CLINCAL TRIAL PROTOCOL (MASTER)

Document Number:		**c23362215-04**
EudraCT No.	2018-002344-81	
BI Trial No.	1381-0009	
BI IMP(s)	Ezabenlimab (BI 754091[anti-PD-1])	
Title	An open-label, Phase II, platform trial evaluating safety and efficacy of multiple ezabenlimab anti-PD-1 based combination regimens in PD-(L)1 naïve and PD-(L)1 pretreated patient populations with advanced and/or metastatic solid tumours who have had at least one line of systemic therapy	
Lay Title	Platform trial evaluating safety and efficacy of ezabenlimab anti-PD-1 based combination therapies in PD-(L)1 naïve and PD-(L)1 pretreated patient populations with advanced/metastatic solid tumours.	
Clinical Phase	Phase II	
Clinical Trial Leader	[redacted] Phone: [redacted]	
Coordinating Investigator	[redacted] Phone: [redacted]	
Status	Final protocol (Revised Protocol [based on Global Amendment 3])	
Version and Date	**Version: 4**	**Date: 12 JUN 2023**

CLINICAL TRIAL PROTOCOL SYNOPSIS (MASTER)

Company name	Boehringer Ingelheim International GmbH
Name of finished product :	N.A.
Name of active ingredient :	Ezabenlimab (BI 754091)
Protocol date	08 AUG 2018
Revision date	12 JUN 2023
BI trial number	1381-0009
Title of trial	An open-label, Phase II, platform trial evaluating safety and efficacy of multiple ezabenlimab anti-PD-1 based combination regimens in PD-(L)1 naïve and PD-(L)1 pretreated patient populations with advanced and/or metastatic solid tumours who have had at least one line of systemic therapy
Coordinating Investigator	[redacted]
Trial site(s)	This multicentre trial will be conducted in North America and the United Kingdom.
Clinical phase	Phase II
Trial rationale	The focus of this study will be to identify biological similarities across tumour types to increase the understanding of immunobiological prerequisites for different treatment regimens to be effective. There may be the potential to identify patterns of responsiveness that are not limited to specific tumour types but are present across multiple settings. In this study, ezabenlimab will be administered to small groups of patients with different tumour types in combination with other agents that are expected to increase responsiveness to checkpoint inhibitors. The tumour types to be included were selected based on high unmet medical need and the expectation that the combination therapy planned may be effective in some patients with these tumour types. This Master protocol design document will support the operational aspects of the trial while the 'Modules' will be applied to specify drug combination. Ezabenlimab will be combined with a Boehringer-Ingelheim (BI) agent(s) for which there is scientific evidence and rationale to

	support the combination in a specific patient population. Separate Modules will be appended to the Master protocol for each of the planned ezabenlimab treatment combinations. The Module will describe the clinical and nonclinical information for the additional agent, rationale, benefit/risk, eligibility criteria, treatment administration, trial assessments and other guidances. Agents combined with ezabenlimab will have been previously tested. A protocol amendment with relevant clinical and non-clinical data will be implemented when a new Module is added prior to enrolling patients.
Trial objective(s)	The main objective of this research trial is to evaluate patient clinical response to ezabenlimab in combination with combination partners presented in individual Modules.
Trial endpoints	Primary Endpoint: • Objective response (OR), defined as the best overall response of complete response (CR) or partial response (PR) according to RECIST v1.1 as assessed by the Investigator. Secondary Endpoints: • Duration of response (DoR), defined as the time from first documented CR or PR (RECIST v1.1) until the earlier of disease progression or death among patients with OR. • Disease control (DC), defined as best overall response of CR, PR, or stable disease (SD) according to RECIST v1.1 as assessed by the Investigator. • Progression-free survival (PFS), defined as the time from first treatment until PD or death from any cause, whichever occurs earlier.
Trial design	Open-label, multicentre, Phase II, Master design with treatment-specific Modules
Total number of patients randomised	Not applicable
Number of patients on each treatment	Patient numbers will be defined in each of the treatment-specific Modules. New Modules will be developed and appended as an amendment to the Master protocol.
Diagnosis	Advanced solid tumours as specified in the treatment-specific Modules.

Main inclusion and exclusion criteria	Inclusion For inclusion in the trial, patients must fulfil all of the following criteria as well as the inclusion criteria in the treatment-specific Module in which eligible solid tumours are defined. • Adult patients at least 18 years of age and a life expectancy of at least 12 weeks. • Eastern Cooperative Oncology Group (ECOG) performance status 0 or1. • Patient must agree to a pre-treatment biopsy (if archival tissue is not available) and on-treatment tumour tissue biopsy. Patients moving from one module to another must have prior immune-related adverse events (irAEs) resolved to a degree that would allow for restart of checkpoint inhibitor therapy according to the irAE management guidelines in the protocol. Exclusion Patients must not enter the trial if any of the criteria below or any of the exclusion criteria described in the treatment-specific Module are fulfilled. • Any investigational treatment anti-tumour treatment within 4 weeks or within 5 half-life periods (whichever is shorter) prior to the initiation of trial treatment. • More than one anti-PD-(L)1-based treatment regimen prior to entering study, more specifically defined in the modules. Note: Once in a trial Module, patients may crossover to a different Module if all other eligibility criteria are met. • Major surgery (‘major’ according to the Investigator’s and/or Medical Monitor’s assessment) performed within 12 weeks prior to first trial treatment or planned within 12 months after screening, e.g., hip replacement. • Inadequate organ function or bone marrow reserve as demonstrated by the laboratory values presented in Table 3.3.3: 1 • Known history of severe hypersensitivity reactions to other monoclonal antibodies (mAbs) or known hypersensitivity to the trial drugs or their excipients. • Presence of central nervous system (CNS) metastases, unless treated and asymptomatic and off corticosteroids and/or anti-convulsant therapy for at least 2 weeks prior to start of treatment. • Immunosuppressive corticosteroid doses (>10 mg prednisone daily or equivalent) within 4 weeks prior to the first dose of study treatment. • Active autoimmune disease or a documented history of autoimmune disease, except vitiligo or resolved childhood asthma/atopy, or a patient who was permanently discontinued from previous anti-PD-1 or anti-PD-L1 therapy because of an irAE.

Test product(s)	Ezabenlimab will be administered in all Modules associated with this clinical trial. Test agents to be administered in combination with ezabenlimab: specified in the treatment-specific Modules.
dose(s)	The ezabenlimab dose will be 240mg Q3W Doses of combination agent will be defined in the treatment-specific Modules.
method and route of administration	Ezabenlimab intravenous infusion
Comparator product(s)	Not applicable.
dose	Not applicable.
method and route of administration	Not applicable.
Duration of treatment	Treatment will continue until progression of disease (PD), according to RECIST v1.1 (R09-0262) and/or iRECIST (R15-2005), withdrawal of patient consent, an unacceptable toxicity, or 1 year of treatment is completed, whichever occurs first. Patients will be allowed to stay on treatment in the case of initial radiological PD, if the Investigator feels that it is in the patient's best interest. If the patient is benefiting clinically at 1 year from ezabenlimab, he/she may continue beyond 1 year of treatment after a case-by-case review with the Medical Monitor and the sponsor. The duration of test agents to be administered in combination with ezabenlimab will be specified in the treatment-specific Modules. Patients that progress on treatment in a given Module may be offered treatment in another Module if deemed appropriate by the Investigator and Sponsor. The patient must sign an approved ICF for the subsequent Module, be screened prior to entering the new Module, and must meet all Master and Module-specific inclusion criteria. The transition time between Modules (last dose of previous Module and screening visit of subsequent Module) will be a maximum of 2 months. Patients will be allowed multiple crossovers into subsequent Modules.
Statistical methods	For the response endpoints (i.e., OR, DC), a Bayesian hierarchical modelling approach will be used, if applicable. Shrinkage estimators per cohort as well as the overall estimate will be considered. The shrinkage estimators allow for borrowing information across cohorts while taking the multiplicity of the different cohorts into account. The details of the specific hierarchical model to be applied as well as the related parameters and priors used will be described within each Module. Additionally, descriptive statistics of these endpoints will be provided. Kaplan-Meier estimates will be used to analyse PFS with 95% confidence intervals, using Greenwood's variance estimate.

FLOW CHART

Detailed flow charts are located in each Module.

Master flow chart for screening

Trial Periods	**Screening[a]**
Visit	**1**
Assessment (Days)	-28 to -1
Informed Consent	X
Inclusion/Exclusion Criteria	X
Medical History and Demographics	X
Physical Examination	X
ECOG Performance Status	X
Vital Signs	X
12-Lead Digital Electrocardiogram	X[b]
Archival or Fresh Tumour Tissue Required	X[e]
Haematology and Clinical Chemistry Laboratory Tests	X
Thyroid panel (TSH, free T4 and free T3)	X
Urinalysis	X
Pregnancy Test for Women of Child-Bearing Potential	X[c]
Concomitant Medications	X
Adverse Events	X
Tumour Assessment	X[d]

a Safety laboratory assessments including haematology, serum biochemistry, and urinalysis will be performed locally. The screening medical history and demographics, physical examination and Eastern Cooperative Oncology Group (ECOG) performance status, vital signs, electrocardiogram (ECG), haematology, clinical chemistry (sodium, potassium, phosphate, chloride, creatinine, calcium, albumin, total protein, aspartate aminotransferase [AST], alanine aminotransferase [ALT], alkaline phosphatase, bilirubin, lactate dehydrogenase, serum glucose, creatine phosphokinase, troponin I (only at screening, C1D1, C1D8, C1D15, C2D1, C3D1, C4D1 and anytime CPK is elevated), serum urea nitrogen [or urea], serum uric acid, thyroid panel [TSH, free T4, and free T3]), urinalysis, and screening pregnancy test should be done ≤14 days prior to initiation of treatment (see Section 5).

b Single digitalised ECGs must be done before blood work or other procedures after 5 minutes of rest at screening (see Section 5.2.4).

c Women of child-bearing potential must have a serum beta human chorionic gonadotropin (βHCG) pregnancy test at screening (see Section 5.2.3).

d Tumour assessments (scans) should be performed ≤28 days prior to initiation of treatment and copies may be collected by the sponsor or designee. Refer to Section 5.1 for additional details. Tumour assessments should be done according to RECIST v1.1 and iRECIST and should include computed tomography/positron emission tomography (CT/PET) scans of the chest and abdomen and, if clinically indicated, imaging of any other known or suspected sites of disease (e.g., pelvis, brain) using an appropriate method (CT/PET scan or magnetic resonance imaging [MRI]). The same radiographic procedure must be used throughout the trial. In case of suspected (but not confirmed) bone metastasis at screening, tumour assessment at screening should include a bone scan. If bone lesions are already known or confirmed at screening, correlative imaging (X-ray or CT scan) should be performed.

e All patients must have tissue samples (fresh or archived [see requirements]) available for retrospective central testing (see Section 3.3.2).

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ABBREVIATIONS

[redacted]

AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Aminotransferase
aPTT	Activated Partial Thromboplastic Time
AST	Aspartate Transaminase
ßHCG	Beta Human Chorionic Gonadotropin
BHM	Bayesian Hierarchical Model
BI	Boehringer Ingelheim
CA	Competent Authority
CI	Confidence Interval
CK	Creatinine Kinase
CKD-EPI	Chronic Kidney Disease Epidemiology
C_{max}	Maximum Concentration
CML	Clinical Monitor Local
CPK	Creatinine Phosphokinase
CR	Complete Response
CRA	Clinical Research Associate
CRF	Case Report Form, paper or electronic (sometimes referred to as "eCRF")
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events

[redacted]

CTP	Clinical Trial Protocol
DBL	Database Lock
DC	Disease Control
DILI	Drug Induced Liver Injury
DLT	Dose-Limiting Toxicity
DOiR	Duration of Immune Response
DoR	Duration of Response
EC	Ethics Committee
ECG	Electrocardiogram

ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EF	Ejection Fraction
eGFR	Estimated Glomerular Filtration Rate
EOT	End of Treatment
EudraCT	European Clinical Trials Database
FFPE	Formalin fixed and paraffin embedded
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HIV	Human Immunodeficiency Virus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonization
iCPD	Immune Confirmed Progressive Disease
iCR	Immune Complete Response
iDC	Immune Disease Control
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
INR	International Normalized Ratio
iOR	Immune Objective Response
iPR	Immune Partial Response
irAE	Immune-Related Adverse Event
IRB	Institutional Review Board
iRECIST	Immune Response Evaluation Criteria in Solid Tumours
IRT	Interactive Response Technology
ISF	Investigator Site File
IUD	Intrauterine Device
IUS	Intrauterine Hormone-Releasing System
i.v.	Intravenous
LPLT	Last Patient Last Treatment
mAb	Monoclonal Antibody
MDSC	Myeloid-Derived Suppressor Cell

MedDRA	Medical Dictionary for Drug Regulatory Activities
MRI	Magnetic Resonance Imaging
NSCLC	Non-Small-Cell Lung Cancer
OR	Objective Response
ORR	Overall Response Rate
OS	Overall Survival
PD	Progression of Disease
PDc	Pharmacodynamic
PD-1	Programmed Cell Death Protein-1
PD-L1	Programmed Death Ligand-1
PET	Positron Emission Tomography
PFS	Progression-Free Survival
PK	Pharmacokinetics
[redacted]	
PR	Partial Response
PT	Prothrombin Time
q3w	Every 3 weeks
QT	ECG interval measured from the onset of the QRS complex to the end of the T wave
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using Fridericia's formula
RECIST	Response Evaluation Criteria in Solid Tumours
REP	Residual Effect Period
SAE	Serious Adverse Event
SC	Steering Committee
SD	Stable Disease
SOP	Standard Operating Procedure
$t_{1/2}$	Half Life Time
t_{max}	Timepoint of Maximum Plasma Concentration
TMF	Trial Master File
TSAP	Trial Statistical Analysis Plan
ULN	Upper Level of Normal
WHO	World Health Organization

WOCBP	Woman of childbearing potential

1. INTRODUCTION

This is a Phase II, open-label, multicentre trial in patients with advanced/metastatic solid tumours who may benefit from immune-checkpoint inhibitor therapy. This Master protocol is designed with 'Modules' which allow for the simultaneous development of ezabenlimab in combination with other checkpoint inhibitors or anticancer medications in various tumour types.

The Master protocol document contains the operational components common to the conduct of the trial regardless of treatment-specific Module (e.g., safety, administrative structure). The treatment-specific Modules contain further details particular to each treatment combination, such as Module-specific or treatment-specific eligibility criteria, treatment administration, trial assessments and other guidances.

1.1 MEDICAL BACKGROUND

Despite the recent advancements in cancer treatment, cancer remains a leading cause of death globally. Approximately 1,685,210 new cancer cases were expected to be diagnosed in 2016 (excluding carcinoma *in situ* [noninvasive cancer] of any site except urinary bladder and basal cell or squamous cell skin cancers). Approximately 595,690 people in the United States were expected to die of cancer in 2016. In the majority of cases, the disease is diagnosed in late stages and the vast majority of patients progress on available treatment and succumb to their disease. These statistics clearly highlight the urgent need for novel therapeutic agents and treatment strategies to improve the treatment outcome for cancer patients.

The normal role of the immune system is to protect the body against the invasion of foreign antigens such as bacteria, viruses, and parasites as well as the body's own malfunctioning cells. Once a mounted immune response (adaptive or innate) completes its task of eliminating the threat, the immune system deploys the immune-checkpoint program to dampen the immune response and minimise collateral immune-mediated damage to healthy tissue.

