CLINCAL TRIAL PROTOCOL MODULE A (BI 754091+BI 754111)

Document Number:		**c25025479-03**
EudraCT No.	2018-002344-81	
BI Trial No.	1381-0009	
BI Investigational Medicinal Product(s)	BI 754091 (anti-PD-1) BI 754111 (anti-LAG3)	
Title	An open-label, Phase II trial evaluating the safety and efficacy of BI 754111 in combination with BI 754091 in 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 module evaluating safety and efficacy of BI 754111 in combination with BI 754091 in PD-(L)1 naïve and PD-(L)1 pretreated patient populations with advanced/metastatic solid tumours.	
Clinical Phase	Phase II	
Trial Clinical Monitor	[redacted] Phone: [redacted] Fax: [redacted]	
Coordinating Investigator	[redacted] Phone: [redacted]	
Status	Final protocol (Revised Protocol [based on Global Amendment 2])	
Version and Date	**Version: 3**	**Date: 14 JUL 2021**

CLINICAL TRIAL PROTOCOL SYNOPSIS MODULE A (BI 754091 + BI 754111)

Company name	Boehringer Ingelheim
Name of finished product :	N.A.
Name of active ingredient :	BI 754091 and BI 754111
Protocol date	08 AUG 2018
Revision date	14 JUL 2021
BI trial number	1381-0009
Title of trial	An open-label, Phase II trial evaluating the safety and efficacy of BI 754111 in combination with BI 754091 in 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] [redacted] [redacted] Phone: [redacted]
Trial site(s)	This multicentre trial will be conducted in North America and the United Kingdom.
Clinical phase	Phase II
Trial rationale	Refer to Master protocol.
Trial objective(s)	The main objective of this Module is to assess the antitumour response of BI 754091 combined with BI 754111 in patients previously exposed to anti-PD-1 or anti-PD-L1 based therapy
Trial endpoints	Refer to the Master protocol.
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	Approximately 110 patients are planned for Module A.

Diagnosis	Cohort 1 GEC: Locally advanced, unresectable or metastatic gastric adenocarcinoma or gastro-oesophageal adenocarcinoma with prior anti-PD-1 or anti-PD-L1 based treatment. Cohort 2 Patients with secondary resistance to anti-PD-1 or anti-PD-L1 based therapy: Any advanced or metastatic solid tumour with previously anti-PD-1 or anti-PD-L1 based treatment who progressed after achieving benefit (at least SD with a minimum duration of benefit of 6 months and minimum treatment duration of 2 months on the previous anti-PD-1 or anti-PD-L1 based treatment without experiencing disease progression during that period). For patients with NSCLC who received anti-PD-1 or anti-PD-L1 based treatment as a first line regimen, the minimum duration of benefit is 8 months with a minimum treatment duration of 2 months on the previous anti-PD-1 or anti-PD-L1 based treatment without experiencing disease progression during that period. Cohort 3 Patients with primary resistance to anti-PD-1 or anti-PD-L1 based therapy: Select advanced or metastatic solid tumour types with previous anti-PD-1 or anti-PD-L1 based treatment without achieving benefit (RECIST v1.1 SD <6 months or progressive disease in <6 months while on previous anti-PD-1 or anti PD-L1 based treatment).
Main in- and exclusion criteria	Abbreviated Inclusion Criteria 1. Measurable lesions according to RECIST v1.1 2. Patient must agree to pre- and on-treatment tumour biopsies. If archived tumour tissue is available from the last treatment failure, sections may be supplied instead of a pre-treatment biopsy. If the patient is not biopsiable because of a safety concern the patient could be considered for study after discussion with the Medical Monitor to allow for inclusion of patients with a tumour type of particular interest.
	Abbreviated Exclusion Criteria 1. Any exclusion criteria listed in the Master protocol. 2. Previous treatment with an anti-LAG-3 agent
Test product(s)	BI 754091 will be co-administered in combination with BI 754111.
dose(s)	BI 754091: a fixed dose of 240 mg once every 3 weeks. BI 754111: 600 mg once every 3 weeks.
method and route of administration	BI 754091 and BI 754111 by 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), unacceptable toxicity, a maximum treatment duration of 1 year, or withdrawal of patient consent. Patients will be allowed to stay on treatment in case of initial radiological PD, if the Investigator feels that is in the patient's best interest. If the patient is benefiting clinically at 1 year, he/she may continue on treatment after a case-by-case review with the Medical Monitor and the sponsor.
Statistical methods	For the response endpoints (i.e., OR, DC), a Bayesian hierarchical modelling approach will be used. An adjustment for different expected response rates across the cohorts will be applied as described in R18-2260. Median shrinkage estimators together with related credible intervals will be considered. 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 MODULE A BI 1381.9

Module A flow chart

		Trial Treatment Days[a,b] Cycle = 21 Days							**Post-Treatment Days**		
	Screening[c]	**Cycles 1**				**Cycles 2-4**	**Cycles 5-11**	**Cycles 12-16**	**End-of-Treatment (EOT) Visit**	**30-Day Safety Follow-up**	**PFS Follow-up[h]**
Assessments (Days)	**-28 to -1**	**1**	**2**	**8 (±1)**	**15 (±1)**	**1 (±2)**	**1 (±2)**	**1 (±2)**	**(within 7 days of EOT)**	**(+2)**	
Informed Consent[b]	X										
Inclusion/Exclusion Criteria	X										
Medical History and Demographics[d]	X										
Physical Examination[c, d, e]	X	X			X	X	X	X	X	X	
ECOG Performance Status[c, d, e]	X	X				X	X	X	X	X	
Vital Signs[c, d]	X	X	X	X	X	X	X	X	X	X	
12-Lead Digital Electrocardiogram[c, d, f]	X								X	(X)	
Haematology and Clinical Chemistry Labs[c, d]	X	X		X	X	X	X	X	X	X	
Urinalysis[c, d]	X	X		X		X	X	X	X		
Pregnancy Test for Women of Child-Bearing Potential[c, d, g]	X	X				X	X	X	X		
Concomitant Medications[c]	X	X	X	X	X	X	X	X	X	X	X
Adverse Events[c]	X	X	X	X	X	X	X	X	X	X	X

		Trial Treatment Days[a,b] Cycle = 21 Days							**Post-Treatment Days**		
	Screening[c]	**Cycles 1**				**Cycles 2-4**	**Cycles 5-11**	**Cycles 12-16**	**End-of-Treatment (EOT) Visit**	**30-Day Safety Follow-up**	**PFS Follow-up[h]**
Assessments (Days)	**-28 to -1**	**1**	**2**	**8 (±1)**	**15 (±1)**	**1 (±2)**	**1 (±2)**	**1 (±2)**	**(within 7 days of EOT)**	**(+2)**	
Tumour Assessments[c, d, i]	X	X	Every 6 weeks ±3 days for the first 6 months (then every 9 weeks ±3 days thereafter)								
Survival[h]											X
Administration of Pre-Treatment Medication[n]		X				X	X	X			
BI 754111 and BI 754091 Infusions[j,l]		X				X	X	X			
Archival (at screening) or Fresh Tumour Biomarker Assessments[m]	X					X (C3 only)[m]	X (at 4 months-optional)		X (at PD)		
Blood Sample for PK BI 754091[k]		X	X		X	X	X (C5, 6 & 8)[o]	X (C12 & 16)[o]	X[o]	X[o]	
Blood Sample for PK BI 754111[k]		X	X		X	X	X (C5, 6 & 8)[o]	X C12 & 16)[o]	X[o]	X[o]	
[redacted]											

		Trial Treatment Days[a,b] Cycle = 21 Days							Post-Treatment Days		
	Screening[c]	Cycles 1				Cycles 2-4	Cycles 5-11	Cycles 12-16	End-of-Treatment (EOT) Visit	30-Day Safety Follow-up	PFS Follow-up[h]
Assessments (Days)	**-28 to -1**	**1**	**2**	**8 (±1)**	**15 (±1)**	**1 (±2)**	**1 (±2)**	**1 (±2)**	**(within 7 days of EOT)**	**(+2)**	
[redacted]		X				X (C3 only)[k]			X[o]		
		X		X	X	X (C2 only)			X[o]		

Flow Chart Footnotes

a All cycles are 3 weeks (21 days) in duration. Days are calculated as calendar days. Patients will continue treatment with the study drugs until disease progression (PD) by RECIST v1.1 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 trial beyond 1 year on a case-by-case basis after discussion with the Medical Monitor and the sponsor. A new IC will be required if the patient remains on study with radiological PD. Day 1 of Cycle 1 is defined as the first day when the combination of BI 754111 and BI 754091 is administered.

b Informed consent for Module A must be obtained ≤28 days prior to the initiation of treatment.

c Screening assessments required in the Master protocol and the Module obtained ≤14 days prior to Cycle 1 Day 1 do not need to be repeated unless otherwise noted.

d 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, troponin I (only at screening, C1D1, C1D8, C1D15, C2D1, C3D1, C4D1 and anytime CPK is elevated), creatine phosphokinase (CPK) [if CPK is elevated, then CPK-MB, troponin I, and myoglobin should be reactively tested], serum urea nitrogen (or urea), serum uric acid, and thyroid panel [TSH, free T4, and free T3]), urinalysis, and screening pregnancy test should be done ≤14 days prior to initiation of treatment. Additionally, amylase and lipase should be analysed in case of symptoms of pancreatitis. If these assessments are performed within 72 hours of initiation of treatment, they do not need to be repeated on Cycle 1 Day 1 with the exception of the ECOG performance status, an abbreviated physical examination, vital signs (pre- and post-infusion), and a single ECG required prior to first trial dose. Tumour assessments (scans) should be performed ≤28 days prior to initiation of treatment and copies may be collected by the sponsor or designee. Baseline PD-L1 expression level, microsatellite instability (MSI), and tumour mutation burden (TMB) information will be collected in the eCRF, if locally available. Refer to the Master protocol for additional details. Vital signs are checked at every visit.

e Physical examinations will be done at screening, on Day 1 of each treatment cycle, at the EOT visit, and at the 30-day safety follow-up visit. However, patients will have an additional abbreviated physical examination (focused on the specific disease, at the Investigator's discretion) on Cycle 1 Day 15. ECOG performance status will be done at screening, on Day 1 of Cycles 1 and 2, on Day 1 of every other cycle beginning with Cycle 3, at the EOT visit, and at the 30-day follow-up visit.

f Single digitalised ECGs must be done at the EOT visit and whenever the Investigator deems it necessary. An ECG is optional at the 30-day safety follow-up visit if the EOT visit ECG was normal and no drug-related abnormalities were detected in on-trial ECGs (see Master protocol).

g Women of child-bearing potential must have a serum beta human chorionic gonadotropin (β-HCG) pregnancy test at screening. Thereafter, this test can be done in either serum or urine on Day 1 of each cycle, and at the EOT visit (see Master protocol).

h Additional progression-free survival (PFS) follow-up visits after the 30-day safety follow-up visit will only be performed for patients who did not progress on treatment. These will be performed once every 12 weeks at least until PD, introduction of a new anti-cancer treatment, death, loss to follow-up, withdrawal of consent, or end of July 2021. As of July 2021, sites may conduct one final PFS visit for each patient that is being followed. For patients who remain on treatment after July 2021, no separate PFS visits will be done (the 30-day post treatment safety visit will be their last study visit).

i 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. Assessments will be performed by the Investigator at screening and every 2 cycles (6 weeks ±3 days) for the first 6 months of treatment, once every 3 cycles (9 weeks ±3 days) thereafter, at the EOT visit (if not performed within the previous 4 weeks), and at the discretion of the Investigator and copies will be collected by the sponsor or designee.

j Dosing of BI 754111 and BI 754091 is described in Module A Section 4.1.

k Blood samples for PKs, [redacted] will be collected from all patients as presented in Module A Section 10.4.

l If the decision is made to permanently discontinue study treatments during a scheduled visit, both BI 754091 and BI 754111 should be discontinued together and the EOT visit should be performed instead of the scheduled visit.

m Pre-treatment and on-treatment (Cycle 3 Day 1) tumour biopsies are mandatory for the study. For fresh biopsies always use the equivalent of no less than two 14-16 gauge needle biopsies (one for IHC and one for transcriptomics/genomics analyses).
Mandatory: The equivalent of no less than two 14-16 gauge needle biopsies (one for IHC and one for transcriptomics/genomics analyses) must be taken between screening and the day before the first study drug treatment. If medically counterindicated, archived tumour tissue available from the last treatment failure may be supplied instead of a pre-treatment biopsy. The archival submission should include 26 (4-5 µm) sections from the archival formalin-fixed paraffin-embedded FFPE block pre-treatment biopsy. Another mandatory biopsy will be collected at C3D1 (±5 days).
Optional: Patients with stable disease over 4 months should be asked for a tumour tissue biopsy at that time point. An optional biopsy is also requested at the time of PD (according to RECIST v1.1 and iRECIST), if possible. Patients enrolling in a second Module will be required to provide pre- and on-treatment tumour biopsy samples. In addition, an optional biopsy should be taken after treatment discontinuation, if possible.
Refer to the Laboratory Manual for collection, storage and shipping details.

n Pre-treatment medications (antihistamine and acetaminophen or paracetamol) should be administered at sufficient time prior to initiation of infusion to allow the agents to exert their influence.

- As of 01 July 2021, PK, [redacted] samples are no longer collected, including the End of Treatment, or the 30-day follow-up.

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ABBREVIATIONS

[redacted]	[redacted]
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Aminotransferase
AST	Aspartate Transaminase
βHCG	Beta Human Chorionic Gonadotropin
BHM	Bayesian Hierarchical Model
BI	Boehringer Ingelheim
BM	Biomarker
CA	Competent Authority
CNS	Central Nervous System
CPK	Creatinine Phosphokinase
CR	Complete Response
CRC	Colorectal Cancer
CRF	Case Report Form, paper or electronic (sometimes referred to as “eCRF”)
CRO	Contract Research Organization
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
[redacted]	[redacted]
CTP	Clinical Trial Protocol
DBL	Database Lock
DC	Disease Control
DILI	Drug Induced Liver Injury
DoR	Duration of Response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EOT	End of Treatment
EudraCT	European Clinical Trials Database
FFPE	Formulin fixed and paraffin embedded
GCP	Good Clinical Practice

GEC	Gastro-oesophageal Adenocarcinoma
GEJ	Gastro-oesophageal Junction
GI	Gastrointestinal
HCC	Hepatocellular Carcinoma
HIV	Human Immunodeficiency Virus
i.v.	Intravenous
IB	Investigator's Brochure
ICF	Informed consent form
IEC	Independent Ethics Committee
IHC	Immunohistochemistry
irAE	Immune-related adverse events
IRB	Institutional Review Board
ISF	Investigator Site File
LAG-3	Lymphocyte-activation gene 3
LPLT	Last Patient Last Treatment
mAb	Monoclonal antibody
MDSC	Myeloid-Derived Suppressor Cell
MedDRA	Medical Dictionary for Drug Regulatory Activities
MHC-II	Major histocompatibility complex Class II
MRI	Magnetic resonance imaging
NSCLC	Non-Small-Cell Lung Cancer
OR	Objective Response
OS	Overall Survival
PD	Progression of disease
PD-1	Programmed cell death 1 (receptor)
PDc	Pharmacodynamics
PD-L1	Programmed cell death ligand 1
PET	Positron Emission Tomography
PFS	Progression-Free Survival
PK	Pharmacokinetics
[redacted]	[redacted]
PR	Partial Response
PTM	Planned Time

RECIST	Response Evaluation Criteria in Solid Tumours
REP	Residual Effect Period
SAE	Serious Adverse Event
SCLC	Small-Cell Lung Cancer
SD	Stable Disease
SUSAR	Suspected Unexpected Serious Adverse Reactions
TNM	Classification of Malignant Tumours
ULN	Upper Level of Normal
[redacted]	[redacted]

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Refer to the Master protocol document to review the medical background information.

1.2 DRUG PROFILE

1.2.1 BI 754111

BI 754111 is a humanised IgG4Pro mAb against LAG-3 that is being developed as an intravenous (*i.v.*) infusion for the treatment of cancer. BI 754111 has highly human frameworks and a low predicted immunogenicity score.

1.2.2 BI 754091

Refer to the Master protocol.

1.3 RATIONALE FOR PERFORMING THE TRIAL

Lymphocyte-activation gene 3 (LAG-3) is a cell-surface negative regulator of immune response involved in maintaining immunological tolerance via regulation of T-cell activation, proliferation, and response (R15-3588; R16-5355; R16-5359). LAG-3 is expressed on activated cytotoxic, helper and regulatory T-cells (T-regs). LAG-3 binds to major histocompatibility complex Class II (MHC-II) glycoproteins and negatively regulates T-cell activity (R16-5357; R16-5358). LAG-3 also regulates T-cell response via T-regs as loss of LAG-3 expression on T-regs results in loss of T-reg function (R16-5355).

Tumours use the immune-checkpoint pathways (such as the PD-1 and LAG-3 pathways) to evade anti-tumour immune responses. Tumour-infiltrating lymphocytes frequently express high levels of PD-1 in combination with other immune-checkpoint inhibitors including LAG-3 (R16-0876, R16-5358), while the ligands for these checkpoint inhibitors (i.e., PD-L1/L2 and MHC-II, respectively) are expressed within the tumour microenvironment. Engagement of the co-inhibitory receptors PD-1 and LAG-3 by their respective ligands inhibits T-cell function preventing an anti-tumour immune response. It is now well established that blockade of the PD-1 axis of the immune-checkpoint program results in reactivation of T-cell function and the antitumour immune response leading to tumour growth inhibition in some patients.

Immune-checkpoint inhibition based therapy is now well established as the standard of care at multiple treatment lines for many cancers including NSCLC, melanoma, renal cancer, bladder cancer and many others. However, only a subset of patients achieve durable response to this therapy. The limited success achieved with checkpoint-inhibitor monotherapy (up to 80% of treated patients do not respond; R15-3588, R15-3778) in some studies may, in part, be attributed to redundancy in immune-checkpoint inhibitor pathways. Therefore, it is postulated that blockade of multiple checkpoint-inhibitor pathways may result in better anti-tumour activity and improved clinical outcome in a higher percentage of patients compared to checkpoint-inhibitor monotherapy. There is now sufficient evidence that show that blockage

of the PD-1 pathway leads to over-expression of other checkpoint inhibitors, including LAG-3. This over expression of other checkpoint inhibitors may represent an escape pathway from the PD-1 pathway blockade. Therefore, it is possible that blocking multiple checkpoint inhibitors at the same time would lead to better response and potentially rescue some of the patients that have failed the PD-1 single-agent blockade, including patient with NSCLC (R15-3696, R16-0868, R16-0881, R16-2707, R16-5335, R16-5545). Multiple immune-checkpoint inhibitor combinations are currently in development including the combination of anti-PD-1 and anti-LAG-3 mAbs with encouraging preliminary results (R16-5204, R16-5218).

New, more tolerable, combinations of immune-therapy treatment are needed to continue to improve the outcome for patients. BI 754111 in combination with BI 754091 has the potential to be such a combination.

The patient populations to be included in this trial were selected on the high unmet medical need (including poor response to currently available regimens or limited treatment options) of these patients and the potential for the combination checkpoint inhibitor therapy to provide clinical benefit for these patients.

1.4 BENEFIT - RISK ASSESSMENT

Significant improvement in checkpoint inhibitor effect has been achieved with checkpoint inhibitor combination therapy. The combination of nivolumab and ipilimumab, for example, has resulted in significant improvement in ORR, compared to checkpoint inhibitor monotherapy in patients with NSCLC and melanoma (R16-5545, R15-3696, R16-5544). Unfortunately, the improved efficacy of combined nivolumab and ipilimumab was associated with a significant increase in the rate and severity of AEs. Grade 3 and 4 AE rates of 53% to 55% were reported with the full-dose combination of nivolumab and ipilimumab in patients with melanoma (R15-3696, R16-5544) and 33% to 37% with reduced dose and dosing frequency of the ipilimumab component in NSCLC compared to approximately 10% for nivolumab monotherapy in these populations (R15-3696, R16-5544).

Treatment with BI 754111 and BI 754091 is anticipated to be associated with a similar pattern of AEs as nivolumab and ipilimumab. Infusion-related reactions have been reported with checkpoint-inhibitor treatments. These reactions occur infrequently and are typically managed based on symptoms using treatments ranging from histamine antagonists in mild cases to administration of epinephrine when symptoms of anaphylaxis are detected. Detailed irAE management guidelines are presented in Appendix 10.2.

BI 754091 combined with BI 754111 should be permanently discontinued (and withheld at least temporarily until recovery in the case of some lower grade events, e.g., pneumonitis) for Common Terminology Criteria for Adverse Events (CTCAE) Version 5 Grade 3 or 4 pneumonitis, Grade 3 or 4 adrenal insufficiency, Grade 3 or 4 or recurrent colitis of any grade, Grade 4 diabetes mellitus, Grade 4 hypophysitis, Grade 4 rash, any grade encephalitis, any recurrent Grade 3 or 4 AE, transaminase values >5 times the upper limit of normal (ULN) or total bilirubin >3 times ULN, inability to taper steroids to 10 mg or less prednisone

or equivalent within 12 weeks, or persistent Grade 2 or 3 AEs that do not recover to Grade 1 or less within 12 weeks. Additional information of management of irAEs is provided in Appendix 10.2

Based on these pre-clinical data, as well as clinical data obtained with BI 754091 and other anti-PD-1 mAbs, the inhibitory effects of the combination of BI 754111 and BI 754091 may translate into clinical benefit in cancer patients.

Therefore, treatment with BI 754111 and BI 754091 is expected to provide patients with clinical benefit at an acceptable risk.

Even so, patients should be advised of the potential risks of side effects from investigational trial treatments (e.g., relatlimab and nivolumab reports of a few cases of myocarditis). While some may be anticipated, others may be rare and unknown with irreversible and/or life-threatening effects. Patients should also be advised that there are other unknown risks associated with participation in a clinical trial.

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 patient safety (refer to the Master protocol).

Infusion-related reactions have been reported in approximately 7% (6/86) of patients treated with the combination of BI 754091 and BI 754111, and none were reported with BI 754091 monotherapy. The majority of the events were reported in patients receiving 240 mg of BI 754091 in combination with 600 mg of BI 754111, with 2 events reported in patients receiving 240 mg of BI 754091 in combination with 20 mg of BI 754111. The majority were CTCAE Grade 2. Two events were Grade 3 and led to treatment discontinuation. The reported infusion-related reactions occurred during the infusion mostly during Cycle 2 or Cycle 3.

2. TRIAL OBJECTIVES AND ENDPOINTS

Refer to the Master protocol for a complete list of objectives and endpoints for the trial.

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

2.1.1 Main objectives

The main objective of this treatment-specific Module is to assess the antitumour response of BI 754091 combined with BI 754111 in patients previously exposed to anti-PD-1 or PD-L1 based therapy and patients who achieved benefit from or failed to respond to the previous anti-PD-1or anti-PD-L1 therapy.

2.1.2 Primary endpoint

Refer to the Master protocol document for the primary endpoint.

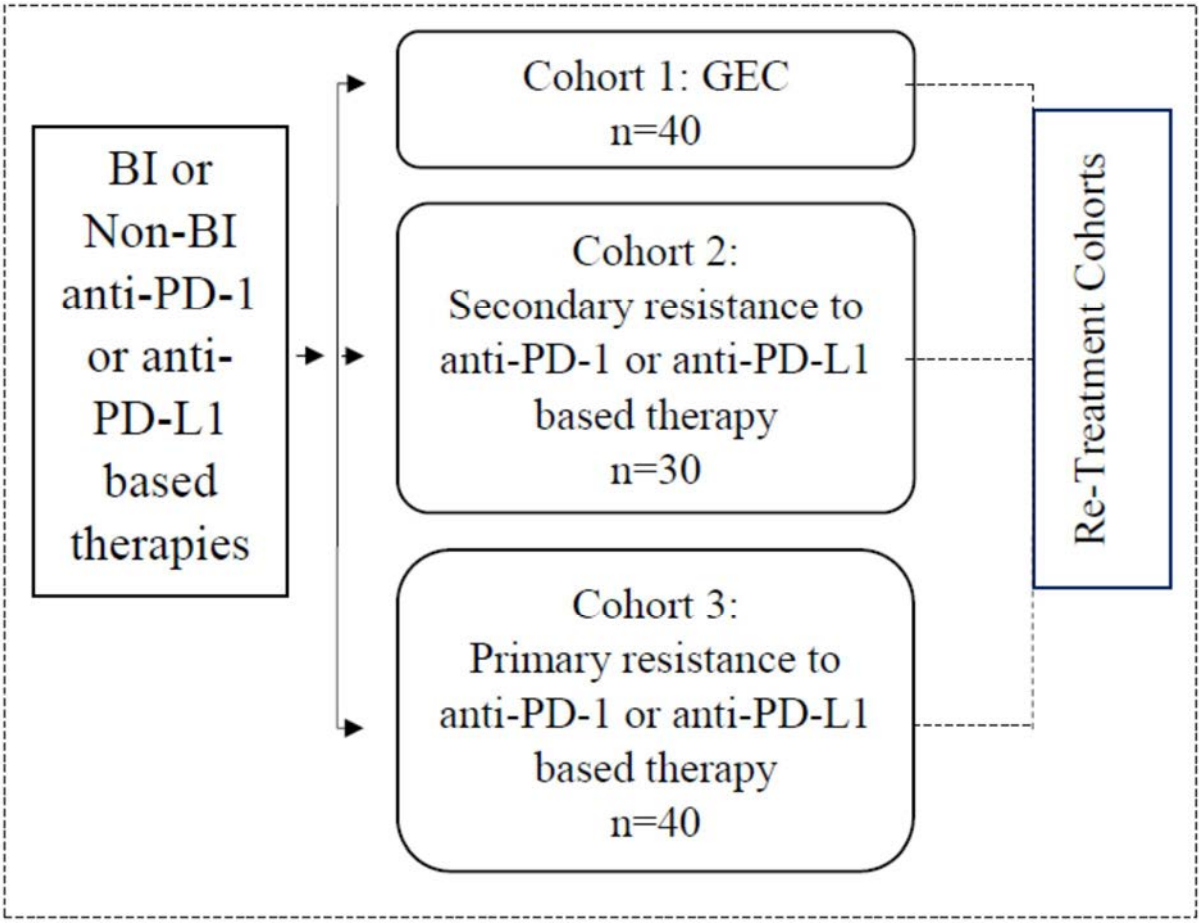
2.1.3 Secondary endpoints

Refer to the Master protocol document for a list of the secondary endpoints.

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

This is a Phase II, open-label, non-randomised, multicentre trial of BI 754111 administered in combination with BI 754091 to patients in one of three cohorts shown below.



Cohort 1 GEC: Locally advanced, unresectable or metastatic gastric adenocarcinoma or gastro-oesophageal adenocarcinoma with prior anti-PD-1 or anti-PD-L1 based treatment.

Cohort 2 Patients with secondary resistance to anti-PD-1 or anti-PD-L1 based therapy: Any advanced or metastatic solid tumour with previously anti-PD-1 or anti-PD-L1 based treatment who progressed after achieving benefit (at least SD with a minimum duration of benefit of 6 months and minimum treatment duration of 2 months on the previous anti-PD-1 or anti-PD-L1 based treatment without experiencing disease progression during that period). For patients with NSCLC who received anti-PD-1 or anti-PD-L1 based treatment as a first line regimen, the minimum duration of benefit is 8 months with minimum treatment duration of 2 months on the previous anti-PD-1 or anti-PD-L1 based treatment without experiencing disease progression during that period.

Cohort 3 Patients with primary resistance to anti-PD-1 or anti-PD-L1 based therapy: Select advanced or metastatic solid tumour types with previous anti-PD-1 or anti-PD-L1 based treatment without achieving benefit (SD <6 months or progressive disease in <6 months while on previous anti-PD-1 or anti PD-L1 based treatment.

Patients in this Module of the clinical trial will receive BI 754111 combined with BI 754091 by i.v. infusion after signing the Master and Module informed consent forms and completing the screening processes. Treatment cycles will be administered every 3 weeks (21 days). Safety laboratory assessments will be performed locally according to the Flow Chart (See Module A flow chart).

Tumour assessments will be done using Response Evaluation Criteria in Solid Tumours RECIST v1.1 and/or Immune-Related Response Evaluation Criteria in Solid Tumours (iRECIST) at screening and reassessed every 2 cycles (6 weeks ±3 days) for the first 6 months, then every 9 weeks using the same radiographic procedure. Pharmacokinetic and biomarker samples will be collected throughout the study as described in Section 10.4 and Section 10.4.1.

Patients will continue study treatment until disease progression (PD) according to RECIST v1.1 or iRECIST, withdrawal of patient consent, or an unacceptable toxicity occurs, whichever occurs first; maximum treatment duration is 1 year. 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 treatment beyond 1 year on a case-by-case basis after discussion with the Medical Monitor and the sponsor. The patient will be required to sign a new ICF to continue treatment.

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

Not applicable.

3.3 SELECTION OF TRIAL POPULATION

Screening of patients for this Module of the trial is competitive, i.e. screening for this Module of the trial will stop at all sites at the same time once a sufficient number of patients has been screened. Investigators will be notified about screening completion and will then not be allowed to screen additional patients for this Module of the 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) in the Master protocol for the documentation requirements pertaining to the inclusion and exclusion criteria. Patients must have one of the tumour types described item number 2, Section 3.3.2.

3.3.2 Inclusion criteria

For inclusion in the Module, patients must fulfil all of the following criteria in addition to the inclusion criteria described in the Master protocol.

1. Patient must have completed the screening process according to the Master protocol. Provision of signed and dated, written ICF prior to any trial-specific procedures, sampling, or analyses (Master ICF and Module ICF).
2. Histologically confirmed diagnosis of one of the following cohorts:
    - Cohort 1 GEC - Locally advanced, unresectable or metastatic gastric adenocarcinoma or gastro-oesophageal adenocarcinoma (GEC) (defined as primary tumour localisation below the gastro-oesophageal junction (GEJ) with prior anti-PD-1 or anti-PD-L1 based treated tumour.
        - Must have had ≥1 line of prior treatment; only 1 prior anti-PD-1/PD-L1 based therapy with the exception of BI PD-1 investigational agent allowed (prior chemotherapy plus anti-PD-L1 combination is allowed).
        - Previous anti-PD-1 or anti-PD-L1 based therapy in a clinical trial setting is allowed as long as it is confirmed that the patient did receive anti-PD-1 or anti-PD-L1 based therapy in the trial (i.e., not placebo).
    - Cohort 2 Patients with secondary resistance to anti-PD-1 or anti-PD-L1 based therapy: Any advanced or metastatic solid tumour with previously anti-PD-1 or anti-PD-L1 based treatment who progressed after achieving benefit
        - Must have had ≥1 line of prior treatment; only one prior anti-PD-1/PD-L1 based therapy with the exception of BI PD-1 investigational agent allowed.
        - Prior anti-PD-1 or anti-PD-L1 secondary resistance is defined as a minimum duration of benefit (i.e., at RECIST v1.1 SD) of 6 months and minimum treatment duration of 2 months on the previous anti-PD-1 or anti-PD-L1 based treatment without experiencing disease progression during that period. For patients with NSCLC who received anti-PD-1 or anti-PD-L1 based treatment as a first line regimen, the minimum duration of benefit is 8 months with minimum treatment duration of 2 months on the previous anti-PD-1 or anti-PD-L1 based treatment without experiencing disease progression during that period.
    - Cohort 3 Patients with primary resistance to anti-PD-1 or anti-PD-L1 based therapy: Select advanced or metastatic solid tumour types with previous anti-PD-1/PD-L1 based treated tumour without achieving benefit.
        - Must have had ≥1 line of prior treatment; only 1 prior anti-PD-1/PD-L1 based therapy with the exception of BI PD-1 investigational agent allowed.
        - Anti-PD-1 or anti-PD-L1 with primary resistance is defined as RECIST v1.1 stable disease (SD) less than 6 months or progressive disease in less than 6 months while on previous anti-PD-1 or anti-PD-L1 based treatment.
        - Included tumour types:
            - Previously treated CRC
            - Merkel cell carcinoma
            - Squamous cell skin carcinoma
            - Other squamous cancers: head and neck, cervical, anal, penile, oesophageal and vulvar

- Other gastrointestinal (GI) cancers: hepatocellular carcinoma (HCC), biliary tract
- Other thoracic cancers: small-cell lung cancer (SCLC) and mesothelioma
- Other tumour types for whom no therapy of proven efficacy exists, or who are not amenable to standard therapies and where anti-PD-1/PD-L1 therapy may be considered exceptional cases upon discussion with the Medical Monitor.

3. All patients must have measurable lesions according to RECIST v1.1
4. Patient must agree to pre- and on-treatment tumour biopsies. 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 an archival tumour tissue sample and is not biopsiable because of a safety concern the patient could be considered for study after discussion with the Medical Monitor to allow for a tumour type of interest.

3.3.3 Exclusion criteria

Patients must not enter the trial if any of the following exclusion criteria are fulfilled:

1. Any exclusion criteria listed in the Master protocol.
2. Previous treatment with an anti-LAG-3 agent

3.3.3.1 Withdrawal of patients from treatment or assessments

Refer to the Master protocol for withdrawal of patients from treatment or assessments guidance.

4. TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

4.1.1 Identity of the Investigational Medicinal Products

4.1.1.1 BI 754111

Details of the drug product, BI 754111, are presented in Table 4.1.1.1: 1 Additional details are presented in the BI 754111 IB and the Module A Pharmacy Manual.

Table 4.1.1.1: 1 BI 754111

Substance:	BI 754111
Pharmaceutical formulation:	Solution for infusion
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	20 mg/mL
Posology:	Infusion on Day 1 of each 3-week cycle
Route of administration:	I.V. infusion

4.1.1.2 BI 754091

Details of the drug product BI 754091 are presented in Table 4.1.1.2: 1. Additional details are presented in the BI 754091 IB and the Module A Pharmacy Manual.

Table 4.1.1.2: 1 BI 754091

Substance:	BI 754091
Pharmaceutical formulation:	Solution for infusion
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	20 mg/mL
Posology:	Infusion on Day 1 of each 3-week cycle
Route of administration:	I.V. infusion

4.2 SELECTION OF DOSES IN THE TRIAL

BI 754111 and BI 754091 will be diluted and administered via i.v. infusion once every three weeks according to the details in the Module A Pharmacy Manual.

4.2.1 BI 754111

The selected dose of BI 754111 to be used in combination with 240 mg BI 754091 is 600 mg administered via i.v. infusion once every 3 weeks. This dose of BI 754111 in combination with the selected dose of BI 754091 240 mg was selected based on the dose escalation data obtained in the ongoing trial 1381.2 (refer to the BI 754091 Investigator's Brochure (IB) and the BI 754111 IB).

4.2.2 BI 754091

The selected dose of BI 754091 to be used in combination with other agents is 240 mg every 3 weeks. This dose was selected by using the most recent clinical information from the ongoing trial 1381.1, administering BI 754091 monotherapy to patients with advanced solid tumours. PK data were collected and clinical response was observed during the conduct of trial 1381.1, providing a basis to investigate a combination approach (BI 754091 Investigator Brochure).

4.2.3 Method of assigning patients to treatment groups

After assessment of all inclusion and exclusion criteria, each eligible patient will be assigned to the applicable open cohort. Site personnel will enter the medication number in the CRF.

4.2.4 Blinding and procedures for unblinding

Not applicable in this open-label trial.

4.2.5 Packaging, labelling, and re-supply

Refer to the Master protocol for this information.

4.2.6 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.

4.2.7 Drug accountability

Refer to the Master protocol for this information.

4.2.8 Dose modifications

Dose reductions or escalations of BI 754111 or BI 754091 are not permitted in any one patient. Treatment administration may be delayed for a patient for one cycle, plus an additional 3 weeks, because of AEs, following discussion with the Medical Monitor.

If treatment is held or discontinued due to an AE(s), both BI 754091 and BI 754111 will be held or discontinued together. If treatment is to be restarted after resolution (≤ Grade 1) of the AE(s), both BI 754091 and BI 754111 must be restarted together.

The study drug(s) should be permanently discontinued for Grade 3 to 4 pneumonitis (for Grade 2 pneumonitis interrupt study drugs until resolution), Grade 3 to 4 adrenal insufficiency, Grade 4 diabetes mellitus, any grade encephalitis, Grade 4 hypophysitis, Grade 4 rash, Grade 3 to 4 colitis or recurrent colitis of any grade, any recurrent Grade 3 to 4 AE, transaminase increases >5 times ULN or total bilirubin >3 times ULN (unless unequivocally attributed to another cause), inability to taper steroids to 10 mg or less prednisone or equivalent within 12 weeks, or persistent Grade 2 to 3 AEs that do not recover to Grade 1 or less within 12 weeks. Study drug(s) should also be permanently discontinued for Grade 3 to 4 AEs that are classified as immune-related by the Investigator that are not listed in Appendix 10.1. Study drug(s) should be discontinued if ≥ Grade 4 drug-related AEs are reported. Please see Appendix 10.2 for guidelines for management of immune-related adverse events.

To reduce the risk of infusion-related reactions, patients are to be pre-treated with an antihistamine and acetaminophen or paracetamol. Pre-treatment should be administered at sufficient time prior to initiation of infusion to allow the agents to exert their effect.

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, study drug(s) will be permanently discontinued (refer to the safety section in the Master protocol) and adequate therapy should be initiated to treat the AE.

4.3 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

4.3.1 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.

4.3.2 Restrictions

4.3.2.1 Restrictions regarding concomitant treatment

Concomitant therapy, with reasons for the treatment, must be recorded in the electronic case report form (eCRF) during the screening and treatment periods, starting at the date of signature of ICF and ending at the 30-day follow-up visit. After the 30-day follow up, only concomitant therapy indicated for treatment of a related AE has to be reported. If a new anti-cancer treatment is started, it will be documented in the eCRF, on a separate page of follow-up therapy, different from the concomitant therapies pages.

4.3.2.2 Permitted concomitant medications

- If medically feasible, patients taking regular medication should be maintained on it throughout the trial.
- Pre-medication will not be required, but may be utilised following the first dose of BI 754111 or the first dose of combination therapy, as appropriate. This includes medications for the management of nausea, diarrhoea, and vomiting for which the patient must be treated according to institutional standards.
- Supportive care and other medications that are considered necessary for the patient's well-being may be given at the discretion of the Investigator.
- Blood transfusions are allowed at any time during the trial, except to meet inclusion criteria. There must be at least 4 weeks between a patient's last transfusion and their screening laboratory assessment. Exceptions to this will be considered by the sponsor on a case-by-case basis.
- Patients already receiving erythropoietin at the time of screening for the trial may continue it, provided they have been receiving it for more than one month at the time trial treatment is started. Prophylactic erythropoietin should not be started during the first 3 weeks of any cohort, but may be started thereafter. Immunosuppressive medications including, but not limited to systemic corticosteroids at doses exceeding 10 mg/day of prednisone or equivalent, methotrexate, azathioprine, and tumour necrosis factor-alpha blockers are prohibited. Use of immunosuppressive medications for the management of investigational product-related AEs or in patients with contrast allergies is acceptable, and does not necessarily warrant immediate treatment discontinuation. In addition, use of inhaled, topical, intranasal corticosteroids or local steroid injections (e.g., intra-articular injection) is permitted. Temporary uses of corticosteroids for concurrent illnesses (e.g., food allergies, computed tomography (CT) scan contrast hypersensitivity) are acceptable upon discussion with the Medical Monitor.
- To reduce the risk of infusion related reactions, patients are to be pre-treated with an antihistamine and acetaminophen or paracetamol. Pre-treatment should be administered at sufficient time prior to initiation of infusion to allow the agents to exert their effect.

4.3.2.3 Prohibited concomitant medications

- Live attenuated vaccines are prohibited during the trial through 30 days after the last dose of investigational product.
- Herbal preparations/medications are not allowed throughout the trial unless agreed to by the Principal Investigator. These herbal medications include, but are not limited to: St. John's wort, kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, and ginseng. If instructed by the Principal Investigator, patients should stop using these herbal medications 7 days prior to first dose of study treatment.
- Granulocyte colony stimulating factors should not be used prophylactically during the first 3 weeks treatment. Thereafter, prophylactic colony stimulating factors may be used according to institutional standards.
- Palliative radiotherapy is not allowed during the first cycle. Lesions that have been exposed to radiotherapy are no longer evaluable, and may not be included in the assessment of the non-target lesions and the overall assessment. Unless in emergency situations, the Medical Monitor should be contacted prior to the administration of palliative radiotherapy in the expansion phase.

4.3.2.4 Restrictions on diet and life style

No restrictions to diet or life style have been identified for BI 754091 or BI 754111.

4.3.2.5 Contraception requirements

Refer to the Master protocol Section 4.2.2.3).

4.4 TREATMENT COMPLIANCE

Refer to the Master protocol Section 4.3).

5. ASSESSMENTS

5.1 ASSESSMENT OF EFFICACY

To review the section on assessing efficacy according to RECIST v1.1 (R09-0262) and iRECIST (R15-2005) refer to the Master protocol.

5.2 ASSESSMENT OF SAFETY

The safety of BI 754091 and BI 754111 will be assessed by a descriptive analysis of incidence and severity of AEs graded according to CTCAE (Version 5), laboratory data, and results of physical examinations. Safety will be assessed in a descriptive way without confirmatory analysis.

Refer to the Master protocol for descriptions of the safety assessments (physical examination, vital signs, laboratory parameters, and electrocardiogram).

5.2.1 Other safety parameters

Not applicable.

5.2.2 Assessment of adverse events

Refer to the Master protocol for assessment of adverse events.

5.3 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

5.3.1 Assessment of pharmacokinetics

Blood for pharmacokinetic analysis of BI 754091 and BI 754111 will be collected at the visits specified in the **Module A flow chart** and in Appendix 10.4.

Pre-dose plasma concentrations shortly before the next infusion and the plasma concentrations after end of infusion of BI 754091 and BI 754111 will be evaluated descriptively according to BI internal Standard Operating Procedure (SOP) (001-MCS-36-472_RD-01 [2.0] and [redacted] SOP 'SOP-1.PKA.03 Non-compartmental PK/PD Analysis').

Sampling in the study will be limited to sparse sampling to primarily support an exploratory model based analysis. The plasma concentrations observed in study 1381.0009 will be pooled with data from other studies for a pooled model based analysis. The model based analysis will be planned and documented separately according to internal and external guidelines and BI SOP.

5.3.2 Methods of sample collection

Blood samples should not be obtained from the arm used for infusion. In case a central venous access is used for infusion, the blood sample can be collected from either forearm or central line. The actual sampling date and time (24-hour time clock) for each sample has to be recorded accurately.

For quantification of analyte plasma concentrations, blood will be drawn for both BI 754091 and BI 754111 at the time points specified in the PK time schedule in Appendix 10.4.

Samples may be used for further methodological investigations, e.g., stability testing. However, only data related to this trial, the analyte or bioanalytical assay will be generated by these additional investigations (i.e., using the sample for ADA or biomarker for PK if sample volume allowed). The trial samples will be discarded after completion of the additional investigations.

Details on sample collection for BI 754111 and BI 754091 characteristics, processing, handling, and shipment are provided in the Module A Laboratory Manual.

[redacted]

5.3.4 Pharmacokinetic – pharmacodynamic relationship

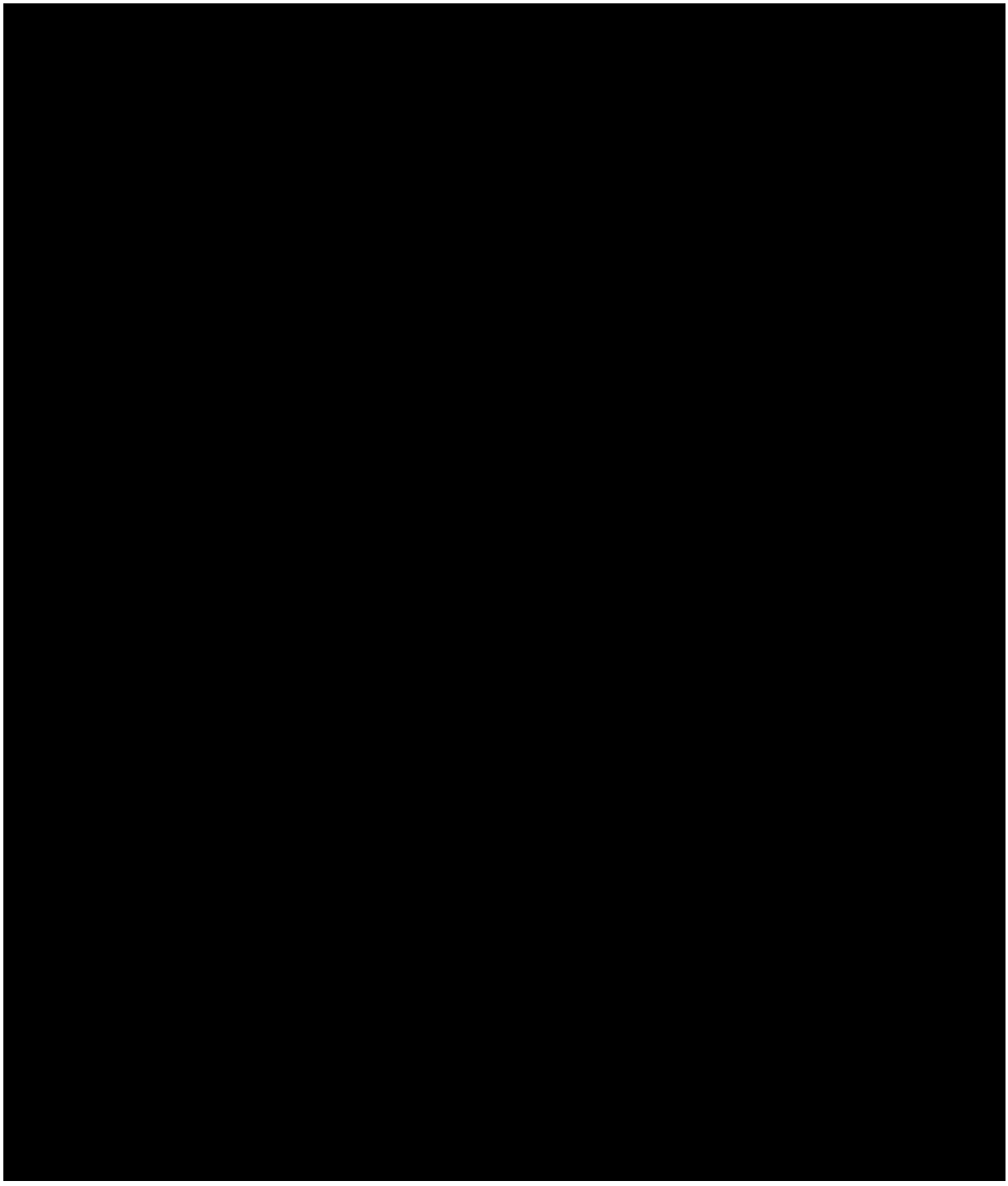
No formal analysis of a PK/PD relationship is planned.

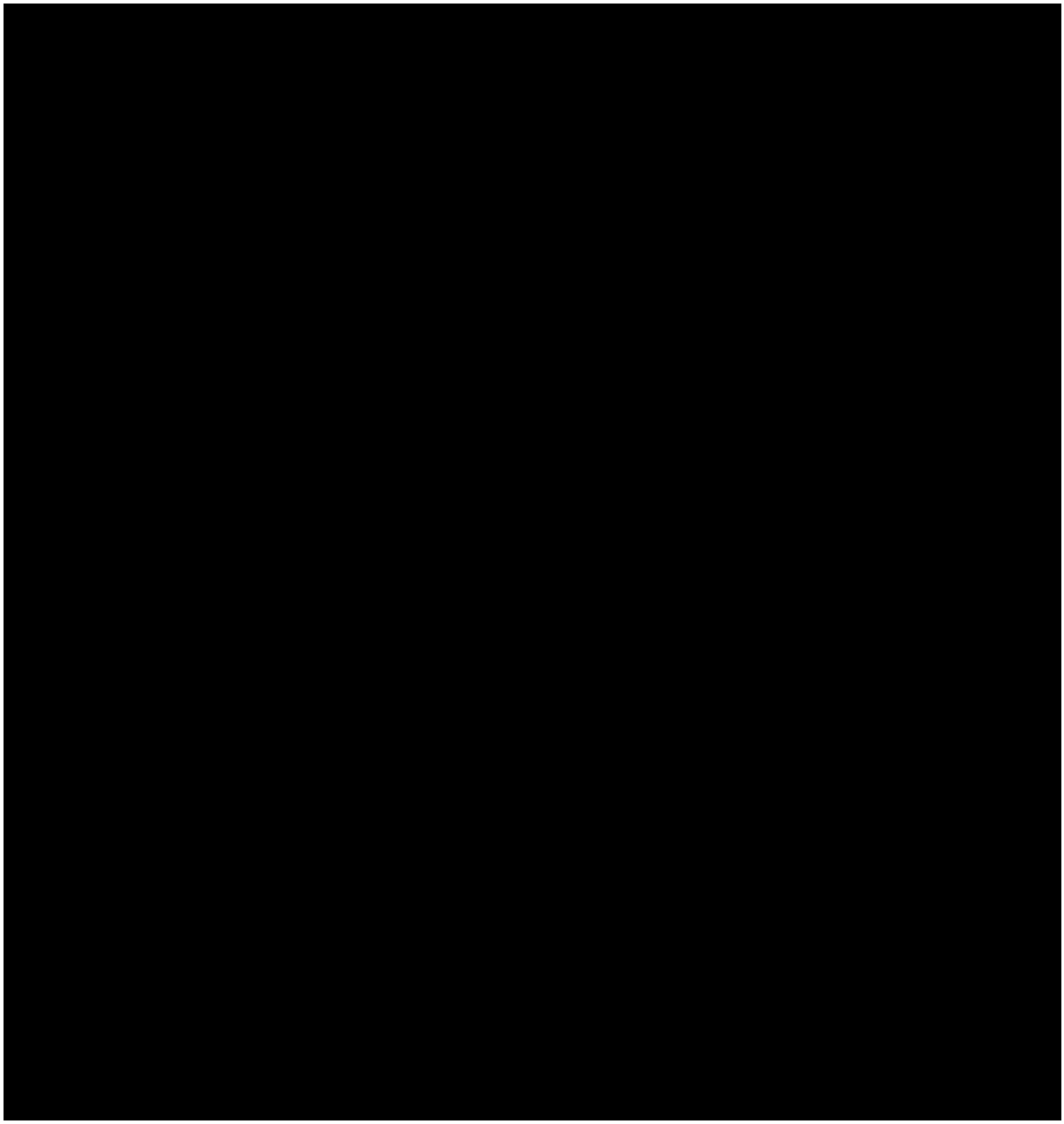
[redacted]

5.4.1 Methods of sample collection

Pre-treatment and on-treatment tumour biopsy collections for biomarker and PD analyses will be mandatory from all patients in the trial. If the patient is not biopsiable because of a safety concern the patient could be considered for study after discussion with the Medical Monitor

to allow for a tumour type of interest. Patients enrolling in a second Module will be required to provide pre- and on-treatment tumour biopsy samples. In addition, an optional biopsy should be taken after treatment discontinuation, if possible. If the patient enters another module, this biopsy could be considered a pre-treatment sample. All samples must be adequately labelled by the trial site personnel. Details about tumour tissue and blood sample collection, plasma/serum preparation, required tubes, labelling of tubes, storage and shipment (frequency and addresses) will be provided in the ISF.





5.5 BIOBANKING

Participation in biobanking is voluntary and not a prerequisite for participation in the trial. Biobanking will only occur after biobanking informed consent has been given in accordance with local ethical and regulatory requirements. Banked samples may be analysed in the future for scientific evaluations or to further, for example, the mechanistic understanding of drug effects and/or to identify genetic or other factors associated with response to therapy or the risk of adverse drug reactions.

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 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, including an audit trail for clinical data and samples to identify and destroy such samples according to ICF is in place
- A fit for 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 consent.

The leftovers of biopsied samples as specified in Module A Section 5.4.2.4 may be banked.

5.7 APPROPRIATENESS OF MEASUREMENTS

All assessments have been planned in accordance with traditional oncology Phase II trial methodology.

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

Patients meeting the inclusion and exclusion criteria for the Master and the Module A and who have signed a written ICF (Master and Module A), are eligible for participation in this Module. Patients will visit the clinical site at the time points specified in the flow chart (see **Module A flow chart**). If a patient misses a scheduled visit, and reports to the Investigator between the missed visit and the next scheduled visit, the assessments for the missed visit must be done with the actual date and the reason must be given for the delayed visit.

Once the decision for any reason is made for a patient to stop the treatment with the combination of BI 754111 plus BI 754091, an EOT visit must occur as soon as possible (preferably within 7 days). After the EOT visit, the patient must undergo a follow-up evaluation 30 (+2) days after the last administration of study therapy.

Additional PFS follow-up visits after the 30-day safety follow-up visit will only be performed for patients who did not progress on treatment. These will be performed once every 12 weeks at least until PD, introduction of a new anti-cancer treatment, death, loss to follow-up, withdrawal of consent, or end of the whole trial.

The trial will be conducted according to the principles of GCP.

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

The procedures required at each trial visit in both portions of the trial are presented in the relevant flow charts of this protocol (**Module A flow chart**). The key procedures required include:

- Reporting of all AEs occurring from signing the ICF onwards until end of residual effect period (REP).
- Baseline and on-treatment blood biomarker and immunogenicity assessments
- Tumour assessments (based on CT/PET and/or MRI scan) according to RECIST v1.1 and iRECIST must be performed once every 2 cycles (meaning every 6 weeks if there are no delays in cycles but as close as possible to the end of the second of the 2 cycles of treatment if there was a delay) after the start of BI 754111 for the first 6 months, and then every 3 cycles (9 weeks) thereafter.

6.2.1 Screening period

The screening period may occur over a period of 28 days (period within the trial and before the first intake of BI 754111 and BI 754091). For the detailed description of the tests to be performed during this period and their timing, please refer to the appropriate flow chart.

6.2.2 Treatment period

Please refer to the **Module A flow chart** for a detailed presentation of each visit during the treatment period.

6.2.3 Follow-up period and trial completion

6.2.3.1 End-of-treatment visit

The EOT visit will be performed after permanent discontinuation of trial medication for any reason, as soon as possible but no later than 7 days after discontinuation of the trial medication or when the Investigator decided with the patient to permanently discontinue the trial medication or became aware that the trial medication had been terminated.

The assessments of the EOT visit will then be performed instead of at the next planned visit. If the patient finishes active treatment without having PD, tumour assessment/imaging must be performed at the time of treatment discontinuation, unless it has been done within the past 4 weeks.

6.2.3.2 30-day post-treatment safety visit

The safety follow-up visit is performed 30 (+2) days after discontinuation of the trial medication. The information collected at this visit must include all new AEs that occurred after the EOT visit, and a follow-up of AEs ongoing at EOT.

A patient will be considered as having completed the trial if he/she discontinues because of PD and has performed the safety follow-up visit 30 days after EOT, or was lost to follow up, or withdrew consent for further evaluation at the EOT visit. If the patient discontinues for any other reason, he/she will be considered as withdrawn.

6.2.3.3 Progression-free survival visits

Additional follow-up visits after the 30-day safety follow-up visit will only be performed for patients who did not progress on treatment. These will be performed once every 12 weeks at least until PD, introduction of a new anti-cancer treatment, death, loss to follow-up, or end of July 2021. Sites may conduct one final PFS visit for each patient that had been followed until July 2021. For patients who remain on treatment after July 2021, no separate PFS visits will be done (the 30-day post treatment safety visit will be their last study visit).

6.2.3.4 Overall survival visits

These will be performed once every 12 weeks at least on the same schedule as PFS survival visits until death, loss to follow-up, or end ofuly 2021. As of July 2021, no further OS data needs to be collected. Sites may collect one final OS visit for each patient they had been following. For patients who remain on treatment after July 2021, no separate OS visit will be done (the 30-day post treatment safety visit will be their last study visit).

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN – MODEL

Refer to the Master protocol for the description of a Bayesian hierarchical model (BHM) approach, which effectively uses the information from different patients' cohorts in the assessment of the efficacy.

Prior distribution
A non-informative normal distribution with mean 0 and standard deviation of 2 is specified for the mean μ. For the inter-cohort heterogeneity parameter τ, a half normal distribution with parameter 1 is used which is a very conservative assumption regarding between-cohort variability and hence leads to only little borrowing of data across patient cohorts because there is little prior information on the strength of the correlation between the treatment effects across cohorts

7.2 NULL AND ALTERNATIVE HYPOTHESES

This is an exploratory trial. No formal hypothesis testing is planned in this trial.

7.3 PLANNED ANALYSES

7.3.1 Primary endpoint analyses

Refer to the Master protocol.

7.3.2 Secondary endpoint analyses

Refer to the Master protocol.

[redacted]

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 AEs with an onset between start of treatment and end of the REP, a period of 30 days after the last dose of trial medication, 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.

Statistical analysis and reporting of AEs will concentrate on treatment-emergent adverse events, i.e. all AEs occurring between start of treatment and end of the REP. Adverse events that start before first drug intake and deteriorate under treatment will also be considered as 'treatment-emergent'.

Frequency, severity, and causal relationship of AEs will be tabulated by system organ class and preferred term after coding according to the current version of 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.

7.3.5 Pharmacokinetic and pharmacodynamic analyses

Please refer to Section 5.3.1.

7.4 INTERIM ANALYSES

Refer to the Master protocol.

An interim futility analysis will be performed for each cohort in the Module. Until any decision from the futility analysis is done, the enrolment of further patients will not be stopped. The two-stage design is planned to stop further recruitment of patients if the defined efficacy boundary (see Table 7.7: 1) is not met at the first stage.

The interim analyses will be conducted when:

- After the 20th patient in cohort 1 and 3 or 15th patient in cohort 2 has completed the third on-treatment imaging assessment (i.e. end of cycle 6).

If the 20th patient in cohort 1 and 3 or 15th patient in cohort 2 discontinues earlier than the third on-treatment imaging, the interim futility analysis will be triggered at approximately 4 months after the first administration of that patient.

In addition, interim analyses may be performed as each cohort is finished.

7.5 HANDLING OF MISSING DATA

Refer to the Master protocol.

7.6 RANDOMISATION

For general aspects please refer to the Master protocol. If at a later time-point there is more than one treatment option available, the respective randomisation procedure will be described in the related Module.

7.7 DETERMINATION OF SAMPLE SIZE

For all three cohorts, no literature is available for the target patients. As there are no treatments of proven efficacy for this population, ORR is assumed to be around 5% (cohorts 1 and 2) and 0% (cohort 3) respectively with anti-PD-1 antibody monotherapy.

The futility boundary and early stopping probability for each cohort is described in Table 7.7: 1.

About 40 patients each will be included in Cohorts 1 and 3, and 30 patients will be included in Cohort 2. The target response $\tilde{p}_j$'s are 20%, 20% and 10% respectively. Different homogeneous scenarios and heterogeneous scenarios are considered in the simulations to assess the frequentist operating characteristics of the BHM approach. The simulation results as shown in Table 7.7: 1 below show that, with the proposed cohort size, the BHM approach has reasonable probability of reaching the pre-specified response rate under a wide range of scenarios.

Table 7.7: 1 Operating characteristics of the Bayesian Hierarchical Modelling approach for final analysis under different scenarios with interim analysis based on observed ORR

Scenario (ORR (%) in each patient cohort)	Early stopping criterion (observed ORR)	Early stopping probability	Probability of shrinkage estimator of the ORR ≥ (20%, 20%, 10%) in at least one cohort at final	Probability of shrinkage estimator of the ORR ≥ (20%, 20%, 10%) in each cohort at final
(25, 25, 15)	(<10%, <10%, <5%)	8% / 9% / 17%	96%	83% / 80% / 81%
(15, 15, 7.5)	(<10%, <10%, <5%)	41% / 33% / 56%	32%	13% / 14% / 19%
(5, 5, 0)	(<10%, <10%, <5%)	90% / 86% / 100%	0%	0% / 0% / 0%
(5, 25, 15)	(<10%, <10%, <5%)	92% / 7% / 19%	86%	0% / 67% / 74%
(25, 25, 0)	(<10%, <10%, <5%)	9% /7% / 100%	86%	74% / 73% / 0%
(25, 5, 0)	(<10%, <10%, <5%)	9% / 83% / 100%	64%	64% / 0% / 0%
(5, 5, 15)	(<10%, <10%, <5%)	92% / 83% / 17%	67%	0% / 0% / 67%

Number of simulations = 1000

Therefore, a total sample size of approximately 110 patients is expected.

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

Refer Section 8 in the Master protocol for this information.

8.1 TRIAL APPROVAL, PATIENT INFORMATION INFORMED CONSENT

Refer to the Master protocol.

8.2 DATA QUALITY ASSURANCE

Refer to the Master protocol.

8.3 RECORDS

Refer to the Master protocol.

8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

Refer to the Master protocol.

8.5 STATEMENT OF CONFIDENTIALIT AND PATIENT PRIVACY

Refer to the Master protocol.

8.6 TRIAL MILESTONES

Refer to the Master protocol.

9. REFERENCES

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10. APPENDICES

10.1 IMMUNE-RELATED ADVERSE EVENTS OF SPECIAL INTEREST

Refer to the Master protocol Appendix 10.1.

10.2 MANAGEMENT OF IMMUNE-RELATED ADVERSE EVENTS

Refer to the Master protocol Appendix 10.2.

10.3 PHARMACOKINETIC METHODS AND ANALYSES

Not applicable.

10.4 TIME SCHEDULE FOR PHARMACOKINETIC (PK) BLOOD SAMPLING

10.4.1 Schedules for PK, [redacted] blood sampling

Protocol Version 3 or later: As of 01 July 2021, PK, [redacted] samples are no longer collected, including the End of Treatment, or the 30-day follow-up.

Table 10.4.1:1 Time schedule for PK, [redacted] blood sampling in Cycle 1

Treatment Cycle	Day	Time Point Description	CRF Time (= Planned Time, PTM) [hh:mm]	PK BI 754091	PK BI 754111	[redacted]					
1	1	Before start of infusion	-0:05	X	X	X	X	X	X	X	X
		Start of infusion	0:00								
		2 h after start of infusion	2:00	X	X						
	2	24 h after start of infusion	24:00	X	X			X	X		

Treatment Cycle	Day	Time Point Description	CRF Time (= Planned Time, PTM) [hh:mm]	PK BI 754091	PK BI 754111	[redacted]					
	8	168 h after start of infusion	168:00					X	X	X	
	15	336 h after start of infusion	336:00	X	X	X	X	X	X	X	

[redacted]; EOT = end of treatment; FU = Follow-up; [redacted]; PK = Pharmacokinetics; [redacted]

The planned infusion duration is 1 hour. Actual date and clock time of start of infusion, end of infusion and blood draws have to be recorded.
The following time windows are specified for PK sampling for procedural reasons:

- Predose (PTM -0:05): within 1 hour **before** next drug infusion
- 2 hours post start of infusion (PTM 2:00): anytime from the end of drug infusion up to 4 hours post-infusion
- 24 hours post start of infusion (PTM 24:00): ±2 hour
- 168 hours post start of infusion (PTM 168:00): ±1 day
- 336 hours post start of infusion (PTM 336:00): ±1 day

Table 10.4.1: 2 Time schedule for PK, [redacted] blood sampling from Cycle 2 onwards

Treatment Cycle	Day	Time Point Description	CRF Time (= Planned Time, PTM) [hh:mm]	PK BI 754091	PK BI 754111	[redacted]					
2, 4, 8	1	Before start of infusion	-0:05	X	X	X (C4 & C8)	X (C4 & C8)	X (C2)	X (C2)	X (C2)	
		Start of infusion	0:00								
		2 h after start of infusion	2:00	X	X						
3, 5, 6	1	Before start of infusion	-0:05	X	X	X (C3 only)	X (C3 only)				X (C3)
12, 16	1	Before start of infusion	-0:05	X	X	X	X				
EOT				X	X	X	X	X	X	X	X
30-days FU				X	X	X	X				

[redacted]; CRF = Case Report Form; EOT = end of treatment; FU = Follow-up; [redacted]; PK = Pharmacokinetics; VEGF = Vascular Endothelial Growth Factor

The planned infusion duration is 1 hour. Patients will be requested to provide samples of blood prior to their first treatment, on-treatment (Cycle 3 Day 1), and at disease progression or EOT.Actual date and clock time of start of infusion, end of infusion and blood draws have to be recorded.

The following time windows are specified for PK sampling for procedural reasons:

- Predose (PTM -0:05): within 1 hour **before** next drug infusion
- 2 hours post start of infusion (PTM 2:00): anytime from the end of drug infusion up to 4 hours post-infusion

10.4.2 Stability testing

Additional blood sample for stability testing:

In order to assess the stability of BI 754091 and BI 754111 in whole blood, one additional blood sample per analyte will be taken from 3 subjects at one pre-selected site. Please refer to the lab manual for details. The results of the analysis of these samples will not be reported within the clinical trial report but will be used for bioanalytical assay validation and therefore included in the corresponding method validation report.

10.5 TRIAL BIOMARKER PLAN

Biomarker collections are included in Appendix 10.4.1.

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

This is the original protocol.

11.1 GLOBAL AMENDMENT 1

Date of amendment		07 May 2019
EudraCT number **EU number**		2018-002344-81
BI Trial number		1381-0009
BI Investigational Medicinal Product(s)		BI 754091 (anti-PD-1) BI 754111 (anti-LAG3)
Title of protocol		An open-label, Phase II trial evaluating the safety and efficacy of BI 754111 in combination with BI 754091 in 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		**Synopsis Main in- and exclusion criteria**
Description of change		Abbreviated Exclusion Criteria 1. Any exclusion criteria listed in the Master protocol. 2. Previous treatment with an anti-LAG-3 agent ~~3. The use of systemic steroids~~ ~~4. Autoimmune disease~~
Rationale for change		Both exclusion criteria were removed from Module A since they were both in the Master.
Section to be changed		**Flow Chart MODULE A BI 1381.9**
Description of change		A new row **"Administration of Pre-Treatment Medication[n]** "and footnote "**n- Pre-treatment medications (antihistamine and acetaminophen or paracetamol) should be administered at sufficient time prior to initiation of infusion to allow the agents to exert their influence.**" were added.
Rationale for change		Pre-treatment medication have been added to the study prior to administration of the study treatment in order to reduce the risk of infusion-related reactions.
Section to be changed		**Flow Chart MODULE A BI 1381.9**

Description of change		**d … Baseline PD-L1 expression level, microsatellite instability (MSI), and tumour mutation burden (TMB) information will be collected in the eCRF, if locally available….**
Rationale for change		Additional baseline data for a deeper analysis was added.
Section to be changed		**Flow Chart MODULE A BI 1381.9** Blood Samples for [redacted]
Description of change		X (**C3 &** C4 only)
Rationale for change		An additional blood collection was added on C3D1to better track [redacted]
Section to be changed		**Flow Chart MODULE A BI 1381.9** footnote m
Description of change		Another mandatory biopsy will be collected at C3D1 **(±5 days).**
Rationale for change		A 5 day window was added to allow for flexibility in the collection of the C3D1 biopsy tissue.
Section to be changed		Section 1.4 BENEFIT – RISK ASSESSMENT
Description of change		**Infusion-related reactions have been reported in approximately 7% (6/86) of patients treated with the combination of BI 754091 and BI 754111, and none were reported with BI 754091 monotherapy. The majority of the events were reported in patients receiving 240 mg of BI 754091 in combination with 600 mg of BI 754111, with 2 events reported in patients receiving 240 mg of BI 754091 in combination with 20 mg of BI 754111. The majority were CTCAE Grade 2. Two events were Grade 3 and led to treatment discontinuation. The reported infusion-related reactions occurred during the infusion mostly during Cycle 2 or Cycle 3.**
Rationale for change		The risk of infusion-related reactions has been described based on the most recent safety information.
Section to be changed		3.2 DISCUSSION OF TRIAL DESIGN, INCLUDING THE CHOICE OF CONTROL GROUPS
Description of change		**Not applicable**
Rationale for change		To clarify the text.
Section to be changed		3.3.2 Inclusion criteria
Description of change		2. Histologically confirmed diagnosis of one of the following cohorts: • Cohort 1 GEC - Locally advanced, unresectable or metastatic gastric adenocarcinoma or gastro-oesophageal adenocarcinoma (GEC) (defined as

		primary tumour localisation below the gastro-oesophageal junction (GEJ) with prior anti-PD-1 or anti-PD-L1 based treated tumour. - Must have had ≥1 line of prior treatment; only 1 prior anti-PD-1/PD-L1 based therapy **with the exception of BI PD-1 investigational agent** allowed (prior chemotherapy plus anti-PD-L1 combination is allowed). - Previous anti-PD-1 or anti-PD-L1 based therapy in a clinical trial setting is allowed as long as it is confirmed that the patient did **receive** ~~revive~~ anti-PD-1 or anti-PD-L1 based therapy in the trial (i.e not placebo). • Cohort 2 Patients with secondary resistance to anti-PD-1 or anti-PD-L1 based therapy: Any advanced or metastatic solid tumour with previously anti-PD-1 or anti-PD-L1 based treatment who progressed after achieving benefit - Must have had ≥1 line of prior treatment; only one prior anti-PD-1/PD-L1 based therapy **with the exception of BI PD-1 investigational agent** allowed. - Prior anti-PD-1 or anti-PD-L1 secondary resistance is defined as a minimum duration of benefit (i.e., at RECIST v1.1 SD) of 6 months and minimum treatment duration of 2 months on the previous anti-PD-1 or anti-PD-L1 based treatment without experiencing disease progression during that period. For patients with NSCLC who received anti-PD-1 or anti-PD-L1 based treatment as a first line regimen, the minimum duration of benefit is 8 months with minimum treatment duration of 2 months on the previous anti-PD-1 or anti-PD-L1 based treatment without experiencing disease progression during that period. • Cohort 3 Patients with primary resistance to anti-PD-1 or anti-PD-L1 based therapy: Select advanced or metastatic solid tumour types with previous anti-PD-1/PD-L1 based treated tumour without achieving benefit. - Must have had ≥1 line of prior treatment; only 1 prior anti-PD-1/PD-L1 based therapy **with the exception of BI PD-1 investigational agent** allowed. - Anti-PD-1 or anti-PD-L1 with primary resistance is defined as RECIST v1.1 stable disease (SD)

		less than 6 months or progressive disease in less than 6 months while on previous anti-PD-1 or anti-PD-L1 based treatment. - Included tumour types: o Previously treated CRC o Merkel cell carcinoma o Squamous cell skin carcinoma o Other squamous cancers: head and neck, cervical, anal, penile, oesophageal and vulvar o Other gastrointestinal (GI) cancers: hepatocellular carcinoma (HCC), biliary tract o Other thoracic cancers: small-cell lung cancer (SCLC) and mesothelioma o Other tumour types for whom no therapy of proven efficacy exists, or who are not amenable to standard therapies and where anti-PD-1/PD-L1 therapy may be considered exceptional cases upon discussion with the Medical Monitor.
Rationale for change		Additional text has been added to clarify that prior use of PD-1 investigational agents is not exclusionary.
Section to be changed		Section 3.3.3 Exclusion criteria
Description of change		~~3 The use of systemic steroids~~ ~~4 Autoimmune disease~~
Rationale for change		Both exclusion criteria were removed from Module A since they were both in the Master.
Section to be changed		4.2.8 Dose modification
Description of change		**To reduce the risk of infusion-related reactions, patients are to be pre-treated with an antihistamine and acetaminophen or paracetamol. Pre-treatment should be administered at sufficient time prior to initiation of infusion to allow the agents to exert their effect.** In the event of an infusion-related reaction ≤ Grade 2, **treat the symptoms accordingly with antihistamine or corticosteroids if needed. T**~~t~~he 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, study drug(s) will be permanently discontinued (refer to the

		safety section in the Master protocol) **and adequate therapy should be initiated to treat the AE.**
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.
Section to be changed		4.3.2.2 Permitted concomitant medications
Description of change		• **To reduce the risk of infusion related reactions, patients are to be pre-treated with an antihistamine and acetaminophen or paracetamol. Pre-treatment should be administered at sufficient time prior to initiation of infusion to allow the agents to exert their effect.**
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.
Section to be changed		Section 5.3.2 Methods of sample collection
Description of change		The trial samples will be discarded after completion of the additional investigations.~~but not later than 5 years after the final trial report has been signed.~~
Rationale for change		The 5 year limit on holding trial samples has been removed to allow for more flexibility.
Section to be changed		[redacted]
Description of change		
Rationale for change		
Section to be changed		
Description of change		
Rationale for change		
Section to be changed		Section 6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS
Description of change		Reporting of all AEs ocuring from signing the ICF onwards until **end of residual effect period (**REP).
Rationale for change		To clarify that AEs will be reported through the entirety of the REP.
Section to be changed		7.4 INTERIM ANALYSES

Description of change		**An interim futility analysis will be performed for each cohort in the Module. Until any decision from the futility analysis is done, the enrolment of next patient will not be stopped. The two-stage design is planned to stop further recruitment of patients if the defined efficacy boundary (see Table 7.7: 1) is not met at the first stage.** **The interim analyses will be conducted when:** • **After the 20th patient in cohort 1 and 3 or 15th patient in cohort 2 has completed the third on-treatment imaging assessment (i.e. end of cycle 6).** **If the 20th patient in cohort 1 and 3 or 15th patient in cohort 2 discontinues earlier than the third on-treatment imaging, the interim futility analysis will be triggered at approximately 4 months after the first administration of that patient.** In addition, interim **analyses** ~~analysis~~ may be performed as each cohort is finished.
Rationale for change		An interim futility analysis has been added to the study.
Section to be changed		7.7 DETERMINATION OF SAMPLE SIZE
Description of change		**For all three cohorts, no literature is available for the target patients. As there are no treatments of proven efficacy for this population, it is assumed around 5% (cohorts 1 and 2) and 0% (cohort 3) respectively with anti-PD-1 antibody monotherapy.** **The futility boundary and early stopping probability for each cohort is described in** Table 7.7: 1**.** About 40 patients each will be included in Cohorts 1 and ~~3~~**2**, and 30 patients will be included in Cohort 2. The target response $\tilde{p}_j$'s are **20**~~35~~%, 20% and 10% respectively
Rationale for change		The text was added to provide more detail about the target patient enrollment sizes.
Section to be changed		10.3 PHARMACOKINETIC METHODS AND ANALYSES
Description of change		**Not applicable**
Rationale for change		To clarify the text.
Section to be changed		10.4.1 Schedule for PK, [redacted] sampling

Description of change

Table 7.7: 1 **Operating characteristics of the Bayesian Hierarchical Modelling approach for final analysis under different scenarios with interim analysis based on observed ORR** ~~Operationg cheacteristics of the Baysean Hierarchical Modeling approach under different scenarios~~

Scenario (ORR (%) in each patient cohort)	Early stopping criterion (observed ORR)	Early stopping probability	Probability of shrinkage estimator of the ORR ≥ (20%, 20%, 10%) in at least one cohort at final	Probability of shrinkage estimator of the ORR ≥ (20%, 20%, 10%) in each cohort at final
(25, 25, 15)	(<10%, <10%, <5%)	8% / 9% / 17%	96%	83% / 80% / 81%
(15, 15, 7.5)	(<10%, <10%, <5%)	41% / 33% / 56%	32%	13% / 14% / 19%
(5, 5, 0)	(<10%, <10%, <5%)	90% / 86% / 100%	0%	0% / 0% / 0%
(5, 25, 15)	(<10%, <10%, <5%)	92% / 7% / 19%	86%	0% / 67% / 74%
(25, 25, 0)	(<10%, <10%, <5%)	9% /7% / 100%	86%	74% / 73% / 0%
(25, 5, 0)	(<10%, <10%, <5%)	9% / 83% / 100%	64%	64% / 0% / 0%
(5, 5, 15)	(<10%, <10%, <5%)	92% / 83% / 17%	67%	0% / 0% / 67%

		~~Scenario (objective response rate (%) in each patient cohort)~~ / ~~Probability of shrinkage estimator of the objective response rate ≥ (35%, 20%, 10%) in at least one cohort~~ / ~~Probability of shrinkage estimator of the objective response rate ≥ (35%, 20%, 10%) in each cohort~~ ~~(40, 25, 15)~~ / ~~97%~~ / ~~79% / 83% / 93%~~ ~~(30, 15, 7.5)~~ / ~~40%~~ / ~~17% / 15% / 27%~~ ~~(15, 5, 0)~~ / ~~0%~~ / ~~0% / 0% / 0%~~ ~~(15, 25, 15)~~ / ~~84%~~ / ~~0% / 60% / 74%~~ ~~(40, 25, 0)~~ / ~~84%~~ / ~~68% / 70% / 10%~~ ~~(40, 5, 0)~~ / ~~58%~~ / ~~58% / 0% / 0%~~ ~~(15, 5, 15)~~ / ~~58%~~ / ~~0% / 0% / 58%~~
Rationale for change		Updated Baysean Hierarchical Modelling parameters were updated based in updated projected ORR.
Section to be changed		Table 10.4.1: 2 Time schedule for PK, [redacted] blood sampling from Cycle 2 onwards
Description of change		**X (C3 only)**
Rationale for change		An additional blood collection was added on C3D1to better track [redacted].
Section to be changed		10.5 TRIAL BIOMARKER PLAN
Description of change		[redacted] collections are included in Appendix 10.4.1. ~~Appendix 10.1 and Appendix 10.2~~
Rationale for change		The text has been corrected to right appendix number.

11.10 GLOBAL AMENDMENT 2

Number of global amendment		2
Date of CTP revision		14 Jul 2021
EudraCT number **EU number**		2018-002344-81
BI Trial number		1381-0009
BI Investigational Medicinal Product(s)		BI 754091 (anti-PD-1) BI 754111 (anti-LAG3)
Title of protocol		An open-label, Phase II trial evaluating the safety and efficacy of BI 754111 in combination with BI 754091 in 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		
Additions to the text are bolded and deletions from the text are crossed-off. Only the parts of sections with changes are presented. Please note that formatting changes and minor changes to punctuation, spelling, and abbreviations that do not affect meaning are not noted in this summary.		

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		Flowchart and footnote f
Description of change		On study electrocardiograms were removed from the flowchart until the EOT visit, and footnote f was changed to . Single digitalised ECGs must be done ~~before blood work or other procedures after 5 minutes of rest at screening, on Day 1 of every cycle,~~at the EOT visit~~,~~ and whenever the Investigator deems it necessary
Rationale for change		Electrocardiograms are no longer required until the EOT visit unless
Section to be changed		Flowchart: footnote h
Description of change		Additional progression-free survival (PFS) follow-up visits after the 30-day safety follow-up visit will only be performed for patients who did not progress on treatment. These will be performed once every 12 weeks at least until PD, introduction of a new anti-cancer treatment, death, loss to follow-up, withdrawal of consent, or end of **July 2021. As of July 2021, sites may conduct one final PFS visit for each patient that is being followed. For patients who remain on treatment after July 2021, no separate PFS visits will be done (the 30-day post treatment safety visit will be their last study visit).** ~~the whole trial.~~
Rationale for change		The sponsor has determined that sufficient PFS and OS data has been collected and very few patients remain on study drug.
Section to be changed		Flowchart: footnote o
Description of change		**As of 01 July 2021, PK, [redacted] samples are no longer collected, including the End of Treatment, or the 30-day follow-up.**
Rationale for changes		As of July 2021, sufficient PK, [redacted] samples have been collected and analyzed. The additional collection of samples will not

		contribute to a better understanding of the characteristics of the molecule. In order to reduce the burden of collection of further samples from patients, PK, [redacted] samples no longer need to be collected.
Section to be changed		6.2.3.3 Progression-free survival visits
Description of change		Additional follow-up visits after the 30-day safety follow-up visit will only be performed for patients who did not progress on treatment. These will be performed once every 12 weeks at least until PD, introduction of a new anti-cancer treatment, death, loss to follow-up, or end of **July 2021**~~the whole trial~~. **Sites may conduct one final PFS visit for each patient that had been followed until July 2021. For patients who remain on treatment after July 2021, no separate PFS visits will be done (the 30-day post treatment safety visit will be their last study visit).**
Rationale for changes		The sponsor has determined that sufficient PFS data has been collected and very few patients remain on study drug.
Section to be changed		**6.2.3.4 Overall survival visits**
Description of change		These will be performed once every 12 weeks at least on the same schedule as PFS survival visits until death, loss to follow-up, or end of **July 2021**~~the whole trial as in the safety and efficacy sections in the Master~~. **As of July 2021, no further OS data needs to be collected. Sites may collect one final OS visit for each patient they had been following. For patients who remain on treatment after July 2021, no separate OS visit will be done (the 30-day post treatment safety visit will be their last study visit).** ~~If the sponsor determines that enough OS data has been collected from select cohorts, sites could be instructed to discontinue OS visits for those cohorts.~~
Rationale for changes		The sponsor has determined that sufficient OS data has been collected and very few patients remain on study drug.
Section to be changed		**10.4.1 Schedule for PK, [redacted] blood sampling**
Description of change		**As of 01 July 2021, PK, [redacted] samples are no longer**

		collected, including the End of Treatment, or the 30-day follow-up.
Rationale for changes		As of July 2021, sufficient PK, [redacted] samples have been collected and analyzed. The additional collection of samples will not contribute to a better understanding of the characteristics of the molecule. In order to reduce the burden of collection of further samples from patients, PK, [redacted] samples no longer need to be collected.

APPROVAL / SIGNATURE PAGE

Document Number: c25025479 **Technical Version Number:3.0**

Document Name: clinical-trial-protocol-version-03-module-a

Title: An open-label, Phase II trial evaluating the safety and efficacy of BI 754111 in combination with BI 754091 in PD-(L)1 naive 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]	15 Jul 2021 05:04 CEST
Author-Trial Clinical Pharmacokineticist	[redacted]	15 Jul 2021 07:48 CEST
Author-Trial Statistician	[redacted]	15 Jul 2021 16:03 CEST
Approval-Therapeutic Area [redacted]	[redacted]	15 Jul 2021 17:52 CEST
Approval-Translational Medicine Expert	[redacted]	15 Jul 2021 18:56 CEST
Approval-Team Member Medicine	[redacted]	16 Jul 2021 15:54 CEST
Verification-Paper Signature Completion	[redacted]	26 Jul 2021 03:12 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed