



CLINICAL STUDY PROTOCOL

ABX196-001

Sponsor:	ABIVAX 5, rue de la Baume 75008 Paris FRANCE
Investigational product:	Not Available
Product code:	ABX196
Therapeutic indication:	A Phase 1-2 Study of ABX196 in Combination with Nivolumab in Patients with Hepatocellular Carcinoma.
IND:	140329
Study code:	ABX196-001
Version number:	7.0
Release date:	January 12 th , 2021

CONFIDENTIALITY STATEMENT

*Information and data contained herein are proprietary and confidential.
This information should not be disclosed to any third party without the prior written consent of ABIVAX*

CLINICAL STUDY PROTOCOL

Study code	ABX196-001
Investigational product code	ABX196
Detailed Title	Open-label, uncontrolled, phase 1-2 study to evaluate the safety, tolerability, pharmacodynamic effects, and preliminary efficacy of ABX196 administered in combination with nivolumab in patients with hepatocellular carcinoma
Study Phase	Phase 1-2
Coordinating Investigator	Dr. Darren SIGAL, MD Scripps Clinic Torrey Pines 10666 N Torrey Pines Rd La Jolla, CA 92037
Sponsor	ABIVAX 5 rue de la Baume 75008 Paris Tel: +33 (0) 1 53 83 08 41 Fax: +33 (0) 1 53 83 07 48
Date/Version	January 12 th , 2021

CONTACTS

Sponsor	ABIVAX 5 rue de la Baume 75008 PARIS - France [REDACTED] VP, Chief Medical Officer Tel: + [REDACTED] [REDACTED] VP, Clinical Operations Tel: + [REDACTED]
Coordinating investigator	Dr. Darren SIGAL, MD Scripps Clinic Torrey Pines 10666 N Torrey Pines Rd La Jolla, CA 92037 USA
Study Conduct, Data management and Statistical Analysis	C3 Research Associates 113 Cherry St., #77114, Seattle, WA 98104 USA
Central Laboratory	PPD Laboratories 2 Tesseneer Drive Highland Heights, KY41076, USA
Flow Cytometry	Neogenomics Laboratories, Inc. 31 Columbia Alison Viejo, CA 92656 USA
Immunohistochemistry	Neogenomics Laboratories, Inc. 31 Columbia Alison Viejo, CA 92656 USA
Pharmacokinetics	Atlanbio (Bioanalyses) ZI de Brais 1 Rue Graham Bell BP 40309 44605 Saint-Nazaire France
Pharmacovigilance	IntuVigilance Limited Scotsbridge House, Scots Hill Rickmansworth WD3 3BB Hertfordshire UK

CONFIDENTIALITY AND INVESTIGATOR STATEMENT

Protocol ABX196-001

Open-label, uncontrolled, phase 1-2 study to evaluate the safety, tolerability, pharmacodynamic effects, and preliminary efficacy of ABX196 administered in combination with nivolumab in subjects with hepatocellular carcinoma.

I have carefully read all the pages of this clinical study protocol and I agree to the following:

- To conduct the study as outlined in the protocol, any mutually agreed future protocol amendments and with all the terms and conditions set out by ABIVAX.
- Not to implement any changes in the procedures described in the protocol without the prior approval of the sponsor and prior to review and written approval by the Ethics Committee and/or Regulatory Authorities, unless instructed otherwise by the Regulatory Authorities or the wellbeing of patients is jeopardized.
- To conduct the study in accordance with the ICH GCP (R2) guidelines, US 21 Code of Federal Regulations dealing with clinical studies (including parts 50 and 56 concerning informed consent and IRB regulations), the European Union Clinical Trials Directive 2005/28/EC, EudraLex GMP guidelines Annex 13, the provisions of the Helsinki Declaration, and relevant legislation in force.
- I am thoroughly aware of the study drug specifications and adverse events as described in the protocol and the current Investigator's Brochure and any other information provided by the Sponsor.
- To ensure that sub-investigator(s) and other relevant members of my staff involved in the study are fully aware of their responsibilities regarding this study and will conduct the study according to the protocol.

Investigator's Name:

Investigator's Signature:

Date:

TABLE OF CONTENTS

CONTACTS	3
TABLE OF CONTENTS.....	5
LIST OF ABBREVIATIONS	7
SYNOPSIS.....	8
1 INTRODUCTION AND RATIONALE	13
1.1 BACKGROUND INFORMATION	13
1.1.1 THE IMMUNE MICROENVIRONMENT IN HCC	13
1.1.2 NIVOLUMAB IN HCC	14
1.1.3 ABX196, AN INKT AGONIST.....	14
1.1.4 RATIONALE FOR COMBINING ABX196 WITH AN ANTI-PD-1 ANTIBODY IN PATIENTS WITH HCC	15
1.1.5 PRECLINICAL PHARMACOLOGY AND TOXICOLOGY	17
1.2 STUDY RATIONALE	17
1.3 RISKS AND BENEFITS	17
2 STUDY OBJECTIVES.....	19
2.1 PRIMARY OBJECTIVES	19
2.2 SECONDARY OBJECTIVES	19
2.3 EXPLORATORY OBJECTIVES	19
2.4 PRIMARY ENDPOINTS	19
2.5 SECONDARY ENDPOINTS	19
2.6 EXPLORATORY ENDPOINTS	20
3 INVESTIGATIONAL PLAN	21
3.1 STUDY DESIGN	21
3.1.1 DOSE ESCALATION PHASE.....	22
3.1.2 EXPANSION PHASE.....	22
3.2 INVESTIGATIONAL SITES	22
3.3 PATIENT ASSIGNMENT METHODS	22
4 STUDY POPULATION.....	23
4.1 NUMBER OF PATIENTS	23
4.2 ELIGIBILITY CRITERIA	23
4.2.1 INCLUSION CRITERIA.....	23
4.2.2 EXCLUSION CRITERIA	24
4.3 SCREENING FAILURES.....	24
4.4 DEVIATION FROM INCLUSION/EXCLUSION CRITERIA	24
5 STUDY PROCEDURES	25
5.1 SCHEDULE OF ASSESSMENTS	25
5.2 SCREENING.....	25
5.3 TREATMENT PERIOD: CYCLES 1-12.....	26
5.3.1 CYCLE 1	26
5.3.2 EVEN CYCLES (CYCLES 2, 4, 6, 8, 10 AND 12)	28
5.3.3 ODD CYCLES (CYCLES 3, 5, 7, 9, 11)	29
5.4 STUDY TERMINATION/EARLY TERMINATION.....	30
5.5 SURVIVAL FOLLOW-UP.....	30
5.6 UNSCHEDULED VISITS	30
5.7 DESCRIPTION OF PROCEDURES	31
5.7.1 SAFETY PROCEDURES	31
5.7.2 PHARMACOKINETICS	32
5.7.3 NIVOLUMAB ANTI-DRUG ANTIBODIES	33
5.7.4 IMMUNE MICROENVIRONNEMENT ANALYSIS (OPTIONAL PROCEDURE)	33
5.7.5 EFFICACY PROCEDURES	33
5.7.6 SUMMARY OF BLOOD SAMPLES	34
6.1 ABX196 AND NIVOLUMAB DOSAGE AND ADMINISTRATION	35
6.2 DOSE PREPARATION AND METHOD OF ADMINISTRATION	35
6.3 DOSE ESCALATION PROCEDURES AND MAXIMUM TOLERATED DOSE	35
6.4 DEFINITION OF DOSE-LIMITING TOXICITIES (DLTs)	36
6.5 EXPANSION PHASE DOSING	37
6.6 DOSE MODIFICATIONS OR DELAYS	37
6.7 PACKAGING.....	38
6.8 STORAGE.....	39
6.9 DRUG ACCOUNTABILITY	39
6.10 DISPOSITION OF USED AND UNUSED VIALS OF STUDY MEDICATION	39
6.11 ORDERING DRUG	39
6.12 CONCOMITANT AND EXCLUDED THERAPY	39
7 PATIENT COMPLETION AND WITHDRAWAL.....	41
7.1 CRITERIA FOR TERMINATION	41
7.2 DOCUMENTATION	41

7.3	PROCEDURES FOR PATIENTS WHO WITHDRAW EARLY	41
7.4	REPLACEMENT OF PATIENTS	41
8	ADVERSE EVENTS.....	42
8.1	DEFINING ADVERSE EVENTS	42
8.1.1	SERIOUS ADVERSE EVENTS.....	42
8.1.2	NONSERIOUS ADVERSE EVENTS.....	42
8.2	DOCUMENTING ALL ADVERSE EVENTS.....	43
8.2.1	GRADING OF ADVERSE EVENTS.....	43
8.2.2	RELATIONSHIP TO STUDY DRUG	43
8.3	ABNORMAL LABORATORY TEST RESULTS AS ADVERSE EVENTS.....	44
8.4	REPORTING AND DOCUMENTING SERIOUS ADVERSE EVENTS	44
8.5	FOLLOW UP OF ADVERSE EVENTS	45
8.6	DATA SAFETY MONITORING BOARD.....	45
8.7	OVERDOSE	45
8.8	APPARENT TOXICITY	46
8.8.1	GRADING OF TOXICITY	46
8.8.2	MONITORING AND TREATMENT OF TOXICITY.....	46
8.9	REPORTING OF SAEs TO ABIVAX OR IT DESIGNEE.....	46
8.10	REPORTING OF SAEs TO REGULATORY AUTHORITIES	47
9	STATISTICS.....	48
9.1	GENERAL PROCEDURES.....	48
9.2	SAMPLE SIZE.....	48
9.3	PATIENT DISPOSITION	48
9.4	RANDOMIZATION AND BLINDING OF TREATMENT ASSIGNMENT.....	48
9.5	BASELINE COMPARABILITY	48
9.6	STATISTICAL ANALYSES.....	48
9.6.1	PRIMARY AND SECONDARY ENDPOINT ANALYSES.....	48
9.6.2	EFFICACY ANALYSES	49
9.6.3	EXPLORATORY ENDPOINT ANALYSES	49
9.7	INTERIM ANALYSIS.....	49
9.8	PROCEDURES FOR ACCOUNTING FOR MISSING, UNUSED, AND SPURIOUS DATA	49
10	CONDITIONS FOR INITIATING, MODIFYING, OR TERMINATING THE STUDY.....	50
10.1	MODIFICATIONS AND AMENDMENTS.....	50
10.2	PROTOCOL DEVIATIONS	50
10.3	TERMINATION	50
10.4	ADDITIONAL PRECAUTIONS	50
11	ETHICAL AND LEGAL CONSIDERATIONS	51
11.1	COMPLIANCE WITH IRB/IEC REGULATIONS	51
11.2	ETHICAL CONDUCT OF THE STUDY	51
11.3	PROTECTION OF HUMAN PATIENTS.....	51
11.3.1	COMPLIANCE WITH INFORMED CONSENT REGULATIONS.....	51
11.3.2	PATIENT CONFIDENTIALITY	52
11.3.3	PATIENT PRIVACY	52
12	ADMINISTRATIVE CONSIDERATIONS.....	53
12.1	ADMINISTRATIVE STRUCTURE.....	53
12.1.2	DOCUMENTATION	53
12.1.3	SOURCE DOCUMENTS.....	53
12.1.4	STUDY FILES AND RETENTION OF STUDY RECORDS.....	53
12.2	STUDY MONITORING	54
12.3	QUALITY MANAGEMENT.....	54
12.4	NON-PROTOCOL RESEARCH.....	54
13	STUDY REPORT AND PUBLICATIONS	55
14	CONFIDENTIALITY.....	56
15	REFERENCES	57
16	APPENDICES	58
	APPENDIX I – SCHEDULE OF ASSESSMENTS.....	59
	APPENDIX II – ALLOWED WINDOW FOR BLOOD SAMPLES TIMEPOINT COLLECTION	61
	APPENDIX III- EASTERN COOPERATIVE ONCOLOGY GROUP (ECOG) PERFORMANCE SCORE SCALE	62
	APPENDIX IV - RESPONSE EVALUATION CRITERIA IN SOLID TUMORS (RECIST) V1.1.....	63
	APPENDIX V – POSSIBLE DOSES TO APPLY IN CASE OF TOXICITY	67

LIST OF ABBREVIATIONS

AE	Adverse event
AFP	Alpha-fetoprotein
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BP	Blood pressure
BQL	Below the quantification limit
CBC	Complete blood count
CBR	Clinical Benefit Rate
Cdiff	Blood Count Differential
CPI	Checkpoint inhibitor
CR	Complete response
CRA	Clinical research associate
CRF	Case report form
CT	Computed tomography
CTCAE	Common Toxicity Criteria for Adverse Events
DCR	Disease Control Rate
DLT	Dose-limiting toxicity
DOR	Duration of response
eCRF	Electronic case report form
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic data capture
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HBV	Hepatitis B Virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C Virus
HIV	Hepatitis D Virus
HR	Human Immunodeficiency Virus
HR	Heart rate
IC ₅₀	Inhibitory concentration 50%
ICF	Informed consent form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IHC	Immunohistochemistry
IM injection	Intramuscular injection
iNKT	Invariant Natural killer T cell
INR	International normalized ratio
IRB	Institutional Review Board
IUD	Intrauterine device
IV or i.v.	Intravenous(ly)
Kg	Kilogram
L	Liters
LLT	Lowest level term
LFT	Liver Function Test
Ug	Microgram
Mg	Milligram
MAD	Maximal Administrated Dose
Min	Minute
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
MTD	Maximum tolerable dose
ORR	Objective response rate
OTC	Over the counter
PD-1	Programmed cell Death protein-1
PDX	Patient-derived xenograft
PFS	Progression-free survival
PK	Pharmacokinetic
PR	Partial response
PT	Preferred term
QA	Quality assurance
QC	Quality control
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommended Phase II dose
RR	Respiratory rate
SAE	Serious adverse event
SOC	System organ class
SOP	Standard operating procedures
TEAE	Treatment-emergent adverse event
TKI	Tyrosine Kinase Inhibitor
TTP	Time to Progression
ULN	Upper limit of normal
US	United States
WHO	World Health Organization

SYNOPSIS

Study n°	ABX196-001	Clinical Phase	1-2
		Type of Study	Safety, Efficacy, Dose-Ranging Study
Study title	Open-label, uncontrolled, phase 1-2 study to evaluate the safety, tolerability, pharmacodynamic effects, and preliminary efficacy of ABX196 administered in combination with nivolumab in patients with hepatocellular carcinoma.		
Short title	Phase 1-2 study of ABX196 in Combination with Nivolumab in Patients with Hepatocellular Carcinoma.		
Investigators and study centers	This study will be conducted at 2-4 sites in the United States (US).		
Study duration	Following a recruitment phase of an estimated 18 months, eligible patients may participate in the treatment phase until disease progression (or meeting other early withdrawal criteria defined in the study protocol section 7.1). After that point, patients will enter a maximum 12 months follow-up phase for disease (for patients who withdraw early) and survival status.		
Study drug: (dose/ route/ regimen)	ABX196 will be administered as an intramuscular (IM) injection 120 minutes (+/- 15 minutes) after the completion of the nivolumab infusion on Day 1 of every other 28-Day treatment cycle (i.e., every 8 weeks). Cycles will be continued until confirmed progressive disease or unacceptable toxicity. For the Dose Escalation portion of the study ABX196 will be administered in ascending dose groups of 0.1, 0.2, and 0.4 µg or until the maximum tolerable dose (MTD) has been determined. Initially, 3 patients will be enrolled at a given dose level. If no dose-limiting toxicities (DLT) are observed in the 3 patients, 3 patients will be enrolled at the next highest dose level. If 1 DLT is observed out of 3 enrolled patients at any given dose level, an additional 3 patients will be enrolled at that dose level. If no additional patients experience a DLT, that dose will be considered the MTD. If at any particular dose level two patients develop a dose-limiting toxicity (DLT), then the maximum tolerated dose will have been exceeded, this dose level will be defined as the maximum administered dose, and the previous dose level will be considered as the MTD. However, if only 3 patients had been enrolled to the dose level immediately below the maximum administered dose, then three additional patients will be enrolled to this dose level. If zero or one of the six patients at the lower dose level experiences a DLT, this dose level will be identified as the MTD. Therefore, the MTD is defined as the highest dose level studied that results in DLTs in at most one out of six patients.		
Reference drug: (dose/ route/ regimen)	Nivolumab administered, consistent with the US prescribing information, as an intravenous (IV) infusion on Days 1 and 15 of each 28-Day cycle. Cycles will be continued until confirmed progressive disease or unacceptable toxicity.		
Study design and methodology	Dose escalation of ABX196 in combination with standard dose nivolumab followed by a two-stage phase 2 design to determine the objective response rate for the combination.		

Study objectives	Primary Objectives - To explore the safety, tolerability and maximum tolerated dose of ABX196 in combination with standard-dose nivolumab (dose escalation and expansion phases); - To evaluate objective response rate (ORR) per RECIST v1.1 (dose expansion phase of the study). Secondary Objectives - To evaluate duration of response (DOR), disease control rate (DCR), time to progression (TTP), and progression-free survival (PFS) per RECIST v1.1; - To evaluate the immunogenicity of nivolumab. Exploratory Objectives [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED]
Study endpoints:	Primary Endpoints <i>Safety</i> - Incidence and severity of adverse events (AEs) and dose limiting toxicities and determination of the maximum tolerated dose - Changes in safety laboratory parameters, vital signs, and weight - Dose limiting toxicities (DLTs) <i>Efficacy</i> - Objective Response Rate (ORR) Secondary Endpoints - Duration of response (DOR) - Disease control rate (DCR) - Progression-free survival (PFS) - Time to disease progression (TTP) - Clinical benefit rate (CBR) - Change in alpha fetoprotein serum concentrations - Frequency of development of anti-drug antibodies to nivolumab Exploratory endpoints [REDACTED] [REDACTED] [REDACTED]

Target population:	Patients with confirmed diagnosis of hepatocellular carcinoma (HCC) not amenable to curative surgery or local therapy and with documented objective radiographic progression after treatment with sorafenib or lenvatinib (or intolerance to sorafenib or lenvatinib) and who are eligible to be treated with nivolumab.
Main selection criteria	Inclusion criteria: 1. Men or women, Age ≥ 18 years 2. Patients with ECOG performance status 0 or 1 3. Patients with confirmed diagnosis of HCC (i.e. histologically or by any other acceptable method for diagnosis) not amenable to curative surgery or local therapy. 4. Patients who are intolerant to or who progressed on at least one line of Tyrosine Kinase Inhibitor (TKI) and/or Checkpoint Inhibitor (CPI) therapy. Patients who have had stable disease for at least 4 cycles of CPI therapy are also eligible 5. Patients eligible to be treated with nivolumab; Prior use of nivolumab is also acceptable providing treatment was not taken in association with ipilimumab; 6. Patients already under treatment with Nivolumab can be recruited, providing they have not achieved an objective response after at least 3 months of treatment. Patients with progressive disease under nivolumab may also be eligible if they meet other eligibility criteria 7. Patients with measurable disease based on RECIST v1.1 8. Patients with Child-Pugh class A liver score within 7 days of first study dose 9. Patients with no history of hepatic encephalopathy 10. Patients with no prior or current clinically significant ascites as measured by physical examination and that requires active paracentesis for control (patients with ascites only on radiographic imaging are eligible) 11. Patients with Hepatitis B Virus (HBV) infection must have received antiviral therapy for at least 12 weeks and HBV viral load must be documented to be <100 IU/mL within 7 days of first study dose 12. Patients with no active co-infection with HBV and HCV or HBV and HDV 13. Patients with no active drug or alcohol abuse 14. Patients with adequate organ function at screening: a. Neutrophils $\geq 1000/\mu\text{L}$ b. Platelets $\geq 50,000/\mu\text{L}$ c. Hemoglobin ≥ 9.0 g/dL d. Creatinine clearance ≥ 40 mL/min according to the Cockcroft-Gault formula e. ALT and AST ≤ 5 x upper limit of normal each f. Total bilirubin ≤ 3 mg/dL g. International Normalized Ratio (INR) ≤ 2.3 or prothrombin time ≤ 6 seconds above control h. Albumin ≥ 2.8 g/dL Main exclusion criteria: 1. Patients with tyrosine kinase inhibitor treatment within 2 weeks of first study dose 2. Patients with esophageal or gastric variceal bleeding within the past 6 months

	3. Patients with portal vein invasion at the main portal (Vp4) or the inferior vena cava or cardiac involvement of HCC based on imaging 4. Patients with previous solid organ or hematologic transplantation 5. Patients with active autoimmune disease requiring systemic treatment in the past 2 years 6. Patients with diagnosis of immunodeficiency or receiving systemic steroid therapy or other immunosuppressive therapy within 7 days before first study dose 7. Patients with previous locoregional therapy or major surgery to the liver within 6 weeks before first study dose 8. Patients with minor surgery to liver or another site within 1 week before first study dose 9. Patient treated with an investigational drug within 2 weeks before first study dose
Concomitant medications	Any treatments for HCC other than nivolumab and ABX196 are prohibited during the study. All other medications and blood products (prescription and over-the-counter, including herbal preparations) taken within 14 days of Cycle 1/Day 1 will be recorded on the appropriate case report form (CRF) by the investigator (or designee). The reason(s) for treatment, dosage, and dates of treatment should also be recorded. All concomitant medications taken by the patient through the final study follow-up visit will be recorded on the appropriate CRF by the investigator (or designee). In addition, concomitant medications used to treat AEs occurring up to 30 days after the last dose of study drug will be recorded.
Premature trial discontinuation	Patients are free to discontinue (withdraw) at any time during this clinical trial. If a patient withdraws from participation in the study during the treatment period, he or she should be encouraged to return for an Early Termination Visit for evaluation of safety. The investigator has the right to discontinue any patient from study drug administration or study participation. Reasons for patient discontinuation may include, but are not limited to, the following: • Clinically significant deterioration of the patient's condition; • Disease progression; • Requirement for other anti-tumor therapy during the study; • Noncompliance; • Pregnancy; • Significant AE; • Elevated serum creatinine that is confirmed on repeat testing; • Patient's right to withdraw from the study at any time, with or without stated reason; • Significant protocol violation; • Lost to follow-up; • Death; • Any other reason that, in the opinion of the principal investigator, would justify the removal of a patient from the study; and • ABIVAX's discretion to terminate the study at any time. The primary consideration in any determination to discontinue a patient's participation must be the health and welfare of the patient.

Patient Follow-up	From the last administration of ABX196, all patients will be followed up for disease and survival status every 3 months until 12 months (1 year) or until confirmed progressive disease, whichever comes first.
Data Safety Monitoring Board	A Data Safety Monitoring Board (DSMB) with expertise and experience in the management of hepatocellular carcinoma will review the safety of the trial. During the dose-escalation phase, the DSMB will review safety data once 3 patients are recruited in a given cohort and when the last recruited patient of the cohort has finished the first cycle of the treatment period, and will provide recommendations to either recruit 3 more patients in the same cohort or at the anticipated maximal tolerated dose level cohort, or to open the next cohort. During the expansion phase, the DSMB will review the safety data every two months until the last ongoing patient has finished the study. In addition, DSMB will be review all potential causally-related Serious Adverse Events and DLTs within 7 days of the initial report by the site staff.
Data monitoring	Monitoring of the study site will be performed by the Sponsor's Clinical Monitor or designee. Monitoring visits will be conducted according to the US CFR Title 21 parts 50, 56, and 312; and ICH Guideline for GCP. Study sites, the study database, and study documentation will be monitored regularly and may be subject to a quality assurance (QA) audit during the study by the Sponsor or its designee on behalf of the Sponsor. In addition, inspections may be conducted by regulatory agencies at their discretion. Following written standard operating procedures (SOPs), the monitors will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements (e.g., Good Laboratory Practice [GLP], Good Manufacturing Practices [GMP]). The investigational site will provide direct access to all trial-related sites, source data/documents, and reports for the purpose of monitoring and auditing by the Sponsor, and inspection by local and regulatory authorities.
Sample size	A maximum of 49 patients will be enrolled in this study: 18 in the dose escalation phase and 37 in the dose expansion phase (patients treated at the MTD in the dose escalation phase will be included in the expansion patient population).
Statistical methods:	A standard 3+3 design will be used for the dose escalation phase of the study. Simon's two-stage design will be used for the cohort expansion phase of the study. The null hypothesis that the true response rate is 0.15 (15%) will be tested against a one-sided alternative. In the first stage, 18 patients will be accrued. If there are less than 3 responses in these 18 patients, the study will be stopped. Otherwise, 19 additional patients will be accrued for a total of 37. The null hypothesis will be rejected if 9 or more responses are observed in 37 patients. This design yields a type I error rate of 10% and power of 80% when the true response rate is 30%.

1 INTRODUCTION AND RATIONALE

1.1 Background Information

ABX196 is a synthetic agonist of invariant Natural Killer T (iNKT) cells. ABX196 shows anti-tumoral activity and generates a functional and effective immune response at very low doses in animal models when used in association with anti-PD-1 antibody therapy, therapeutic vaccination or chemotherapy. ABX196 demonstrates a capacity to turn on a cold non-responsive tumor in a hot responsive tumor with proof of concept established in three preclinical cancer models. Preclinical data indicate that administration of an iNKT agonist such as ABX196 concurrently with an anti-PD-1 antibody such as nivolumab may augment the activity of ABX196 and prevent the induction of iNKT anergy observed with administration of an iNKT agonist alone [Parekh, 2009].

Hepatocellular carcinoma (HCC) is an incurable disease with poor prognosis. Anti-PD-1 antibody therapy with nivolumab (Opdivo, BMS/Ono) received accelerated approval by the FDA for the treatment of patients with HCC who received prior sorafenib therapy based on an objective response rate (ORR) of only 15-20%.

The current study is designed to evaluate the combination of ABX196 and nivolumab for the treatment of HCC as a strategy to overcome the immunosuppressive microenvironment in this disease and with a view to allowing a greater proportion of patients to achieve objective responses to immunotherapy.

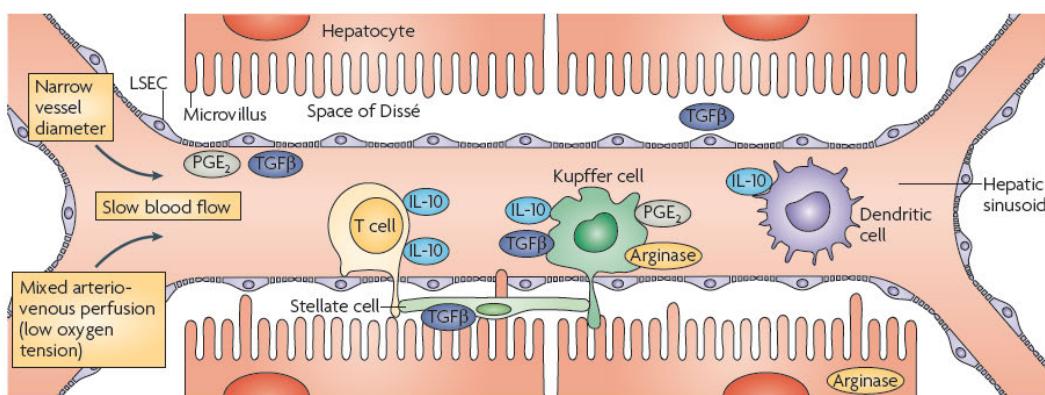
1.1.1 The Immune Microenvironment in HCC

The immune microenvironment in HCC is influenced by several unique features:

The liver as tolerogenic organ:

Due to its dual vasculature, the liver receives nutrients and pathogen-derived molecules from the portal vein as well as oxygenated blood from the systemic circulation via the hepatic artery. This unique macroscopic anatomy leads to persistent exposure to gut-borne pathogens as well as exogenous nonpathogenic molecules. As such, the immunologic composition of the liver, which contains the largest concentration of immune effectors in the body, is designed to play a central role in host defense and in the maintenance of self-tolerance. Antigen presenting cells of the liver, including liver sinusoidal endothelial cells (LSECs) and Kupffer cells (KCs) express high levels of PD-L1 and low levels of costimulatory molecules, limiting their ability to effectively activate CD4 and CD8 T cells. Both LSECs and KCs express low levels of MHC molecules, produce inhibitory cytokines such as IL-10 and preferentially expand regulatory T cells (Tregs) [Harding, 2016]. The liver therefore represents a tolerogenic organ in which HCC develops with key anatomic and cellular features depicted in Figure 1 [Aravalli, 2017]:

Figure 1: Anatomic Location of Hepatic APCs and Factors Regulating Their Function



HCC arising in the setting of chronic inflammation:

HCC is a tumor which almost always develops in an environment of chronic liver inflammation, either as a result of viral hepatitis, autoimmune hepatitis, or nonalcoholic fatty liver disease. These chronic inflammatory conditions create a microenvironment that favors immune cell exhaustion. Exhausted immune cells have the capacity to

recognize both foreign and cancer neoantigens; however, they exist in a chronic hyporesponsive state, expressing high levels of coinhibitory receptors, such as PD-1 and CTLA-4, express low concentrations of effector cytokines, all leading to impaired cytotoxicity necessary for an immune response. Other factors that contribute to the immunosuppressive phenotype of chronic inflammation which fosters HCC growth include high levels of IL-10 and TGF- β , increased frequencies of Tregs, and impaired antigen presentation [[Harding, 2016](#)].

HCC is an immunogenic tumor:

Tumor-associated antigens identified from patients with HCC include alfa-fetoprotein, glypican 3, NY-ESO-1, MAGE-A, Wilms tumor 1, and human telomerase reverse transcriptase and have led to functional cytotoxic T-cell responses. In one series, patients who developed CD8 response to in vitro antigen stimulation with AFP, MAGE-A, glypican 3, or NY-ESO-1 had an improved survival compared with patients without CD8 responses [[Flecken, 2014](#)]. These data suggest that HCC is an immunogenic tumor and that strategies that overcome the immunosuppressive microenvironment may lead to clinical benefit.

The activity of anti-PD-1 antibodies confirm the immune responsiveness of HCC:

As HCC develops within the immunosuppressive environment of the chronically inflamed liver, overexpression of coinhibitory receptors is common, as is resultant T cell dysfunction and exhaustion. Consequently, anti-PD-1 antibodies have been tested in HCC patients and found to be effective (ORR 15-20%).

1.1.2 Nivolumab in HCC

Nivolumab received accelerated approval by the FDA in September 2017 for patients with HCC previously treated with sorafenib based on durable objective responses observed in the CheckMate 040 study [[Opdivo US prescribing information, Revised 03/2019](#)]. This study enrolled 262 patients with advanced HCC, treating them with the anti-PD-1 monoclonal antibody nivolumab at 0.1 to 10 mg/kg in the dose-escalation phase (n = 48) and at 3 mg/kg in the dose-expansion phase (n = 214) [[El-Khoueiry, 2017](#)]. Previous treatment with sorafenib was allowed (70%), though some patients (30%) were sorafenib naive. The study included patients with hepatitis C virus infection (2) or hepatitis B virus infection (2) as well as patients who were uninfected (50%). Median follow-up was 13.3 months in the dose-escalation phase and 10.5 months in the dose-expansion phase.

By investigator assessment, in the 70% of patients previously treated with sorafenib, the objective response rate was 16.2% in the dose-escalation cohort and 18.6% in the dose-expansion cohort, with complete responses achieved in each group (by blinded independent central review, the response rate was 18.9% and 14., respectively); stable disease was shown in 43.2% and 45., respectively. As first-line treatment, the response rate to nivolumab in the dose-expansion cohort was 21.7%, and stable disease was achieved in 43%. Responses were observed irrespective of the expression of PD-1 on tumor cells or the hepatitis status of the patients. The duration of response was long with a median duration of response in sorafenib treated patients of 17.1 months in the dose-escalation cohort and was not reached in the dose-expansion group.

1.1.3 ABX196, an iNKT Agonist

ABX196 is a synthetic analog of the parent iNKT agonist α -GalCer.

A first-in-human phase 1 study in healthy male volunteers of ABX196 in a liposomal formulation (with preferential hepatic uptake) has been completed assessing not only safety but also immune regulatory and adjuvant activities of ABX196 in the context of a prophylactic vaccine against hepatitis B [[Tefit, 2014](#)]. ABX196 was administered at three doses: [REDACTED] μ g, in 29 patients. In all the individuals injected with ABX196, peripheral blood NKT cells displayed hallmarks of activation, and 4 of them had measurable circulating IFN- γ 24 h after the first administration. More importantly, the addition of ABX196 to the minimally immunogenic HBs antigen resulted in protective anti-HBs antibody responses in a majority of patients, demonstrating the adjuvant properties of ABX196 in humans.

Key observations from this phase I first-in-human study are the following:

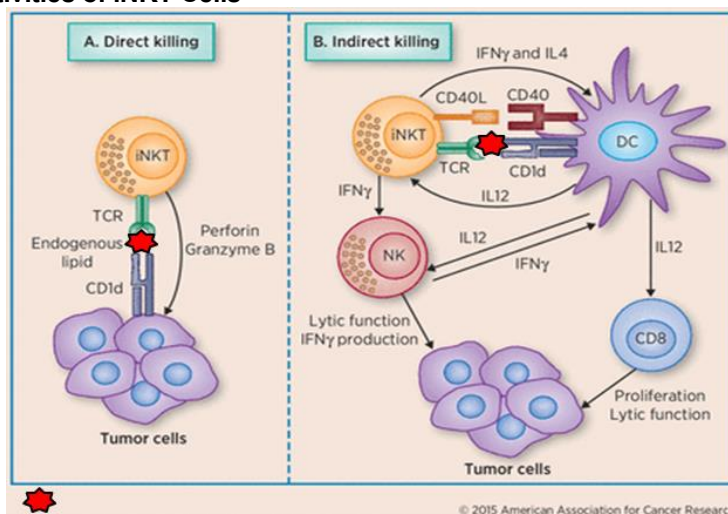
- [REDACTED]

- [REDACTED]
- [REDACTED]
- [REDACTED]

1.1.4 Rationale for Combining ABX196 with an Anti-PD-1 Antibody in Patients with HCC

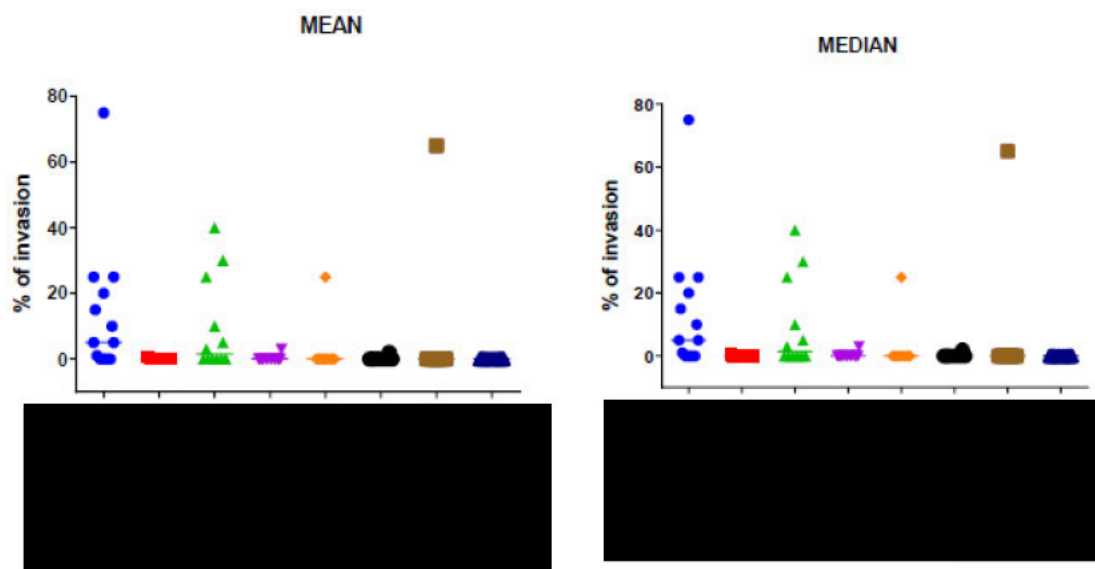
iNKT cells are a known immune cell population with higher prevalence within the liver. These cells are important in the priming phase of the immune response by cross-priming dendritic cells (DCs) through DC binding via MHC-like CD1d receptors to the iNKT T cell receptors, leading to expression of the DC-activating ligand CD40L; they can activate natural killer cells (NK) and overcome an immunosuppressive tumor microenvironment (TME) through interferon gamma (IFN γ) and interleukin 4 (IL-4) secretion; in addition, they can augment the effector phase of the antitumor response leading to direct tumor cell death similar to CD8 effector T cells (CD8) on CD1d expressing tumor cells. The mechanisms of iNKT antitumor effects are summarized in Figure 2 [McEwen-Smith, 2009]:

Figure 2: Antitumor Activities of iNKT Cells



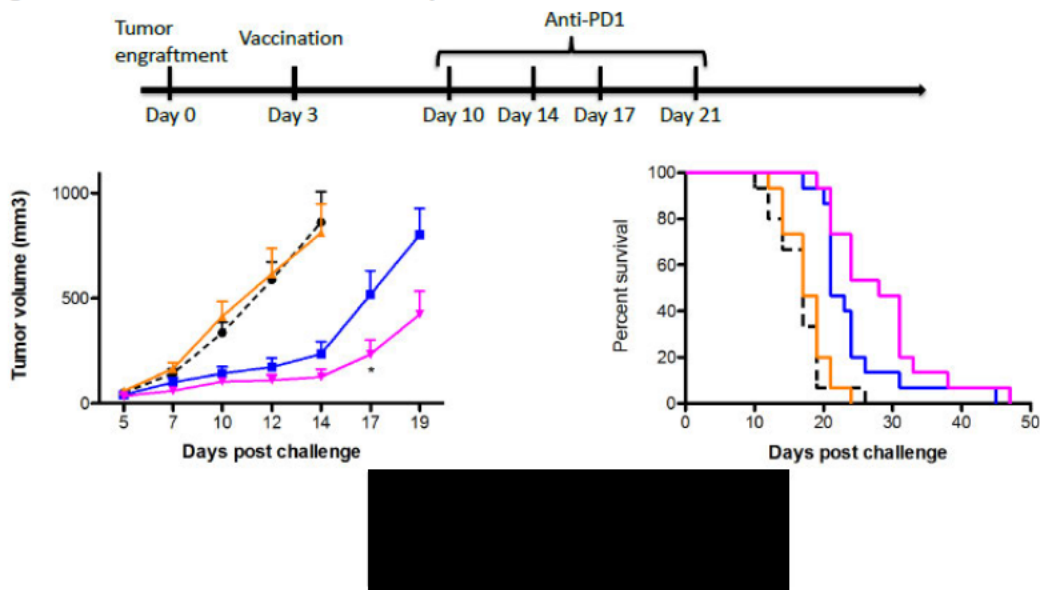
ABX196 shows anti-tumoral activity and generates a functional and effective immune response at very low doses when used in association with anti-PD-1 antibody therapy, therapeutic vaccination or chemotherapy. An orthotopic study evaluating ABX196, anti-PD-1 antibody, sorafenib, and doxorubicin has been conducted in the Hepa 1-6 murine HCC orthotopic model. The percentage of tumor invasion at study day 19-20 demonstrated effective tumor growth control by both ABX196 and anti-PD-1 (with less effective control by sorafenib) as summarized in Figure 3:

Figure 3: % Invasion Day 19-Day 20 in the Hepa 106 Xenograft



A separate experiment of ABX196 (with TRP2 peptide) or anti-PD-1 or in combination demonstrated an active response with the anti-PD-1 in combination with ABX/peptide but no activity of the anti-PD-1 as a monotherapy. This suggests that ABX196/peptide initiated an immune response which was then sustained with the addition of PD-1 blockade. These experimental results are summarized in Figure 4:

Figure 4: ABX196/TRP2 Confers Responsiveness to Anti-PD-1



Similar to observations of ABX196, previous studies of the iNKT agonist α -GalCer in mice demonstrated robust cytokine production upon activation followed by loss of circulating iNKT cells due to downregulation of the iNKT TCR, leading to profound and persistent iNKT anergy [Parekh, 2005]. The same group later updated their results and determined that α GalCer-activated iNKT cells rapidly up-regulated expression of PD-1 at their cell surface, this increased expression persisted for at least one month [Parekh, 2009].

Blockade of the interaction between PD-1 and its ligands, PD-L1 and PD-L2, at the time of α GalCer treatment prevented the induction iNKT cell anergy but was unable to reverse established iNKT cell anergy. Consistently, injection of α GalCer into PD-1-deficient mice failed to induce iNKT cell anergy. These authors demonstrated that

blockade of PD-1/PD-L interactions enhanced the antimetastatic activities of α GalCer and suggested that this finding could represent a path forward for development of immunotherapies.

In the light of the previous research, it follows that administering ABX196 concurrently with an anti-PD-1 antibody such as nivolumab may augment the activity of ABX196 and prevent the induction of iNKT anergy. From an early clinical development perspective, a rapid proof of concept would be obtained if addition of ABX196 to anti-PD-1 antibody therapy increases the objective response rates from the current 15-20% observed with single-agent anti-PD-1 antibody therapy with acceptable tolerability.

1.1.5 Preclinical Pharmacology and Toxicology

See Investigator's Brochure.

1.2 Study Rationale

Nivolumab has been approved for the treatment of previously treated advanced hepatocellular carcinoma, but objective responses with either checkpoint inhibitors are only observed in a minority of treated patients. The liver is a tolerogenic organ and hepatocellular carcinoma arises in the immunosuppressive environment of chronic inflammation. Anti-PD-1 antibodies may prevent the severity of ABX196-induced iNKT anergy and ABX196-induced iNKT activation may enhance the T cell immune response to anti-PD-1 antibodies. Hence, the combination has the potential for increasing the proportion of patients benefiting from immunotherapy.

The dose of nivolumab is the standard US approved dose for the drug. The dose of ABX196 will be escalated from doses below and up to the maximum dose found to be well tolerated in healthy adult volunteers. This is a range of doses that have been shown to be pharmacologically active when used as a prophylactic adjuvant for hepatitis B in healthy adult volunteers. This study will evaluate tolerability and pharmacodynamics and will provide a preliminary assessment of efficacy of ABX196 in combination with nivolumab in patients with previously treated advanced hepatocellular carcinoma.

1.3 Risks and Benefits

Patients in this study have advanced hepatocellular carcinoma and longstanding liver dysfunction. Anti-PD1 antibodies and ABX196 are both immunostimulatory molecules; these drugs individually and in combination may lead to acute liver inflammation and may place the patient at risk for autoimmune side effects, however, the combination may also promote the immune control of the patient's advanced refractory cancer.

While key observations from the phase I first-in-human study administering ABX196 showed clinical adverse events to be mild to moderate, and common events to include headache and asthenia mostly occurring within the first few days after a single dose of ABX196 administration, dose-dependent transient elevations in liver enzymes (AST/ALT) were also observed in most patients. These AST/ALT elevations peaked at 24-48 hours post dosing with maximum values in some patients at the higher two doses of 5x to approximately 10x the upper limit of normal. However, these elevations were mostly resolved by one week (representing SAEs in two patients dosed at 0.4 μ g and one patient dosed at 2.0 μ g). Minimum changes in total bilirubin and alkaline phosphatase were observed.

During nivolumab therapy, mild-to-moderate serum aminotransferase elevations are not uncommon (~10%) but are usually self-limited and resolve even with continuing cyclic therapy. Serum ALT elevations above 5 times the upper limit of normal (ULN) occur in 0.3% to 1.6% of patients, and a proportion of these individuals develop clinically apparent liver injury that can be severe. The onset of such injury is usually after 2 to 6 cycles, 1 to 3 months after initiation of treatment. The pattern of enzyme elevation is usually hepatocellular but can be mixed, particularly at the onset. Liver histology demonstrates an acute hepatitis-like pattern with focal or confluent necrosis and prominent lymphocytic infiltrates of activated T cells, which is compatible with an immune mediated hepatic injury. However, autoantibodies are usually not present. Restarting nivolumab can result in recurrence of injury, although corticosteroid treatment may block recurrence.

Guidelines for management of patients receiving nivolumab recommend monitoring of liver tests and use of corticosteroids for patients who develop serum aminotransferase elevations above 5 times the ULN, initiating therapy with high doses of intravenous methylprednisolone and switching to oral prednisone after 1 to 2 days, continuing tapering doses for at least 30 days. Most cases of hepatitis due to nivolumab resolve with prompt

institution of immunosuppressive therapy. The few fatal cases that have been reported during immunotherapy with checkpoint inhibitors occurred in patients who had other severe immune related adverse events (Stevens Johnson syndrome, capillary leak syndrome) or who had a delay in starting corticosteroid therapy. There is little information on the safety of restarting nivolumab or other checkpoint inhibitors after occurrence of clinically apparent liver injury from their use. In some situations, therapy can be restarted safely after resolution of an immune mediated adverse event, but in other situations immunosuppressive therapy is required to control the adverse event.

In the CheckMate 040 study of nivolumab in patients with HCC, twenty-five percent of patients experienced Grade 3/4 or greater adverse events, including AST increase (10%), ALT increase (6%) and lipase increase (13%). While hematologic liver parameters are of particular concern to the HCC patient population, these were considered manageable and did not result in hepatitis and the relatively mild toxicity profile of nivolumab monotherapy in these pretreated HCC patients was encouraging. Only of patients required systemic corticosteroid therapy for immune-mediated hepatitis. Also, nivolumab was not associated with exacerbation of either HBV or HCV when present in this HCC population.

In contrast, the benefits of this research remain considerable as HCC remains an incurable disease with poor prognosis, and this study will explore the potential to increase the immune control of the disease in patients not amenable to curative surgery or local therapy and with documented objective radiographic progression during or after treatment with sorafenib (or intolerance to/refusal to receive sorafenib).

This trial will be conducted in compliance with the Declaration of Helsinki, current Good Clinical Practices (GCP) and all other applicable laws and regulations.

2 STUDY OBJECTIVES

2.1 Primary Objectives

The study primary objectives are:

- To explore the safety, tolerability and maximum tolerated dose of ABX196 in combination with standard-dose nivolumab (dose escalation and expansion phases);
- To evaluate objective response rate (ORR) per RECIST v1.1 (dose expansion phase of the study).

2.2 Secondary Objectives

The study secondary objectives are:

- To evaluate duration of response (DOR), disease control rate (DCR), time to progression (TTP), and progression-free survival (PFS) per RECIST v1.1;
- To evaluate the immunogenicity of nivolumab.

2.3 Exploratory Objectives

The study exploratory objectives are:

- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]

2.4 Primary Endpoints

The study primary safety endpoints are:

- The incidence and severity of adverse events (AEs) and dose limiting toxicities and determination of the maximum tolerated dose;
- The changes in safety laboratory parameters, vital signs, and weight;
- The occurrence of DLTs.

The study primary efficacy endpoint is:

- The objective response rate (ORR).

2.5 Secondary Endpoints

The study secondary efficacy endpoints are:

- The duration of response (DOR);
- The disease control rate (DCR);
- The progression-free survival (PFS);

- The time to disease progression (TTP);
- The clinical benefit rate (CBR);
- The change in alpha fetoprotein serum concentrations;
- The frequency of development of anti-drug antibodies to nivolumab.

2.6 Exploratory endpoints

The study exploratory endpoints are:

- [REDACTED]
- [REDACTED];
- [REDACTED]

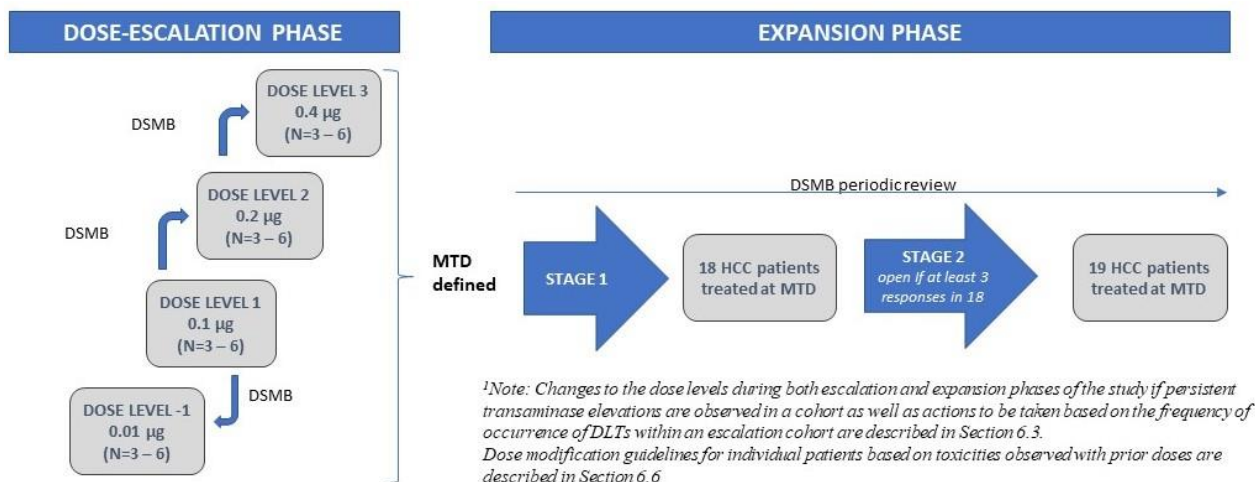
3 INVESTIGATIONAL PLAN

3.1 Study Design

This is an open-label, uncontrolled phase 1-2 study to evaluate the safety, tolerability, pharmacodynamic effects, and preliminary efficacy of ABX196 administered in combination with nivolumab in patients with hepatocellular carcinoma.

The study consists of 2 phases, a Dose Escalation Phase (Section 3.1.1) and an Expansion Phase (Section 3.1.2). The overall study design is presented in Figure 5.

Figure 5: ABX196-001 Overall Study Design¹



During the dose escalation phase, three (3) patients will be initially enrolled into Dose Level 1. If there is no DLT observed in any of these patients, the trial proceeds to enroll additional patients into the next Dose Level, following DSMB recommendations. If one patient out of three develops a DLT at a specific dose, an additional three patients are enrolled into that same Dose Level. Development of DLTs in more than 1 of 6 patients in a specific Dose Level indicates that the MTD has been exceeded, and further dose escalation is not pursued. The previous dose level will be considered as the MTD.

However, if only 3 patients had been enrolled to the dose level immediately below the maximum administered dose, then three additional patients will be enrolled to this dose level. If zero or one of these six patients experiences a DLT, this dose level will be identified as the MTD. Therefore, the MTD is defined as the highest dose level studied that results in DLTs in at most one of six patients.

Besides, if a DLT occurs in more than 1 of 6 patients in the Dose Level 1, the Dose Level -1 will be started upon the DSMB recommendation.

Once MTD is defined, the Expansion Phase will start.

Nivolumab will be administered, consistent with the US prescribing information, as an IV infusion on Days 1 and 15 of each 28-Day cycle.

ABX196 will be administered as an IM injection 120 minutes (+/- 15 minutes) after the completion of the nivolumab infusion on Day 1 of every odd cycle (i.e., cycle 1, 3, 5, 7, 9 and 11). Cycles will be repeated until confirmed progressive disease or until unacceptable toxicity.

Patients included in the dose escalation phase of the study will be observed in the hospital/clinic setting, if possible, for at least 24 hours (but preferably 36 hours) after the first dose to be observed for any early toxicities and for blood sampling. If any signs of side effects appear after the first ABX196 dosing, patients must be kept for a second hospitalization once ABX196 is administered.

This in-hospital/clinic observation period will not be required during the expansion phase.

3.1.1 Dose Escalation Phase

The Dose Escalation Phase is designed to determine maximally tolerated dose (MTD) of ABX196 administered as a single IM injection 120 minutes (+/- 15 minutes) after the completion of the nivolumab infusion on Study Day 1 of the first 28 Day treatment cycle.

Each dose level must include a minimum of 3 patients but can enroll up to 6 patients for the determination of the MTD. Dose escalation procedures are described in Section 6.3.

As anti-PD-1 antibodies may augment the response of iNKT cells to ABX196 treatment, the initial dose (0.1 µg) is one half of the well tolerated dose from the prior first-in-man trial (0.2 µg) which was not associated with any transaminase elevations in healthy volunteers.

3.1.2 Expansion Phase

Once the MTD has been established, patients will be enrolled into an expansion phase to obtain a preliminary assessment of the safety and activity of the combination.

Simon's two-stage design (Simon, 1989) will be used for the cohort expansion phase of the study. The null hypothesis that the true response rate is 0.15 (15%) will be tested against a one-sided alternative. In the first stage, 18 patients will be recruited. If there are two or fewer responses in these 18 patients, the study will be terminated. Otherwise, 19 additional patients will be recruited for a total of 37 patients. The null hypothesis will be rejected if nine or more responses are observed in 37 patients.

This design yields a type I error rate of 10% and power of 80% when the true response rate is 30%.

3.2 Investigational Sites

This study will be conducted at two to four sites in the United States.

3.3 Patient Assignment Methods

This is an open-label study. All patients enrolling into this study will be treated with ABX196 and nivolumab.

4 STUDY POPULATION

4.1 Number of Patients

Approximately 9-18 patients (3 cohorts of 3 to 6 patients) with HCC will be enrolled in the Dose Escalation Phase. Additional cohorts of patients might be enrolled in case of persistent non-transient transaminase elevations requiring more conservative subsequent dose escalations.

In the Dose Expansion Phase up to 18 evaluable patients will be enrolled in Stage 1 (including patients in the dose escalation portion who were treated at the MTD) plus up to 19 more in Stage 2 for a total of 37 efficacy-evaluable patients.

4.2 Eligibility Criteria

All patients must meet all of the inclusion criteria (Section 4.2.1), and none of the exclusion criteria (Section -h);

4.2.1 Inclusion Criteria

A patient will be eligible to participate in this study if ALL the following criteria are met:

1. Men or women, Age ≥ 18 years;
2. Patients with ECOG performance status 0 or 1;
3. Patients with confirmed diagnosis of HCC (i.e. histologically or by any other acceptable method for diagnosis) not amenable to curative surgery or local therapy;
4. Patients who are intolerant to or who progressed on at least one line of Tyrosine Kinase Inhibitors and / or Checkpoint Inhibitors (CPI) therapy. Patients who have had stable disease for at least 4 cycles of CPI therapy are also eligible;
5. Patients eligible to be treated with nivolumab; Prior use of nivolumab is also acceptable providing treatment was not taken in association with ipilimumab.
6. Patients already under treatment with nivolumab can be recruited, providing they have not achieved an objective response after at least 3 months of treatment. Patients with progressive disease under nivolumab may also be eligible if they meet other eligibility criteria
7. Patients with measurable disease based on RECIST v1.1;
8. Patients with Child-Pugh class A liver score within 7 days of first study dose;
9. Patients with no history of hepatic encephalopathy;
10. Patients with no prior or current clinically significant ascites as measured by physical examination and that requires active paracentesis for control (patients with ascites only on radiographic imaging are eligible);
11. Patients with HBV infection must have received antiviral therapy for at least 12 weeks and HBV viral load must be documented to be <100 IU/mL within 7 days of first study dose;
12. Patients with no active co-infection with HBV and HCV or HBV and HDV;
13. Patients with no active drug or alcohol abuse;
14. Patients with adequate organ function at screening:
 - a. Neutrophils $\geq 1000/\mu\text{L}$
 - b. Platelets $\geq 50,000/\mu\text{L}$
 - c. Hemoglobin ≥ 9.0 g/dL
 - d. Creatinine clearance ≥ 40 mL/min according to the Cockcroft-Gault formula
 - e. ALT and AST ≤ 5 x upper limit of normal each
 - f. Total bilirubin ≤ 3 mg/dL
 - g. International Normalized Ratio (INR) ≤ 2.3 or prothrombin time ≤ 6 seconds above control
 - h. Albumin ≥ 2.8 g/dL.

4.2.2 Exclusion Criteria

Patients who meet any of the following exclusion criteria will be excluded from the study:

1. Patients with tyrosine kinase inhibitor treatment within 2 weeks of first study dose;
2. Patients with esophageal or gastric variceal bleeding within the past 6 months;
3. Patients with portal vein invasion at the main portal (Vp4) or the inferior vena cava or cardiac involvement of HCC based on imaging;
4. Patients with previous solid organ or hematologic transplantation;
5. Patients with active autoimmune disease requiring systemic treatment in the past 2 years;
6. Patients with diagnosis of immunodeficiency or receiving systemic steroid therapy or other immunosuppressive therapy within 7 days before first study dose;
7. Patients with previous locoregional therapy or major surgery to the liver within 6 weeks before first study dose;
8. Patients with minor surgery to liver or another site within 1 week before first study dose.
9. Patient treated with an investigational drug within 2 weeks before first study dose

4.3 Screening Failures

Screening failures are defined as patients who consent to participate in the clinical study but are not subsequently entered in the study.

Individuals who do not meet the criteria for participation in this study (screening failure) may be rescreened.

4.4 Deviation from Inclusion/Exclusion Criteria

All patients must meet all of the inclusion criteria (Section 4.2.1) and none of the exclusion criteria (Section h). Deviations, if any, will be managed as per protocol section 10.2 "Protocol deviation".

5 STUDY PROCEDURES

Once preliminary eligibility has been established by history, inspection of medical records, and protocol-required evaluations, and after the patient or guardian has provided an informed consent, the investigator or designee will contact ABIVAX or its designee via email providing the date of expected C1D1 for enrollment authorization.

Patients are expected to participate until progression of the disease with continued follow-up for survival until 12 months (1 year) after last administration of ABX196 or, for patients who withdraw early, until confirmed progressive disease, whichever occurs first.

Please refer to Appendix I, for the Schedule of Assessments. Patients who withdraw from the study before all follow-up procedures have been performed will be managed and documented as described in Section 7.

5.1 Schedule of Assessments

A summary of visits and clinical procedures is found in Appendix I.

Patients will participate in the study following the below schedule:

- Screening Period: Up to 21 days-prior to Cycle 1 Day 1
- Treatment Period: Up to confirmed progressive disease (or other treatment termination criteria met)
- End of treatment visit: Approximately 1 to 2 weeks after the last dose of study medication
- From the last ABX196 administration, all patients will be followed up for disease and survival status every 3 months until 12 months (1 year) from last dose or until confirmed progressive disease, whichever comes first.

All patients will be screened within 21 days prior to Cycle 1/Day 1.

Vital signs, clinical laboratory test results, weight, and AEs will be used to assess safety. Efficacy will be assessed based on tumor assessments (ORR and DOR) conducted at intervals during the study.

5.2 Screening

During Screening, candidates for the study will be fully informed about the nature of the study and possible risks and will receive a copy of the informed consent for review. Candidates must read the consent form and sign the document after the Investigator has answered all questions to the candidate's satisfaction. Further procedures can begin only after the consent form has been signed. The original signed consent form will be retained by the Investigator and a copy will be given to the candidate.

Candidates will be evaluated for entry into the study according to the stated inclusion and exclusion criteria (Section 4.2). The Investigator will evaluate the results of all examinations, including clinical laboratory tests, and will determine each candidate's suitability for the study. The Investigator must know the baseline results before enrollment. The pregnancy test for females of reproductive potential must be negative for those patients to proceed to enrollment. All Screening procedures must be done within 21 days of Cycle 1/Day 1, unless otherwise specified. The following procedures will be performed to establish each candidate's general health and qualifications for possible enrollment into the study:

- Obtain signed, written informed consent and permission to use protected health information, (in accordance with the Health Insurance Portability and Accountability Act or HIPAA). Refusal to sign informed consent and permission excludes an individual from the study.
- Record medical history, including cancer history, histology of primary tumor (including degree of differentiation), cancer stage at diagnosis, site of primary tumor, date of cancer diagnosis, date of diagnosis of metastatic disease (if applicable), types and dates of prior anti-tumor therapy (including surgery, radiation therapy, systemic therapy), and date of most recent disease progression (if applicable) including supportive tumor marker results.
- Optional: Obtain archival tumor tissue for assessment of immune status including IHC localization and counting of iNKT cells (including CD4, CD8, and double negative cells; CD69 activation marker; and PD-1

expression), NK, DC, and CD8 T cells; measurement of PD-L1 on tumor and immune cells and CD1d on tumor cells.

- Record best response to prior therapy (if applicable) and date of progression. If tumor measurements before and after therapy are available, RECIST v1.1 should be used for these tumor assessments (see Appendix III).
- Record recent medication history, including vitamins, herbal preparations, blood products, and other over the counter (OTC) drugs (all concomitant medications taken within 14 days of Day 1 must be documented on the CRF for enrolled patients).
- Record blood pressure (BP), heart rate (HR), respiratory rate (RR) and temperature measurements. These measurements will be done according to the standard instructions (see Section 5.7.1.3).
- Perform a complete physical examination, including height and weight.
- Tumor assessments will be conducted with computed tomography scans of the chest, abdomen, and pelvis, including contrast-enhanced triphasic computed tomography scans of the abdomen, at baseline, every six weeks for one year or until disease progression according to RECIST v1.1 (see Appendix IV). If a patient is found to have disease progression but is tolerating and benefiting from treatment per investigator assessment, the patient may continue study therapy until disease progression is confirmed.
- Assess ECOG performance status score (see Appendix II).
- Obtain blood samples for hematology and iNKT cell count.
- Obtain serum samples for chemistry (including thyroid function parameters), cytokines and AFP (see Section 5.7.1.4).
- Obtain serum sample for serum human chorionic gonadotropin (HCG) pregnancy test in female patients of child-bearing potential (all female patients unless surgically sterilized or at least 1-year post-menopausal). For patients with cancers known to produce HCG, a presumed false positive pregnancy test should be confirmed by pelvic ultrasound.
- Review inclusion and exclusion criteria (see Section 4.2).

5.3 Treatment Period:

All patients will be on treatment until disease progression or until early withdrawal based on the criteria indicated in protocol Section 7.1.

See Appendix I - Schedule of Events, for an overview of study procedures during the Treatment Period, and Appendix II for allowed windows applicable to specific blood analysis timepoint collection.

During the whole course of the study, CT scans will be performed every 6 weeks for tumor assessment regardless of a specific cycle/day visit. A frequency of every 12 weeks will be applied for bones scans.

Patients in the dose escalation phase of the study should remain in the hospital/clinic setting for at least 24 hours (but preferably 36 hours) to observe for side effects and for blood sampling. If any side effects is observed following this first ABX196 administration, patients can be kept for a second day of hospitalization.

The following procedures will be performed during the Treatment Period.

5.3.1 Cycle 1

Cycle 1 consists of 5 onsite visits, as follow:

Day1:

- Perform a limited physical examination, including weight, to focus on treatment emergent adverse events and tumor disease status;
- Measure and record vital signs (BP, HR, RR, temperature):

- before nivolumab infusion,
- within 1 hour after the nivolumab infusion and again within 1 hour prior to the ABX196 IM injection,
- and 1 hour (+/- 10 minutes) after the ABX196 IM injection;
- Assess ECOG performance status score;
- Collect blood samples for the following tests:
 - iNKT Cell count before drug administration (pre-dose),
 - Lymphocyte immunophenotyping before drug administration (pre-dose) and 4 hours post ABX196 administration,
 - Serum cytokines before drug administration (pre-dose) and 4 hours post ABX196 administration,
 - Hematology panel,
 - Biochemistry panel (including thyroid function exploration),
 - Serum pregnancy test (when applicable),
 - Alpha Fetoprotein (AFP)
 - PK parameters ABX196 at the following timepoints: pre-dose, 10 min, 30 min, 60 min, 2 h, 4h, and 6h (6h timepoint collection is optional) after the ABX196 IM injection
 - Nivolumab anti-drug antibodies assessment (before Nivolumab administration)
- Administer nivolumab 240 mg
- Administer ABX196 as an IM injection 120 minutes (+/- 15 minutes) after the completion of the nivolumab infusion administration
- Record concomitant medications, including vitamins, herbal preparations, blood products, and other OTC drugs since the last visit.
- Record any adverse event starting from the first administration.

Day 2:

- Perform a limited physical examination, to focus on treatment emergent adverse events and tumor disease status;
- Record vital signs (BP, HR, RR, temperature);
- Collect blood samples for the following tests:
 - iNKT Cell count 24 hours post ABX196 dosing
 - Lymphocyte immunophenotyping 24 hours post ABX196 dosing
 - Serum cytokines 24 hours post ABX196 dosing
 - PK parameters ABX196 24 hours post dose
 - Hematology panel
 - Serum chemistry panel
- Record concomitant medication if any changes occurred since Day 1
- Record any adverse event

Day 4 & Day 8:

- Perform a limited physical examination, to focus on treatment emergent adverse events and tumor disease status;
- Record vital signs (BP, HR, RR, temperature);
- Collect blood samples for the following tests:
 - Serum cytokines (non-timepoint)
 - Hematology panel
 - Serum chemistry panel

- Record concomitant medication if any changes occurred since Day 1
- Record any adverse event

Day 15:

- Perform a limited physical examination to focus on treatment emergent adverse events and tumor disease status;
- Measure and record vital signs (BP, HR, RR, temperature);
- Assess ECOG performance status score;
- Collect blood samples for the following tests:
 - Lymphocyte immunophenotyping (non-timepoint),
 - Serum cytokines (non-timepoint),
 - Hematology panel,
 - Serum chemistry panel,
 - Nivolumab anti-drug antibodies assessment (before Nivolumab administration);
- Administer nivolumab 240 mg
- Record concomitant medication if any changes occurred since Day 1;
- Record any adverse event;
- Collect a fresh biopsy (Optional procedure) from the tumor: ideally, biopsy should be taken from the liver and from the same location as the archival tissue collected at screening. However, when it is not possible, biopsies from other nodules or location are acceptable.

5.3.2 Even Cycles (cycles 2, 4, 6, 8, 10 ,12, etc.)

For all even cycles from cycle 2 onwards, the patient will be invited to come back for 2 on-site visits as follows:

Day 1:

- Perform a limited physical examination, including weight, to focus on treatment emergent adverse events and tumor disease status;
- Measure and record vital signs (BP, HR, RR, temperature): before nivolumab infusion, and within 1 hour after the nivolumab infusion,
- Assess ECOG performance status score;
- Collect blood samples for the following tests:
 - Hematology panel,
 - Biochemistry panel (including thyroid function exploration),
 - Serum pregnancy test (when applicable),
 - Alpha Fetoprotein (AFP)
 - Nivolumab anti-drug antibodies assessment (before Nivolumab administration) (not measured after cycle 12);
- Administer nivolumab 240 mg
- Record concomitant medication if any changes occurred since previous visit;
- Record any adverse event;

Day 15:

- Measure and record vital signs (BP, HR, RR, temperature): before nivolumab infusion, and within 1 hour after the nivolumab infusion,

- Assess ECOG performance status score;
- Collect blood sample for nivolumab anti-drug antibodies assessment (before Nivolumab administration) (not measured after cycle 12);
- Administer nivolumab 240 mg;
- Record concomitant medication if any changes occurred since previous visit;
- Record any adverse event;

NB! Perform imaging for tumor assessment every 6 weeks (or 12 weeks for bones scans).

5.3.3 Odd cycles (Cycles 3, 5, 7, 9, 11, etc.)

For all odd cycles from cycle 3 onwards, the patient will be invited to come back for 3 on-site visits as follows:

Day 1:

- Perform a limited physical examination, including weight, to focus on treatment emergent adverse events and tumor disease status;
- Measure and record vital signs (BP, HR, RR, temperature):
 - before nivolumab infusion,
 - within 1 hour after the nivolumab infusion and again 1 hour prior to the ABX196 IM injection,
 - and 1 hour (+/- 10 minutes) after the ABX196 IM injection;
- Assess ECOG performance status score;
- Collect blood samples for the following tests:
 - iNKT Cell count before drug administration (pre-dose) (not measured after cycle 12),
 - Hematology panel,
 - Serum chemistry panel (including thyroid function exploration),
 - Serum pregnancy test (when applicable),
 - Alpha Fetoprotein (AFP),
 - PK parameters ABX196 (optional after cycle 1; 1 post-dose sample needed; can be collected at either day 1 or day 2) (not measured after cycle 12),
 - Nivolumab anti-drug antibodies assessment (before nivolumab administration) (not measured after cycle 12);
- Administer nivolumab 240 mg
- Administer ABX196 as an IM injection 120 minutes (+/- 15 minutes) after the completion of the nivolumab infusion administration
- Record concomitant medication if any changes occurred since previous visit;
- Record any adverse event;

Day 2:

- Collect blood samples for the following tests:
 - iNKT Cell count 24 hours post ABX196 dosing (not measured after cycle 12)
 - PK parameters ABX196 24 hours post dose (optional after cycle 1; to be done if PK samples were collected at day1 of the cycle) (not measured after cycle 12),
- Record concomitant medication if any changes occurred since previous visit;
- Record any adverse event;

Day 15:

- Measure and record vital signs (BP, HR, RR, temperature): before nivolumab infusion, and within 1 hour after the nivolumab infusion,
- Assess ECOG performance status score;
- Collect blood sample for nivolumab anti-drug antibodies assessment (before Nivolumab administration) (not measured after cycle 12);
- Administer nivolumab 240 mg;
- Record concomitant medication if any changes occurred since previous visit;
- Record any adverse event;

NB! Perform imaging for tumor assessment every 6 weeks (or 12 weeks for bones scans).

5.4 Study Termination/Early Termination

The Study Termination Visit will occur 1-2 weeks following the last dose of treatment on study. The following will be done at the Study Termination/Early Termination Visit:

- Record concomitant medications if any changes occurred since previous visit;
- Record AEs since the last visit;
- Perform a complete physical examination, including weight;
- Assess ECOG performance status score;
- Measure and record vital signs (BP, HR, RR, temperature);
- Collect blood samples for the following tests:
 - Lymphocyte immunophenotyping (non-timepoint),
 - iNKT cell count
 - Serum cytokines (non-timepoint),
 - Hematology panel,
 - Serum chemistry panel (with thyroid function exploration)
 - Serum pregnancy test (when applicable),
 - Alpha Fetoprotein (AFP),
- Perform tumor assessments, using the same imaging assessments done at baseline, if not done within past 6 weeks.
- Collect a fresh biopsy (Optional procedure) from the tumor: ideally, biopsy should be taken from the liver and from the same location as the archival tissue collected at screening. However, when it is not possible, biopsies from other nodules or location are acceptable.

In accordance with good medical practice, any ongoing study drug-related AE present at study termination, including a clinically significant laboratory test abnormality, will be followed until resolved or until the event stabilizes and the overall clinical outcome has been ascertained.

Adverse events starting up to 30 days after the last dose of study medication may be collected by telephone contacts.

5.5 Survival Follow-Up

From the last administration of ABX196, patients will be followed up for disease (early withdrawn patients only) and survival status every 3 months until 12 months (1 year) from last ABX196 dose administration or until confirmed progressive disease, whichever comes first.

Patients and/or family member will be contacted in that case.

5.6 Unscheduled visits

The need to ask a patient to come at a non-scheduled visit will be left to the investigator's judgement.

A visit to the emergency room won't be considered as unscheduled visit and should be reported as an adverse event with regards to the definitions described in this protocol.

During an unscheduled visit, the following assessments are mandatory:

- Record concomitant medications, including vitamins, herbal preparations, blood products, and other OTC drugs since the last visit;
- Record AEs since the last visit;

Every effort should be done to get the followings (optional procedures and measurements):

- A complete physical examination, including weight;
- ECOG performance status score;
- vital signs values (BP, HR, RR, temperature);
- Blood/serum samples for hematology and biochemistry panels analysis (including thyroid function parameters and serum HCG pregnancy test in female patients of child-bearing potential)
- Tumor assessments, using the same imaging assessments done at baseline, if not done within past 6 weeks (or 12 weeks for bones scans).

5.7 Description of Procedures

5.7.1 Safety Procedures

5.7.1.1 Adverse Event Assessments

Adverse events will be graded according to the Common Toxicity Criteria for Adverse Events (CTC-AE version 5.0). Adverse events will be summarized by relationship to study drug, grade, and seriousness (See Section 0).

5.7.1.2 Physical Examination

A complete physical examination will be performed at Screening and at the Study Termination/Early Termination Visit. Results will be recorded on the appropriate CRF by the investigator (or designee).

Limited physical examination will be done at specified timepoints.

The results of the physical examinations will be used for safety monitoring purposes only. At each study visit, according to good medical practice, the patient's general health (e.g., appearance, adequacy of hydration, presence of illness or injury, temperature, and vital signs indicative of a concurrent illness) will be assessed to determine whether continued dosing is appropriate.

5.7.1.3 Vital Signs

Blood pressure and HR measurements should be obtained with the patient's arm unconstrained by clothing or other material and with the appropriate cuff size from the opposite arm to that used for blood sampling, where possible. The arm should be supported at the level of the heart. All BP measurements will be obtained from the same arm throughout the dosing period. The cuff should be placed on the designated arm at least 10 minutes prior to taking BP measurements.

5.7.1.4 Clinical Laboratory Testing

Samples will be obtained for the tests listed in this section (see also Appendix I, Schedule of Assessments). Additional follow-up samples should be obtained as clinically indicated.

Routine parameters will be analyzed at local laboratories where results will be transcribed onto the CRF.

Blood samples will be collected for the following clinical laboratory tests:

Serum Chemistry	Hematology	Other
Glucose Urea Nitrogen Creatinine Electrolytes: Sodium Potassium Chloride CO2 Calcium Phosphorus Total protein Albumin Total bilirubin Alkaline phosphatase Alanine aminotransferase (ALT) Aspartate aminotransferase (AST) Gamma-Glutamyl Transferase (GGT) Lactate dehydrogenase Uric acid	White Blood Cell Count Red Blood Cell Count Hemoglobin Hematocrit Platelet Count Differential and absolute Neutrophils Lymphocytes Monocytes Eosinophils Basophils INR	Serum HCG Pregnancy Test AFP T3, T4, TSH

5.7.1.5 iNKT cell counting

Blood samples will be collected at specified timepoints at each ABX196 administrations up to cycle 12 inclusive (see Appendix I, Schedule of Assessments), to document the effect of ABX196 on circulating iNKT cell.

On odd cycles, blood samples will be collected before and 24h post each ABX196 dose. This analysis will be done on fresh blood by flow cytometry.

These determinations will be performed at central laboratories.

5.7.1.6 Lymphocyte Phenotyping, Cytokine Serum Concentrations

Blood and serum samples will be collected at specified timepoints up to cycle 12 inclusive (see also Appendix I, Schedule of Assessments) during the study, to document effects of ABX196 and nivolumab on T cell, NK and dendritic cell concentrations as well as on cytokines that may be associated with systemic symptoms and/or transaminase elevations (TNF, IL-1, IL-6, CRP) or activity (IFNg, IL-12).

These determinations will be performed at central laboratories.

Immunophenotyping	Cytokines
CD3 (Mature T cells) CD4 (Helper T cells) CD8 (Cytotoxic T cells) CD19 (B cells) CD16/CD56 (NK cells) Dendritic cells iNKT cells (CD4, CD8, Double Negative; CD69; PD-1; CXCR6)	TNF, IL-1, IL-6, CRP, IFNg, IL-12

5.7.2 Pharmacokinetics

The main objective of the PK analysis is to evaluate potential PK specificities of ABX196 in patients suffering from HCC.

PK analysis will be performed in all patients enrolled in this study at the first ABX196 administration. A first blood sample (reference) will be collected on the first day of treatment before any drug administration then blood samples will be collected for PK purpose at 10 min, 30 min, 60 min, 2 h, 4h, 6h, 24h post-dose samples after the first ABX196 IM injection (timepoint collection at 6 hours is optional depending on the site internal organization).

As optional, ABX196 PK can take place at each ABX196 dosing (Day 1 or Day 2 of every odd cycle) (not measured after cycle 12) .

Blood samples collected for PK purpose will be sent to ATLANBIO for Bioanalyses.

Blood samples for determination of ABX196 will be collected from all patients using direct venipuncture or an indwelling catheter.

Then, the following PK parameters will be derived for ABX196 for each patient:

- C_{max} , t_{max} : the maximum plasma concentration (C_{max}) and the time taken to reach C_{max} (t_{max}) will be obtained directly from the concentration-time data.
- $AUC_{0-\tau}$: the area under the concentration-time curve from time zero to the time of dosing interval τ . If no concentration can be measured at this time point, AUC_{0-last} (from time zero to the last quantifiable concentration) will be calculated. Both parameters will be presented independently. For both parameters, a linear trapezoidal method will be used.

Moreover, evaluation of steady-state will be made by visual inspection of the pre-dose concentration measurement collected over the study duration.

5.7.3 Nivolumab anti-drug antibodies

Serum samples will be collected at different time points up to cycle 12 inclusive (see also Appendix I, Schedule of Assessments) to assess the possible antibody response against nivolumab.

Samples will be collected at screening and at Day 1 and Day 15 of each cycle before nivolumab administration.

These determinations will be performed at central laboratory.

5.7.4 Immune microenvironnement analysis (Optional Procedure)

If available at screening, archival tumor tissue will be obtained for assessment of immune status including IHC localization (CD4, CD8 cells; PD-1 and PD-L1 expression) in tumors at the beginning of the study, before ABX196 and nivolumab treatment.

Then, if medically acceptable and only if the patient has consented to this optional procedure, two liver biopsies will be performed at D15 Cycle 1 and at termination / early termination, as well as at screening if there is no archival/historic biopsies available.

From each sample, one piece of the block will be prepared and sent to the dedicated central laboratory for immunohistochemistry analysis to assess effect of ABX196 / nivolumab on the immune environment in the liver.

Biopsy should be preferentially taken at the same site than the historical biopsy. Primary tumor or liver metastasis are preferred. If it's not medically feasible then other sites/nodules are allowed.

5.7.5 Efficacy Procedures

5.7.5.1 Tumor assessments

Tumor response will be performed using the RECIST v1.1 (see Appendix IV). The following outcome measures will be determined:

- ORR: Partial and Complete Responses
- DOR: Defined as time from date of first response to date of disease progression or death on study
- PFS: Defined as time from first dose of study drug to disease progression or death on study.

5.7.5.2 Tumor markers

Alpha Fetoprotein (AFP) will be assessed to determine baseline and change from baseline in AFP and number of patients categorized as responders. Responders will be defined as a greater than 50% reduction in AFP from baseline in patients with baseline AFP values $\geq 20\text{ng/mL}$.

5.7.5.3 Performance Status

Performance status will be scored using the 6-point ECOG performance score scale (see Appendix II).

5.7.6 Summary of blood samples

The Table 1 below summarizes the volume of blood to be sampled at each study visit.

Up to 415,5 mL is needed for the whole study duration.

Table 1: Blood Volume

			CYCLE 1						ALL EVEN CYCLES		CYCLE 3 AND ALL ODD CYCLES				
	REQUIRED VOLUME	COLLECTION TUBE	SCR	D1	D2	D4	D8	D15	D1	D15	D1	D2	D15	EOS	UNS
Hematology (Hemoglobin, Hematocrit, Red Cell Count, MCV, MCHC, Platelets, White cell count with diff.)	0.5mL EDTA blood	2mL EDTA tube	2	2	2	2	2	2	2		2			2	2
Biochemistry panel incl Serum Pregnancy, AFP	2 mL serum	5 mL serum gel tube	5	5	5	5	5	5	5		5			5	5
Thyroid function (T3,T4, TSH)	Performed within biochemistry panel (when applicable)		X	X					X		X			X	X
Neutralizing antibodies (biologics)**	0.75 mL serum	2.5mL serum gel tube	2.5	2.5				2.5	2.5	2.5	2.5		2.5		
iNKT**	16 mL of blood	2 x 10mL EDTA 1 x 6mL EDTA tube	16	16	16						16	16		16	
Cytokines**	5 mL serum	2x 5mL tube	10	20*	10	10	10	10						10	
Immunophenotyping**	30 ml of blood	3 x 10mL EDTA tube		60*				30						30	
PK samples**	1.0 mL plasma	2mL EDTA tube		14*	2						7 x 2**	2**			
Total per visit			35,5	119,5	35	17	17	49,5	9,5	2,5	39,5	18	2,5	63	7

*Values take into account pre-dose and post-dose volumes / **PK analysis is optional after cycle 1.

**Not measured during treatment after cycle 12. Will be performed at EOS if indicated in Schedule of Assessments.

6 INVESTIGATIONAL PRODUCT(S)

6.1 ABX196 and Nivolumab Dosage and Administration

Nivolumab will be administered according to the US prescribing information, i.e., nivolumab 240 mg an IV infusion Day 1 and 15 of each 28-Day cycle until confirmed progressive disease or unacceptable toxicity.

ABX196 will be administered as an IM injection 120 minutes (+/- 15 minutes) after the completion of the nivolumab infusion on Study Day 1 of every other 28-Day cycle (i.e., every 8 weeks).

6.2 Dose Preparation and Method of Administration

On the day of administration, the pharmacist will transfer 1 mL of the Investigational Product in 10 mL glass vials containing sterile 9 mL 0.9% saline chloride to reach 0.1 µg/mL ABX196.

Depending on the dose level (0.1/0.2/0.4 µg), 1/2/4 mL respectively will be injected IM in either the deltoid, the ventrogluteal or vastus lateralis areas, depending on the volume to be injected. For the 0.4 µg dose (i.e. 4 mL), two IM administrations should be performed, 2 mL each (2mL being the maximal volume to be administered as a single injection).

If the -1 cohort dose of 0.01 µg is required, 1 mL of the initially diluted product (i.e. 0.1 µg/mL) will be added to an additional 10 mL glass vial containing sterile 9 mL 0.9% saline chloride to reach 0.01 µg/mL ABX196; 1 mL of this product will then be administered to the patient for a total dose of 0.01 µg.

6.3 Dose Escalation Procedures and Maximum Tolerated Dose

This study will use a classic 3 + 3 dose escalation design to determine the maximal tolerated dose (MTD) of ABX196 in combination with nivolumab based on the frequency of dose limiting toxicities (DLTs) observed during the first 28 Day cycle.

The dose of ABX196 will be escalated in cohorts of 3-6 patients.

Dosing will begin with Cohort 1 (Dose Level 1: 0.1 µg ABX196); a single patient will be treated initially at each dose level with a two-week safety follow up assessment made before subsequent patients are treated; a total of at least 3 patients will be enrolled in that cohort.

If none of the patients experience a DLT during Cycle 1, the dose will be increased through successive dose level cohorts (specified in Table 2) until a maximum dose level of 0.4 µg, a dose previously found to be well tolerated in healthy volunteers.

Any patient developing a DLT during cycle 1 will be removed from the study treatment and will be followed up for survival/disease progression as per the study protocol.

If one patient develops a DLT at a specific dose, an additional three patients will be enrolled into that same Dose Level. Development of DLTs in more than 1 of 6 patients in a specific Dose Level indicates that the MTD has been exceeded, and further dose escalation is not pursued. The previous dose level will be considered as the MTD.

However, if only 3 patients had been enrolled to the dose level immediately below the maximum administered dose, then three additional patients will be enrolled to this dose level. If zero or one of the six total patients experiences a DLT, this dose level will be identified as the MTD.

Table 2. ABX196 Dose Escalation Schedule

Dose Level	ABX196 Dose
-1	0.01 µg
1 (Starting dose)	0.1 µg
2	0.2 µg
3	0.4 µg

It is anticipated that the highest dose in this study (0.4 µg) will be well tolerated and pharmacologically active based on previous healthy volunteer research. However, as a cancer population, patients' sensitivity to side effects may be altered and furthermore, ABX196 is being administered in combination with nivolumab, which may present increased risk of side effects.

Consequently, dose escalation will be performed according to the following rules for MTD determination:

1. If 1 of the first 3 patients in a dose level cohort experiences a CTC-AE Version 5 Grade 1 worsening in LFTs (AST, ALT, GGT, or total bilirubin) that is considered possibly related to study treatment and lasts more than 7 days during the first cycle (i.e., $> 3.0 \times \text{ULN}$ if normal at baseline or $> 3.0 \times \text{baseline}$ if baseline was abnormal for AST, ALT, GGT; $> 1.5 \times \text{ULN}$ if normal at baseline or $> 1.5 \times \text{baseline}$ if baseline was abnormal for total bilirubin), up to 3 additional patients will be treated at that dose level.
2. If 2 or more patients at a given dose level experience a Grade 1 worsening in LFTs that is considered possibly related to study treatment and lasts more than 7 days during the first cycle, then the dose escalation schedule for subsequent dose escalation groups will be modified to only increase by 30%, e.g., if 2 Grade 1 LFT elevations lasting more than 7 days are observed in 2 patients treated at Dose Level 1 (for example 0.1 µg but no DLTs are observed, then the next higher Dose Level will be 0.13 µg).
3. If no toxicities described in points 1 and 2 above are observed in the interim dose cohort; the next dose escalation will be as described in figure 5 - ABX196-001 Overall Study Design.
4. If toxicities described in points 1 and 2 above are observed; the steps outlined in points 1 and 2 will be repeated.
5. If dose limiting toxicities (Section 6.4) or worsening liver toxicity occurs as described in points 1 and 2 above; ABX196 is withheld and the patient will be removed from the study.

This procedure is implemented as persistent non-transient transaminase elevations in this study population dictates that more conservative subsequent dose escalations should be implemented.

At each dose level, when all patients have completed cycle 1 and before proceeding to each new dose level, the Data and Safety Monitoring Board (DSMB) will review and discuss the available relevant safety data. Patients who experience DLTs after cycle 1 may continue to receive ABX196 treatment according to the Dose Modification Guidelines described in Section 6.6. Intra-patient dose escalation is not allowed. Appendix V details all the doses that can be applied with regards to the procedure for dose modifications in case of toxicity (see section 6.6).

Dose Level -1 will be built into the study if patients experience excessive toxicity at Dose Level 1.

6.4 Definition of Dose-Limiting Toxicities (DLTs)

A DLT will include toxicities that are at least possibly related to study treatment which occur from Day 1 of Cycle 1 onwards. A patient experiencing a DLT in the first cycle will be removed from the study treatment and will be followed up for survival/disease progression as per the study protocol.

A DLT is defined as:

- Febrile neutropenia
- Grade 3 nausea, vomiting or diarrhea lasting longer than 24 hours despite optimal medical management or any Grade 4 vomiting or diarrhea
- Grade 3 alanine aminotransferase (ALT) or aspartate aminotransferase (AST) elevation lasting >7 days or with concomitant bilirubin $>2 \times \text{ULN}$ that is not clearly related to another process (other than study drug)

- Grade 4 neutropenia lasting >5 days
- Grade 3 thrombocytopenia with clinically significant bleeding
- Grade 4 thrombocytopenia (or any requirement for platelet transfusion)
- Grade 3 or 4 non-hematologic toxicities
- Any Grade 2 non-hematologic toxicity that does not resolve to Grade 0 or 1 toxicity by the start of the next cycle which, in the judgment of the investigator is considered a DLT
- The inability to begin the next cycle of treatment within 2 weeks of the scheduled dosing date due to unresolved toxicity.

All patients in a dose level cohort will be followed for the first cycle (or until DLT) before enrolling patients at the next higher dose level. Dose escalations are not allowed within individual patients. Patients who do not complete all doses during Cycle 1 and who do not experience a DLT will be replaced.

Before proceeding to the next dose level, available relevant safety data will be reviewed by the Data Safety Monitoring Board and discussed with the Investigators.

6.5 Expansion Phase Dosing

Once the MTD is determined in the Dose Escalation Phase, patients will be enrolled into the Expansion Phase.

6.6 Dose Modifications or Delays

After the completion of Cycle 1, dose modifications (modifications reductions or treatment discontinuation) for ABX196 will be based on treatment-related toxicities observed with prior doses.

Modification guidelines for ABX196 are as follows:

Toxicity observed with the prior ABX196 dose	Action
Grade 3 infusion-associated signs or symptoms, including cytokine release	• Reduce subsequent doses by 30% • If Grade 1 or less infusion-associated signs or symptoms are observed with this dose reduction, then subsequent doses should be at this dose level • If Grade 2 or 3 infusion-associated signs or symptoms recur with this dose reduction, then permanently discontinue ABX196 dosing
Grade 2 or greater LFT (AST, ALT, GGT, total bilirubin) elevations lasting > 7 days	• If LFTs have returned to within 10% of baseline by the next scheduled dose (up to 2-week delay allowed), reduce subsequent doses by 30%. If LFTs are still elevated > 10% of baseline by the time of the next scheduled dose, then discontinue further ABX196 dosing • If no Grade 2 or greater LFT elevations lasting > 7 days recur with this dose reduction, then subsequent doses should be at this dose level • If Grade 2 or greater LFT elevations lasting > 7 days recur with this dose reduction, then permanently discontinue ABX196 dosing
Grade 4 neutropenia or febrile neutropenia	• If the absolute neutrophil count has returned to within 10% of baseline by the next scheduled dose (up to 2-week delay allowed), reduce subsequent doses by 30%. If the absolute neutrophil count is still elevated > 10% of baseline by the time of the next scheduled dose, then discontinue further ABX196 dosing • If no Grade 4 neutropenia or febrile neutropenia recurs with this dose reduction, then subsequent doses should be at this dose level • If Grade 4 neutropenia or febrile neutropenia recur with this dose reduction, then permanently discontinue ABX196 dosing
Grade 3 or Grade 4 thrombocytopenia	• If the platelet count has returned to within 10% of baseline by the next scheduled dose (up to 2-week delay allowed), reduce subsequent doses by 30%. If the platelet count is still elevated > 10% of baseline by the time of the next scheduled dose, then discontinue further ABX196 dosing • If no Grade 3 or Grade 4 thrombocytopenia recurs with this dose reduction, then subsequent doses should be at this dose level

	If Grade 3 or Grade 4 thrombocytopenia recurs with this dose reduction, then permanently discontinue ABX196 dosing
Other Grade 3 or 4 non-hematologic toxicities	- If the observed non-hematologic toxicities have resolved by the next scheduled dose (up to 2-week delay allowed), reduce subsequent doses by 30%. If the observed non-hematologic toxicities persist beyond Grade 1 by the time of the next scheduled dose, then discontinue further ABX196 dosing - If the observed non-hematologic toxicities do not recur to more than Grade 1 with this dose reduction, then subsequent doses should be at this dose level - If the observed non-hematologic toxicities recur with a severity of Grade 2 or higher with this dose reduction, then permanently discontinue ABX196 dosing

One expected overlap in toxicities between anti-PD-1 antibodies and ABX196 is that both types of agents can be associated with transaminase elevations. ABX196 administration is associated with acute transaminase elevations with onset within the first day of injection, with peak levels within the first week, and with resolution within the first two weeks. The etiology is likely a transient hepatocyte response to intrahepatic cytokine release from iNKT, NK and dendritic cells activated secondary to the iNKT activation by ABX196. Repeat doses of ABX196 should only be administered if LFTs (AST, ALT, GGT, total bilirubin) are within 10% of baseline values. Dosing may be delayed for up to 2 weeks from the planned dosing; if longer delays are required then further ABX196 dosing should be discontinued.

Anti-PD-1 antibody-associated transaminase elevations occur after one or two cycles of treatment and are considered due to an immune-mediated hepatitis. This hepatitis is reportedly responsive to nivolumab treatment interruption and systemic glucocorticoid treatment as detailed in the package insert.

The modifications for nivolumab with respect to hepatotoxicity are as follows:

Liver Function Test Severity	Nivolumab Dose Modification
- If AST/ALT is within normal limits at baseline and increases to >3-5x the ULN - If AST/ALT is >1-3x at baseline and increases to >5-10x the ULN - If AST/ALT is >3-5x ULN at baseline and increases to >8-10x the ULN - If AST/ALT > 10x ULN after the first dose (in combination with ABX196)	Withhold dose (resume treatment when AST/ALT returns to baseline)
If AST or ALT increases to >10x the ULN after the second or later nivolumab dose	Permanently discontinue
If total bilirubin increases to >3x the ULN	Permanently discontinue

In addition, it is recommended to administer prednisone equivalent corticosteroids at a dose of 1 to 2 mg/kg/day followed by corticosteroid taper in the event that nivolumab is withheld or discontinued due to immune-mediated hepatitis.

Standard dose modification guidelines as outlined in the nivolumab Opdivo US prescribing information should be followed for this study [Opdivo US prescribing information, Revised 03/2019].

6.7 Packaging

The ABX196 investigational product (IP) is a liposomal suspension in phosphate buffered sucrose containing 1.0 µg/mL ABX196 drug substance embedded into liposomes composed of [REDACTED]

[REDACTED] The drug product composition is presented in Table 3.

Table 3. Drug product composition

Component	Function	Concentration
Drug substance	Active ingredient	1.0 µg/ml
████████████████████	████████████████████	██████
████████████████████	████████████████████	██████
████████████████████	████████████████████	██████
████████████████████	████████████████████	██████
████████████████████	████████████████████	██████
████████████████████	████████████████████	██████
████████████████████	████████████████████	██████

The ABX196 IMP is supplied in 2 mL glass vials (Type I), with a stopper and aluminum flip-off cap. The total volume will be 1 mL.

6.8 Storage

The ABX196 IP must be stored at ██████████

6.9 Drug Accountability

The investigator is responsible for the control of drugs under investigation. Adequate records of the receipt and disposition of all study drug shipped to the site will be maintained. Records will include dates, quantities received, quantities dispensed, and the identification codes of the patients who received study drug. The individual administering the study drug will write the study number, patient number, date, and start/stop times of administration on the study drug label, the CRF and the Drug Accountability Record, as appropriate.

6.10 Disposition of Used and Unused Vials of Study Medication

All used, partially used, and unused vials must be retained by the pharmacist. Periodically throughout and at the conclusion of the study, inventory checks and accountability of study materials will be conducted by a representative of ABIVAX or its designated agent. Once accountability is completed, an ABIVAX representative will authorize the return to a designated facility or release for local destruction of all used, partially used, and unused vials. Partially used or empty vials may be destroyed prior to ABIVAX's review per the site's standard institutional procedures and local and federal regulations as applicable, and with appropriate documentation after two study staff members have reconciled and documented the count on an Accountability Record. The completed Drug Accountability and Drug Return/Destruction Record(s) will be returned to ABIVAX.

The investigator's copy of the Drug Return/ Destruction Record(s) must accurately document the destruction of all study drug supplies. Records will also include dates, lot numbers, and quantities returned to ABIVAX, its designated agent or destroyed locally.

6.11 Ordering Drug

Investigators will order the study drug from the designated clinical research associate (CRA). Referring to the study manual provided by ABIVAX for CRA contact information and instructions for ordering study drug. Delivery typically will take 10 working days for processing and delivery of drug orders.

6.12 Concomitant and Excluded Therapy

All medications and blood products (prescription and over-the-counter including herbal preparations) taken within 14 days of Cycle 1/Day 1 will be recorded on the appropriate case report form (CRF) by the investigator (or designee). The reason(s) for treatment, dosage, and dates of treatment should be recorded in the source documents.

All concomitant medications taken by the patient through the final study follow-up visit will be recorded on the appropriate CRF by the investigator (or designee). In addition, concomitant medications used to treat AEs occurring up to 30 days after the last dose of study drug will be recorded.

Therapies prohibited during the conduct of this trial include any treatments for HCC other than nivolumab and ABX196.

7 PATIENT COMPLETION AND WITHDRAWAL

7.1 Criteria for Termination

Patients are free to discontinue (withdraw) at any time during this clinical trial. If a patient withdraws from participation in the study during the treatment period, he or she should be encouraged to return for an Early Termination Visit for evaluation of safety (see Section 5.4).

The investigator has the right to discontinue any patient from study drug administration or study participation. Reasons for patient discontinuation may include, but are not limited to, the following:

- Clinically significant deterioration of the patient's condition
- Disease progression;
- Requirement for other anti-tumor therapy during the study
- Noncompliance
- Pregnancy
- Significant AE
- Elevated serum creatinine that is confirmed on repeat testing
- Patient's right to withdraw from the study at any time, with or without stated reason
- Significant protocol violation
- Lost to follow-up
- Death
- Any other reason that, in the opinion of the principal investigator, would justify the removal of a patient from the study
- ABIVAX's discretion to terminate the study at any time.

The primary consideration in any determination to discontinue a patient's participation must be the health and welfare of the patient.

All patients will be instructed on the importance of complying with the requirements of the study. It is expected that patients will complete all of the necessary visits. If a patient does not return for follow-up visits as directed or does not adhere to the study requirements, the investigator and the ABIVAX-designated medical monitor will determine if early withdrawal should occur.

If there is any question as to whether a patient should be withdrawn from the study, the investigator should contact the ABIVAX-designated medical monitor.

7.2 Documentation

The primary reason for early removal of a patient from the study must be documented clearly on the patient's CRF and must be completed for any patient who has received any amount of drug during the treatment period. If the reason for early withdrawal is an AE or an abnormal laboratory value, the specific event or test result must also be recorded on the patient's CRF.

7.3 Procedures for Patients Who Withdraw Early

Following early termination, the patient should be informed about which evaluations are necessary to monitor his or her safety. In addition, patients should be encouraged to complete any procedures or evaluations outlined in Section 5.4.

7.4 Replacement of Patients

Patients participating in the Dose Escalation component of the study and who do not complete all doses during Cycle 1 and who do not experience a DLT will be replaced. All other patients who receive any study drug and who withdraw or are prematurely discontinued from the study will not be replaced. Patients who do not receive ABX196 will be replaced. Patient enrollment numbers are unique and will not be re-assigned.

8 ADVERSE EVENTS

A physician (either the investigator or physician designated by the investigator) will assess the seriousness, severity, and causality of an AE based on the following definitions.

8.1 Defining Adverse Events

An adverse event (AE) is any undesirable event occurring to or in a patient enrolled in a clinical trial, whether the event is considered related to the study drug (ABX196). This includes the time periods beginning after the first administration of study drug until 30 days after the last dose of study drug. Adverse events include the following types of occurrences:

1. Suspected adverse reactions;
2. Other medical experiences, regardless of their relationship to the study drug, such as injury, causes for surgery, accidents, increased severity of pre-existing symptoms, apparently unrelated illnesses, and significant abnormalities in clinical laboratory values, physiological testing, or physical examination findings; and
3. Reactions from drug overdose, abuse, withdrawal, sensitivity, or toxicity.

8.1.1 Serious Adverse Events

A serious adverse event (SAE) is any adverse experience that occurs at any dose and results in any of the following outcomes:

- Death. This includes any death that occurs during the conduct of the clinical study, including deaths that appear to be completely unrelated to the study drug (e.g., car accident). However, deaths that occur due to disease progression are not considered SAEs, but should be reported as a death on study on the death CRF. If a patient dies during the study, and an autopsy is performed, the autopsy results should be sent to ABIVAX, in addition to the patient's CRF. Possible evidence of organ toxicity and the potential relationship of the toxicity to the study drug are of particular interest. The autopsy report should distinguish between the relationship between the underlying diseases, their side effects, and the cause of death.
- Life-threatening adverse experience. This includes any AE during which the patient is, in the view of the investigator, at immediate risk of death from the event as it occurs. This definition does not include any event that may have caused death if it had occurred in a more severe form.
- Persistent or significant disability or incapacity
- Inpatient hospitalization or prolongation of existing hospitalization
- Congenital anomaly or birth defect
- Other medically important event which, according to appropriate medical judgment, may require medical or surgical intervention to prevent one of the outcomes listed above.

8.1.2 Nonserious Adverse Events

A nonserious AE includes any AE that is not defined as an SAE.

8.1.3 Unexpected Adverse Events

An unexpected AE is any AE that is not identified in nature, severity or frequency in the Investigator's Brochure for the current study.

8.2 Documenting All Adverse Events

All AEs will be recorded on the patient's CRF as descriptive findings (symptoms, or laboratory, physical exam, or vitals abnormalities) or diagnoses if etiology is known. Included are all AEs that occur after the start of treatment to within 30 days of administration of the last dose of study drug. Record AEs of any severity and AEs that are assessed as serious or not serious.

Note: Unchanged, chronic conditions and cancer symptoms present at baseline are **NOT** AEs and should not be recorded on AE pages of the CRF unless there is an exacerbation or worsening in severity of a chronic condition or cancer symptom after the first administration of study drug until 30 days after the last dose of study drug. Chronic conditions and/or cancer symptoms that exacerbate or worsen in severity should be documented on the AE CRF as a "worsening" condition. Death due to disease progression and measures of disease progression collected as efficacy endpoints (e.g., increasing tumor size or new lesions) are not considered adverse events, but should be collected as termination reasons (if applicable) and/or noted in tumor assessment CRFs as appropriate. Other reasons for death occurring during the AE reporting period are SAEs and should be reported as such.

Detailed information regarding an SAE must also be recorded on the ABIVAX Serious Adverse Event Reporting Form. Whenever possible, the investigator will group together into a single term the signs and symptoms that constitute a single diagnosis. For example, cough, rhinitis, and sneezing might be grouped together as "upper respiratory infection" if the investigator is confident of the diagnosis.

Adverse event information will be elicited from each patient by indirect questioning using a nonleading question, such as "Has anything bothered you since your last visit or is anything bothering you now?" Adverse event data may also be volunteered by the patient to the investigator (or the investigator's designee).

8.2.1 Grading of Adverse Events

Severity of AEs or clinically significant laboratory test results will be assessed in accordance with the grading scale presented in the CTC-AE version 5.0. A copy of this document can be found at the following internet site: <http://ctep.info.nih.gov/reporting/ctc.html> and will also be provided as a separate document to the sites upon request. Clinically significant abnormal laboratory results and lab results requiring an intervention will be recorded as AEs and should describe whether the lab result was increased or decreased. The following definitions for rating severity of AEs will be used for events not covered in the CTC-AE.

- Grade 1: Mild; awareness of signs or symptoms that are easily tolerated, are of minor irritant type, cause no loss of time from usual activities, do not require medication or further medical evaluation, and/or are transient.
- Grade 2: Moderate; signs or symptoms sufficient to interfere with function but not activities of daily living.
- Grade 3: Severe; signs or symptoms sufficient to interfere with activities of daily living; signs and symptoms may be of a systemic nature or require further medical evaluation and/or treatment.
- Grade 4: Disabling or with life-threatening consequences. (This definition does not include any event that might have caused death if it had occurred in a more severe form.)
- Grade 5: Death

8.2.2 Relationship to Study Drug

Using the following criteria, investigators will assess whether there is a reasonable possibility that the study drug (ABX196) caused or contributed to the AE.

- Yes:
 - The time sequence between the onset of the AE and study drug administration is consistent with the event being related to study drug; and/or
 - There is a possible biologic mechanism for study drug causing or contributing to the AE; and the AE may or may not be attributed to concurrent/underlying illness, other drugs, or procedures.

- No:
Another cause of the AE is most likely; and/or
The time sequence between the onset of the AE and study drug administration is inconsistent with a causal relationship; and/or
A causal relationship is considered biologically unlikely.

8.3 Abnormal Laboratory Test Results as Adverse Events

The investigator will monitor the laboratory test results and determine the clinical significance of any result that falls outside of the reference range. In accordance with good medical practice, any clinically significant abnormal laboratory test results must be followed until resolved or stabilized. Abnormal laboratory test results should not be reported as AEs unless, in the opinion of the investigator, the results constitute or are associated with a clinically relevant condition or require intervention. All such cases must be reported on the AE CRF.

In the event of unexplained, clinically significant abnormal laboratory test results, the tests should be repeated immediately and followed up until the values have returned to within the reference range or to baseline for that patient.

8.4 Reporting and Documenting Serious Adverse Events

Serious adverse events that occur at any time point after the first dose of study drug until 30 days after the last dose of study drug must be reported.

The following steps will be taken to promptly report and accurately document any SAE, even if it may not appear to be related to the study drug:

1. Report the SAE to the sponsor **by entering the SAE into the Electronic Data Capture (EDC) database within 24 hours** of becoming aware that a patient has experienced an SAE (a separate instruction manual will be provided for use of the SAE EDC database).

Using the additional bottom section of the Adverse Event form pertaining to SAEs, submit all known patient information (listed below) **within 24 hours of knowledge of the SAE occurrence**. The following information should also be entered in the database (or as much as possible to obtain and still report the event within 24 hours):

- a) Patient's Demographic Data
 - b) Patient's weight
 - c) Description of SAE, including date of onset and duration, severity, and outcome
 - d) All dosing data of study drugs administered up to the date the SAE occurred
 - e) Action taken regarding study drug administration
 - f) Relationship of SAE to study drugs
 - g) Concomitant medications, including regimen and indication
 - h) Intervention, including concomitant medications used to treat SAE
 - i) Pertinent laboratory data/diagnostic tests conducted and date
 - j) Pertinent medical history of patient
 - k) Date of hospital admission/discharge (if applicable)
 - l) Date of death (if applicable)
2. Perform appropriate diagnostic tests and therapeutic measures, and submit all follow-up substantiating data, such as diagnostic test reports and autopsy report to ABIVAX.

3. Conduct appropriate consultation and follow-up evaluations until the events are resolved, stabilized, or otherwise explained by the principal investigator.
4. Review each SAE report and evaluate the relationship of the SAE to study treatment and to the underlying disease. ABIVAX will determine whether the SAE is unexpected in nature.
5. Based on a cooperative assessment of the SAE with ABIVAX, a decision for any further action will be made. The primary consideration is patient safety. If the discovery of a new SAE related to the study drug raises concern over the safety of its continued administration to patients, ABIVAX will take immediate steps to notify the Agency, and all participating investigators in this study.
6. The investigator must report all SAEs and unexpected problems promptly to his or her IRB/IEC, as appropriate (see ICH Guidelines, Good Clinical Practice [E6]).

Other actions regarding SAEs might include the following:

- Protocol amendment
- Discontinuation or suspension of the protocol
- Modification of informed consent to include recent findings
- Informing current study participants of new findings
- Identification of specific AEs as drug-related

8.5 Follow Up of Adverse Events

All AEs are followed until they are resolved or determined to be irreversible or otherwise explained by the principal investigator.

8.6 Data Safety Monitoring Board

A Data Safety Monitoring Board (DSMB) with expertise and experience in oncology will review the safety of the trial. During the dose-escalation phase, the DSMB will review safety data once 3 patients are recruited in a given cohort and when the last recruited patient of the cohort has finished the 2 first cycle of the treatment period, and will provide recommendations to either (but not limited to):

- recruit 3 more patients in the same cohort, or
- recruit 3 more patients at the anticipated maximal tolerated dose level cohort, or
- to open the next cohort, or
- to open the expansion phase 1, or
- to open the expansion phase 2.

During the expansion phase, the DSMB will review the safety data every two months until the last ongoing patient has finished the study.

In addition, DSMB will review all potential causally-related Serious Adverse Events and DLTs within 7 days of the initial report by the site staff.

8.7 Overdose

Any instance of overdose (suspected or confirmed and irrespective of whether it involved ABX196) must be communicated to ABIVAX or a specified designee within 24 hours and be fully documented as an SAE. Details of any signs or symptoms and their management should be recorded including details of any antidote(s) administered.

8.8 Apparent Toxicity

Comprehensive assessments of any apparent toxicity experienced by the patient will be performed throughout the course of the study. Study site personnel will report any clinical AE, whether observed by the investigator or reported by the patient (see Section 8 for further details regarding the definition, management, and reporting of AEs).

8.8.1 Grading of Toxicity

Clinical AEs or abnormal laboratory test results will be assessed by the principal investigator or other designated other physician, in accordance with the grading scale presented in Section 8.2.1.

8.8.2 Monitoring and Treatment of Toxicity

A physician (either the investigator or a physician designated by the investigator) will manage and treat any toxicity. Patients should be referred to an ophthalmologist for evaluation if clinically significant ophthalmologic abnormalities are noted. The ophthalmologist should be directed to perform examinations as clinically indicated.

8.9 Reporting of SAEs to Abivax or its designee

Throughout the study, the reporting of SAEs to the Sponsor or its designee will be done through the SAE forms.

It is the investigator's responsibility to ensure that the SAE report is submitted to **IntuVigilance Limited within 24 hours after knowledge of the event(s).**

IntuVigilance Limited
Scotsbridge House, Scots Hill
Rickmansworth WD3 3BB
Hertfordshire, UK
Hotline phone: [REDACTED]
Email Address: [REDACTED]
Fax number: [REDACTED]

Legislative guidance requires the investigator to also ensure that any related SAEs are reported after the patient finished the study if the investigator becomes aware of them.

The study specific SAE form should be completed as thoroughly as possible, with all the available details of the event and signed by the investigator or designee. The investigator will assess causality between the study drug and the adverse event (AE) / serious adverse event (SAE) according to the table outlined below:

Related	A clinical event, including laboratory test abnormality, occurs in a plausible time relationship to treatment administration, and which concurrent disease or other drugs or chemicals cannot explain.
Probably related	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the treatment, unlikely to be attributed to concurrent disease or other drugs or chemicals.
Possibly related	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the treatment, but which could also be explained by concurrent disease or other drugs or chemicals.
Unlikely to be related	A clinical event, including laboratory test abnormality, with a temporal relationship to treatment administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations.
Unrelated	A clinical event, including laboratory test abnormality, with little or no temporal relationship with treatment administration. Typically explained by extraneous factors (e.g., concomitant disease, environmental factors or other drugs or chemicals).

An assessment of causality should always be provided at the time of the initial report. If the investigator or designee does not have all information regarding the SAE, he/she should not wait to receive additional information before completing the form and notifying IntuVigilance Limited.

Additional or follow-up information relating to the initial SAE report, will be requested, if necessary. Again, this information is to be completed and submitted through the SAE forms within 24 hours of receipt of the information.

In the rare occasion when the facsimile equipment does not work and in the absence of, the investigator should notify IntuVigilance Limited by telephone within the given timeframe and send a copy of the SAE report form by email.

8.10 Reporting of SAEs to Regulatory Authorities

ABIVAX has a legal responsibility to notify, as appropriate, both the local regulatory authorities and other regulatory agencies about the safety of the investigational medicinal product. It is therefore important that the investigator notifies promptly (within 24 hours) ABIVAX or designee of any SAEs, in order for legal obligations and ethical responsibilities towards other patients to be met.

In addition, the investigator or designee, will comply with the local regulatory requirements (when applicable) in reporting of SAEs to the ethics committee and, if required, to the relevant government authority.

Safety reports on adverse events that are serious AND unexpected AND causally associated with the investigational product are prepared according to ABIVAX's policy and applicable regulations and are forwarded to the investigators. These reports are filed with the investigator brochure or other appropriate study documentation. It is the Sponsor or its designee and/or investigator's responsibility to notify the IRB or IEC of these reports, if applicable according to local requirements.

9 STATISTICS

Detailed procedures for statistical analyses to be performed for this study will be provided in a separate Statistical Analysis Plan that will be finalized before database lock.

9.1 General Procedures

All analyses of safety and efficacy for this open-label Phase I/II study will be descriptive in nature and presented by dose group and overall, as appropriate. The incidence and duration of treatment-emergent adverse events (TEAEs) will be assessed.

Descriptive statistics (e.g., number of observations, means, standard deviations, medians, minimum and maximum values) will be used to summarize continuous variables. Frequencies, proportions, and the exact confidence interval (CI), when appropriate, will be used to summarize categorical variables. Patient listings will also be provided.

9.2 Sample Size

The Dose Escalation Phase of the study includes up to 3 dose levels (as well as a -1 level in case the initial dose level is not tolerated), with 3-6 patients per dose level. This represents a total of 12-18 patients.

Simon's two-stage design will be used for the cohort expansion phase of the study. The null hypothesis that the true response rate is 0.15 (15%) will be tested against a one-sided alternative. In the first stage, 18 patients will be recruited. If there are two or fewer responses in these 18 patients, the study will be stopped. Otherwise, 19 additional patients will be recruited for a total of 37. The null hypothesis will be rejected if nine or more responses are observed in 37 patients. This design yields a type I error rate of 10% and power of 80% when the true response rate is 30%.

9.3 Patient Disposition

Disposition of all patients included in the study will be reported overall and by investigational site. Tabulations will include eligibility status, study completion status, and reason for study withdrawal. Patients who are enrolled but do not receive study drug will be excluded from analyses.

9.4 Randomization and Blinding of Treatment Assignment

This is an open-label study. Investigators, patients, and the Sponsor will not be blinded to treatment dose.

9.5 Baseline Comparability

Demographics and baseline characteristics including age, sex, ethnic origin, time since diagnosis, time since diagnosis of advanced disease, and number of prior regimens of chemotherapy will be listed for all patients and will be summarized by dose level. Treatment arms will be analyzed separately. The Expansion Phase cohorts will be analyzed separately and will include patients from the Dose Escalation cohort who meet the eligibility for the Expansion Phase and were treated at the MTD. Any comparisons of groups will utilize analysis of variance for numerical data and the chi-square test for categorical data. Any comparisons will be used for baseline summaries and no adjustments in subsequent analyses are planned.

9.6 Statistical Analyses

9.6.1 Primary and Secondary Endpoint Analyses

9.6.1.1 Safety Analyses

All enrolled patients who receive study drug will be included in the safety analysis and summaries. Safety data will be summarized by dose level.

The MedDRA® (Medical Dictionary for Regulatory Activities) thesaurus will be used to map the AE verbatim to lowest level term (LLT), preferred term (PT) and System Organ Class (SOC) for summary purposes. All AEs

including the AE verbatim term and the associated AE thesaurus PT will be provided in the patient data listings. Analyses of AEs will be performed by relationship to study drug, grade, and seriousness. The rate of hospitalization will be summarized.

Concomitant medications used during the study will be summarized. The World Health Organization (WHO) Drug Dictionary will be used to map the medication name to the Anatomical Therapeutic Chemical (ATC) classification codes for summary purpose. If a medication can map to more than one ATC-code, a unique ATC-code will be selected based on the condition treated and/or route of administration. The summary will be created based on the grouping variables generated from ATC-codes.

Laboratory values will be tabulated in patient listings with abnormal values flagged. Pre-dose urine and blood samples will be used for baseline values. Changes from baseline will be summarized. If appropriate, analyses by number and by type of prior chemotherapy will be performed.

Vital signs and change in body weight will be summarized.

9.6.2 Efficacy Analyses

The Dose Expansion cohort will be utilized for preliminary efficacy assessments. RECIST v1.1 response will be summarized for all patients receiving study drug for confirmed response and best response (confirmed or unconfirmed). The ORR (complete response [CR] + partial response [PR]) as well as the rates for the individual categories of response (CR, PR) will be estimated as the number of complete or partial responders divided by the number of patients receiving study drug. The percent of patients with a best response of stable disease will also be calculated. The precision of these estimates will be estimated using CIs.

Radiographic examinations may be collected to allow an outside independent review facility to assess response or to investigate radiographic features that may be predictive of clinical benefit.

Duration of response (PR and CR), defined as time from first response to disease progression, and PFS, defined as time from start of treatment to disease progression, will be estimated using the Kaplan-Meier method. Patients without evidence of progression will be censored at their last response assessment.

9.6.3 Exploratory Endpoint Analyses

[REDACTED]

9.7 Interim Analysis

Objective Response Rate (CR + PR) will be reported once 18 patients are recruited in the dose expansion phase of the study (including the patients enrolled at the same dose level in the dose escalation phase) If there are two or fewer responses in these 18 patients, the study will be stopped. Otherwise, 19 additional patients will be recruited for a total of 37 in dose expansion.

9.8 Procedures for Accounting for Missing, Unused, and Spurious Data

Missing values will not be imputed unless otherwise specified in the Statistical Analysis Plan. All data will be included in data listings.

10 CONDITIONS FOR INITIATING, MODIFYING, OR TERMINATING THE STUDY

10.1 Modifications and Amendments

Protocol modifications, except those intended to reduce immediate risk to study patients, may be made only by ABIVAX. A protocol change intended to eliminate an apparent immediate hazard to patients may be implemented immediately, provided the IRB/IEC is notified within 5 days.

Any permanent change to the protocol must be handled as a protocol amendment. The written amendment must be submitted to the IRB/IEC and the investigator must await approval before implementing the changes. ABIVAX will submit protocol amendments to the appropriate regulatory authorities for approval.

If in the judgment of the IRB/IEC, the investigator, and/or ABIVAX, the amendment to the protocol substantially changes the study design and/or increases the potential risk to the patient and/or has an impact on the patient's involvement as a study participant, the currently approved written informed consent form will require similar modification. In such cases, informed consent will be renewed for patients enrolled in the study before continued participation.

10.2 Protocol Deviations

ABIVAX will consider any deviations from the protocol on a case-by-case basis. The investigator or other health professional in attendance must contact ABIVAX as soon as possible to discuss the associated circumstances. The principal investigator and ABIVAX will then decide whether the patient should continue to participate in the study. All protocol deviations and the reasons for such deviations must be noted in the source documents.

10.3 Termination

Although there are no predefined criteria for termination, if ABIVAX or the investigator(s) discover conditions during the course of the study that indicate it should be discontinued, an appropriate procedure for terminating the study will be instituted, including notification of the appropriate regulatory agencies and IRB/IEC at all study sites. ABIVAX reserves the right to terminate the study at any time and for any reason.

10.4 Additional Precautions

Information regarding precautions and AEs associated with ABX196 can be found in the current Investigator's Brochure provided by ABIVAX. Information regarding precautions and AEs associated with nivolumab in patients with HCC can be found in the Opdivo package insert.

11 ETHICAL AND LEGAL CONSIDERATIONS

11.1 Compliance with IRB/IEC Regulations

This study is to be conducted in accordance with IRB regulations (US 21 Code of Federal Regulations [CFR] Part 56.103), IEC regulations, or applicable local regulations. The protocol, ICFs, recruitment materials, and all patient materials will be submitted to the IRB/IEC for review and approval. Approval of both the protocol and the consent form must be obtained before any patient is enrolled, and the investigator must submit written approval to the Sponsor, before enrolling any patient. The investigator is responsible for informing the IRB/IEC of any amendment to the protocol in accordance with local requirements. The protocol must be re-approved by the IRB or IEC on receipt of amendments and annually, as local regulations require.

All changes to the consent form must be approved by the IRB/IEC; a determination will be made regarding whether previously consented patients need to be re-consented.

The Sponsor is to be notified immediately if the responsible IRB/IEC has been disqualified or if proceedings leading to disqualification have begun. Copies of all IRB/IEC correspondence with the investigator should be provided to the Sponsor.

Progress reports and notifications of serious adverse drug reactions will be provided to the IRB or IEC according to local regulations and guidelines.

11.2 Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/GCP and applicable regulatory requirements.

The investigator will ensure that the study procedures outlined in this protocol will be conducted in accordance with applicable country and local regulations.

11.3 Protection of Human Patients

11.3.1 Compliance with Informed Consent Regulations

Written informed consent is to be obtained from each patient before enrollment into the study, and/or from the patient's legally authorized representative.

The investigator(s) at each center will ensure that the patient is given full and adequate oral and written information about the nature, purpose, possible risk, and benefit of the study. Patients must also be notified that they are free to discontinue from the study at any time. The patient should be given the opportunity to ask questions and allowed time to consider the information provided.

- The informed consent form (ICF) will contain all the elements required by ICH (R2) guidelines for GCP and any additional elements required by local regulations.
- The ICF must include information about the possible retention of biological samples at the conclusion of this study; with the patient's permission, samples may be retained for future determination of active metabolite concentrations and possible biomarkers related to drug response.
- The patient's signed and dated ICF must be obtained before conducting any study procedures.
- The investigator(s) must maintain the original, signed ICF. A copy of the signed ICF must be given to the patient.
- The ICF must include information about the possible retention of biological samples at the conclusion of this study; with the patient's permission, blood, plasma, serum and tissue samples may be obtained for future analysis to help identify biomarkers of disease or ABX196 treatment.

The investigator(s) must maintain the original, signed ICF. A copy of the signed ICF must be given to the patient.

11.3.2 Patient Confidentiality

To maintain patient privacy, all source documents, study reports, and communications will identify the patient by initials and the assigned patient number. The investigator will grant monitor(s) and auditor(s) from the Sponsor or its designee and regulatory authority(ies) access to the patient's original study records for verification of data gathered on source documents and to audit the data collection process. The patient's confidentiality will be maintained and will not be made publicly available to the extent permitted by applicable laws and regulations.

11.3.3 Patient Privacy

The investigator or designee must explain to each patient, before enrollment into the study, that for evaluation of study results, the patient's protected health information obtained during the study may be shared with the Sponsor, regulatory agencies, and IRB/IEC. It is the investigator's (or designee's) responsibility to obtain written permission to use protected health information per country-specific regulations from each patient or, if appropriate, the patient's legally authorized representative. If permission to use protected health information is withdrawn, it is the investigator's responsibility to obtain a written request, to ensure that no further data will be collected from the patient, and the patient will be removed from the study.

Written authorization is to be obtained from each patient before enrollment into the study, and/or from the patient's legally authorized representative in accordance with the applicable privacy requirements.

12 ADMINISTRATIVE CONSIDERATIONS

12.1 Administrative Structure

This trial will be sponsored and managed by ABIVAX. Data management will be performed by ABIVAX or its designee. An Independent Review Facility may be used to evaluate tumor response.

12.1.1 Independent Radiology Review

Baseline and follow up radiology studies and other relevant clinical information used for tumor assessment may be collected and forwarded to an Independent Review Facility after each tumor assessment. An independent review of tumor response may be performed in patients in the Expansion Phase cohorts.

12.1.2 Documentation

12.1.2.1 Electronic Case Report Forms and Study Records

The investigator must generate and maintain complete, adequate, accurate, reliable, and consistent records to enable full documentation of study conduct. Study data will be captured on electronic CRFs (eCRFs). Investigators must retain all original source documents, and the Sponsor or its designee will notify investigators in writing when the trial-related records are no longer needed.

12.1.2.2 Access to Source Documentation

The Sponsor or its representative will be allowed to conduct site visits to the investigational facilities for the purpose of monitoring any aspect of the study. The investigator agrees to allow the monitor to inspect the drug storage area, study drug stocks, drug accountability records, patient charts and source documents, and other records relative to study conduct.

By signing the protocol, the investigator agrees that, within local regulatory restrictions and institutional and ethical considerations, authorized representatives of the Sponsor, a regulatory authority, and/or an IRB/IEC may visit the site to perform audits or inspections, including the drug storage area, study drug stocks, drug accountability records, patient charts and source documents, and other records relative to study conduct. The purpose of a Sponsor audit or inspection is to systematically and independently examine all study-related activities and documents (e.g., laboratory reports, x-rays, workbooks, patients' medical records) to determine whether these activities were conducted, and data recorded, analyzed, and accurately reported according to the protocol, GCP guidelines of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), and any applicable regulatory requirements.

The investigator should contact the Sponsor immediately if contacted by a regulatory agency regarding an inspection.

12.1.3 Source Documents

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Examples of these original documents and data records include, but are not limited to, a patient's medical records, hospital charts, clinic charts, the investigator's patient study files, as well as the results of diagnostic tests such as x-rays, laboratory tests, and electrocardiograms (ECGs). All data entered into the eCRFs must be substantiated by a source document.

12.1.4 Study Files and Retention of Study Records

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified.

Study documents should be retained for a minimum of 2 years after the last approval of a marketing application or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by local regulations. No

records will be destroyed without the written consent of the Sponsor, if applicable. It is the responsibility of the Sponsor to inform the investigator when these documents no longer need to be retained.

Patient identification codes (patient names and corresponding study numbers) will be retained for this same period of time. These documents may be transferred to another responsible party, acceptable to the Sponsor, who agrees to abide by the retention policies. Written notification of transfer must be submitted to the Sponsor. The investigator or designee must contact the Sponsor before disposing of any study records.

12.2 Study Monitoring

Monitoring of the study site will be performed by the Sponsor's Clinical Monitor or designee.

- Monitoring will be performed in accordance with applicable federal regulations and guidance.
- Monitoring will include regular site visits and communication with the investigator and site staff as appropriate to discuss and answer study questions; ensure compliance with the protocol; and ensure quality and integrity of the data.
- Monitors will ensure the site maintains an adequate supply of investigational products; any necessary supplies and ensure that appropriate storage conditions are maintained.
- Monitoring visits will be conducted according to the US CFR Title 21 parts 50, 56, and 312; and ICH E6 (R2) GCP guidelines

12.3 Quality Management

Study sites, the study database, and study documentation will be monitored regularly and may be subject to a quality assurance (QA) audit during the study by the Sponsor or its designee on behalf of the Sponsor. In addition, inspections may be conducted by regulatory agencies at their discretion.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written standard operating procedures (SOPs), the monitors will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements (e.g., Good Laboratory Practice [GLP], Good Manufacturing Practices [GMP]).

The investigational site will provide direct access to all trial-related sites, source data/documents, and reports for the purpose of monitoring and auditing by the Sponsor, and inspection by local and regulatory authorities.

12.4 Non-Protocol Research

ABIVAX has a legal responsibility to report fully to regulatory authorities all results of administration of investigational drugs to humans. No investigative procedures other than those described in this protocol will be undertaken on the enrolled patients without the agreement of the IRB/IEC and ABIVAX.

13 STUDY REPORT AND PUBLICATIONS

ABIVAX is responsible for preparing and providing the appropriate regulatory authorities with clinical study reports according to the applicable regulatory requirements.

The publication policy of ABIVAX is discussed in the investigator's Clinical Research Agreement.

14 CONFIDENTIALITY

All information generated in this study is considered highly confidential and must not be disclosed to any person or entity not directly involved with the study unless prior written consent is gained from ABIVAX. However, authorized regulatory officials, IRB/IEC personnel, ABIVAX and its authorized representatives are allowed full access to the records.

Identification of patients and CRFs shall be by initials, screening and treatment numbers only. If required, the patient's full name may be made known to an authorized regulatory agency or other authorized official.

15 REFERENCES

- Aravalli RN, Steer CJ. Immune-mediated therapies for hepatocellular carcinoma. *Genes* 2017;8:
- El-Khoueiry AB, Sangro B, Yao T, et al. Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial. *Lancet* 2017;389:2492-2502.
- Flecken T, Schmidt N, Hild S, et al. Immunodominance and functional alterations of tumor-associated antigen-specific CD8+ T-cell responses in hepatocellular carcinoma. *Hepatology* 2014;59:1415-1426.
- Harding JJ, El Dika I, Abou-Alfa GK. Immunotherapy in hepatocellular carcinoma: Primed to make a difference? *Cancer* 2016;122:367-377.
- McEwen-Smith RM, Salio M, Cerundolo V. The regulatory role of invariant NKT cells in tumor immunity. *Cancer Immunol Res* 2015;3:425-435.
- Parekh VV, Lalani S, Kim S, et al. PD-1/PD-L blockade prevents anergy induction and enhances the anti-tumor activities of glycolipid-activated invariant NKT cells. *J Immunol* 2009;182:2816-2826.
- Parekh VV, Wilson MT, Olivares-Villagómez D, et al. Glycolipid antigen induces long term natural killer T cell anergy in mice. *J Clin Invest* 2005;115:2572-2583.
- Simon R. Optimal two-stage designs for phase II clinical trials. *Controlled Clinical Trials* 1989;10:1-10.
- Tefit JN, Crabé S, Orlandini B, et al. Efficacy of ABX196, a new NKT agonist, in prophylactic human vaccination. *Vaccine* 2014;32:6138-6145.
- Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst*. 2000;92:205-16.
- US Prescribing Information Opdivo® - March 2019

16 APPENDICES

APPENDIX I - SCHEDULE OF ASSESSMENTS

	Screening ¹	TREATMENT PERIOD											Survival Follow-up
		CYCLE 1					EVEN CYCLES		ODD CYCLES			Termination/ Early Termination ¹⁶ / Unscheduled ¹⁷	
Assessment	<i>Within 21 days of cycle 1/ day 1</i>	D1¹⁵	D2	D4	D8	D15	D1	D15	D1	D2	D15		<i>Every 3 months</i>
Informed consent & eligibility confirmation	X												
Medical, Cancer, Medication History	X												
Concomitant medication		X	X	X	X	X	X	X	X	X	X	X	
Complete physical exam (*including height measurement)	X*											X	
Limited physical exam ²		X	X	X	X	X	X		X				
Weight	X	X					X		X			X	
Vital signs & temperature ³	X	X	X	X	X	X	X	X	X		X	X	
ECOG performance status	X	X				X	X	X	X		X	X	
iNKT Cell count ⁴ (*with pre-dose)	X	X*	X						X	X		X	
Lymphocyte immunophenotyping ⁵ (*pre-dose)		X*	X			X						X	
Serum cytokines ⁶	X	X	X	X	X	X						X	
Hematology & Biochemistry *With thyroid function exploration: T3, T4, TSH	X*	X*	X	X	X	X	X*		X*			X*	
Serum Pregnancy test ⁷	X	X					X		X			X	
Alpha Fetoprotein (AFP)	X	X					X		X			X	
Tumor assessments ⁸	X	CT scans every 6 weeks for the whole study duration. For bones scans a frequency of every 12 weeks is allowed											
Tumor FFPE block/slides for immune microenvironment analysis (e.g. PD-L1, iNKT, DC, NK) ⁹ – optional procedure	(X)					(X)						(X)	
Nivolumab anti-drug antibody ¹⁰	X	X				X	X	X	X		X		
Nivolumab administration ¹¹		X				X	X	X	X		X		
ABX196 administration ¹²		X							X				
PK parameters ABX196 ¹³		X	X						(X)	(X)			
Adverse event assessment		X	X	X	X	X	X	X	X	X	X	X	
Survival Follow up ¹⁴													X

**All visits should be performed according to the schedule of assessment. No visit window will be tolerated between CxD1 and CxD2. A visit window of +/- 1 day for all others time points.

1. **Screening:** within 21 days prior to Cycle 1 Day 1.
2. **Complete and limited physical examination:** Complete physical exams to be done at Screening and at the Study Termination/ Early Termination Visit. Limited physical examinations will be performed at each visit of Cycle 1, and at Day 1 of every other cycle.
3. **Vital signs & temperature:** blood pressure, heart rate, respiration rate and temperature will be measured before and within 1 hour after the nivolumab infusion and prior to ABX196 injection (for appropriate cycles), then 1 hour (+/- 10 minutes) after ABX196 injection.
4. **iNKT Cell Count:** At screening, pre-dose Days 1 and 24h after the ABX196 IM injection up to cycle 12.
5. **Lymphocyte immunophenotyping:** Day 1 (Predose and 4 hours post ABX196 dose), Day 2, and 15 of Cycle 1, then at termination visit
6. **Serum cytokines:** to be done at the same time than samples for immunophenotyping. To be done also at C1 Day 4 72 hours (+/- 7 hours) after ABX196 dosing and at C1 Day 8, and Day 15 then at termination visit.
7. **Pregnancy Test:** Serum testing at Screening and Study Termination/Early Termination, and at day 1 of any cycle. Results must be known prior to dosing. Urine test is acceptable when a serum test has been done, but results are not available at the time of dosing.
8. **Tumor assessments:** Tumor-appropriate spiral CT scans (and bone scans for patients with bone metastases) at Screening, every 6 weeks for one year and at Termination if not done within 6 weeks of termination or until additional anti-tumor therapy is started. For bone scans, a frequency of every 12 weeks is acceptable
9. **Tumor FFPE block/slides for immune microenvironment analysis (e.g., PD-L1, iNKT, DC, NK):** Optional Procedure.
10. **Nivolumab anti-drug antibody:** At screening, pre-dose Days 1 and Days 15 before Nivolumab administration up to cycle 12.
11. **Nivolumab administration:** Administer nivolumab 240 mg as an IV infusion Day 1 and 15 of each 28 Days cycle until confirmed progressive disease or unacceptable toxicity.
12. **ABX196 administration:** Administer ABX196 as an IM injection 120 minutes (+/- 15 minutes) after the completion of the nivolumab infusion every 8 weeks starting on Day 1 of cycle 1 (i.e. Day1 of cycles 1, 3, 5, 7, 9 and 11).
13. **ABX196 PK parameters:** Pre-dose Day 1 and 10min, 30 min, 60 min, 2 h, 4 h, 24 h after the ABX196 IM injection. of Cycle 1. Timepoint collection at 6h post dose on cycle 1 and PK sample collection after each other ABX196 dosing are optional and not measured after cycle 12.
14. **Survival follow up:** All patients will be followed up every 3 months for survival through 1 year after the last dose of ABX196 administration (whether patients completed the study or early withdrawn).
15. **Safety laboratory parameters at Cycle 1 Day 1:** can be collected the day before;
16. **Obtain all required evaluations for early termination as required for the termination visit.** Termination Visit will occur 1-2 weeks following the last dose of treatment on study. Tumor assessments only required if not done within the past 6 weeks.
17. **Unscheduled visits:** Concomitant medications and adverse events recording are mandatory. All efforts should be done to get the followings: physical examination, ECOG performance status score, vital signs, blood sample collection for hematology and biochemistry panel analysis, as well as tumor assessment (if not done within the past 6 weeks). No other exam is required.

APPENDIX II – ALLOWED WINDOW FOR BLOOD SAMPLES TIMEPOINT COLLECTION

Treatment period	Screening	Cycle 1					Even Cycles		Odd Cycles			Termination
Visit Name	Screening	D1	D2	D4	D8	D15	D1	D15	D1	D2	D15	
iNKT*	Non-Timepoint	Pre-dose	24h Post (+/-1hr)						Pre-dose	24h Post		Non-Timepoint
Immunophenotyping		Pre-dose 4h post-dose (+/- 20')	24h Post (+/-1hr)			Non-Timepoint						Non-Timepoint
Cytokines	Non-Timepoint	Pre-dose 4h post-dose (+/- 20')	24h Post (+/-1hr)	Non-Timepoint	Non-Timepoint	Non-Timepoint						Non-Timepoint
ABX196 PK*		Pre-dose 10 min post-dose 30 min post-dose 60 min post-dose (+/- 5') 2h post-dose (+/- 10') 4h post-dose (+/-20') optional : 6h post-dose (+/- 30')	24h Post (+/-1hr)						Optional (Within 24h post-dose)			
Nivolumab ADA*	Pre-dose	Pre-dose				Pre-dose	Pre-dose	Pre-dose	Pre-dose		Pre-dose	

*Not measured after cycle 12.

APPENDIX III- EASTERN COOPERATIVE ONCOLOGY GROUP (ECOG) PERFORMANCE SCORE SCALE

Grade	Description
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 selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

APPENDIX IV - RESPONSE EVALUATION CRITERIA IN SOLID TUMORS (RECIST) V1.1

'Response assessment in solid tumours (RECIST): Version 1.1 and Supporting Papers' European Journal of Cancer, Volume 45, Issue 2 Jan. 2009: 225-310.

https://ctep.cancer.gov/protocoldevelopment/docs/recist_guideline.pdf

RECIST 1.1: Criteria Handout

Image Acquisition

- CT
 - Slice thickness ≤ 5 mm if possible, contiguous
 - IV and oral contrast used (3-phase liver if appropriate)
 - Field of view adjusted to body habitus (include the whole body, out to the skin)
- MRI
 - Axial T1 and T2, axial T1 post contrast
 - ≤ 5 mm contiguous slices if possible
 - Use the same machine for all timepoints
- PET/CT
 - Not required but may be useful for assessment of new lesions on future timepoints. CT portion of PET/CT is usually of lower quality, and should not be used instead of dedicated diagnostic CT. If the CT is of high quality, with oral and IV contrast. Additional information from PET may bias CT assessment
 - Use the same machine for all timepoints
- Calipers - Reproducibility difficult
 - Include ruler in photograph for skin lesions
- Chest x-ray – Use in place of CT (When CT is not available)
- Ultrasound – Not reproducible

Measurable Lesions

- Tumor ≥ 10 mm in longest diameter (LD) on an axial image on CT or MRI with ≤ 5 mm reconstruction interval
 - If slice thickness > 5 mm, LD must be at least 2 times the thickness
- Tumor ≥ 20 mm LD by chest x-ray (if clearly defined and surrounded by aerated lung); CT is preferred (even without contrast)
- Tumor ≥ 10 mm LD on clinical evaluation (photo) with electronic calipers; skin photos should include ruler
- Lesions which cannot be accurately measured with calipers should be recorded as non-measurable
- Lymph nodes ≥ 15 mm in short axis on CT (CT slice thickness recommended to be no more than 5 mm)
- Ultrasound cannot be used to measure lesions

Non-Measurable Lesions

- All other definite tumor lesions
 - Masses < 10 mm
 - Lymph nodes 10-14 mm in short axis
 - Leptomeningeal disease
 - Ascites, pleural or pericardial effusion
 - Inflammatory breast disease
 - Lymphangitic involvement of skin or lung
 - Abdominal masses or organomegaly identified by physical exam which cannot be measured by reproducible imaging techniques
- Benign findings are NEVER included. Also, do not include equivocal ('cannot exclude') findings

Special Lesion Types

- Bone Lesions
 - NMBS, PET scans & plain films can be used to confirm the presence or disappearance of bone lesions, but NOT for measurement. These should be confirmed by CT
 - Bone lesions with identifiable soft tissue components seen on CT or MR can be measurable if the soft tissue component meets the definition above
 - Blastic bone lesions are unmeasurable
- Cystic Lesions
 - Simple cysts are not included as lesions
 - Cystic metastases may be selected, but prefer to use non-cystic lesions as 'target'
 - Clarify with sponsor as to acceptability before study start

Target Lesions

- Choose up to 5 lesions in total
 - Up to 2 per organ
- Add up longest diameters (LD) of non-nodal lesions (axial plane)
- Add short axis diameters of nodes
- This is the 'sum of diameters'

Baseline Documentation

- Target Lesions
 - A maximum of five (5) target lesions in total (up to two (2) per organ)
 - Select largest reproducibly measurable lesions
 - If the largest lesion cannot be measured reproducibly, select the next largest lesion which can be
 - Lesions in previously irradiated areas (or areas treated with local therapy) should not be selected as target lesions
- Non-Target Lesions
 - It is possible to record multiple non-target lesions involving the same organ as a single item on the eCRF (e.g. 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases')

Evaluating Response at Each Timepoint

- Measure previously chosen target lesions
 - Even if they are no longer the largest
- Evaluate all previously identified non-target lesions
- Look for new definite neoplastic lesions
- Combine lesion responses into timepoint response using appropriate table

Target Lesion Evaluation

- Measure LD (axial plane) for each non-nodal target lesion
- Measure short axis for target lymph nodes
- Add these measurements to get the sum of the longest diameters
- If too small to measure, a default value of 5 mm is assigned. If the lesion disappears completely, the measurement is recorded as 0 mm. If an accurate measurement can be obtained, use actual measurement even if smaller than 5 mm as long as the measurement is greater than the slice thickness
- Splitting or coalescent lesions
 - If a target lesion fragments into multiple smaller lesions, the LDs of all fragmented portions are added to the sum
 - If target lesions merge, the LD of the resulting merged lesion is added to the sum

Response	Definition
Complete Response (CR)	Disappearance of all extranodal target lesions. All pathological lymph nodes must have decreased to <10 mm in short axis
Partial Response (PR)	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters
Progressive Disease (PD)	Sum of diameters increased by at least 20% from the smallest value on study (including baseline, if that is the smallest) The sum of diameters must also demonstrate an absolute increase of at least 5mm. (Two lesions increasing from 2 mm to 3 mm, for example, does not qualify.)
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD

Missing Assessments and Non-evaluable Designation

- If all lesions cannot be evaluated due to missing data or poor image quality the patient is inevaluable (NE) at that time point
- If only a subset of lesions can be evaluated at an assessment, the visit is also considered NE, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response
 - E.g. PD based on other findings

Non-Target Lesion Evaluation

Response	Definition
Complete Response (CR)	– Disappearance of all extranodal non-target lesions. – All lymph nodes must be non-pathological in size (<10 mm short axis.) – Normalization of tumor marker level
Non CR / Non PD	Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits
Progressive Disease (PD)	Unequivocal progression of existing non-target lesions. (Subjective judgement by experienced reader)*

**Be cautious when calling progression based on non-target lesions. If target lesions are also present, there must be substantial worsening in nontarget disease overall such that, even in presence of SD or PR in target disease, the disease burden has increased enough to merit discontinuation of therapy. A modest increase in non-target lesions is usually not sufficient to qualify for unequivocal progression status.*

New Lesions

- Should be unequivocal and not attributable to differences in scanning technique or findings which may not be a tumor
 - Does not have to meet criteria to be 'measurable'
- If a new lesion is equivocal, continue to next timepoint. If confirmed then, PD is assessed at the date when the lesion was first seen
- Lesions identified in anatomic locations not scanned at baseline are considered new
- New lesions on US should be confirmed on CT/MRI

FDG-PET

- FDG-PET can be used to help detect progression
 - A 'positive' FDG-PET scan lesion means one with uptake greater than twice that of the surrounding tissue on the attenuation corrected image

- Negative PET at baseline and positive PET at follow-up: Progressive Disease (PD) based on a new lesion
- No PET acquired at baseline and positive PET at follow-up: If there is a corresponding new or growing lesion on CT, this is PD. If a later CT confirms appearance or growth of a lesion, the date of PD is the date of the initial positive PET scan
- No PET acquired at baseline and positive PET at follow-up: If there is a corresponding preexisting lesion on CT that is stable, this is not PD

Recurrence of Lesions

- For a patient with Stable Disease (SD)/Partial Response (PR), a target lesion which disappears and then reappears will continue to be measured and added to the sum
 - Response will depend on the status of the other lesions
- For a patient with Complete Response (CR), reappearance of a target lesion would be considered Progressive Disease (PD)

Evaluation of Overall Timepoint Response for Patients with Measurable Disease at Baseline

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

CR = Complete Response, PR = Partial Response, SD = Stable Disease, PD = Progressive Disease, NE = Inevaluable

**When target lesions show SD/PR and some subset of non-target lesions is inevaluable, a careful decision must be made whether to call the overall response at this timepoint SD/PR or NE. This is based on whether the inevaluable lesions, if they showed growth, could cause an overall response of PD in the context of the other lesion responses seen. If the inevaluable non-target lesions comprise a significant proportion of the overall disease burden, the appropriate timepoint response is NE.*

APPENDIX V – POSSIBLE DOSES TO APPLY IN CASE OF TOXICITY

Please refer to protocol section 6.3 and 6.6 for the detailed procedure.

		amount µg	IMP concentration (µg/mL)	Description	total volume to be injected (mL)
Level -1				TARGET DOSE	
Possible dose reductions & escalations starting from target dose 1	Target dose - L1D1			TARGET DOSE	
	L1D2 (reduction of % of L1D1)			Dose reduction in case of toxicity observed with target dose D1 (level 1)	
	L1D3 (increase of % of L1D1)			Interim dose level: Dose escalation following toxicity events during D1 (level 1)	
	L1D4 (reduction of % L1D3)			Dose reduction in case of toxicity observed with interim dose D3 (level 1)	
	L1D5 (increase of % of L1D3)			Interim dose level: Dose escalation following toxicity events during D3 (level 1)	
	L1D6 (reduction of % L1D5)			Dose reduction in case of toxicity observed with interim dose D5 (level 1)	
Possible dose reductions & escalations starting from target dose 2	Target dose - L2D1			TARGET DOSE	
	L2D2 (reduction of % of D1)			Dose reduction in case of toxicity observed with target dose D1 (level 2)	
	L2D3 (increase of % of D1)			Interim dose level: Dose escalation following toxicity events during D1 (level 2)	
	L2D4 (reduction of % of D3)			Dose reduction in case of toxicity observed with interim dose D3 (level 2)	
	L2D5 (increase of % of D3)			Interim dose level: Dose escalation following toxicity events during D3 (level 2)	
	L2D6 (reduction of % of D5)			Dose reduction in case of toxicity observed with interim dose D5 (level 2)	
Possible dose reductions & escalations starting from target dose 3	Target dose - L3D1			TARGET DOSE	
	L3D2 (reduction of % of D1)			Dose reduction in case of toxicity observed with target dose D1 (level 3)	