T-cell activation is a highly regulated process that promotes T-cell proliferation, differentiation, survival, and cytokine production. Up-regulation of multiple co-regulatory receptors on activated T-cells provides a mechanism of fine-tuning the immune response. The programmed cell death protein-1 (PD-1) and programmed death ligand-1 (PD-L1) pathway was the first negative immune co-regulatory (immune-checkpoint inhibitor) pathway described (R16-2361; R16-2363). Indeed, genetic inactivation of the PD-1/PD-L1 pathway in mice resulted in various autoimmune phenotypes (R16-2362; R16-2364). PD-1 expression in humans is largely restricted to immune cells (T-cells, B-cells, natural killer T-cells, activated monocytes and dendritic cells) and is upregulated upon T-cell activation (R15-6038; R16-2364), whereas PD-L1 protein is expressed on the surface of a wide range of human cancer cells (R16-2371). The physiologic function of the PD-1 pathway is to down-regulate the immune response once the antigen that stimulated the response is eliminated, thereby limiting collateral tissue damage. The primary study drug in this trial, ezabenlimab, targets the PD-1 pathway.

Treatment of patients with advanced melanoma, non-small-cell lung cancer (NSCLC), renal cell carcinoma, and many other tumour types with anti-PD-1 (nivolumab or pembrolizumab) or anti-PD-L1 (atezolizumab, durvalumab, and avelumab) monoclonal antibodies (mAbs) has resulted in highly durable responses in approximately 15% to 30% of patients (R15-3715; R15-3776; R15-3778; R15-6023; R16-0663; R16-0864; R16-0876; R16-1225; R16-1588; R16-3547).

For the patients that either lack a response to initial anti-PD-(L)1 therapy or progress following an anti-PD-(L)1 response, research efforts to date are focusing on achieving clinical benefit using a combination therapy approach. In particular, preclinical and clinical research data present strong evidence of tumour regression effects when combining other agents, such as immunomodulatory and targeted therapies, with a PD-(L)1 antagonist.

In this study, the planned ezabenlimab treatment combination will include the clinical and nonclinical information for the agent being combined and presented in individual Modules. The rationale, benefit/risk, treatment-specific eligibility criteria, treatment administration, trial assessments and other guidances will be described in the Module. Additional Modules and agents may be added to the Master. Agents combined with ezabenlimab will have been previously tested.

1.2 DRUG PROFILE

Ezabenlimab will be combined with other agents in each of the Modules. The profiles for the agents to be combined with ezabenlimab will be described in the respective Module.

1.2.1 Ezabenlimab

Ezabenlimab is a humanised IgG4Pro mAb that is being developed as an i.v. infusion for the treatment of cancer. Ezabenlimab has highly human frameworks and a low predicted immunogenicity score.

For a more detailed description of the ezabenlimab profile, please refer to the Investigator's Brochure (IB).

1.3 RATIONALE FOR PERFORMING THE TRIAL

The aim of this study is to assess the efficacy of ezabenlimab in combination with other checkpoint inhibitors or anticancer medications in different tumour types covered by the trial cohorts, and to identify potential patterns of responsiveness that are not limited to specific tumour types but are present across multiple settings. Patients that progress on treatment in a given Module may be offered treatment in another Module if deemed appropriate by the Investigator and Sponsor. Such patients will help explore potential longitudinal efficacy of treatment cross-over from one treatment-specific Module to another.

This Master protocol design document (referred to as the Master) will describe the common operational aspects of the trial while the treatment-specific 'Modules' (referred to as Modules) will contain further details particular to that treatment combination, such as eligibility criteria, dose and treatment administration, trial assessments, and other guidances.

The trial will begin with one treatment Module (ezabenlimab in combination with BI 754111); additional Modules will be added by protocol amendment. Clinically ineffective or completed Modules will be closed. Patients receiving treatment in one Module with disease progression or tolerability issues may be eligible for cross-over to a different Module.

Ezabenlimab will be combined with anticancer agent(s) with scientific evidence and a rationale to support the combination in a specific patient population. Agents combined with ezabenlimab will have at least completed dose escalation in combination with ezabenlimab in patients with solid tumours in a separate trial prior to inclusion of that treatment-specific Module in this study. These agents may be Boehringer Ingelheim-developed agents or other agents.

In order to be able to address future scientific questions, patients will be asked to voluntarily donate biopsied biospecimens for banking (see the treatment-specific module for details). If the patient agrees, banked samples may be used for future biomarker research and drug development projects, e.g. to identify patients that are more likely to benefit from a treatment or experience an adverse event (AE), or to gain a mechanistic or genetic understanding of drug effects and thereby better match patients with therapies.

The trial populations for the trial (as defined in each module) were selected based on the current high unmet medical need with limited treatment options as well as the expectation that the combination therapy may be a viable treatment option for these patients.

1.4 BENEFIT - RISK ASSESSMENT

The role of the immune-checkpoints within a normal immune response is to dampen the immune response after the trigger (antigen) is resolved, minimising collateral immune-mediated damage to healthy tissue. Immune-checkpoints also play a major role in promoting and maintaining self-tolerance by inactivating auto-reactive T-cells. Therefore, inhibition of immune-checkpoint pathways unleashes the immune system and comes with a higher risk of inducing immune dysfunction, leading to immune-related adverse events (irAEs). Indeed, mice deficient in PD-1 or its ligands (PD-Ll and PD-L2) were found to be highly prone to development of autoimmune diseases (R16-2364; R16-2969; R16-2970).

Immune-checkpoint inhibition has been shown to be a promising therapeutic strategy in a subset of patients. The limited success achieved with checkpoint-inhibitor monotherapy in some studies (up to 80% of treated patients do not respond [R15-3588; R15-3778]) may, in part be attributed to redundancy in immune-checkpoint inhibitor pathways. Understanding that multiple, diverse mechanisms may contribute to checkpoint-inhibitor resistance, a goal of this trial is to improve upon checkpoint-inhibitor monotherapy results thus far, assessing multiple novel approaches to therapy.

As of 30-November-2018, 50 patients with advanced/metastatic solid tumours have been treated with ezabenlimab as monotherapy in the 1381.1 trial.

The most frequently reported AEs (reported in >10% of the patients) were fatigue (40%), nausea (28.0%), decreased appetite (18.0%), arthralgia (16.0%), cough (16.0%), abdominal

pain (14.0%), constipation (14.0%), diarrhoea (14.0 %), vomiting (14.0), back pain (12.0%) and dyspnoea (12.0%). Headache, hypokalaemia, muscular chest pain, myalgia, pruritis and rash, each occurred at a frequency of 10.0%. The majority of these AEs were CTCAE Grade 1 and 2.

Grade 3 and 4 AEs were reported in 38.0% and 4.0% of patients, respectively. Of the Grade 3 events, only the AST elevation event was reported as related to trial drug. The reported Grade 4 AEs were 1 (2.0%) case of disease progression and 1 (2.0%) case of sepsis, neither of which was deemed treatment related.

Consistent with the similar drug class labels, most irAEs were reported in the GI, skin and endocrine system organ class (SOCs). The majority of the irAEs were Grades 1 or 2; the only Grade 3 irAE was AST increase.

Preliminary efficacy analyses for study 1381.1 indicate that there have been 6 patients with partial response (PR) and 20 patients with stable disease (SD) as best response on ezabenlimab monotherapy. The PRs were reported in two patients with triple negative breast cancer, one patient with fallopian tube cancer, one patient with renal cancer, one patient with stomach cancer and one patient with endometrial cancer. All of these PRs occurred in patients receiving the 240 mg q3w dose of ezabenlimab.

A similar safety profile of ezabenlimab monotherapy was observed in 6 Japanese patients with solid tumours evaluated in the Asian trial 1381.4.

The details of the preliminary analysis are provided in section 6.2 of the ezabenlimab IB.

Trial procedures such as blood sampling, imaging with contrast media, and tumour biopsies, are part of standard of care in these advanced cancer patients. The additional blood samplings increase the risk for anaemia which can be corrected by appropriate transfusion, if necessary. While the imaging performed can bring additional long-term radiation it is the only method to detect early progression or early response to avoid unnecessary further treatment or a premature stop while the trial treatment would be beneficial to the patient.

There is an added risk for pain, swelling, and bleeding for those patients who will undergo tumour biopsies at screening and during the trial, under treatment. Additional treatment-specific benefit-risk assessments are described in the respective Modules.

Although rare, the potential for drug-induced liver injury (DILI) is under constant surveillance by sponsors and regulators. Therefore, this trial requires timely detection, evaluation, and follow-up of laboratory alterations in selected liver laboratory parameters to ensure patients safety.

A Safety Review Committee (SRC) as described in Section 8.7 will be established for the study.

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

Objectives common across all Modules are described in the following sections. Distinct and important objectives applicable to each treatment plan are described in the treatment-specific Modules.

2.1.1 Main objective

The aim of this study is to assess the efficacy of ezabenlimab in combination with other checkpoint inhibitors or anticancer medications in diverse tumour type cohorts.

2.1.2 Primary endpoint

The primary endpoint of the trial is objective response (OR), defined as best overall response of complete response (CR) or partial response (PR) according to RECIST v1.1 as assessed by the Investigator.

2.1.3 Secondary endpoint(s)

The secondary endpoints of the trial will include:

- Duration of response (DoR), defined as the time from first documented CR or PR (RECIST v1.1) until the earlier of disease progression or death among patients with OR.
- Disease control (DC), defined as best overall response of CR, PR, or stable disease (SD) according to RECIST v1.1 as assessed by the Investigator.
- Progression-free survival (PFS), defined as the time from first treatment until PD or death from any cause, whichever occurs earlier.

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

This Phase II, multi-drug, open-label multi-centre trial will be conducted in North America and the United Kingdom. The Master trial design will include several different ezabenlimab-based combinations, which are defined in treatment-specific Modules appended to the Master. Each Module will investigate the anti-PD-1 mAb ezabenlimab combined with other agents. Within each Module selection criteria will identify patients to be assigned by cohort based on their previous exposure or lack of exposure to cancer anti-PD-1 or anti-PD-L1 treatment and tumour type. The safety, tolerability, PK profile and antitumour activity of the treatments in each Module will be determined.

Initial screening assessments are described in the Master protocol. Patients will sign a Master informed consent form (ICF) for screening. Upon module assignment, the patient will sign the corresponding module ICF. Further screening assessments will be performed to determine eligibility for the Module the patient is assigned to.

Once determined eligible for a Module and treatment has begun, the patient will continue study treatment in the Module with the study drugs until disease progression (PD) according to RECIST 1.1 (R09-0262) and/or iRECIST (R15-2005), withdrawal of patient consent, an unacceptable toxicity occurs, or 1 year of treatment is completed, whichever occurs first. Patients will be allowed to stay on treatment in the case of initial radiological PD, if the Investigator feels that it is in the patient's best interest. In addition, patients without PD may stay on trial beyond 1 year of treatment on a case-by-case basis after discussion with the Medical Monitor and the sponsor. Patients that progress on treatment in a given Module may be offered treatment in another Module if deemed appropriate by the Investigator and Sponsor. Patients that discontinue for reasons other than PD will not be eligible for other Modules.

3.2 DISCUSSION OF TRIAL DESIGN, INCLUDING THE CHOICE OF CONTROL GROUPS

The primary reason for using this type of design is to answer questions and deliver results expeditiously, thus benefitting future patients and the research community. A Master design protocol will streamline the exploration of an agent of interest given in combination with ezabenlimab, a PD-1 inhibitor, and allow for assessments of patterns of responsiveness across multiple tumour types and treatment combinations.

A Safety Review Committee (SRC) as described in Section 8.7 will be established for the study.

3.3 SELECTION OF TRIAL POPULATION

The inclusion and exclusion criteria for enrolment in the Master protocol are described below. Each Module will have additional inclusion/exclusion criteria to be met prior to enrolment into that Module.

Screening of patients for this trial is competitive, i.e. screening for the trial will stop at all sites at the same time once a sufficient number of patients have been screened. Investigators will be notified about screening completion and will then not be allowed to screen additional patients for this trial.

A log of all patients enrolled into the trial (i.e. who have signed informed consent) will be maintained in the Investigator Site File (ISF) irrespective of whether they have been treated with investigational drug or not.
If a patient is enrolled in error (does not meet all inclusion criteria or meets one or more exclusion criteria on the day of enrolment), the sponsor should be contacted immediately.

3.3.1 Main diagnosis for trial entry

Please refer to Section 8.3.1 (Source Documents) for the documentation requirements pertaining to the inclusion and exclusion criteria.

3.3.2 Inclusion criteria

Patients must fulfil all of the following Master inclusion criteria below and the inclusion criteria described in the particular Module to be eligible.

1. Provision of signed and dated, written Master informed consent form (ICF) prior to any trial-specific procedures, sampling, or analyses.
2. Several cohorts of patients with various solid tumours have been defined. Details are given in the respective treatment-specific Modules.
3. Patient moving from one module to another must have prior irAEs resolved to a degree that would allow for restart of checkpoint inhibitor therapy according to the irAE management guidelines in the protocol.
4. Patient ≥18 years of age at the time of signature of the ICF.
5. Eastern Cooperative Oncology Group (ECOG) score: 0 or 1.

6. Patient must agree to a pre-treatment biopsy (if archival tissue is not available) and on-treatment tumour biopsy. If archived tumour tissue is available from the last treatment failure, sections may be supplied instead of a pre-treatment biopsy.
7. Life expectancy of at least 12 weeks after the start of the treatment according to the Investigator's judgement.
8. Male or female patients. Women of childbearing potential (WOCBP)[1] and men able to father a child must be willing and able to use highly effective methods of birth control (that result in a low failure rate of less than 1% per year when used consistently and correctly) during trial participation and for at least 6 months after the last administration of trial medication. Acceptable highly effective methods of contraception include total sexual abstinence when this is in line with the preferred and usual lifestyle of the study participant (periodic abstinence such as calendar, ovulation, symptothermal, post-ovulation methods and withdrawal are not acceptable methods of contraception), an intrauterine device or intrauterine hormone-releasing system, bilateral tubal ligation, and vasectomised partner (with post-vasectomy proof of absence of sperm). Male patients with partners of childbearing potential must agree to use condoms and ensure their partners are using an additional highly-effective method of birth control, during the trial and until at least 6 months after the end of the trial treatment.

3.3.3 Exclusion criteria

Patients must fulfil none of the Master exclusion criteria below or any exclusion criteria described in the particular Module to be eligible:

1. Any investigational treatment, anti-tumour treatment within 4 weeks or within 5 half-life periods (whichever is shorter) prior to the initiation of trial treatment.
2. More than one anti-PD-(L)1-based treatment regimen prior to entering study, more specifically defined in the modules. Note: once in a trial Module, patients may crossover to different Module if all other eligibility criteria are met.
3. Major surgery ('major' according to the Investigator's assessment and/or Medical Monitor's) performed within 12 weeks prior to first trial treatment or planned within 12 months after screening, e.g., hip replacement.
4. Presence of other active invasive cancers other than the one treated in this trial within 5 years prior to screening, with the exception of appropriately treated basal-cell carcinoma of the skin, *in situ* carcinoma of the uterine cervix, or other local tumours considered cured by local treatment.
5. Active infection requiring systemic treatment (antibacterial, antiviral, or antifungal therapy) at start of treatment in this trial. Patients may be enrolled onto the study following an 7-day washout period after the end of systemic treatment for active infection.
6. Patient has received allogeneic bone marrow or solid organ transplant.

[1] A woman is considered of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile.
Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.
Tubal ligation is NOT a method of permanent sterilisation.
A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

7. Inadequate organ function or bone marrow reserve as demonstrated by the laboratory values presented in Table 3.3.3: 1.
8. Any of the following cardiac criteria:
   - Mean resting corrected QT interval (QTc) >470 msec
   - Any clinically important abnormalities (as assessed by the Investigator) in rhythm, conduction, or morphology of resting ECGs, e.g., complete left bundle branch block, third degree heart block
   - Any factors that increase the risk of QTc prolongation or risk of arrhythmic events such as heart failure, hypokalaemia, congenital long QT syndrome, family history of long QT syndrome or unexplained sudden death under 40 years-of-age, or any concomitant medication known to prolong the QT interval
   - Patients with an ejection fraction (EF) <55% or the lower limit of normal of the institutional standard (if the lower limit of normal of institutional standard is higher than 55%) will be excluded. Only in cases where the Investigator (or the treating physician or both) suspects cardiac disease with negative effect on the EF will the EF be measured during screening using an appropriate method according to local standards to confirm eligibility (e.g., echocardiogram, multi-gated acquisition scan). An historic measurement of EF no older than 6 months prior to first administration of trial drug can be accepted provided that there is clinical evidence that the EF value has not worsened since this measurement in the opinion of the Investigator or of the treating physician or both.
9. Known history of human immunodeficiency virus infection or an active hepatitis B or C virus infection.
10. Active autoimmune disease or a documented history of autoimmune disease, except vitiligo or resolved childhood asthma/atopy. Patients who were permanently discontinued from previous anti-PD-1 or anti-PD-L1 therapy because of an immune-related adverse event (irAE).
11. Known history of severe hypersensitivity reactions to other mAbs or known hypersensitivity to the trial drugs or their excipients.
12. Presence of central nervous system (CNS) metastases, unless treated and asymptomatic and off corticosteroids and anti-convulsant therapy for at least 2 weeks prior start of treatment.
13. Immunosuppressive corticosteroid doses (>10 mg prednisone daily or equivalent) within 4 weeks prior to the first dose of study treatment.
14. Patients who must or wish to continue the intake of restricted medications (see Section 4.2.2.1) or any drug considered likely to interfere with the safe conduct of the trial.
15. Chronic alcohol or drug abuse or any condition that, in the Investigator's and/or Medical Monitor's opinion, makes him/her an unreliable trial subject, unlikely to complete the trial, or unable to comply with the protocol procedures.
16. Women who are pregnant, nursing, or who plan to become pregnant while in the trial and for at least 6 months after the last administration of trial medication.
17. Men who plan to father a child while in the trial and for at least 6 months after the last administration of trial medication.

Table 3.3.3: 1 Laboratory values demonstrating inadequate organ function

Laboratory Parameter	Values for solid tumours
Absolute neutrophil count	<1.5 x 10^9/L (<1500/mm^3)
Alanine aminotransferase (ALT)	>2.5 X ULN if no demonstrable liver metastases or >5 X ULN in the presence of liver metastases
Aspartate aminotransferase (AST)	>2.5 X ULN if no demonstrable liver metastases or >5 X ULN in the presence of liver metastases
Haemoglobin	<9 g/dL
International Normalized Ratio (INR) (only tested if clinically indicated)	>1.5 X ULN (If treated with anticoagulants, prolonged INR is acceptable)
Platelet count	<100 x 10^9/L
Serum Creatinine	>1.5 X ULN or estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2 (Chronic Kidney Disease Epidemiology [CKD-EPI] Collaboration equation); confirmation of eGFR is only required when creatinine is >1.5 X ULN.
Total bilirubin	>1.5 X ULN, except for patients with Gilbert's syndrome who are excluded if total bilirubin >3.0 X ULN or direct bilirubin >1.5 X ULN

3.3.3.1 Withdrawal of patients from treatment or assessments

Patients may discontinue trial treatment or withdraw consent to trial participation as a whole ('withdrawal of consent') with very different implications; please see Sections 3.3.3.2 and 3.3.3.3 below.

Every effort should be made to keep the patients in the trial, if possible on treatment, or at least post-treatment discontinuation to collect important trial data.

Patients whose disease progresses while receiving therapy in a given Module in this study may be offered treatment with a different investigational Module if deemed appropriate by the Investigator. A signed Module-specific ICF will be required prior to treatment. The transition time between Modules (last dose of previous Module and screening visit of subsequent Module) will be a maximum of 2 months.

Measures to control the withdrawal rate include careful patient selection and appropriate explanation of the trial requirements and procedures prior to trial enrolment, as well as the explanation of the consequences of withdrawal.

The decision to discontinue trial treatment or withdraw consent to trial participation and the reason must be documented in the patient files and CRF. If the reason for discontinuation is death other than due to PD, this should be reported on the SAE form as well, regardless of causal relationship.

3.3.3.2 Discontinuation of trial treatment

An individual patient will discontinue trial treatment if:

- The patient wants to discontinue trial treatment, without the need to justify the decision.
- The patient has repeatedly shown to be non-compliant with important trial procedures and, in the opinion of both the Investigator and sponsor representative, is not willing or able to adhere to the trial requirements in the future.
- The patient needs to take concomitant medication that interferes with the investigational medicinal product or other trial treatment.
- The patient can no longer receive trial treatment for medical reasons (such as surgery, adverse events, other diseases, or pregnancy). For pregnancy see Section 5.2.6.2.4.

Even if the trial treatment is discontinued, the patient will remain in the trial and, given his/her agreement, will undergo the procedures for early treatment discontinuation and follow up (see the treatment-specific module for details).

3.3.3.3 Withdrawal of consent to trial participation

Patients may withdraw their consent to trial participation at any time without the need to justify the decision.

If a patient wants to withdraw consent, the investigator should be involved in the discussion with the patient and explain the difference between trial treatment discontinuation and withdrawal of consent to trial participation, as well as explain the options for continued follow-up after trial treatment discontinuation (please see Section 3.3.3.2 above).

3.3.3.4 Discontinuation of the trial by the sponsor

Boehringer Ingelheim reserves the right to discontinue the trial overall, a specific Module, or at a particular trial site at any time for the following reasons:

1. Failure to meet expected enrolment goals overall or at a particular trial site.
2. Emergence of any efficacy/safety information invalidating the earlier positive benefit-risk assessment that could significantly affect the continuation of the trial.
3. Violation of GCP, the trial protocol, or the contract impairing the appropriate conduct of the trial.
4. Completion of treatment by all patients and the sponsor determines that sufficient data have been collected.

The Investigator/ trial site will be reimbursed for reasonable expenses incurred in case of trial termination (except in case of the third reason).

4. TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

This is an open-label study. Specific dosing and treatment regimens for each of the ezabenlimab combinations are described in the individual Modules. Selection of the treatment-specific Module will be determined by the patient's tumour type, prior treatment, and algorithm (such as Interactive Response Technology [IRT]) for patient assignment. Patients will sign a Master ICF prior to any Master screening procedures and will sign the Module ICF prior to the occurrence of any Module-specific procedures.

For agents to be combined with ezabenlimab, selection of doses, method of assignment to treatment, any dose modification instructions, drug administration, and drug accountability are described in the respective Modules of this clinical protocol.

Dose reductions or escalations of ezabenlimab are not permitted. Treatment administration may be delayed to manage AEs by one cycle, plus an additional 3 weeks, following discussion with the Medical Monitor.

4.1.1 Identity of the Investigational Medicinal Products

Ezabenlimab will be administered in each of the Modules. The agent to be paired with ezabenlimab will be described in detail in the treatment-specific Module.

4.1.2 Selection of doses in the trial

Refer to the treatment-specific Module.

4.1.3 Method of assigning patients to treatment groups

After assessment of all inclusion and exclusion criteria from the Master and the Module, each eligible patient will be assigned to a module and the corresponding appropriate medication number. Note that the medication number is different from the patient number (the latter is assigned directly after informed consent is obtained). The assignment will be determined by person(s) independent from the site using predefined algorithm and entered into the Interactive Response Technology (IRT) System. Site personnel will enter the medication number in the CRF.

4.1.3.1 Method of assigning patients to a second, or subsequent, Module(s)

Patients whose disease progresses while receiving a modular treatment may be offered treatment in a different Module if deemed appropriate by the Investigator. The process will be the same as if the patient were new to the trial. All the Module-specific inclusion and exclusion criteria must be met and the patient must sign an approved ICF for the Module. The

assignment will be based on a predefined algorithm if patients are eligible for more than one Module.

The patient must sign an approved ICF for the subsequent Module, be screened prior to entering the new Module, and must meet all Master and Module-specific inclusion criteria. The transition time between Modules (last dose of previous Module and screening visit of subsequent Module) will be a maximum of 2 months. The assignment will be based on predefined algorithm if patients are eligible for more than one Module. Patients will be allowed multiple crossovers into subsequent Modules.

Patients that cross over to a new Module will not reduce the preplanned number of patients allocated to that module (i.e. A Module that is planned to have a specific number of patients will have that number of patients recruited irrespective of the number of patients that cross over from other modules.)

4.1.4 Blinding and procedures for unblinding

Not applicable in this open-label trial.

4.1.5 Packaging, labelling, and re-supply

The investigational products will be provided by BI. They will be packaged and labelled in accordance with the principles of Good Manufacturing Practice. Each site will be provided with an initial shipment of trial drug supply. The Investigator or designee is responsible to monitor that supply to ensure the site has enough for current and potential patients. [redacted] will monitor expiry dates of trial drug to trigger replacement supplies as needed. The IRT system and DS Team will monitor drug supply at site, expiry dates, and upcoming patient visits to ensure adequate supplies. If supply is low at a site, the IRT will trigger replacement supplies. Additional details on resupply and setup for IRT drug monitoring will be provided in the associated IRT Specific Documentation.

Upon receipt of the request, [redacted] will trigger drug supply for the site using an IRT system.

For details of packaging and the description of the label, refer to the Investigator Site File (ISF).

4.1.6 Storage conditions

Drug supplies will be kept in their original packaging and in a secure limited access storage area according to the recommended storage conditions on the medication label. A temperature log must be maintained for documentation.

If the storage conditions are found to be outside the specified range, the local clinical monitor (as provided in the list of contacts) must be contacted immediately.

4.1.7 Drug accountability

The Investigator, or designee, will receive the investigational drugs delivered by the sponsor when the following requirements are fulfilled:

- Approval for the Master protocol, applicable Modules and ICFs by the Institutional Review Board (IRB)
- Availability of a signed and dated clinical trial contract between the sponsor and the head of the investigational site
- Approval/notification of the regulatory authority, e.g. competent authority for the Master protocol and applicable Modules
- Availability of the curriculum vitae of the Principal Investigator
- Availability of a signed and dated CTP
- Availability of the proof of a medical license for the Principal Investigator
- Availability of signed and dated Form 1572 (U.S. only).

The Investigator, or designee, must maintain records of the products' delivery to the trial site, the inventory at the site, the use by each patient, and the return to the sponsor or alternative disposal of unused products.

These records will include dates, quantities, batch / serial numbers, expiry ('use-by') dates, and the unique code numbers assigned to the investigational products and trial patients. The Investigator, or designee, will maintain records that document adequately that the patients were provided the specified doses and reconcile all investigational products received from the sponsor. Unused and partially used trial drugs will be destroyed on site at the end of the trial (after relevant reconciliations have been completed and records reviewed by the clinical monitor).

4.1.8 Dose modifications

Refer to the treatment-specific Module.

4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

Refer to the treatment-specific Modules.

4.2.1 Other treatments and emergency procedures

There are no other mandatory treatments to be used in this trial or special emergency procedures to be followed. Recommendations for the management of immune-related AEs can be found in Appendix 10.2.

Rescue medications to reverse the actions of ezabenlimab are not available. Therefore, potential side effects of ezabenlimab have to be treated symptomatically. Rescue medications for other investigational medicinal products will be described in the respective Module.

Appropriate measures according to institutional standards should be taken to limit any risk of bleeding for patients who are on full anti-coagulation therapy.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

No other investigational therapy or anticancer agent should be given to patients. If such agents are required for a patient, then the patient must first be withdrawn from the trial.

4.2.2.2 Restrictions on diet and life style

No restrictions to diet or life style have been identified for ezabenlimab.

Refer to each Module for any additional restrictions.

4.2.2.3 Contraception requirements

Women of childbearing potential and men able to father a child must use highly effective methods of birth control per ICH M3 (R2) that result in a low failure rate of less than 1% per year when used consistently and correctly. A list of contraception methods meeting these criteria is provided below.

WOCBP and men able to father a child must use medically approved methods of birth control throughout the trial, and for a period of at least 6 months after last trial drug intake.

Male patients:
Male patients with partners of childbearing potential must agree to use condoms and ensure their partners are using an additional highly-effective method of birth control, during the trial and until at least 6 months after the end of the trial treatment.

Female patients:
WOCBP must use highly effective methods of birth control per ICH M3 (R2) that results in a low failure rate of less than 1% per year when used consistently and correctly during the trial, and for a period of at least 6 months after the last dose of trial drug.

Highly-effective methods of contraception include:
- Total sexual abstinence when this is in line with the preferred and usual lifestyle of the study participant, OR
- Bilateral tubal ligation, OR
- Vasectomised partner (with appropriate post-vasectomy documentation of the absence of sperm in the ejaculate and provided that partner is the sole sexual partner of the WOCBP CT participant), OR
- Intrauterine device or intrauterine hormone-releasing system

4.3 TREATMENT COMPLIANCE

Study drug will be administered at the sites by the Investigator and/or trained site personnel, and dosing will be recorded in the eCRF. Therefore, actual dosing is expected to precisely follow the prescribed drug regimen in the applicable Module. Missed or interrupted doses will be recorded in the eCRF with the associated reasons. The method of collecting dosing information assures that total exposure can be calculated programmatically taking into account any missing doses.

5. ASSESSMENTS

5.1 ASSESSMENT OF EFFICACY

The tumour response in patients with solid tumours will be evaluated according to RECIST Version 1.1 (R09-0262) for the primary endpoin [redacted]

The assessment by the Investigator and/or the local radiologist will be the basis for continuation or discontinuation of the trial medication in an individual patient (in addition to safety). The baseline imaging must have been performed within 4 weeks prior to treatment with the trial medication and the Investigator will record the target and non-target lesions in the eCRF. The same method of assessment and the same technique must be used to characterise each reported lesion at baseline and during treatment. Lesions in previously irradiated areas may not be used as target lesions. Tumour assessments will be performed at screening (as close as possible to the treatment start and no more than 28 days before the start of study treatment), every 6 weeks (±3 days) for the first 6 months, then every 9 weeks (±3 days) thereafter, and at the EOT visit (if not performed within the previous 4 weeks). The length of cycles will be defined in the respective Modules.

If the patient stops trial medication intake for a reason other than PD based on RECIST, the tumour assessment according to RECIST and iRECIST will be performed according to standard of care until the last follow-up needed according to the protocol (PD, death, lost to follow-up, end of the trial).

Patients will continue treatment with the study drugs until disease progression (PD) by RECIST and/or iRECIST, withdrawal of patient consent, an unacceptable toxicity occurs, or 1 year of treatment is completed, whichever occurs first. Patients will be allowed to stay on treatment in the case of initial radiological PD, if the Investigator feels that it is in the patient's best interest. In addition, patients without PD may stay on study drug (s) beyond 1 year of treatment on a case-by-case basis after discussion with and approval by the Medical Monitor and the sponsor.

Digital copies of disease evaluation scans (CT/MRI/PET) are to be collected by the sponsor and stored centrally for later radiomics assessment. It is planned to explore the potential for enhanced and improved baseline and on-treatment markers/patterns of early efficacy based on comprehensive quantitative CT metrics, i.e., radiomics features, assessed in standard-of-care medical imaging data.

5.2 ASSESSMENT OF SAFETY

The safety of ezabenlimab in combination with other agents will be assessed by a descriptive analysis of incidence and severity of AEs graded according to CTCAE (version 5.0), laboratory data, and results of physical examinations. Safety will be assessed in a descriptive way without confirmatory analysis.

5.2.1 Physical examination

A complete physical examination will be performed at the time points specified within each module (see the treatment-specific module for details). It includes at a minimum general appearance, neck, lungs, cardiovascular system, abdomen, extremities, skin, and neurological systems.

Measurement of height and body weight will be performed at the specific time points (see the treatment-specific module for details).

During the physical examination, the patient should be assessed for possible adverse events. The results must be included in the source documents available at the site.

5.2.2 Vital signs

Vital signs will be evaluated at the time points specified to the modules, prior to blood sampling and trial treatment administration (see the treatment-specific module for details). This includes body temperature, systolic and diastolic blood pressure and pulse rate (electronically or by palpation count for 1 minute). All except body temperature need to be taken in a seated position after 5 minutes of rest. Oxygen saturation will be measured, if needed.

Blood pressure and heart rate may also be measured after infusion of ezabenlimab or at any time that the Investigator deems it is necessary.

5.2.3 Safety laboratory parameters

Safety laboratory testing will occur at the time points specified in the respective modules (see the treatment-specific module for details). All analyses will be performed locally. Patients do not have to be fasted for the blood sampling for the safety laboratory tests.

Instructions regarding sample collection, sample handling / processing and sample shipping are provided in the Laboratory Manual in the ISF.

Clinically relevant abnormal findings as judged by the Investigator will be reported as adverse events (please refer to Section 5.2.6).

In case the criteria for hepatic injury are fulfilled, a number of additional measures will be performed (please see Section 5.2.6.1.3 and the DILI Checklist provided in the ISF). The amount of blood taken from the patient concerned will be increased due to this additional sampling.

Safety laboratory tests will include the following parameters:

Haematology
The standard haematology panel will consist of: haemoglobin, red blood cell count, haematocrit, mean corpuscular volume, white blood cell count, differential blood count (preferably expressed in absolute values), and platelets.

Biochemistry
The standard biochemistry panel will consist of glucose, sodium, potassium, chloride, calcium, phosphate, urea, creatinine, AST, ALT, alkaline phosphatase, lactate dehydrogenase, bilirubin (direct and indirect bilirubin in case of elevated total bilirubin values), total protein, albumin, urea nitrogen, uric acid, Troponin I (only at screening, C1D1, C1D8, C1D15, C2D1, C3D1, C4D1 and anytime CPK is elevated), and creatinine kinase (CK). A thyroid panel (TSH, free T4, and free T3) will be done during at the time of each standard biochemistry panel.

If symptoms of pancreatitis are observed, amylase and lipase should be tested at the discretion of the Investigator.

Coagulation
Activated partial thromboplastin time (aPTT) and prothrombin time (PT) (expressed either in seconds or as a percentage) will be tested according to the treatment-specific module.

Urine
Urine (pH, glucose, erythrocytes, leukocytes, protein, and nitrite) will be analysed by dipstick (semi-quantitative measurements).

Pregnancy test
A beta human chorionic gonadotropin (β-HCG) pregnancy test in serum will be performed for women of childbearing potential (WOCBP) at screening. Thereafter, this test may be done in serum or urine on Day 1 of each cycle, at the EOT visit, and at the 30-day safety follow-up visit.

If laboratory safety investigations have been performed >72 hours prior to the first trial treatment, the results of the new safety laboratory investigations performed within 72 hours of first treatment must be available to reconfirm eligibility.

5.2.4 Electrocardiogram

Standard 12-lead (I, II, III, aVR, aVL, aVF, V1 - V6) resting electrocardiograms (ECGs) will be obtained and digitally recorded. See the treatment-specific modules for details outlining which visits will require single ECGs.

The ECG should be obtained after the patient has been resting supine for at least 5 minutes. All ECGs should be recorded with the patient in the same physical position. If necessary, additional ECGs may be recorded for safety reasons.

The ECG recordings must also be analysed and checked for abnormality by the Investigator (or designated physician) who will also calculate the QTcF. Particular attention must be paid to T wave inversions. Clinically relevant abnormal findings will be reported either as baseline condition (if identified at the screening visit) or otherwise as adverse events and will be followed up and/or treated as medically appropriate. CTCAE version 5.0 will be used for the grading of prolonged QTcF intervals.

In case of related ECG changes and whenever the Investigator deems necessary, additional ECG monitoring will be performed in the respective and later courses of treatment.

In case of QTcF prolongation to >500 ms AFTER receiving therapy, the Investigator will initiate further ECG monitoring and diagnostics (e.g., check electrolytes and check concomitant therapy that may be contributing to QTcF prolongation) and if required provide adequate treatment according to medical standards. The patient will be discharged from the investigational site only after resolution of ECG findings as assessed by the Investigator.

In case of occurrence of symptoms suggestive of arrhythmia related to QTcF prolongation, a cardiologic evaluation will be performed, and treatment will be provided according to medical standards at the discretion of the Investigator.

5.2.5 Other safety parameters

Refer to the treatment-specific Modules.

5.2.6 Assessment of adverse events

5.2.6.1 Adverse event

An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The following should also be recorded as an AE in the CRF and BI SAE form (if applicable):
- Worsening of pre-existing conditions.
- Changes in vital signs, ECG, physical examination and laboratory test results, if they are judged clinically relevant by the investigator.

If such abnormalities already exist prior to trial inclusion, they will be considered as baseline conditions and should be collected in the eCRF only.

5.2.6.1.1 Serious adverse event

A serious adverse event (SAE) is defined as any AE, which fulfils at least one of the following criteria:

- results in death,
- is life-threatening, which refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if more severe,
- requires inpatient hospitalisation,
- requires prolongation of existing hospitalisation,
- results in persistent or significant disability or incapacity,
- is a congenital anomaly / birth defect,
- is deemed serious for any other reason if it is an important medical event when based on appropriate medical judgement which may jeopardise the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation or development of dependency or abuse.

Patients may be hospitalised for administrative reasons during the trial, including hospitalisation for respite care. These as well as hospitalisations/surgical procedures which were planned before the patient signed informed consent need not be reported as SAEs if they have been documented at or before signing of the informed consent and have been performed as planned (the condition requiring hospitalisation/surgical procedure has not changed/worsened after signing informed consent).

5.2.6.1.2 AEs considered ‘Always Serious’

Every new occurrence of cancer of new histology must be classified as a serious event regardless of the time since the discontinuation of the trial medication and must be reported as described in Section 5.2.6.2, subsections ‘AE Collection’ and ‘AE reporting to sponsor and timelines’.

In accordance with the European Medicines Agency initiative on Important Medical Events, Boehringer Ingelheim has set up a list of further AEs, which by their nature, can always be considered to be ‘serious’ even though they may not have met the criteria of an SAE as defined above. The latest list of ‘Always Serious AEs’ can be found in the electronic document system. These events should always be reported as SAEs as described above.

5.2.6.1.3 Adverse events of special interest

The term adverse events of special interest (AESI) relates to any specific AE that has been identified at the project level as being of particular concern for prospective safety monitoring and safety assessment within this trial, e.g. the potential for AEs based on knowledge from other compounds in the same class. AESIs need to be reported to the sponsor’s Pharmacovigilance Department within the same timeframe that applies to SAEs, please see Section 5.2.6.2.2.

For this trial, infusion-related AEs, potential DILI events, hepatic injury, and qualifying irAEs, as defined in the treatment-specific Modules and Appendix 10.1, are AESIs.

Immune-related adverse events (irAEs)

Immune-related AEs are AEs associated with immunotherapy treatments that appear to be associated with the immune therapy's mechanism of action. These adverse reactions, which can be severe, may involve the gastrointestinal, skin, liver, endocrine, respiratory, renal, or other organ systems. All immune-related events are to be reported as AEs. Some irAEs also need to be reported as AESIs as defined by the sponsor in Appendix 10.1. If an Investigator determines a Grade 3 event of an AE that is not mentioned on the list of immune-related AEs, the Investigator should also report that event as an AESI.

Recommendations for the management of irAEs are presented in Appendix 10.2.

Infusion-related reactions

In the event of an infusion-related reaction ≤ Grade 2, treat the symptoms accordingly with antihistamine or corticosteroids if needed. The infusion rate of ezabenlimab may be decreased by 50% or interrupted until resolution of the event and re-initiated at 50% of the initial rate until completion of the infusion. In patients experiencing infusion-related reactions ≤ Grade 2, subsequent infusions may be administered at 50% of the initial rate. If an infusion-related reaction to trial medications is Grade 3 or higher in severity at any point during the study, permanently discontinue study drug(s).

If a patient experiences an infusion-related reaction, acetaminophen and/or an antihistamine (e.g., diphenhydramine) and/or corticosteroid or equivalent medication per institutional standard may be administered prior to subsequent infusions at the discretion of the Investigator for secondary prophylaxis of infusion-related reactions. If an infusion-related reaction is Grade 3 or higher in severity at any point during the study, treatment with ezabenlimab will be permanently discontinued.

As with any mAb, allergic reactions to dose administration are possible. Appropriate drugs and medical equipment to treat acute anaphylactic reactions must be immediately available, and trial personnel must be trained to recognise and treat anaphylaxis. The trial site must have immediate access to emergency resuscitation teams and equipment in addition to the ability to admit patients to an intensive care unit if necessary.

The following terms describe those events that are to be considered potential infusion-related AEs. Regardless of grade, these events are considered as AESIs and must be reported to the [redacted] Safety group within 24 hours of the event:

- Allergic reaction
- Anaphylaxis
- [redacted]-release syndrome
- Serum sickness
- Infusion reactions
- Infusion-like reactions

If the Investigator determines that another event (not on the list) may be a potential infusion-related AE, the Investigator may also report that event as an AESI.

Hepatic injury and potential drug-induced liver injury (DILI)

During the course of the trial the Investigator will remain vigilant for increases in liver biochemistry. The Investigator is responsible for determining whether a patient meets the hepatic injury definition or potential Hy's Law criteria at any point during the trial.

The Investigator participates, together with the Medical Monitor and BI clinical project representatives, in review and assessment of cases meeting potential hepatic injury and Hy's Law criteria. Hy's Law criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than a DILI caused by the investigational product.

The Investigator is responsible for recording data pertaining to these cases and for reporting them as AEs and/or SAEs according to the outcome of the review and assessment in line with standard safety reporting processes.

Hepatic injury definition:
A hepatic injury is defined by the following alterations of hepatic laboratory parameters:

- an elevation of AST (Aspartate Aminotransferase) and/or ALT (Alanine Aminotransferase) ≥3 fold ULN combined with an elevation of total bilirubin ≥2 fold ULN measured in the same blood draw sample, or
- aminotransferase (ALT, and/or AST) elevations ≥10 fold ULN.

These lab findings constitute a hepatic injury alert and the patients showing these lab abnormalities need to be followed up according to the "Potential DILI Checklist" provided in the ISF.

In case of clinical symptoms of hepatic injury (icterus, unexplained encephalopathy, unexplained coagulopathy, right upper quadrant abdominal pain, etc.) without lab results (ALT, AST, total bilirubin) available, the investigator should make sure these parameters are analysed, if necessary in an unscheduled blood test. Should the results meet the criteria of hepatic injury alert, the procedures described in the "Potential DILI Checklist" (Figure 5.2.6.1.3: 1) should be followed.

Lab values meeting the hepatic injury definition will need to be reported as an AESI. Please follow the flowchart below for reporting hepatic injury / potential DILI cases.

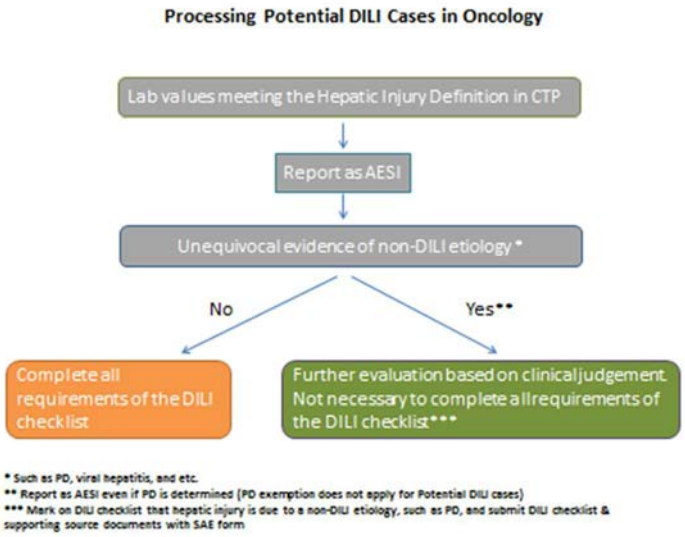


Figure 5.2.6.1.3: 1 Potential DILI Cases in Oncology

Hy's Law cases have the following 3 components:

- The drug causes hepatocellular injury, generally shown by a higher incidence of 3-fold or greater elevations above the ULN of ALT or AST
- Among trial subjects showing such aminotransferase elevations, often with elevations much greater than 3 times ULN, one or more also show elevation of serum total bilirubin to >2 times ULN, without initial findings of cholestasis (elevated serum ALP)
- No other reason can be found to explain the combination of increased aminotransferase and total bilirubin, such as viral hepatitis A, B, or C; pre-existing or acute liver disease; or another drug capable of causing the observed injury.

5.2.6.1.4 Severity of AEs

The severity of AEs should be classified and recorded in the eCRF according to the CTCAE Version 5.

5.2.6.1.5 Causal relationship of AEs

Medical judgement should be used to determine the relationship, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history.

Arguments that may suggest that there is a reasonable possibility of a causal relationship could be:

- The event is consistent with the known pharmacology of the drug.

- The event is known to be caused by or attributed to the drug class.
- A plausible time to onset of the event relative to the time of drug exposure.
- Evidence that the event is reproducible when the drug is re-introduced.
- No medically sound alternative aetiologies that could explain the event (e.g. pre-existing or concomitant diseases, or co-medications).
- The event is typically drug-related and infrequent in the general population not exposed to drugs (e.g. Stevens-Johnson syndrome).
- There was an indication of dose-response (i.e. greater effect size if the dose is increased, smaller effect size if dose is reduced).

Arguments that may suggest that there is no reasonable possibility of a causal relationship could be:

- No plausible time to onset of the event relative to the time of drug exposure is evident (e.g. pre-treatment cases, diagnosis of cancer or chronic disease within days / weeks of drug administration; an allergic reaction weeks after discontinuation of the drug concerned).
- The event continued despite the withdrawal of the medication, taking into account the pharmacological properties of the compound (e.g. after 5 half-lives).
  Of note, this criterion may not be applicable to events whose time course is prolonged despite removing the original trigger.
- The event disappeared even though the trial drug treatment continued or remained unchanged.
- There may be additional arguments amongst those stated before, like alternative explanation (e.g. situations where other drugs or underlying diseases appear to provide a more likely explanation for the observed event than the drug concerned).

5.2.6.2 Adverse event collection and reporting

5.2.6.2.1 AE Collection

The investigator shall maintain and keep detailed records of all AEs in the patient files. The following must be collected and documented on the appropriate CRF(s) by the investigator:

- From signing the ICF onwards until the end of treatment (including the residual effect period (REP); a period of 30 days after the last dose of trial medication) - all AEs (non-serious and serious) and all AESIs.
- After the end of treatment, including REP until the individual patient's end of trial - all related SAEs and all related AESIs and any occurrence of cancer of new histology.
- After the individual patient's end of trial, the Investigator does not need to actively monitor the patient for new AEs but should only report related SAEs and related AESIs and any occurrence of cancer of a new histology of which the investigator may become aware of by any means of communication, e.g. phone call. Those AEs should however, not be reported in the CRF.

The rules for AE reporting exemptions still apply, please see Section 5.2.6.2.5.

All AEs which occurred through the treatment phase and throughout the REP will be considered as on treatment; please see Section 7.3.4. Events which occurred after the REP will be considered as post-treatment events.

5.2.6.2.2 AE reporting to the sponsor and timelines

The Investigator must report SAEs, AESIs, and non-serious AEs that are relevant for the reported SAE or AESI, on the BI SAE form via secure e-mail connection or via fax immediately (within 24 hours) to [redacted] Safety Department:

- Secure email [redacted] mailbox: [redacted] or
- Fax [redacted] safety fax number): [redacted]

For sites outside of the US, country-specific fax numbers will be provided in the ISF/study reference manual.

The same timeline applies if follow-up information becomes available. On specific occasions, the Investigator can inform [redacted] Safety Department upfront via telephone by calling [redacted] reporting phone number ([redacted]). This does not replace the requirement to complete and fax the BI SAE form.

With receipt of any further information about these events, a follow-up SAE form has to be provided. For follow-up information the same rules and timeline apply as for initial information.

5.2.6.2.3 Information required

For each AE, the Investigator should provide the information requested on the appropriate eCRF pages and on the BI SAE form (if applicable).

All (S)AEs, including those persisting after an individual patient's end of trial must be followed up until they have resolved, they have been sufficiently characterised, or no further information can be obtained.

5.2.6.2.4 Pregnancy

In rare cases, pregnancy might occur in a clinical trial. Once a patient has been enrolled in the clinical trial and has taken trial medication, the investigator must report any drug exposure during pregnancy in a trial participant immediately (within 24 hours) by means of Part A of the Pregnancy Monitoring Form to the sponsor's unique entry point.

Similarly, potential drug exposure during pregnancy must be reported if a partner of a male trial participant becomes pregnant. This requires a written consent of the pregnant partner;

Reporting and consenting must be in line with local regulations. The ISF will contain the trial specific information and consent for the pregnant partner.

The outcome of the pregnancy associated with the drug exposure during pregnancy must be followed up and reported to the sponsor's unique entry point on the Pregnancy Monitoring Form for Clinical Trials (Part B).

The ISF will contain the Pregnancy Monitoring Form for Clinical Trials (Part A and B).

As pregnancy itself is not to be reported as an AE, in the absence of an accompanying SAE and/or AESI, only the Pregnancy Monitoring Form for Clinical Trials and not the SAE form is to be completed. If there is an SAE and/or AESI associated with the pregnancy an SAE form must be completed in addition.

5.2.6.2.5 Exemptions to AE/SAE reporting

Disease progression is a trial endpoint for analysis of efficacy and as such is exempted from reporting as an AE or SAE. Progression of the subject's underlying malignancy will be recorded on the appropriate pages of the eCRF as part of efficacy data collection only and will not be reported on the SAE Form. It will therefore not be entered in the safety database (ARISg) and hence not get expeditiously reported. Death due to disease progression is also to be recorded on the appropriate eCRF page and not on the SAE Form. However, when there is evidence suggesting a causal relationship between the study drug or study drugs and the progression of the underlying malignancy, the event must be reported as an SAE on the SAE Form and on the eCRF.

Examples of exempted events of PD may be:

- Progression of underlying malignancy (progressive disease [PD]): if PD is clearly consistent with the suspected progression of the underlying malignancy as defined by the respective response criteria.
- Hospitalisation/procedures due solely to the progression of underlying malignancy (PD)
- Clinical symptoms and/or signs of progression (without confirmation by objective criteria e.g., imaging, clinical measurement): if the symptom can exclusively be determined to be due to the progression/relapse of the underlying malignancy and does meet the expected pattern of progression for the disease under study.

Exempted events are collected and tracked following a protocol specified monitoring plan. Exempted events are monitored at appropriate intervals throughout the study at Safety Review Meetings.

Lab values meeting the hepatic injury definition as defined in Section 5.2.6.1.3 will need to be reported as AESI. PD reporting exemption does not apply to hepatic injury.

5.3 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

Refer to the treatment-specific Modules.

5.6 APPROPRIATENESS OF MEASUREMENTS

Refer to the treatment-specific Modules.

6. INVESTIGATIONAL PLAN

6.1 SCREENING PERIOD

Screening procedures in the Master protocol apply to all patients (See Master flow chart). Refer to the treatment-specific Modules as well.

6.1.1 Baseline conditions

Demographics (sex, birth date, race, and ethnicity where allowed), information on tobacco and alcohol use, and baseline conditions will be collected during the screening visit.

6.1.2 Medical history

History of the patient's cancer and concomitant disease, other diseases, and operations will be obtained. The type of cancer, the date of the first histological diagnosis (month and year may be sufficient), and the primary tumour site will be reported on the eCRF. The differentiation grade (not specified, undifferentiated, poorly differentiated, moderately differentiated, well differentiated) obtained at the time of diagnosis and the location of metastatic sites as well as the stage according to the tumour, (lymph) node, and metastasis (TNM) classification will be provided as obtained at diagnosis and at trial screening. Previous surgeries will be reported.

Previously administered chemotherapy, tyrosine kinase inhibitor treatment, vaccine therapy, antibodies therapy, immune therapy, and hormone therapy will be reported, including start and end dates (month and year may be sufficient), as well as whether therapy was given as neoadjuvant, adjuvant, or palliative therapy. The date of tumour progression after previous lines of treatment will be recorded, if known. Baseline PD-L1 expression level, microsatellite instability (MSI), and tumour mutation burden (TMB) information will be collected in eCRF, if locally available.

6.1.3 Concomitant therapies

Relevant concomitant diagnoses and/or therapies present at trial entry and/or during screening and relevant to the patient's safety during the trial as judged by the Investigator will be recorded in the eCRF. Post-trial therapy for advanced or metastatic disease will also be documented.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN – MODEL

To effectively use the information from these patients' cohorts in the assessment of the efficacy, a Bayesian hierarchical model (BHM) approach (R13-4803), which assumes full exchangeability of model parameters and allows borrowing information across patients' cohorts, will be used to analyse the response rate endpoints (i.e., objective response rate, disease control rate). For cases where the initial assumption of exchangeability may not be valid more general approaches will be considered like the EXNEX (R17-3435). If that is the case the primary model will be described explicitly in the respective Module.

The BHM has 2 main components: a data model and a parameter model, as well as priors for the parameter model. The data model is a binomial sampling model

$$r_j|n_j \sim Binomial\left(n_j, p_j\right), \text{j} = 1, 2, 3, \ldots$$

where n_j and r_j are the number of patients and the corresponding number of patients with response in each patient cohort. The parameter model for the log-odds parameters, including an adjustment for the target rates

$$\theta_j = log\left(\frac{p_j}{1-p_j}\right) - log\left(\frac{\tilde{p}_j}{1-\tilde{p}_j}\right)$$

is specified as

$$\theta_j|\,\mu,\tau \sim N(\mu,\tau^2), \text{j} = 1, 2, 3, \ldots$$

where $\tilde{p}_j$ is the target response rate, μ denotes the "overall" mean of θ_j and τ determines the inter-cohort heterogeneity. A non-informative normal prior is used for the mean parameter μ. For the inter-cohort heterogeneity parameter τ, a prior distribution will be specified in each of the Modules. Based on this model the cohort specific shrinkage estimators for p_j will be evaluated.

7.2 NULL AND ALTERNATIVE HYPOTHESES

This trial is an exploratory trial. No formal hypothesis testing is planned in this trial. Only descriptive analysis will be performed.

7.3 PLANNED ANALYSES

Only one analysis population will be considered for efficacy and safety analyses: the treated set (i.e., patients treated with at least one dose of trial medications).

In the case that a patient switches to another available treatment in the study, the detailed handling rule will be described in the TSAP.

The data from each module will be analysed and reviewed together with the data from other studies in the same combination project to evaluate the safety and efficacy benefit in explored indications/patient populations. Decisions on further development will be made based on an analysis of the aggregated data for each combination via a meta-analytic approach implementing quantitative Go-NoGo rules. Results of the meta-analytic approach will be

summarised as an internal research report and will be used to support the rationale and the benefit-risk assessment for future development trials, if applicable.

7.3.1 Primary endpoint analyses

Overall response will be analysed in terms of ORR, defined as the proportion of patients with best overall response of CR or PR determined according to RECIST v1.1 until the earliest of disease progression, death or last evaluable tumour assessment before start of subsequent anti-cancer therapy. A BHM approach will be used to derive the posterior distribution of the response rate endpoints of each patient cohort within each Module if applicable. The median and 95% credible interval will be used to summarize the posterior. It will be evaluated and described in the Trial Statistical Analysis Plan (TSAP) which cohorts will be included in the model. Data from other trials may be included as well if deemed appropriate. If a different primary model is chosen for a specific Module, e.g. the EXNEX method etc., the details of the analysis method will be illustrated in that Module.

Descriptive statistics regarding e.g., observed response rates will be displayed additionally.

In the case that a patient meets the inclusion and exclusion criteria for more than one cohorts within a Module, the handling rule will also be documented in the TSAP.

The primary analysis will include patients who received only one anti-PD-(L)1 based treatment regimen prior to entering the trial, and additional analyses may be performed taking into account the patients who cross-over from different Modules and therefore will have had more than one prior anti-PD-(L)1 based therapy.

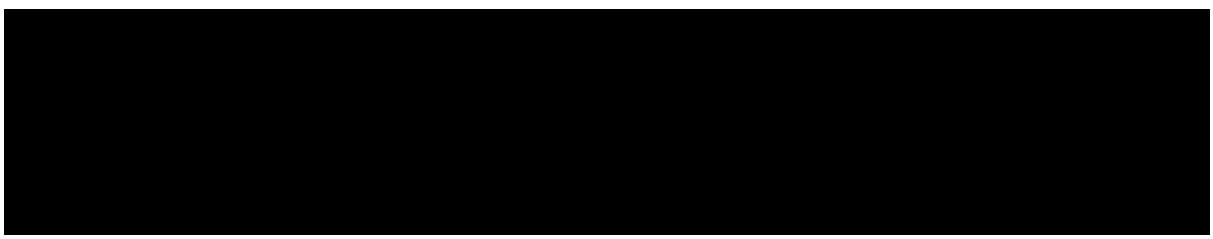
7.3.2 Secondary endpoint analyses

The same method for the analysis of primary endpoint will be used for the analysis of disease control. All the other endpoints will be analysed separately for each cohort.

Descriptive analysis will be performed for DoR.

Kaplan-Meier estimates will be used to analyse PFS with 95% confidence intervals, using Greenwood’s variance estimate.

The censoring rules for PFS and DoR (i.e., outcome and the date of outcome) are described in the TSAP.



7.3.4 Safety analyses

Adverse events will be coded using the Medical Dictionary for Drug Regulatory Activities (MedDRA). Standard BI summary tables and listings will be produced. All adverse events with an onset between start of treatment and end of the REP, defined in each Module, will be assigned to the on-treatment period for evaluation.

All treated patients will be included in the safety analysis. In general, safety analyses will be descriptive in nature and will be based on BI standards. No hypothesis testing is planned. Statistical analysis and reporting of adverse events will concentrate on treatment-emergent adverse events, i.e. all AEs occurring between start of treatment and end of the REP. AEs that start before first drug intake and deteriorate under treatment will also be considered as 'treatment-emergent'.

Frequency, severity, and causal relationship of adverse events will be tabulated by system organ class and preferred term after coding according to the current version of the MedDRA at database lock.

Laboratory data will be analysed both quantitatively as well as qualitatively. The latter will be done via comparison of laboratory data to their reference ranges. Values outside the reference range as well as values defined as clinically relevant will be summarised. Treatment groups will be compared descriptively with regard to distribution parameters as well as with regard to frequency and percentage of patients with abnormal values or clinically relevant abnormal values.

Vital signs, physical examinations, or other safety-relevant data observed at screening, baseline, during the course of the trial and at the end-of-trial evaluation will be assessed with regard to possible changes compared to findings before start of treatment.

7.4 INTERIM ANALYSES

Interim analysis will be performed when deemed necessary. Final/primary analysis for a specific treatment combination or cohort will be considered as interim analysis. A cohort or Module may be closed, if determined to be appropriate based on results on interim analyses. Note that interim analysis will not lead to any modifications within the running trial unless otherwise stated in a Module.

Details will be described in the Trial Statistical Analysis Plan (TSAP).

7.5 HANDLING OF MISSING DATA

In general, no imputation will be performed on missing efficacy data. For PFS data, every effort will be made to obtain date of progression for patients known to have progressed. Detailed censoring rules will be specified in the TSAP. Missing baseline laboratory values will be imputed by the respective values from the screening visit. No other imputations will be performed on missing data although every effort will be made to obtain complete information on all AEs. For partial or missing AE onset and/or end dates, BI internal rules will be followed.

7.6 RANDOMISATION

The treatment assignment will be determined by person(s) independent from the site using predefined criteria and entered into the Interactive Response Technology (IRT) System. If not stated differently in a Module, a balanced randomisation across available treatment groups is the aim.

7.7 DETERMINATION OF SAMPLE SIZE

As sample sizes are in particular depending on assumptions regarding cohort-specific response rates and the number of cohorts to be investigated they will be determined in each of the treatment-specific Modules. Sample sizes are selected to ensure reasonable probabilities of reaching the pre-specified response rate under a wide range of scenarios.

8. INFORMED CONSENT, TRIAL RECORDS, DATA PROTECTION, PUBLICATION POLICY, AND ADMINISTRATIVE STRUCTURE

The trial will be carried out in compliance with the protocol, the ethical principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonized Guideline for Good Clinical Practice (GCP), relevant BI Standard Operating Procedures (SOPs), the EU regulation 536/2014 and other relevant regulations. Investigators and site staff must adhere to these principles.

Standard medical care (prophylactic, diagnostic and therapeutic procedures) remains the responsibility of the treating physician of the patient.

The investigator will inform the sponsor immediately of any urgent safety measures taken to protect the trial patients against any immediate hazard, as well as of any serious breaches of the protocol or of ICH GCP.

The Boehringer Ingelheim transparency and publication policy can be found on the following web page: trials.boehringer-ingelheim.com. The rights of the investigator and of the sponsor with regard to publication of the results of this trial are described in the investigator contract. As a rule, no trial results should be published prior to finalization of the Clinical Trial Report.

The certificate of insurance cover is made available to the investigator and the patients, and is stored in the ISF.

Patients will sign a Master informed consent form (ICF) for screening. Upon module assignment, the patient will sign the corresponding module ICF. Further screening assessments will be performed to determine eligibility for the Module the patient is assigned to.
Patients that progress on treatment in a given Module may be offered treatment in another Module if deemed appropriate by the Investigator and Sponsor, and must sign the ICF for the newly-assigned Module.

8.1 TRIAL APPROVAL, PATIENT INFORMATION, INFORMED CONSENT

This Master protocol and each treatment-specific Module (the trial will begin with one module, Module A) will be initiated only after all required legal documentation has been reviewed and approved by the respective IRB / Independent Ethics Committee (IEC and competent authority (CA) according to national and international regulations. The same applies for the implementation of changes such as additional Modules which will be introduced by amendments. Clinically ineffective or completed Modules will be closed.

Prior to patient participation in the trial, written informed consent must be obtained from each patient (or the patient's legally accepted representative) according to ICH-GCP and to the regulatory and legal requirements of the participating country. Each signature must be personally dated by each signatory and the informed consent and any additional patient-information form retained by the investigator as part of the trial records. A signed copy of the informed consent and any additional patient information must be given to each patient or the patient's legally accepted representative.

The investigator or delegate must give a full explanation to trial patients based on the patient information form. A language understandable to the patient should be chosen, technical terms and expressions avoided, if possible. The patient must be given sufficient time to consider participation in the trial. The investigator or delegate obtains written consent of the patient's own free will with the informed consent form after confirming that the patient understands the contents. The investigator or [redacted] delegate must sign (or place a seal on) and date the informed consent form. If a trial collaborator has given a supplementary explanation, the trial collaborator also signs (or places a seal on) and dates the informed consent.

Re-consenting may become necessary when new relevant information becomes available and should be conducted according to the sponsor's instructions.

The consent and re-consenting process should be properly documented in the source documentation.

8.2 DATA QUALITY ASSURANCE

It is initiated by the assessment of critical data and processes for trial subject protection and reliability of the results as well as identification and assessment of associated risks. An Integrated Quality and Risk Management Plan documents the rationale and strategies for risk management during trial conduct including monitoring approaches, vendor management and other processes focusing on areas of greatest risk.

Continuous risk review and assessment may lead to adjustments in trial conduct, trial design or monitoring approaches.

A quality assurance audit/inspection of this trial may be conducted by the sponsor, sponsor's designees, or by IRB / IEC or by regulatory authorities. The quality assurance auditor will have access to all medical records, the investigator's trial-related files and correspondence, and the informed consent documentation of this clinical trial.

8.3 RECORDS

CRFs for individual patients will be provided by the sponsor. For drug accountability, refer to Section 4.1.7.

8.3.1 Source documents

In accordance with regulatory requirements, the investigator should prepare and maintain adequate and accurate source documents and trial records that include all observations and other data pertinent to the investigation on each trial patient. Source data as well as reported data should follow the 'ALCOA principles' and be **a**ttributable, **l**egible, **c**ontemporaneous, **o**riginal and **a**ccurate. Changes to the data should be traceable (audit trail).
Data reported on the CRF must be consistent with the source data or the discrepancies must be explained.

The current medical history of the patient may not be sufficient to confirm eligibility for the trial and the investigator may need to request previous medical histories and evidence of any diagnostic tests. In this case, the investigator must make three documented attempts to retrieve previous medical records. If this fails, a verbal history from the patient, documented in their medical records, would be acceptable.

Copies of source documents necessary for tumour assessment will be provided to the sponsor. Before sending or uploading those copies, the investigator must ensure that all patient identifiers (e.g. patient's name, initials, address, phone number, social security number) have properly been removed or redacted from any copy of the patients' source documents.

If the patient is not compliant with the protocol, any corrective action e.g. re-training must be documented in the patient file.

For the CRF, data must be derived from source documents, for example:

- Patient identification: gender, year of birth (in accordance with local laws and regulations)
- Patient participation in the trial (substance, trial number, patient number, date patient was informed)
- Dates of patient's visits, including dispensing of trial medication
- Medical history (including trial indication and concomitant diseases, if applicable)
- Medication history
- Adverse events and outcome events (onset date [mandatory], and end date [if available])
- Serious adverse events (onset date (mandatory), and end date [if available])
- Concomitant therapy (start date, changes)
- Originals or copies of laboratory results and other imaging or testing results, with proper documented medical evaluation (in validated electronic format, if available)
- Completion of patient's participation in the trial" (end date; in case of premature discontinuation document the reason for it).
- Prior to allocation of a patient to a treatment into a clinical trial, there must be documented evidence in the source data (e.g. medical records) that the trial participant

meets all inclusion criteria and does not meet any exclusion criteria. The absence of records (either medical records, verbal documented feedback of the patient or testing conducted specific for a protocol) to support inclusion/exclusion criteria does not make the patient eligible for the clinical trial.

8.3.2 Direct access to source data and documents

The investigator /institution will allow site trial-related monitoring, audits, IRB / IEC review and regulatory inspections. Direct access must be provided to the CRF and all source documents/data, including progress notes, copies of laboratory and medical test results, which must be available at all times for review by the CRA, auditor and regulatory inspector (e.g. FDA). They may review all CRFs and informed consents. The accuracy of the data will be verified by direct comparison with the source documents described in Section 8.3.1. The sponsor will also monitor compliance with the protocol and GCP.

8.3.3 Storage period of records

Trial site(s):
The trial site(s) must retain the source and essential documents (including ISF) according to contract or the local requirements valid at the time of the end of the trial (whatever is longer).

Sponsor:
The sponsor must retain the essential documents according to the sponsor's SOPs.

8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

BI is responsible to fulfil their legal and regulatory reporting obligation in accordance with regulatory requirements.

Exemptions from expedited reporting are described in Section 5.2.6.2.5, if applicable.

8.5 STATEMENT OF CONFIDENTIALITY AND PATIENT PRIVACY

Individual patient data obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the exceptions noted in Section 8.7.

Data protection and data security measures are implemented for the collection, storage and processing of patient data in accordance with the principles 6 and 12 of the WHO GCP handbook.

Personalised treatment data may be given to the patient's personal physician or to other appropriate medical personnel responsible for the patient's welfare. Data generated at the site as a result of the trial need to be available for inspection on request by the participating physicians, the sponsor's representatives, by the IRB / IEC and the regulatory authorities.

8.5.1 Collection, storage and future use of biological samples and corresponding data

Measures are in place to comply with the applicable rules for the collection, biobanking and future use of biological samples and clinical data, in particular

- Sample and data usage has to be in accordance with the separate biobanking informed consent
- The BI-internal facilities storing biological samples from clinical trial participants as well as the external banking facility are qualified for the storage of biological samples collected in clinical trials.
- An appropriate sample and data management system, incl. audit trail for clinical data and samples to identify and destroy such samples according to ICF is in place
- A fit for the purpose documentation (biomarker proposal, analysis plan and report) ensures compliant usage
- A fit for purpose approach will be used for assay/equipment validation depending on the intended use of the biomarker data
- Samples and/or data may be transferred to third parties and other countries as specified in the biobanking ICF

8.6 TRIAL MILESTONES

Independent milestones will be defined in each individual Module. Milestones for the Master are not necessary since it is the launching point for each Module.

The start of the trial is defined as the date when the first patient in the whole trial signs informed consent for the Master protocol and treatment-specific Module.

The **end of the trial** is defined as the date of the last visit of the last patient in the whole trial ('Last Patient Completed').

The **'Last Patient Last Treatment'** (LPLT) date is defined as the date on which the last patient in the whole trial is administered the last dose of trial treatment (as scheduled per protocol or prematurely). Individual investigators will be notified of SUSARs occurring with the trial medication until 30 days after LPLT at their site.

Early termination of the trial is defined as the premature termination of the trial due to any reason before the end of the trial as specified in this protocol.

Temporary halt of the trial is defined as any unplanned interruption of the trial by the sponsor with the intention to resume it.

Suspension of the trial is defined as an interruption of the trial based on a Health Authority request.

8.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL

The trial is sponsored by Boehringer Ingelheim (BI).

A Coordinating Investigator is responsible to coordinate investigators at the different sites participating in this trial. Tasks and responsibilities are defined in a contract.

A Steering Committee (SC) consisting of independent experts and sponsor representatives will be established to support the Coordinating Investigator who will be the chair of the SC. The composition of the SC will be documented in the Trial Master File (TMF). The tasks and responsibilities will be agreed in contracts between the SC members and the sponsor and also summarised in a SC charter.

The safety of all patients will be under surveillance by the Safety Review Committee (SRC). The SRC will be responsible for assessing the progress of the clinical trial, including making safety and efficacy assessments at specified intervals. The SRC will have unblinded access to data from this trial.

Members of the SRC will include:

- [redacted] Medical Monitor for the trial
- Principal Investigators, or delegates, from investigational sites
- BI Safety Physician, or delegate
- BI Clinical Program Leader responsible for the project
- BI Project or Trial Statistician.

The BI Safety Physician, BI Clinical Program Leader, or delegate, should always attend the SRC, if there are safety issues for discussion. [redacted], [redacted], Medical Monitor, or delegate, should always be present at the SRC.

The tasks and responsibilities of the SRC will be documented. The SRC will maintain written records of all its meetings.

Relevant documentation on the participating (Principal) Investigators (e.g. their curricula vitae) will be filed in the ISF.

Data Management and Statistical Evaluation will be done by BI according to BI SOPs.

Tasks and functions assigned in order to organise, manage, and evaluate the trial are defined according to BI SOPs. A list of responsible persons and relevant local information can be found in the ISF.

An IRT vendor will be used in this trial. Details will be provided in the IRT Manual are available in the ISF.

9. REFERENCES

9.1 PUBLISHED REFERENCES

R09-0262 Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45:228-47.

R13-4803 Neuenschwander B, Branson M, Gsponer T. Critical aspects of the Bayesian approach to phase I cancer trials. Stat Med. 2008;27:2420-39.

R15-2005 Bohnsack O, Ludajic K, Hoos A. Adaptation of the immune-related response criteria: irRECIST. 39th Ann Cong of the European Society for Medical Oncology (ESMO), Madrid, 26-30 Sep 2014 (Poster).

R15-3588 Topalian SL, Hodi FS, Brahmer JR, Gettinger SN, Smith DC, McDermott DF, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. N Engl J Med. 2012;366(26):2443-54.

R15-3715 Brahmer J, et al. Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. N Engl J Med. 2015;373(2):123-35.

R15-3776 Robert C, Schachter J, Long GV, Arance A, Grob JJ, Mortier L, et al. KEYNOTE-006 Investigators Pembrolizumab versus ipilimumab in advanced melanoma. N Engl J Med, 2015;372(26):2521-32.

R15-3778 Robert C, Ribas A, Wolchok JD, Hodi FS, Hamid O, Kefford R, et al. Anti-programmed-death-receptor-1 treatment with pembrolizumab in ipilimumab-refractory advanced melanoma: a randomised dose-comparison cohort of a phase 1 trial. Lancet. 2014;384:1109-17.

R15-6023 Garon EB, Rizvi NA, Hui, R, Leighl N, Balmanoukian AS, Eder JP, et al., KEYNOTE-001 Investigators. Pembrolizumab for the treatment of non-small-cell lung cancer. N Engl J Med. 2015;372(21):2018-28.

R15-6038 Taube JM, Anders RA, Young GD, Xu H, Sharma R, McMiller TL, et al. Colocalization of inflammatory response with B7-H1 expression in human melanocytic lesions supports an adaptive resistance mechanism of immune escape. Sci Transl Med. 2012;4(127):127ra37.

R16-0663 Antonia S, Goldberg SB, Balmanoukian A, Chaft JE, Sanborn RE, Gupta A, et al. Safety and antitumour activity of durvalumab plus tremelimumab in non-small cell lung cancer: a multicentre, phase 1b study. Lancet Oncol. 2016; (online publication):1-10.

R16-0864 Topalian SL, Sznol M, McDermott DF, Kluger HM, Carvajal RD, Sharfman WH, et al. Survival, durable tumor remission, and long-term safety in patients with advanced melanoma receiving nivolumab. J Clin Oncol. 2014:32(10):1020-30.

R16-0868 Koyama S, et al. Adaptive resistance to therapeutic PD-1 blockade is associated with upregulation of alternative immune checkpoints. Nat Commun. 2016;7:10501.

R16-0876 Herbst RS, Baas P, Kim DW, Felip E, Perez-Gracia JL, Han JY, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. Lancet. 2016;387(10027):1540-50.

R16-1225 Fehrenbacher L, Spira A, Ballinger M, Kowanetz M, Vansteenkiste J, Mazieres J, et al. POPLAR Study Group Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): a multicentre, open-label, phase 2 randomised controlled trial. Lancet. 2016; (online publication). 00587-95.

R16-1588 Rosenberg J, Hoffman-Censits J, Powles T, van der Heijden MS, Balar AV, Neechi A, et al. Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial. Lancet. 2016; (online publication): 00561-4.

R16-2360 Francisco LM, Sage PT, Sharpe AH. The PD-I Pathway in Tolerance and Autoimmunity. Immunol Rev. 2010;236:219-42.

R16-2361 Freeman GJ, Long AJ, Iwai Y, Bourque K, Chernova T, Nishimura H, et al. Engagement of the PD-1 immunoinhibitory receptor by a novel B7 family member leads to negative regulation of lymphocyte activation. J. Exp. Med. 2000;192(7):1027-34.

R16-2362 Nishimura N, Nose M, Hiai H, Minato N, Honjo T. Development of lupus-like autoimmune diseases by disruption of the PD-1 gene encoding an ITIM motif-carrying immunoreceptor. Immunity. 1999;11:141-51.

R16-2363 Ishida Y, Agata Y, Shibahara K, Honjo T. Induced expression of PD-1, a novel member of the immunoglobulin gene superfamily, upon programmed cell death. The EMBO Journal. 1992;11(11):3887-95.

R16-2364 Nishimura H, Okazaki T, Tanaka Y, Nakatani K, Hara M, Matsumori A, et al. Autoimmune dilated cardiomyopathy in PD-1 receptor-deficient mice. Science. 2001;291(5502):319-22.

R16-2371 Dong H, Strome SE, Salomao DR, Tamura H, Hirano F, Flies DB, et al. Tumor-associated B7-H1 promotes T-cell apoptosis: a potential mechanism of immune evasion. Nature Med. 2002;8(8):793-800.

R16-2968 Dong H, Zhu G, Tamada K, Flies DB, Deursen JMA van, Chen L. B7-H1 determines accumulation and deletion of intrahepatic CD8+ T lymphocytes. Immunity. 2004;20(3):327-36.

R16-2969 Nishimura H, Honjo T. PD-1: an inhibitory immunoreceptor involved in peripheral tolerance. Trends Immunol. 2001;22(5):265-68.

R16-2970 Okazaki T, Okazaki I, Wang J, Sugiura D, Nakaki F, Yoshida T, et al. PD-1 and LAG-3 inhibitory co-receptors act synergistically to prevent autoimmunity in mice. J Exp Med. 2011;208(2):395-407.

R16-3547 Massard C, Gordon MS, Sharma S, Rafii S, Wainberg ZA, Luke J, et al. Safety and Efficacy of Durvalumab (MEDI4736), an Anti–Programmed Cell Death Ligand-1 Immune Checkpoint Inhibitor, in Patients With Advanced Urothelial Bladder Cancer. J Clin Oncol. 2016;34:1-9.

R16-4925 American Cancer Society. Cancer facts & figures 2016. http://www.cancer.org/acs/groups/content/@research/documents/document/acspc-0470 79.pdf (access date: 20 October); Atlanta: American Cancer Society 2016.

R16-5335 Huang RY, Francois A, McGray AJR, Miliotto A, Odunsi K. Compensatory upregulation of PD-1, LAG-3 and CTLA-4 limits the efficacy of single agent checkpoint blockade in metastatic ovarian cancer. Oncoimmunology. 2016.

R16-5356 Workman CJ, Vignali DAA. Negative regulation of T cell homeostasis by lymphocyte activation gene-3 (CD223). J Immunol. 2005;174(2):688-95.

R16-5357 Triebel F, Jitsukawa S, Baixeras E, Roman-Roman S, Genevee C, Viegas-Pequignot E, et al. LAG-3, a novel lymphocyte activation gene closely related to CD4. J Exp Med. 1990;171(5):1393–1405.

R16-5358 Huard B, Mastrangeli R, Prigent P, Bruniquel D, Donini S, El-Tayar N, et al. Characterization of the major histocompatibility complex class II binding site on LAG-3 protein. Proc Natl Acad Sci USA. 1997;94:5744-49.

R17-3435 Neuenschwander B, Wandel S, Roychoudhury S, Bailey S. Robust exchangeability designs for early phase clinical trials with multiple strata. Pharm Stat 2105; 15:123-134.

10. APPENDICES

10.1 IMMUNE-RELATED ADVERSE EVENTS OF SPECIAL INTEREST

Table 10.1: 1 Immune-related adverse events of special interest

This table defines immune-related AEs that must be reported as AESIs.

Immune-related adverse events of special interest
Pneumonitis (reported as an AESI if ≥ Grade 2)
• Acute interstitial pneumonitis • Interstitial lung disease • Pneumonitis
Colitis (reported as an AESI if ≥ Grade 2 or any grade resulting in dose modification or use of systemic steroids to treat the AE)
• Intestinal obstruction • Colitis • Colitis microscopic • Enterocolitis • Enterocolitis haemorrhagic • Gastrointestinal perforation • Necrotizing colitis • Diarrhoea
Endocrine (reported as an AESI if ≥ Grade 3 or ≥ Grade 2 and resulting in dose modification or use of systemic steroids to treat the AE)
• Adrenal insufficiency • Hyperthyroidism • Hypophysitis • Hypopituitarism • Hypothyroidism • Thyroid disorder • Thyroiditis • Hyperglycaemia, if ≥ Grade 3 and associated with ketosis or metabolic acidosis
Endocrine (reported as an AESI)
• Type 1 diabetes mellitus (if new onset)

Immune-related adverse events of special interest
Hematologic (reported as an AESI if ≥ Grade 3 or any grade resulting in dose modification or use of systemic steroids to treat the AE)
• Autoimmune haemolytic anaemia • Aplastic anaemia • Thrombotic thrombocytopenic purpura • Idiopathic (or immune) thrombocytopenia purpura • Disseminated intravascular coagulation • Haemolytic-uraemic syndrome • Any Grade 4 anaemia regardless of underlying mechanism
Hepatic (reported as an AESI if ≥ Grade 2, or any grade resulting in dose modification or use of systemic steroids to treat the AE**)**
• Hepatitis • Autoimmune hepatitis • Transaminase elevations (ALT and/or AST)
Infusion Reactions (reported as an AESI)
• Allergic reaction • Anaphylaxis • [redacted] release syndrome • Serum sickness • Infusion reactions • Infusion-like reactions
Neurologic (reported as an AESI)
• Autoimmune neuropathy • Guillain-Barre syndrome • Demyelinating polyneuropathy • Myasthenic syndrome
Ocular (report as an AESI if ≥ Grade 2 or any grade resulting in dose modification or use of systemic steroids to treat the AE)
• Uveitis • Iritis
Renal (reported as an AESI if ≥ Grade 2)
• Nephritis • Nephritis autoimmune • Renal failure • Renal failure acute • Creatinine elevations (report as an irAE if ≥Grade 3 or any grade resulting in dose modification or use of systemic steroids to treat the AE)

Immune-related adverse events of special interest
Skin (reported as an AESI)
• Dermatitis exfoliative • Erythema multiforme • Stevens-Johnson syndrome • Toxic epidermal necrolysis
Skin (reported as an AESI if ≥ Grade 3)
• Pruritus • Rash • Rash generalized • Rash maculopapular • Any rash considered clinically significant in the physician's judgment
Other (reported as an AESI)
• Myocarditis • Pancreatitis • Pericarditis • Any other Grade 3 event that is considered immune-related by the physician

10.2 MANAGEMENT OF IMMUNE-RELATED ADVERSE EVENTS

Management of immune-related adverse event toxicities associated with anti-PD-1 mAbs are presented below. Ezabenlimab should be permanently discontinued for Grade 3-4 pneumonitis, Grade 3-4 adrenal insufficiency, Grade 4 diabetes mellitus, any grade encephalitis, Grade 4 hypophysitis, Grade 4 rash, Grade 3-4 or recurrent colitis of any grade, any recurrent Grade 3-4 AE, transaminase >5 times ULN or total bilirubin >3 times ULN (unless unequivocally attributably to another cause), inability to taper steroids to 10 mg or less prednisone or equivalent within 12 weeks, or persistent Grade 2-3 AEs that do not recover to Grade 1 or less within 12 weeks.

- Pneumonitis:
    - For Grade 2 events, treat with systemic corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 28 days.
    - Add prophylactic antibiotics for opportunistic infections in the case of prolonged steroid administration.
    - For Grade 3-4 events immediately treat with i.v. steroids. Administer additional anti-inflammatory measures, as needed.
    - Ezabenlimab should be permanently discontinued for Grade 3-4 pneumonitis, inability to taper steroids to 10 mg or less prednisone or equivalent within 12 weeks, or persistent Grade 2 AEs that do not recover to Grade 1 or less within 12 weeks.
- Diarrhoea/Colitis:

Subjects should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhoea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus).

- All subjects who experience diarrhoea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via i.v. infusion. For Grade 2 or higher diarrhoea, consider GI consultation and endoscopy to confirm or rule out colitis.
- For Grade 2 diarrhoea/colitis that persists greater than 3 days, administer oral corticosteroids.
- For Grade 3 or 4 diarrhoea that persists >1 week, treat with i.v. steroids followed by high-dose oral steroids.
- For Grade 3 or 4 colitis, or recurrent colitis of any grade, permanently discontinue Ezabenlimab and immediately treat with i.v. steroids followed by high-dose oral steroids.
- When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 28 days.
- Ezabenlimab should be permanently discontinued for Grade 3-4 or recurrent colitis of any grade, inability to taper steroids to 10 mg or less prednisone or equivalent within 12 weeks, or persistent Grade 2-3 AEs that do not recover to Grade 1 or less within 12 weeks.

- Type 1 diabetes mellitus (if new onset, including diabetic ketoacidosis) Grade 3, or ≥ Grade 3 hyperglycaemia, if associated with ketosis (ketonuria) or metabolic acidosis
    - For Type 1 diabetes mellitus Grade 3-4 or Grade 3-4 hyperglycaemia

        - Insulin replacement therapy is recommended for Type I diabetes mellitus and for Grade 3-4 hyperglycaemia associated with metabolic acidosis or ketonuria.
        - Evaluate subjects with serum glucose and a metabolic panel, urine ketones, glycosylated haemoglobin, and C-peptide.
    - Ezabenlimab should be permanently discontinued for Grade 4 diabetes mellitus, any recurrent Grade 3 AE or persistent Grade 2-3 AE that does not recover to Grade 1 or less within 12 weeks.
- Hypophysitis:
    - For Grade 2 events, treat with corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 28 days. Replacement of appropriate hormones may be required as the steroid dose is tapered.
    - For Grade 3 events, treat with an initial dose of i.v. corticosteroids followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 28 days. Replacement of appropriate hormones may be required as the steroid dose is tapered.
    - For Grade 4 events, permanently discontinue ezabenlimab, and treat with an initial dose of i.v. corticosteroids followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 28 days. Replacement of appropriate hormones may be required as the steroid dose is tapered.
    - Ezabenlimab should be permanently discontinued for Grade 4 hypophysitis, any recurrent Grade 3 AE, inability to taper steroids to 10 mg or less prednisone or equivalent within 12 weeks, or persistent Grade 2-3 AEs that do not recover to Grade 1 or less within 12 weeks.
- Hyperthyroidism or Hypothyroidism:
  Thyroid disorders can occur at any time during treatment. Monitor subjects for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders.
    - For Grade 2 hyperthyroidism events (and Grade 3-4 hypothyroidism):
        - In hyperthyroidism, nonselective beta-blockers (e.g., propranolol) are suggested as initial therapy.
        - In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyronine, is indicated per standard of care.
    - For Grade 3-4 hyperthyroidism
        - Treat with an initial dose of i.v. corticosteroid followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 28 days. Replacement of appropriate hormones may be required as the steroid dose is tapered.
    - Ezabenlimab should be permanently discontinued for any recurrent Grade 3-4 AE, inability to taper steroids to 10 mg or less prednisone or equivalent within 12 weeks, or persistent Grade 2-3 AEs that do not recover to Grade 1 or less within 12 weeks.

- Hepatic:
  - For Grade 2 events, monitor liver function tests more frequently until returned to baseline values (consider weekly).
    - Treat with i.v. or oral corticosteroids
  - For Grade 3-4 events, treat with i.v. corticosteroids for 24 to 48 hours.
  - When symptoms improve to Grade 1 or less, a steroid taper should be started and continued over no less than 28 days.
  - Ezabenlimab should be permanently discontinued for any recurrent Grade 3-4 AE, transaminase >5 times ULN or total bilirubin >3 times ULN (unless unequivocally attributably to another cause), inability to taper steroids to 10 mg or less prednisone or equivalent within 12 weeks, or persistent Grade 2-3 AEs that do not recover to Grade 1 or less within 12 weeks.
- Renal failure or nephritis:
  - For Grade 2 events, treat with corticosteroids.
  - For Grade 3-4 events, treat with systemic corticosteroids.
  - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 28 days.
  - Ezabenlimab should be permanently discontinued for any recurrent Grade 3-4 AE, inability to taper steroids to 10 mg or less prednisone or equivalent within 12 weeks, or persistent Grade 2-3 AEs that do not recover to Grade 1 or less within 12 weeks.
- Adrenal insufficiency
  - Ezabenlimab should be permanently discontinued for Grade 3-4 adrenal insufficiency or persistent Grade 2 AEs that do not recover to Grade 1 or less within 12 weeks.
- Rash
  - Ezabenlimab should be permanently discontinued for Grade 4 rash, any recurrent Grade 3 AE or persistent Grade 2-3 AEs that do not recover to Grade 1 or less within 12 weeks.
- Encephalitis
  - Ezabenlimab should be permanently discontinued for any grade encephalitis.
- Infusion reactions:
  Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. In the event of an infusion-related reaction ≤ Grade 2, treat the symptoms accordingly with antihistamine or corticosteroids if needed, the infusion rate of study drug(s) may be decreased by 50% or interrupted until resolution of the event and re-initiated at 50% of the initial rate until completion of the infusion. In patients experiencing infusion-related reactions ≤ Grade 2, subsequent infusions may be administered at 50% of the initial rate. If an infusion-related reaction is Grade 3 or higher in severity at any point during the study, permanently discontinue study drug(s).

10.3 PHARMACOKINETIC METHODS AND ANALYSES

Methods and procedure for handling blood samples are presented in the Laboratory Manual for the individual Modules.

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

This is the original protocol.

11.1 GLOBAL AMENDMENT 1

Date of amendment		7 MAY 2019
EudraCT number **EU number**		2018-002344-81
BI Trial number		BI 1381-0009
BI Investigational Medicinal Product(s)		See Modules
Title of protocol		An open-label, Phase II, platform trial evaluating safety and efficacy of multiple BI 754091 anti-PD-1 based combination regimens in PD-(L)1 naïve and PD-(L)1 pretreated patient populations with advanced and/or metastatic solid tumours who have had at least one line of systemic therapy
To be implemented only after approval of the IRB / IEC / Competent Authorities		X☒
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		☐
Section to be changed		Synopsis - Main inclusion and exclusion criteria
Description of change		Patients moving from one module to another must have prior irAEs resolved to a degree that would allow for restart of checkpoint inhibitor therapy according to the irAE management guidelines in the protocol.
Rationale for change		An additional inclusion criteria was added and included in the list of main inclusion and exclusion criteria to highlight it.

Section to be changed		Synopsis - Main inclusion and exclusion criteria
Description of change		**More than** ~~A maximum of~~ one anti-PD-(L)1-based treatment regimen prior to entering study, more specifically defined in the modules.
Rationale for change		To help clarify the criteria
Section to be changed		Synopsis - Main inclusion and exclusion criteria
Description of change		• Active autoimmune disease or a documented history of autoimmune disease, except vitiligo or resolved childhood asthma/atopy, or a patient **who was permanently discontinued** ~~removed~~ from previous anti-PD-1 or anti-PD-L1 therapy because of a ~~severe~~ immune-related adverse event (irAE).
Rationale for change		To help clarify the criteria
Section to be changed		Synopsis - Duration of Treatment
Description of change		**The patient must sign an approved ICF for the subsequent Module, be screened prior to entering the new Module, and must meet all Master and Module-specific inclusion criteria. The transition time between Modules (last dose of previous Module and screening visit of subsequent Module) will be a maximum of 2 months. Patients will be allowed multiple crossovers into subsequent Modules.**
Rationale for change		The additional text provides further detail about how a crossover to another Module after progression on their previous treatment Module.
Section to be changed		1.2 Drug Profile
Description of change		BI 754091 will be combined with other agents in each of the ~~multiple~~ Modules.
Rationale for change		"Multiple" was removed from the description of modules to avoid implying there would be an unlimited number of modules in the study.
Section to be changed		1.4 BENEFIT – RISK ASSESSMENT
Description of change		~~BI 754091 is currently being tested in patients in the BI 1381.1 clinical trial. Preliminary clinical safety information indicates that BI 754091 monotherapy in 39 patients with advanced metastatic cancer is well tolerated with no reported dose limiting toxicities (DLTs), treatment related SAE or treatment related deaths. Preliminary efficacy analyses indicate that there are 5 patients with partial response (PR) and 17 patients with disease stabilization on BI 754091 monotherapy in the trial 1381.1. The PRs were reported in two patients with triple negative breast cancer,~~

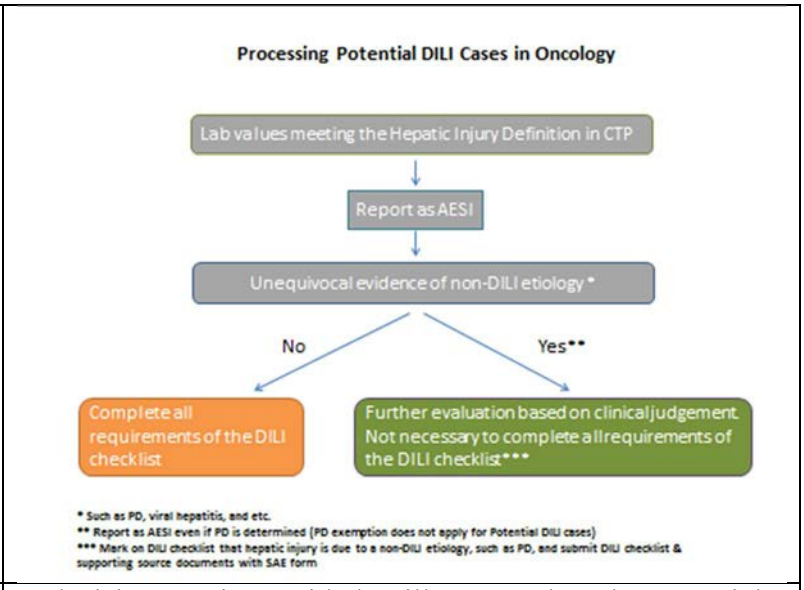
		~~one patient with ovarian cancer, one patient with renal cancer, and one patient with stomach cancer. All of these PRs occurred in patients receiving the 240 mg q3w dose of BI 754091 (BI 754091 Investigator Brochure).~~ **As of 30-November-2018, 50 patients with advanced/metastatic solid tumours have been treated with BI 754091 as monotherapy in the 1381.1 trial.** **The most frequently reported AEs (reported in >10% of the patients) were fatigue (40%), nausea (28.0%), decreased appetite (18.0%), arthralgia (16.0%), cough (16.0%), abdominal pain (14.0%), constipation (14.0%), diarrhoea (14.0 %), vomiting (14.0), back pain (12.0%) and dyspnoea (12.0%). Headache, hypokalaemia, muscular chest pain, myalgia, pruritis and rash, each occurred at a frequency of 10.0%. The majority of these AEs were CTCAE Grade 1 and 2.** **Grade 3 and 4 AEs were reported in 38.0% and 4.0% of patients, respectively. Of the Grade 3 events, only the AST elevation event was reported as related to trial drug. The reported Grade 4 AEs were 1 (2.0%) case of disease progression and 1 (2.0%) case of sepsis, neither of which was deemed treatment related.** **Consistent with the similar drug class labels, most irAEs were reported in the GI, skin and endocrine system organ class (SOCs). The majority of the irAEs were Grades 1 or 2; the only Grade 3 irAE was AST increase.** **Preliminary efficacy analyses for study 1381.1 indicate that there have been 6 patients with partial response (PR) and 20 patients with stable disease (SD) as best response on BI 754091 monotherapy. The PRs were reported in two patients with triple negative breast cancer, one patient with fallopian tube cancer, one patient with renal cancer, one patient with stomach cancer and one patient with endometrial cancer. All of these PRs occurred in patients receiving the 240 mg q3w dose of BI 754091.** **A similar safety profile of BI 754091 monotherapy was observed in 6 Japanese patients with solid tumours evaluated in the Asian trial 1381.4.**

		The details of the preliminary analysis are provided in section 6.2 of the BI 754091 IB.
Rationale for change		More recent safety and efficacy information has been added to update the benefit-risk section of the protocol.
Section to be changed		1.4 BENEFIT – RISK ASSESSMENT
Description of change		Trial procedures such as blood sampling, imaging with ~~e.g.~~ contrast media, **and** tumour biopsies, are part of standard of care in these advanced cancer patients.
Rationale for change		The text was clarified to better describe the standard of care for advanced cancer patients.
Section to be changed		3.3.2 Inclusion Criteria
Description of change		**3 Patient moving from one module to another must have prior irAEs resolved to a degree that would allow for restart of checkpoint inhibitor therapy according to the irAE management guidelines in the protocol.**
Rationale for change		Text has been added to provide safety guidance when a patient moves from one Module to another.
Section to be changed		3.3.2 Inclusion Criteria
Description of change		**Male patients with partners of childbearing potential must agree to use condoms and ensure their partners are using an additional highly-effective method of birth control, during the trial and until at least 6 months after the end of the trial treatment.**
Rationale for change		The additional language provides guidance for male patients with partners of childbearing potential. This also aligns the text with the contraception requirements found in Section 4.2.2.3.
Section to be changed		3.3.3 Exclusion Criteria
Description of change		**2 More than** ~~A maximum of~~ one anti-PD-(L)1-based treatment regimen prior to entering study, more specifically defined in the modules.
Rationale for change		To help clarify the criteria
Section to be changed		3.3.3 Exclusion Criteria
Description of change		**6. Patient has received allogeneic bone marrow or solid organ transplant.**
Rationale for change		To address UK regulatory concern.
Section to be changed		3.3.3 Exclusion Criteria
Description of change		10 Active autoimmune disease or a documented history of autoimmune disease, except vitiligo or resolved

		childhood asthma/atopy, or a patient **who was permanently discontinued** ~~removed~~ from previous anti-PD-1 or anti-PD-L1 therapy because of a ~~severe~~ immune-related adverse event (irAE).
Rationale for change		To help clarify the criteria
Section to be changed		3.3.3.1 Withdrawal of patients from treatment or assessments
Description of change		**The transition time between Modules (last dose of previous Module and screening visit of subsequent Module) will be a maximum of 2 months.**
Rationale for change		The additional text provides further detail about transition timelines between Modules after progression on a previous treatment Module.
Section to be changed		4.1.3.1 Method of assigning patients to a second or subsequent, Module(s)
Description of change		**The patient must sign an approved ICF for the subsequent Module, be screened prior to entering the new Module, and must meet all Master and Module-specific inclusion criteria. The transition time between Modules (last dose of previous Module and screening visit of subsequent Module) will be a maximum of 2 months. The assignment will be based on predefined algorithm if patients are eligible for more than one Module. Patients will be allowed multiple crossovers into subsequent Modules.**
Rationale for change		The additional text provides further detail about how to cross a patient over to another Module after they have had progression on their previous treatment Module.
Section to be changed		Section 4.2.2.3 Contraception requirements
Description of change		WOCBP and men able to father a child must use ~~two~~ medically approved methods of birth control throughout the trial, and for a period of at least 6 months after last trial drug intake. WOCBP must use ~~two~~ highly effective methods of birth control per ICH M3 (R2) that result in a low failure rate of less than 1% per year when used consistently and correctly during the trial, and for a period of at least 6 months after the last dose of trial drug.
Rationale for change		The text was updated to correct the number of highly effective methods of birth control that should be used by a patient.

Section to be changed		Section 4.2.2.3 Contraception requirements
Description of change		~~Acceptable methods of birth control for this trial are:~~ Highly-effective methods of contraception include:
Rationale for change		Redundant language was removed from the text.
Section to be changed		5.2.6.1.3 Adverse events of specific interest
Description of change		For this trial, infusion-related AEs, **potential** DILI events, hepatic injury, and qualifying irAEs, as defined in the treatment-specific Modules and Appendix 10.1, are AESIs.
Rationale for change		Language about drug-induced liver injury has been updated per BI revised template text to clarify that all liver elevations meeting potential Hy's Law criteria require expedited reporting as an AESI on the SAE form.
Section to be changed		5.2.6.1.3 Adverse events of specific interest
Description of change		In the event of an infusion-related reaction ≤ Grade 2, ~~the~~**treat the symptoms accordingly with antihistamine or corticosteroids if needed. The** infusion rate of BI 754111 and/or the combination of BI 754111 plus BI 754091 may be decreased by 50% or interrupted until resolution of the event and re-initiated at 50% of the initial rate until completion of the infusion. In patients experiencing infusion-related reactions ≤ Grade 2, subsequent infusions may be administered at 50% of the initial rate. **If an infusion-related reaction is Grade 3 or higher in severity at any point during the study, permanently discontinue study drug(s).**
Rationale for change		Pre-treatment medication has been added to the study prior to administration of the study treatment in order to reduce the risk of infusion related reactions. In addition, more detail has been provided on what to do in the event of a Grade 3 or higher infusion related reaction.
Section to be changed		5.2.6.1.3 Adverse events of specific interest
Description of change		Hepatic injury and **potential** drug-induced liver injury (DILI)
Rationale for change		Language about drug-induced liver injury has been updated per BI revised template text to clarify that all liver elevations meeting potential Hy's Law criteria require expedited reporting as an AESI on the SAE form.
Section to be changed		5.2.6.1.3 Adverse events of specific interest

Description of change		Hepatic injury definition: ~~In patient with normal baseline hepatic function, hepatic injury is defined by the following alterations in hepatic laboratory parameters:~~ ~~• An elevation of AST and/or ALT ≥3 times the ULN combined with an elevation of total bilirubin ≥2 times the ULN measured in the same blood draw sample, and/or~~ ~~• Marked peak AST and/or ALT elevation ≥10 times the ULN.~~ **A hepatic injury is defined by the following alterations of hepatic laboratory parameters:** • **an elevation of AST (Aspartate Aminotransferase) and/or ALT (Alanine Aminotransferase) ≥3 fold ULN combined with an elevation of total bilirubin ≥2 fold ULN measured in the same blood draw sample, or** • **aminotransferase (ALT and/or AST) elevations ≥10 fold ULN.** **These lab findings constitute a hepatic injury alert and the patients showing these lab abnormalities need to be followed up according to the "Potential DILI Checklist" provided in the ISF.** **In case of clinical symptoms of hepatic injury (icterus, unexplained encephalopathy, unexplained coagulopathy, right upper quadrant abdominal pain, etc.) without lab results (ALT, AST, total bilirubin) available, the investigator should make sure these parameters are analysed, if necessary in an unscheduled blood test. Should the results meet the criteria of hepatic injury alert, the procedures described in the "Potential DILI Checklist" (Figure 5.2.6.1.3: 1) should be followed.** **Lab values meeting the hepatic injury definition will need to be reported as an AESI. Please follow the flowchart below for reporting hepatic injury / potential DILI cases.**

		
Rationale for change		A decision tree is provided to illustrate when the Potential DILI Checklist is initiated and when it can be considered complete.
Section to be changed		5.2.6.2.4 Pregnancy
Description of change		**Similarly, potential drug exposure during pregnancy must be reported if a partner of a male trial participant becomes pregnant. This requires a written consent of the pregnant partner; Reporting and consenting must be in line with local regulations. The ISF will contain the trial specific information and consent for the pregnant partner.**
Rationale for change		Guidance for the pregnant partner of a male trial participant was added.
Section to be changed		5.2.6.2.5 Exemptions to SAE Reporting
Description of change		5.2.6.2.5 Exemptions to **AE**/SAE Reporting
Rationale for change		The header has been corrected to reflect the section content.
Section to be changed		5.2.6.2.5 Exemptions to AE/SAE Reporting
Description of change		**Lab values meeting the hepatic injury definition as defined in section 5.2.6.1.3 will need to be reported as AESI. PD reporting exemption does not apply to hepatic injury.**
Rationale for change		Text stating that PD reporting exemptions do not apply to hepatic injury reporting was added for clarification. Language added to clarify that liver injury is to be reported as an AESI.
Section to be changed		6.1.2 Medical history

Description of change		**Baseline PD-L1 expression level, microsatellite instability (MSI), and tumour mutation burden (TMB) information will be collected in eCRF, if locally available.**
Rationale for change		Additional baseline data for a deeper analysis was added.
Section to be changed		7.3 Planned Analyses
Description of change		**The data from each module will be analysed and reviewed together with the data from other studies in the same combination project to evaluate the safety and efficacy benefit in explored indications/patient populations. Decisions on further development will be made based on an analysis of the aggregated data for each combination via a meta-analytic approach implementing quantitative Go-NoGo rules. Results of the meta-analytic approach will be summarised as an internal research report and will be used to support the rationale and the benefit-risk assessment for future development trials, if applicable.**
Rationale for change		The text clarifies how the data from each module will contribute to the overall development plan for each potential combination and how the data from each module will be used going forward.
Section to be changed		**10.2 MANAGEMENT OF IMMUNE-RELATED ADVERSE EVENTS**
Description of change		**In the event of an infusion-related reaction ≤ Grade 2, treat the symptoms accordingly with antihistamine or corticosteroids if needed, the infusion rate of study drug(s) may be decreased by 50% or interrupted until resolution of the event and re-initiated at 50% of the initial rate until completion of the infusion. In patients experiencing infusion-related reactions ≤ Grade 2, subsequent infusions may be administered at 50% of the initial rate. If an infusion-related reaction is Grade 3 or higher in severity at any point during the study, permanently discontinue study drug(s).**
Rationale for change		More detail has been provided on what to do in the event of an infusion related reaction.

11.2 GLOBAL AMENDMENT 2

Number of Amendment		2
Date of amendment		14 JUL 2021
EudraCT number EU number		2018-002344-81

BI Trial number		BI 1381-0009
BI Investigational Medicinal Product(s)		See Modules
Title of protocol		An open-label, Phase II, platform trial evaluating safety and efficacy of multiple BI 754091 anti-PD-1 based combination regimens in PD-(L)1 naïve and PD-(L)1 pretreated patient populations with advanced and/or metastatic solid tumours who have had at least one line of systemic therapy
To be implemented only after approval of the IRB / IEC / Competent Authorities		X☒
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		☐
Section to be changed		Title page/ BI IMP(s)
Description of change		Added **ezabenlimab**
Rationale for change		BI 754091's INN is "ezabenlimab". The section was updated to show the new name associated with BI 754091
Section to be changed		Coordinating Investigator
Description of change		[redacted], [redacted]
Rationale for change		[redacted] will replace [redacted] as the coordinating investigator.
Section to be changed		Synopsis Main Inclusion and Exclusion Criteria and Section 3.3.2 Inclusion Criteria
Description of change		5 Eastern Cooperative Oncology Group (ECOG) score: 0 ~~to~~ **or** 1.
Rationale for change		To clarify that patients with either an ECOG of 0 or 1 may be enrolled onto the study.

Section to be changed		Synopsis Main Inclusion and Exclusion Criteria and Section 3.3.2 Inclusion Criteria and Section 3.3.3 Exclusion Criteria
Description of change		….the Investigator's **and/or Medical Monitor's**….
Rationale for change		To clarify that the Medical Monitor plays a role in determining if a patient meets the enrollment criteria.
Section to be changed		Synopsis Main Inclusion and Exclusion Criteria and Section 3.3.3 Exclusion Criteria
Description of change		12. ~~Known p~~**P**resence of ~~symptomatic~~ central nervous system (CNS) metastases, unless **treated and** asymptomatic and off corticosteroids and anti-convulsant therapy for at least 2 weeks prior start of treatment.
Rationale for change		To clarify that known, untreated, asymptomatic CNS metastases will also be an exclusion criteria.
Section to be changed		Section 3.3.2 Inclusion Criteria
Description of change		6 Patient must agree to a pre-treatment biopsy (if archival tissue is not available) and on-treatment tumour biopsy. If archived tumour tissue is available from the last treatment failure, sections may be supplied instead of a pre-treatment biopsy. ~~If the patient does not have archival tumour tissue and is not biopsiable because of a safety concern the patient could be considered for study after discussion with the Medical Monitor to potentially allow for inclusion of a patient with for a tumour type of interest.~~
Rationale for change		To prevent the enrollment of ineligible patients.
Section to be changed		Section 3.3.3 Exclusion Criteria
Description of change		5. Active infection requiring systemic treatment (antibacterial, antiviral, or antifungal therapy) at start of treatment in this trial. **Patients may be enrolled onto the study following an 7-day washout period after the end of systemic treatment for active infection.**
Rationale for change		To clarify how soon after an active infection a patient would be allowed to enrol.

11.3 GLOBAL AMENDMENT 3

Date of amendment		12 JUN 2023
EudraCT number **EU number**		2018-002344-81
BI Trial number		1381-0009
BI Investigational Medicinal Product(s)		See Modules

Title of protocol		An open-label, Phase II, platform trial evaluating safety and efficacy of multiple ezabenlimab anti-PD-1 based combination regimens in PD-(L)1 naïve and PD-(L)1 pretreated patient populations with advanced and/or metastatic solid tumours who have had at least one line of systemic therapy
To be implemented only after approval of the IRB / IEC / Competent Authorities		☐
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		☒
Section to be changed		Title Page/Clinical Trial Leader
Description of change		~~Trial Clinical Monitor~~**Clinical Trial Leader** [redacted] ~~Phone:~~ [redacted] **Phone:** [redacted]
Rationale for change		Role of 'Trial Clinical Monitor' changed to 'Clinical Trial Leader' due to update in role title within BI; role changed over to [redacted].
Section to be changed		Title Page/Coordinating Investigator and Synopsis
Description of change		[redacted] Phone: [redacted]

Rationale for change		Updated company name.
Section to be changed		Title page and throughout the document
Description of change		BI 754091 was changed to its INN, 'ezabenlimab'.
Rationale for change		Change was communicated with Global Amendment 2 (14 Jul 2021) but was not introduced to the study title or replaced throughout the document.
Section to be changed		Throughout the document
Description of change		[redacted] updated to [redacted]
Rationale for change		Updated to legal name.
Section to be changed		Section 4.1 Investigational Treatments
Description of change		Selection of the treatment-specific Module will be determined by the patient's tumour type, prior treatment, and algorithm (such as ~~IVRS~~**Interactive Response Technology [IRT]**) for patient assignment.
Rationale for change		Terminology corrected for consistency with rest of the document.
Section to be changed		Section 8.7 Administrative Structure of the Trial
Description of change		'BI Team Member Medicine' changed to 'BI Clinical Program Leader': Members of the SRC will include: • ~~BI Team Member Medicine~~**BI Clinical Program Leader** responsible for the project The BI Safety Physician, ~~BI Team Member Medicine~~**BI Clinical Program Leader**, or delegate, should always attend the SRC, if there are safety issues for discussion.
Rationale for change		Role of 'BI Team Member Medicine' changed to 'BI Clinical Program Leader' due to update in role title within BI.

APPROVAL / SIGNATURE PAGE

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Document Name: clinical-trial-protocol-version-04-master

Title: An open-label, Phase II, platform trial evaluating safety and efficacy of multiple ezabenlimab anti-PD-1 based combination regimens in PD-(L)1 naïve and PD-(L)1 pretreated patient populations with advanced and/or metastatic solid tumours who have had at least one line of systemic therapy

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Clinical Trial Leader	[redacted]	12 Jun 2023 13:05 CEST
Approval-Team Member Medicine	[redacted]	12 Jun 2023 13:10 CEST
Author-Trial Statistician	[redacted]	12 Jun 2023 13:17 CEST
Verification-Paper Signature Completion		27 Jun 2023 09:47 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed