periodic audits of the study processes, including, but not limited to study center, vendors, clinical database, and final clinical study report.

8.2.1 Monitoring

Investigator site monitoring visits will be conducted according to all applicable regulatory requirements and standards. Regular monitoring visits will be made to each center while subjects are enrolled in the study. The monitor will complete written reports to the Sponsor's representative for each contact with the Investigator/site, regardless of whether it is by phone or in person.

8.2.2 Retention of Patient Records and Study Files

Records and documents pertaining to the conduct of this study and the distribution of investigational materials, including Investigational file, eCRFs, ICFs, laboratory test results, and medication inventory records, must be retained by the Investigator for at least 15 years after completion or discontinuation of the study, or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations. However non-records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

8.2.3 Quality Assurance Audit

Study centers, the study database and study documentation may be subject to Quality Assurance audit during the course of the study by the Sponsor or CRO on behalf of Sponsor. In addition, inspections may be conducted by regulatory bodies at their discretion. In the event of a Quality Assurance audit, the auditor(s) will be allowed access to study treatment records at the study center(s) to verify that dispensing has been done accurately.

8.2.4 Site Audits

The Investigators and institutions involved in the study will permit study-related monitoring, audits, IRB/IEC review, and regulatory inspection(s) by providing direct access to all study records. In the event of an audit, the Investigator agrees to allow the Sponsor, Sponsor representatives, or the regulatory agencies access to all study records.

The Investigator should promptly notify the Sponsor or Sponsor representative of any inspection/audits scheduled by any regulatory authorities and promptly forward copies of any finding/audit reports received to the Sponsor or Sponsor representative.

8.3 Ethics

8.3.1 Ethical Conduct of the Study

This study will be conducted, and the informed consent will be obtained according to the ethical principles stated in the Declaration of Helsinki, the applicable guidelines for GCP (CPMP/ICH/135/95), or the applicable drug and data protection laws and regulations of the countries where the study will be conducted.

GCP is an international ethical and scientific quality standard for designing, conducting, recording and reporting studies that involve the participation of human subjects. The study will be conducted in compliance with GCP and the applicable national regulations so as to assure that the rights, safety and well-being of the participating study subjects are protected consistent with the ethical principles that have their origin in the Declaration of Helsinki.

8.3.2 Institutional Review Board or Independent Ethics Committee

An IRB or IEC must review and approve the final protocol, including the final version of the ICF and any other written information and/or materials to be provided to the subjects. The Investigator will provide the Sponsor's representative with documentation of IRB/IEC approval of the protocol and informed consent before the study may begin at the study center(s). The Investigator should submit the written approval to Sponsor or representative before enrollment of any subject into the study.

The Sponsor or representative reviews and approves any modification(s) to the ICF that are needed to meet local requirements.

The Investigator supplies documentation of required IRB/IEC's annual renewal of the protocol, and any approvals of revisions to the informed consent document or amendments to the protocol to the Sponsor's representative.

The Investigator promptly reports to the IRB/IEC, any new information that may adversely affect the safety of subjects or the conduct of the study. Similarly, the Investigator will submit written summaries of the study status to the IRB/IEC annually, or more frequently if requested by the IRB/IEC. Upon completion of the study, the Investigator will provide the ethics committee with a brief report of the outcome of the study, if required.

The Sponsor or Sponsor representative will provide Regulatory Authorities, Ethics Committees and Investigators with safety updates/reports according to local requirements, including Suspected Unexpected Serious Adverse Drug Reactions (SUSAR), where relevant.

Each Investigator is responsible for providing the IRB/IEC with safety reports of any serious and unexpected adverse drug reactions from the study and any other study conducted with the Study Treatment. The Sponsor or Sponsor representative will provide this information to the Investigator so that he/she can meet these reporting requirements.

8.3.3 Subject Information and Informed Consent

The Investigator is responsible for ensuring that informed consent is obtained from each subject, or their legally authorized representative (LAR) only after the subject/LAR has been given ample time and opportunity to inquire about details of the trial and to make a decision regarding participation in the trial. In addition, the Investigator is responsible for ensuring that all questions about the trial have been answered to the satisfaction of the subject or the subject's LAR. The Investigator/designee provides each subject/LAR with a copy of the signed and dated ICF. The Investigator (or designee) is responsible for obtaining the appropriate signatures and dates on the informed consent document prior to the performance of any protocol procedures, including the administration of any Study Treatment.

8.3.4 Confidentiality

The Sponsor maintains confidentiality standards by coding each subject enrolled in the study through assignment of a unique subject identification number. Subject names are not included in data sets that are transmitted to any Sponsor location.

Subject medical information obtained by this study is confidential and may only be disclosed to third parties as permitted by the ICF (or separate authorization for use and disclosure of personal health information) signed by the subject, unless permitted or required by law. Medical information may be given to a subject's personal physician or other appropriate medical personnel responsible for the subject's welfare, for treatment purposes.

8.3.5 Subject Data Protection

The ICF will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation.

8.3.6 Protocol Amendments

Any amendments to the protocol will be require IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects.

8.3.7 Study Closure

The Sponsor has the right to close this study at any time. In addition, the Sponsor, Sponsor representative and or the Investigator have the right to close the study at a particular site(s) at any time. Where possible, the agreement to close the study and/or to close a site(s) should be reached after mutual consultation. The IRB/IEC must be informed, if required by legislation.

Should the study be closed prematurely, all unused HBI-8000 will be reconciled with dispensing records, documented, and returned to the Sponsor. Alternatively, if directed by the Sponsor, unused HBI-8000 (tablets) may be destroyed at the study center after completion of drug accountability by the site monitor.

The Sponsor will notify the Investigators if the study is placed on hold, or if the Sponsor decides to discontinue the study or development program.

8.3.7.1 Study Discontinuation

The clinical trial may be terminated early if the extent (incidence and/or severity) of emerging effects/clinical endpoints is such that the risk/benefit ratio to the trial population as a whole is unacceptable. In addition, further recruitment in the trial or at (a) particular trial site(s) may be stopped due to insufficient compliance with the protocol, GCP and/or other applicable regulatory requirements, procedure-related problems or the number of discontinuations for administrative reasons is too high.

Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to study subjects
- Unsatisfactory subject enrollment.

The Sponsor will notify the Investigator if the study is placed on hold, or if the Sponsor decides to discontinue the study or development program.

8.3.7.2 Site Discontinuation

The Sponsor has the right to replace a site at any time.

Reasons for replacing a site may include, but are not limited to, the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with ICH guidelines for GCP.

In the event the Sponsor prematurely terminates a particular trial site, the Sponsor will promptly notify that trial site’s IRB.

8.4 Study Administration

8.4.1 Data Handling and Record Keeping

It is the Investigator's responsibility to maintain adequate and accurate source documents and trial records, including essential study documents (protocol and protocol amendments, completed eCRFs, signed ICFs, relevant correspondence, and all other supporting documentation). The study site should plan on retaining such documents for approximately 15 years after study completion. Subject identification codes will be retained for this same period of time. These documents may be transferred to another responsible party, acceptable to Sponsor, who agrees to abide by the retention policies. Written notification of transfer must be submitted to Sponsor. The Investigator must contact Sponsor prior to disposing of any study records.

No records can be disposed of without the written approval of the Sponsor.

8.4.2 Direct Access to Source Data/Documents

The Investigator will prepare and maintain adequate and accurate source documents to record all observations and other pertinent data for each subject enrolled into the study.

The Investigator will allow the Sponsor, Sponsor representatives (e.g., CRO), and authorized regulatory authorities to have direct access to all documents pertaining to the study, including individual subject medical records, as appropriate.

8.4.3 Investigator Obligations

This study will be conducted in accordance with the ICH Harmonized Tripartite Guideline for GCP (GCP, 1997); the US CFR Title 21 parts 50, 56, and 312; and the ethical principles that have their origin in the Declaration of Helsinki. The Investigator agrees to conduct the clinical study in compliance with this protocol after the approval of the protocol by the IRB/IEC in compliance with local regulatory requirements. The Investigator and the Sponsor will sign the protocol to confirm this agreement.

8.4.4 Financial Disclosure

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for one year after completion of the study.

8.4.5 Protocol Signatures

Each Investigator is responsible for signing the Investigator Agreement following careful review of the protocol. A copy of the signed page is sent to the Sponsor (or designee). By signing the protocol, the Investigator confirms in writing that he/she has read, understands and will strictly adhere to the study protocol and will conduct the study in accordance with ICH Tripartite Guidelines for GCP and applicable regulatory requirements. The study cannot start at any center where the Investigator has not signed the protocol.

8.4.6 Publication Policy

The data generated by this study are confidential information of the Sponsor. The Sponsor will make the results of the study publicly available. The publication policy with respect to the Investigator and study center will be set forth in the Clinical Trial Agreement. Publication may include any or all of the following: posting of a synopsis online, abstract and/or presentation at a scientific conference, or publication of a full manuscript.

Authorship credit should be based on 1) substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; and 3) final approval of the version to be published. Authors must meet conditions 1, 2 and 3. Significant contributions to trial execution may also be taken into account to determine authorship, provided that contributions have also been made to all three of the preceding authorship criteria. Although publication planning may begin before conducting the trial, final decisions on authorship and the order of authors' names will be made based on participation and actual contributions to the trial and writing, as discussed above.

The Sponsor must have the opportunity to review all proposed abstracts, manuscripts or presentations regarding this trial prior to submission for publication/presentation.

Any information identified by the Sponsor as confidential will be deleted prior to submission.

9. REFERENCES

Barrero MJ. Epigenetic Strategies to Boost Cancer Immunotherapies. Int J Mol Sci 2017; **18**(6).

Beier UH, Wang L, Han R, Akimova T, Liu Y and Hancock WW. Histone deacetylases 6 and 9 and sirtuin-1 control Foxp3+ regulatory T cell function through shared and isoform-specific mechanisms. Sci Signal 2012; **5**(229): ra45.

Borghaei H, Paz-Ares L, Horn L, Spigel DR, Steins M, Ready NE, et al. Nivolumab versus Docetaxel in Advanced Nonsquamous Non-Small-Cell Lung Cancer. N Engl J Med 2015; **373**(17): 1627-1639.

Brahmer J, Reckamp KL, Baas P, Crino L, Eberhardt WE, Poddubskaya E, et al. Nivolumab versus Docetaxel in Advanced Squamous-Cell Non-Small-Cell Lung Cancer. N Engl J Med 2015; **373**(2): 123-135.

Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009; **45**(2): 228-247.

FDA. *Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency – Guidance for Industry, Investigators and Institutional Review Boards*. Rockville, MD; Food and Drug Administration; September 2020.

Gadgeel S, Rodriguez-Abreu D, Speranza G, Esteban E, Felip E, Domine M, et al. Updated Analysis From KEYNOTE-189: Pembrolizumab or Placebo Plus Pemetrexed and Platinum for Previously Untreated Metastatic Nonsquamous Non-Small-Cell Lung Cancer. J Clin Oncol 2020; **38**(14): 1505-1517.

Gandhi L, Rodriguez-Abreu D, Gadgeel S, Esteban E, Felip E, De Angelis F, et al. Pembrolizumab plus Chemotherapy in Metastatic Non-Small-Cell Lung Cancer. N Engl J Med 2018; **378**(22): 2078-2092.

Gao Y, Nihira NT, Bu X, Chu C, Zhang J, Kolodziejczyk A, et al. Acetylation-dependent regulation of PD-L1 nuclear translocation dictates the efficacy of anti-PD-1 immunotherapy. Nat Cell Biol 2020; **22**(9): 1064-1075.

Herbst RS, Baas P, Kim DW, Felip E, Perez-Gracia JL, Han JY, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. Lancet 2016; **387**(10027): 1540-1550.

Herbst RS, Baas P, Perez-Gracia JL, Felip E, Kim DW, Han JY, et al. Use of archival versus newly collected tumor samples for assessing PD-L1 expression and overall survival: an updated analysis of KEYNOTE-010 trial. Ann Oncol 2019; **30**(2): 281-289.

Hontecillas-Prieto L, Flores-Campos R, Silver A, de Álava E, Hajji N and García-Domínguez DJ. Synergistic Enhancement of Cancer Therapy Using HDAC Inhibitors: Opportunity for Clinical Trials. Frontiers in Genetics 2020; **11**(1113).

Horn L, Spigel DR, Vokes EE, Holgado E, Ready N, Steins M, et al. Nivolumab Versus Docetaxel in Previously Treated Patients With Advanced Non-Small-Cell Lung Cancer: Two-Year Outcomes From Two Randomized, Open-Label, Phase III Trials (CheckMate 017 and CheckMate 057). J Clin Oncol 2017; **35**(35): 3924-3933.

Hui R, Garon EB, Goldman JW, Leighl NB, Hellmann MD, Patnaik A, et al. Pembrolizumab as first-line therapy for patients with PD-L1-positive advanced non-small cell lung cancer: a phase 1 trial. Ann Oncol 2017; **28**(4): 874-881.

Mok TSK, Wu YL, Kudaba I, Kowalski DM, Cho BC, Turna HZ, et al. Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally advanced or metastatic

non-small-cell lung cancer (KEYNOTE-042): a randomised, open-label, controlled, phase 3 trial. Lancet 2019; **393**(10183): 1819-1830.

Ning ZQ, Li ZB, Newman MJ, Shan S, Wang XH, Pan DS, et al. Chidamide (CS055/HBI-8000): a new histone deacetylase inhibitor of the benzamide class with antitumor activity and the ability to enhance immune cell-mediated tumor cell cytotoxicity. Cancer Chemother Pharmacol 2012; **69**(4): 901-909.

Nishino M, Giobbie-Hurder A, Gargano M, Suda M, Ramaiya NH and Hodi FS. Developing a common language for tumor response to immunotherapy: immune-related response criteria using unidimensional measurements. Clin Cancer Res 2013; **19**(14): 3936-3943.

Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982; **5**(6): 649-655.

Pan D-S, Yang Q-J, Fu X, Shan S, Zhu J-Z, Zhang K, et al. Discovery of an orally active subtype-selective HDAC inhibitor, chidamide, as an epigenetic modulator for cancer treatment. MedChemComm 2014; **5**(12): 1789-1796.

Pili R, Salumbides B, Zhao M, Altiok S, Qian D, Zwiebel J, et al. Phase I study of the histone deacetylase inhibitor entinostat in combination with 13-cis retinoic acid in patients with solid tumours. Br J Cancer 2012; **106**(1): 77-84.

SEER. SEER Incidence – U.S. Cancer Statistics Public Use Research Database, 2020 submission (2001–2018), United States Department of Health and Human Services, Centers for Disease Control and Prevention and National Cancer Institute. Released June 2021. Available at https://seer.cancer.gov/statfacts/html/lungb.html Accessed Sep. 2021.

Shen L and Pili R. Class I histone deacetylase inhibition is a novel mechanism to target regulatory T cells in immunotherapy. Oncoimmunology 2012; **1**(6): 948-950.

Wang L, Tao R and Hancock WW. Using histone deacetylase inhibitors to enhance Foxp3(+) regulatory T-cell function and induce allograft tolerance. Immunol Cell Biol 2009; **87**(3): 195-202.

Woods DM, Sodre AL, Villagra A, Sarnaik A, Sotomayor EM and Weber J. HDAC Inhibition Upregulates PD-1 Ligands in Melanoma and Augments Immunotherapy with PD-1 Blockade. Cancer Immunol Res 2015; **3**(12): 1375-1385.

APPENDIX 1. PERFORMANCE SCALES – ECOG AND LANKSY

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

Source: [Oken 1982]

APPENDIX 2. NEW YORK HEART ASSOCIATION (NYHA) FUNCTIONAL CLASSIFICATION

Class I

No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation (feeling heart beats), or dyspnea (shortness of breath).

Class II (Mild)

Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea.

Class III (Moderate)

Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea.

Class IV (Severe)

Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.

Source: https://www.havhrt.com/heartfailureclassification

APPENDIX 3. STRONG CYP3A4 INDUCERS AND INHIBITORS

CYP3A4 inducers or inhibitors may affect HBI-8000 exposures since HBI-800 is metabolized by CYP3A4. CYP3A4 inducers may potentially decrease the efficacy of HBI-8000, and CYP3A4 inhibitors may potentially increase the systemic exposure and toxicity of HBI-8000. For this reason, in HBI-8000-305, the following drugs will be used with extreme caution as concomitant medications, at Investigator discretion.

CYP3A4 INDUCERS	CYP3A4 INHIBITORS	
Carbamazepine	Amiodarone	Ketoconazole
Dexamethasone	Anastrozole	Metronidazole
Ethosuximide	Azithromzcin	Mibefradil
Glucocorticoids	Cannabinoids	Miconazole
Griseofulvin	Cimetidine	Nefazodone
Nafcillin	Clarithromycin	Nelfinavir
Nelfinavir	Clotrimazole	Nevirapine
Nevirapine	Cyclosporine	Norfloxacin
Oxcarbazepine	Danazol	Norfluoxetine
Phenobarbital	Delavirdine	Omeprazole
Phenylbutazone	Dexamethasone	Oxiconazole
Phenytoin	Diethyldithiocarbamate	Paroxetine
Primidone	Diltiazem	Propoxyphene
Progesterone	Dirithyromycin	Quinidine
Rifabutin	Disulfiram	Quinine
Rifampin	Entacapone	Quinupristine and dalfopristin
Rofecoxib	Erythromycin	Ranitidine
St John’s wort	Ethinyl estradiol	Ritonavir
Sulfadimidine	Fluconazole	Saquinavir
Sulfinpyrazone	Fluoxetine	Sertindole
Troglitazone	Fluvoxamine	Sertraline
	Gestodene	Troglitazone
	Grapefruit juice	Troleandomycin
	Indinavir	Valproic acid
	Isoniazid	

APPENDIX 4. RECIST V1.1 AND irRECIST

	Lesion Requirements and Response Criteria
Lesion Measurement	Unidimensional
Baseline Lesion Size [a]	≥10 mm
Malignant lymph nodes [b]	For the lymph node (s) to be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm when assessed by CT scan
Baseline Lesion Number	5 lesions total, 2 per organ
Appearance of New Lesions	Always represents PD
Response	CR: disappearance of all lesions
	PR: ≥30% decrease from baseline STD
	SD: when neither PR nor PD can be established
	PD: ≥20% increase in nadir of STD (minimum 5 mm)
Confirmation after first assessment	Yes, if response is primary endpoint

Abbreviations: CR = complete response; PD = progressive disease; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; SD = stable disease; STD = sum of target lesion(s) diameter(s).
[a] CT: 10 mm (when slice thickness is ≤5 mm); or 2× slice thickness (when slice thickness is >5 mm),
Clinical: 10 mm (must be measurable with calipers)
[b] Lymph node: ≥15 mm short axis for target, ≥10 to <15 mm for non-target, <10 mm is non-pathological

Assessment of Overall Response

Target Lesions	**Non-Target Lesions**	**New Lesions**	**Overall Response**
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	Not Evaluable (NE)
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Source: Eisenhauer 2009

irRECIST Summary of measurement and response assessment approaches for bidimensional and unidimensional assessment based on irRC

Table 1. Summary of measurement and response assessment approaches for bidimensional and unidimensional assessment based on irRC

	Bidimensional assessment (the original irRC (7))	Unidimensional assessment
Measurable lesions	≥5 × 5 mm^2 by bidimensional measurements	≥10 mm in the longest diameter
Measurement of each lesion	The longest diameter × the longest perpendicular diameter (cm^2)	The longest diameter (cm)
The sum of the measurements	The sum of the bidimensional measurements of all target lesions and new lesions if any	The sum of the longest diameters of all target lesions and new lesions if any
Response assessment	PD: ≥25% increase from the nadir PR: ≥50% decrease from baseline CR: Disappearance of all lesions	PD: ≥20% increase from the nadir PR: ≥30% decrease from baseline CR: Disappearance of all lesions
New lesions	The presence of new lesion(s) does not define progression. The measurements of the new lesion(s) are included in the sum of the measurements.	
Confirmation	Confirmation by 2 consecutive observations not less than 4 weeks apart was required for CR, PR, and PD	

Source: Nishino 2013