Clinical Trial Protocol

	Document Number:	**c16323837-07**
BI Trial No.:	1381-0004	
BI Investigational Product(s):	BI 754091 and BI 754111	
Title:	An open label, Phase I study of BI 754091 monotherapy and combination therapy of BI 754091 and BI 754111 in Asian patients with advanced solid tumours	
Lay Title:	This study aims to find a safe and effective dose of BI 754091. The study also aims to find safe and effective doses of BI 754091 and BI 754111 in combination. This study is done in Asian patients with different types of cancer	
Clinical Phase:	I	
Clinical Trial Leader:	[redacted] Telephone: [redacted], Fax: [redacted]	
Coordinating Investigator	[redacted] Telephone: [redacted]	
Status:	Final Protocol (Revised Protocol based on global amendment 5)	
Version and Date:	**Version: 6.0**	**Date: 21 Apr 2021**

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Finished product name	NA
Active ingredient name:	BI 754091 and BI 754111
Protocol date	15 Dec 2017
Revision date	21 Apr 2021
Trial number	1381-0004
Title of trial:	An open label, Phase I study of BI 754091 monotherapy and combination therapy of BI 754091 and BI 754111 in Asian patients with advanced solid tumours
Coordinating Investigator	[redacted] Telephone: [redacted]
Trial site(s):	Multi-centre trial conducted in Asia
Clinical phase:	I
Objective(s):	The main objectives of the dose-finding parts (Parts I and II) of the trial are to investigate the following in patients with advanced solid tumours: • Part I: Safety, tolerability, and pharmacokinetics (PK) of BI 754091 as monotherapy. • Part II: Safety, tolerability, and PK of escalating doses of BI 754111 when administered with BI 754091, and PK of BI 754091 when administered with escalating doses of BI 754111. • Parts I and II: Maximum tolerated dose (MTD) and/or recommended dose (RD) of BI 754091 monotherapy and the combination of BI 754091 and BI 754111. The main objectives of the expansion part (Part III) of the trial are: • To further investigate the safety, tolerability, and PK of the RD

	of the combination of BI 754091 and BI 754111 in patients with gastric/esophagogastric junction cancer, esophageal cancer, hepatocellular cancer, or non-small cell lung cancer (NSCLC) • To explore the efficacy of the combination of BI 754091 and BI 754111 at RD in patients with gastric/esophagogastric junction cancer, esophageal cancer, hepatocellular cancer, or NSCLC
Methodology:	Part I (BI 754091 monotherapy dose-finding part): Open-label, single arm dose-finding Part II (Combination dose-finding part): Open-label, single arm dose-finding Part III (Combination dose- expansion part): Open-label, single arm
Number of patients entered:	Approximately 179 patients
Number of patients on each treatment:	Part I: approximately 6 to 12 patients (Japanese patients) Part II: approximately 12 to 18 patients (Japanese patients) Part III: Approximately 155 patients (Asian patients)
Diagnosis :	Part I and II: Patients with a confirmed diagnosis of advanced, unresectable, and/or metastatic solid tumours Part III: Patients with advanced and/or metastatic disease of following tumour types: ▪ Cohort A: Patients with gastric/esophagogastric junction cancer, with no prior treatment with anti-PD-1/PD-L1 antibody, and who received at least one line of systemic medical treatment excluding adjuvant therapy ▪ Cohort B: Patients with esophageal cancer with no prior treatment with anti-PD-1/PD-L1 antibody, and who received at least one line of systemic medical treatment excluding adjuvant therapy ▪ Cohort C: Patients with hepatocellular cancer with no prior treatment with anti-PD-1/PD-L1 antibody, who received at least one line of systemic medical treatment excluding adjuvant therapy, and whose Child-Pugh score is 7 or less ▪ Cohort D: Patients with gastric/esophagogastric junction cancer, esophageal cancer, or hepatocellular cancer with a prior treatment with anti-PD-1/PD-L1 antibody ▪ Cohort E: First line NSCLC patients with wildtype (wt) epidermal growth factor receptor [EGFR] and anaplastic lymphoma kinase [ALK] tumours of squamous or non-squamous origin
Main in- and exclusion criteria	Part I and II: Patients with a confirmed diagnosis of advanced, unresectable, and/or metastatic solid tumours (any type) for whom no therapy of proven efficacy exists, or who are not amenable to standard therapies, with measurable disease according to RECIST

	Version 1.1. Part III: Patients with advanced and/or metastatic disease of selected tumour types, who have measurable disease according to RECIST Version 1.1, with at least 1 tumour lesion amenable to biopsy, and are willing to undergo paired biopsies during the trial. Additional specific criteria for the individual expansion cohorts include: ▪ Cohort A: Patients with gastric/esophagogastric junction cancer, with no prior treatment with anti-PD-1/PD-L1 antibody, and who received at least one line of systemic medical treatment excluding adjuvant therapy ▪ Cohort B: Patients with esophageal cancer with no prior treatment with anti-PD-1/PD-L1 antibody, and who received at least one line of systemic medical treatment excluding adjuvant therapy ▪ Cohort C: Patients with hepatocellular cancer with no prior treatment with anti-PD-1/PD-L1 antibody, who received at least one line of systemic medical treatment excluding adjuvant therapy, and whose Child-Pugh score is 7 or less ▪ Cohort D: Patients with gastric/esophagogastric junction cancer, esophageal cancer, or hepatocellular cancer with a prior treatment with anti-PD-1/PD-L1 antibody ▪ Cohort E: First line squamous or non-squamous NSCLC patients: • Without EGFR mutations or ALK rearrangements • PD-L1 expression level <50%
Test product(s):	BI 754091 and BI 754111
dose:	Part I: BI 754091 starting with 240 mg once every 3 weeks, the BI 754091 RD established in the 1381-0001 trial in Caucasian patients. Dose-finding of BI 754091 will be guided by Bayesian logistic regression model (BLRM) with overdose control. Part II: The starting dose of BI 754111 will be 400 mg, based on the safety information from another ongoing trial, 1381-0002. BI 754111 will be administered once every 3 weeks in combination with BI 754091 at the RD (Part I). Dose-finding of BI 754111 in combination with BI 754091 will be guided by BLRM with overdose control. Part III: The RD of the combination determined in the combination dose-finding part (Part II)
mode of administration:	Intravenous infusion
Comparator products:	Not applicable
dose:	Not applicable
mode of administration:	Not applicable

Duration of treatment:	Administration will continue until progressive disease (PD), unacceptable toxicity, other withdrawal criteria, or a maximum treatment duration of 1 year. If the patient is benefiting clinically at 1 year, he/she may continue after a case-by-case review with the sponsor.
Endpoints	Part I Primary: - Number of patients experiencing DLTs graded according to the Common Terminology Criteria for Adverse Events (CTCAE Version 4.03) observed in the MTD evaluation period (first cycle of treatment; 3 weeks) - MTD of BI 754091 Secondary: - PK parameters for BI 754091: C_{max} and area under the curve $(AUC)_{0-504}$ - Objective Response (OR): confirmed CR or PR according to RECIST v1.1 assessed by the Investigator Part II Primary: - Number of patients experiencing DLTs graded according to CTCAE Version 4.03 observed in the MTD evaluation period (first cycle of treatment; 3 weeks) - MTD of the BI 754091 plus BI 754111 combination Secondary: - PK parameters for BI 754091 and for BI 754111: C_{max} and AUC_{0-504} - OR: confirmed complete response (CR) or partial response (PR) according to RECIST v1.1 assessed by the Investigator Part III Primary: - OR: confirmed CR or PR according to RECIST Version 1.1 as assessed by the Investigator Secondary: - Duration of response: the duration from the date of first documented PR or CR according to RECIST Version 1.1 as assessed by the Investigator to the date of PD or death. - Disease control (DC): CR, PR, or stable disease (SD) according to RECIST Version 1.1, as assessed by the Investigator.
Safety criteria:	Adverse events (AEs) according to CTCAE (Version 4.03 in Parts I and II, Version 5 in Part III), incidence of DLTs for determination of the MTD (dose-finding parts only), results of physical examinations, laboratory evaluations, vital signs, and electrocardiograms (ECGs)

Statistical methods:	Part I Descriptive statistics. Dose-finding will be guided by BLRM with overdose control that will be fitted to binary toxicity outcomes. The estimate of parameters will be updated as data are accumulated using BLRM. At the end of dose finding, the toxicity probability at each dose level will be calculated to determine an estimate of the MTD of BI 754091. Part II Descriptive statistics. Dose escalation will be guided by BLRM with overdose control that will be fitted to binary toxicity outcomes. The estimate of parameters will be updated as data are accumulated using BLRM. At the end of dose escalation, the toxicity probability at each dose (combination) level will be calculated to determine an estimate of the MTD of the combination of BI 754111 plus BI 754091. Part III Efficacy response endpoints will be summarised descriptively. For OR and DC, the frequency and proportion of patients and 95% two-sided confidence interval will be presented. For PFS and duration of response, the median and 95% two-sided confidence interval will be presented using the Kaplan-Meier method. No hypothesis testing is planned in this trial.

FLOW CHART

Flow Chart		Trial Treatment Days[a,b] Cycle = 21 Days							Post-Treatment Days[b]		
	Screening	Cycles 1, 2, and 4						Cycles 3, 5+	End-of-Treatment[p] (EOT) Visit	30-Day Safety Follow-up[r]	FU for PFS/OS[h]
Assessments (Days)	**-28 to -1**	**1 (±2 C2+)**	**2**	**3[s]**	**4[s]**	**8 (±1)**	**15 (±1)**	**1 (±2)**	**within 7 days of**	**(+7)**	
Informed Consent[c]	X										
Inclusion/Exclusion Criteria	X										
Medical History and Demographics[d]	X										
Physical Examination[d, e]	X	X					X[e]	X	X	X	
ECOG Performance Status[d, e]	X	X						X[e]	X	X	
Vital Signs[d]	X	X	X	X	X	X	X	X	X	X	
12-Lead Digital Electrocardiogram[d, f,t]	X	X					X	~~X~~[t] (C3,5,6,8,10, 12, etc and C3D15)	~~X~~[t]	~~(X)~~[t]	
Haematology and Clinical Chemistry Labs[d]	X	X				X	X	X		X	
Troponin	X	X (C4)				X (C1,2)	X (C1)	X (C3,5)			
Urinalysis[d]	X	X						X	X		
Pregnancy Test for Women of Child-Bearing Potential[d, g]	X	X						X	X		
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X

Flow Chart		**Trial Treatment Days[a,b] Cycle = 21 Days**							**Post-Treatment Days[b]**		
	Screening	**Cycles 1, 2, and 4**						**Cycles 3, 5+**	**End-of-Treatment[p] (EOT) Visit**	**30-Day Safety Follow-up[r]**	**FU for PFS/OS[h]**
Assessments (Days)	**-28 to -1**	**1 (±2 C2+)**	**2**	**3[s]**	**4[s]**	**8 (±1)**	**15 (±1)**	**1 (±2)**	**within 7 days of**	**(+7)**	
Progression/Survival[h]											X
Blood Samples for Anti-Drug Antibodies[i,q,t]		X						~~X~~[q,t]	~~X~~[q,t]	~~X~~[q,t]	
(Part I, II) PK Blood Samples [j,q]		X	X	X	X	X	X	X[q]	X[q]	X[q]	
(Part III) PK Blood Samples[j,q,t]		X	X (C1&4)			X (C1&4)	X (C1&4)	~~X~~[q,t]	~~X~~[q]	~~X~~[q,t]	
(Part II and III, only if feasible at study site) Blood Samples and extraction of PBMC for Biomarkers (PBMC [extract])[k,t]		X (C1&2)	X (C1)			X (C1)		X (C3&5)		~~X~~[t]	
(Part III cohort E only) Blood Samples for Biomarkers (PBMC [blood])[k]		X (C1&2)				X(C1)	X(C1)		X		
(Part III only) Plasma Samples for Biomarkers (Cytokines)[k,t]		X	X (C1&4)			X (C1&4)		X (C3D1 only)		~~X~~[t]	
(Part III only) Biopsy[l,t]	X							X (C3D1 only)	~~(X)~~[t]		
Tumour Assessments[d, m]	X	Every 2 cycles ±5 days for 6 months (then every 3 cycles ±5 days thereafter)									
Study Drug Infusion[n]		X						X			
DLT Assessment[o]		X	X	X	X	X	X	X	X		

a All cycles are 3 weeks (21 days) in duration. 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, and the patient provides an additional consent. In addition, patients without PD may stay on trial after 1 year on a case-by-case basis after discussion with the sponsor. Day 1 of Cycle 1 is defined as the day when the study medication is first administered.

b Days are calculated as calendar days.

c Informed consent must be obtained ≤28 days prior to the initiation of treatment.

d Safety laboratory assessments including haematology, clinical biochemistry, and urinalysis will be performed locally (Free T3, Troponin I, and venous HCO_3 will be measured at a central laboratory if study site cannot measure it locally). The screening medical history and demographics, physical examination and Eastern Cooperative Oncology Group (ECOG) performance status (PS), vital signs, ECG, haematology, clinical chemistry (sodium, potassium, phosphate, chloride, creatinine, calcium, venous bicarbonate HCO_3 (if the local lab test is available at the study site), albumin, total protein, aspartate aminotransferase [AST], alanine aminotransferase [ALT], alkaline phosphatase, bilirubin, lactate dehydrogenase, glucose, creatine phosphokinase [CPK: if CPK is elevated, then CPK-MB, troponin (either I or T), and myoglobin should be reactively tested], urea [or blood urea nitrogen (BUN)], 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. 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 PS, an abbreviated physical examination, vital signs (pre- and post-infusion), and a single ECG required prior to first trial dose. Hepatitis B virus (HBV), hepatitis C virus (HCV), and human immunodeficiency virus (HIV) testing should be performed at screening unless test results obtained in routine diagnostics within 14 days before the informed consent date are available (For patients with hepatocellular cancer in Part III Cohorts C and D, if a patient is known to have HBV and/or HCV infection, the diagnostic testing for that item does not need to be repeated). Additionally, amylase and lipase should be analysed in case of symptoms of pancreatitis. 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 5.2 for additional details. Vital signs are checked at every visit. At the visit for the first treatment, vital signs are checked before and after infusion. At subsequent visits for administration, vital signs are checked only before infusion.

e Physical examinations will be done at screening, on Day 1 of each treatment cycle, at the end of treatment (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.

f Single digitalised ECGs must be done before blood sampling or other procedures after 5 minutes of rest at screening, on Day 1 of every cycle through Cycle 6 and then every other cycle thereafter (Cycles 8, 10, 12, etc.), on Day 15 of Cycles 1 through 4, 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 Section 5.2.5).

g Women of child-bearing potential must have a serum beta human chorionic gonadotropin (βHCG) 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 Section 5.2.4.4).

h **Patients enrolled in Part III Cohort E:** Additional overall survival (OS) and progression-free survival (PFS) follow-up visits after the 30-day safety follow-up visit will be performed once every 12 weeks at least (in person or by telephone) until death, loss to follow-up, withdrawal of consent, or end of the whole trial.

All other patients: Additional follow-up visits for PFS after the 30-day safety follow-up visit will only be performed in Part III for patients who did not progress on treatment. The follow-up visits for PFS will be performed once every 12 weeks at least (in person or by telephone) until PD, introduction of a new anti-cancer treatment, death, loss to follow-up, withdrawal of consent, or end of the whole trial.

i Blood samples for anti-drug antibodies (ADAs) will be collected from all patients as presented in Tables 10.4: 1 and 10.4: 2 in Appendix 10.4 .

j Pharmacokinetic (PK) blood sampling: there is extensive PK sampling during Cycles 1, 2, and 4. It is strongly recommended that the visit days and sampling time points outlined in Tables 10.4: 1 and 10.4: 2 in Appendix 10.4 be followed closely. The permitted visit windows noted in the table footnotes should only be used if medically indicated. Please note that there are separate assays for determination of BI 754091 and BI 754111 in Part II and III. Therefore, when PK samples are drawn during combination dosing, 2 tubes must be drawn at each time point.

k Blood samples for biomarkers – following blood samples are taken for biomarker analysis:

- Cytokine: samples will be taken in Part III on Days 1 (pre-treatment only), 2, and 8 of Cycles 1, and 4, on Day 1 (pre-treatment only) of Cycle 2 & 3, and at the 30-day follow-up visit for quantification of cytokines (e.g., IL-2 and IFN-γ) in plasma samples (see Section 5.4.2.2 and Appendix 10.4).
- PBMC (extract): Blood samples will be taken and peripheral blood mononuclear cells (PBMC) will be extracted during Part II and Part III only at study sites in which the sample preparation is possible, on Day 1 (pre-treatment), 2, 8 of Cycle 1, on Day 1 (pre-treatment) of Cycle 2, 3 and 5, and at the 30-day safety follow-up visit.
- PBMC (blood): Blood samples for biomarker PBMC (blood) will be taken only in Part III cohort E during Cycle 1 on Day 1 (pre-treatment), Day 8, Day 15, during Cycle 2 on Day 1 (pre-treatment), and at the end-of-treatment visit. Kits will be provided from a designated laboratory logistics vendor. If the kits are not ready at study sites at the time of patient recruitment, this blood sampling will not be performed.

l All patients in Part III must have tissue samples (fresh or archived [see requirements]) available for retrospective central biomarker testing. The following will be required (see Section 5.4.2.3 for details):

- If available and taken within 6 months of study start and no anti-tumour treatment has been given after the sample is taken, at least 20 (4-5 µm) sections from an archival FFPE block should be collected. If adequate archival tissue is not available, 2 core-needle biopsies must be taken between screening and the day before the first study drug treatment.
- Two core-needle biopsies on treatment at the end of Cycle 2 (after 6 weeks of treatment), preferably from the same lesion.
- Another biopsy (optional) should be taken upon PD (according to RECIST v1.1 or iRECIST), if possible. SD over 4 months would also be qualified as a response, and a biopsy (optional) would be taken at that time point. Subjects with PR will also be asked for biopsies upon confirmation of the response.

m 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. Correlative imaging should then be repeated at each tumour assessment (see Section 5.1.1 for more detail). Assessments will be performed by the Investigator at screening and every 2 cycles (meaning every 6 weeks ±5 days 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) for the first 6 months of treatment, once every 3 cycles (meaning every 9 weeks ±5 days if there are no delays in cycles but as close as possible to the end of the third of the 3 cycles of treatment if there was a delay) thereafter, at the EOT visit (if not performed within the previous 4 weeks), and at the discretion of the Investigator and copies may be collected by the sponsor or designee.

n Dosing of BI 754111 and BI 754091 will be determined by the SMC and communicated to sites as each new cohort opens for recruitment. Refer to Sections 4.1.2.1, 4.1.2.2, and 4.1.3 for further details. 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.

o Dose-limiting toxicities (DLTs) will be collected as adverse events of special interest (AESIs) throughout the trial and will be assessed for dose-finding. (see Section 4.1.5).

p If the decision is made to permanently discontinue study treatments during a scheduled visit, the EOT visit should be performed instead of the scheduled visit assessments. In the combination treatment parts (Part II and III), both BI 754091 and BI 754111 should be discontinued together if necessary.

q PK and ADA blood samplings are to be collected during Cycles 1 through 12, Cycle 14, Cycle 17, at every 3 cycle after Cycle 17 at the EOT visit, and the 30-day safety follow-up (see the tables in Appendix 10.4 for specifics).

r 30-day safety follow-up visit takes place 30 days after EOT visit.

s Visits on days 3 and 4 are to be performed in Part I and Part II only.

t After an interim database lock in 2021, the following procedures are not required: 12-lead ECG (could be performed if clinically indicated with significant abnormalities recorded as AEs), blood samples for Anti-Drug Antibodies, PK blood samples, blood samples and extraction of PBMC for biomarkers (PBMC [extract]), plasma samples for biomarkers, and biopsy

Optional assessments are noted in parentheses. Please refer to the specific footnotes.

TABLE OF CONTENTS

[redacted]

ABBREVIATIONS

ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
ALK	Anaplastic lymphoma kinase
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the Curve
β-hCG	Beta human chorionic gonadotropin
BI	Boehringer Ingelheim
BLQ	below the limit of quantification
BLRM	Bayesian Logistic Regression Model
BOR	Best overall response
BUN	Blood urea nitrogen
CA	Competent authority
C_{EOI}	Plasma concentration at the end of infusion
CKD-EPI	Chronic Kidney Disease Epidemiology
CL	Total clearance of the analyte in plasma following intravascular administration
C_{max}	Maximum measured concentration of the analyte in plasma
C_{min}	Minimum measured concentration of the analyte in plasma
CML	Clinical Monitor Local
CPK	Creatinine phosphokinase
$C_{pre,N}$	Predose measured concentration of the analyte in plasma before the Nth dose
CR	
CRA	Clinical Research Associate
CRF	Case Report Form, paper or electronic (sometimes referred to as “eCRF”)
CRO	Contract Research Organisation
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTL	Clinical Trial Leader
CTLA-4	Cytotoxic T-lymphocyte-associated protein 4
CTR	Clinical Trial Report
DC	Disease control
DCR	Disease control rate
DILI	Drug induced liver injury
DLT	Dose Limiting Toxicity
eDC	electronic Data Capturing
ECG	Electrocardiogram
ECOG	Eastern Co-Operative Oncology Group
EF	Ejection Fraction
EGFR	Epidermal growth factor receptor

eGFR	Estimated glomerular filtration rate
EOT	End of Treatment
EWOC	Escalation With Overdose Control
FFPE	Folmarin fixed paraffin embedded
GCP	Good Clinical Practice
HIV	Human immunodeficiency virus
IB	Investigator's Brochure
iBOR	Best overall response according to iRECIST
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
iCPD	Confirmed progressive disease according to iRECIST
iCR	Complete response according to iRECIST
IDMS	Isotope dilution mass spectroscopy
IEC	Independent Ethics Committee
IFN	Interferon
IHC	Immunohistochemistory
IL	Interleukin
INR	International normalized ratio
IO	Immune Oncology
iPD	Progressive disease according to iRECIST
iPR	Partial response according to iRECIST
IRB	Institutional Review Board
IRT	Interactive Response Technology
iUPD	Unconfirmed progressive disease according to iRECIST
iSD	Stable disease according to iRECIST
ISF	Investigator Site File
irAEs	immune-related adverse events
iUPD	
i.v.	intravenous
LAG-3	Lymphocyte-activation gene 3
LDH	Lactate dehydrogenase
LPDD	last patient drug discontinuation
mAb	Monochronal antibody
MDSC	Myeloid-derived suppressor cell
MedDRA	Medical Dictionary for Drug Regulatory Activities
MHC-II	Major histocompatibility complex Class II
MRI	Magnetic resonance imaging
MTD	Maximum Tolerated Dose
MUGA	Multigated acquisition
NE	Not evaluable
NK	Natural killer
NL	New lesion
NLNT	New lesion non-target
NLT	New lesion target
NOA	Not analysed
NOAEL	No observed adverse effect level
NOR	No valid result

NOS	No sample available
NSCLC	Non-small-cell lung cancer
OPU	Operative Unit
OR	Overall response/objective response
ORR	Overall response rate/objective response reate
PBMC	Peripheral blood mononuclear cells
PD	Progressive Disease
PDc	Pharmacodynamics
PD-1	Programmed cell death protein-1
PD-L1	Programmed death ligand-1
PFS	Progression free survival
PET	Positron emission tomography
PK	Pharmacokinetics
PR	Partial response
PS	Performance status
R_A	Accumulation ratio
RECIST	Response Evaluation Criteria in Solid Tumours
REP	Residual Effect Period
RD	Recommended dose
QTc	Corrected QT interval
SAE	Serious adverse event
SD	Stable disease
SMC	Safety Monitoring Committee
SOC	System organ class
SOP	Standard operating procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
$t_{1/2}$	Terminal half-life of the analyte in plasma
t_{max}	Time from (last) dosing to the maximum concentration of the analyte in plasma
T-regs	regulatory T-cells
TSAP	Trial Statistical Analysis Plan
ULN	Upper limit of normal
Vss	Apparent volume of distribution at steady state following intravascular administration
WHO	World Health Organization
WOCBP	Woman of childbearing potential

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Despite the recent advancements in cancer treatment, cancer remains a leading cause of death globally. In 2012, there were approximately 14 million new cancer cases, and 8.2 million cancer-related deaths worldwide (R15-3504). 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 minimize 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. 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; R16-2360), 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.

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 (R16-5356; R16-5359). LAG-3 is expressed on activated cytotoxic, helper as well as 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 (R16-0868, R16-5335), while the ligands for these checkpoint inhibitors (i.e., PDL1/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. 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).

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 (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 antitumour activity and improved clinical outcome in a higher percentage of patients compared to checkpoint-inhibitor monotherapy. Clinical proof-of-concept for combination checkpoint inhibitor treatment has come from clinical trials evaluating the safety and efficacy of combination anti-PD-1 and anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) mAb in patients with advanced NSCLC, small-cell lung cancer, and melanoma. For example, the combination of nivolumab (anti-PD-1 mAb) with ipilimumab (anti-CTLA-4 mAb) in patients with small-cell lung cancer increased objective response rate (ORR) to 19% to 20% compared to 10% with nivolumab monotherapy (R16-2707). In previously untreated patients with advanced melanoma, the combination of nivolumab and ipilimumab increased median progression-free survival (PFS) to 11.5 months from a PFS of 2.9 and 6.9 months achieved by ipilimumab or nivolumab monotherapies, respectively, in patients with low PD-L1 levels (R15-3696). The combination of nivolumab and ipilimumab has also resulted in a significant improvement in ORR in patients with previously untreated NSCLC (39% to 47% for ipilimumab dosed every 6 weeks or every 12 weeks, respectively) compared to the 23% ORR achieved by nivolumab monotherapy (R16-5545). Unfortunately, the improved efficacy of combined PD-1/CTLA-4 came at the expense of safety. Grade 3 and 4 adverse event (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 (R15-3696; R16-5544). These findings clearly underscore the need for the development of more efficacious and better-tolerated alternative immunotherapy combinations.

Multiple other immune-checkpoint inhibitor combinations are currently in development including the combination of anti-PD-1 and anti-LAG-3 mAbs with encouraging preliminary results. Tumour-infiltrating lymphocytes not only express PD-1, but frequently co-express LAG-3 (R16-0872). Upon binding of PD-1 and LAG-3 to their respective ligands (PD-L1/PD-L2 and MHC-II, respectively), an intracellular signal negatively regulating T-cell responses is induced. Combined neutralisation of PD-1 and LAG-3, using antagonistic mAbs, is expected to enhance reactivation of T-cells and improve tumour rejection beyond the level achieved by PD-1 neutralisation alone. This has been demonstrated in both in vitro and in vivo models (R16-0852, R16-0881). Therefore, compared to anti-PD-1 monotherapy, combined blockade of the co-inhibitory receptors PD-1 and LAG-3 has the potential to better

restore T-cell functionality and improve objective responses (ORs) and prolongation of overall survival in cancer patients. The combination of nivolumab and BMS-986016 (anti-LAG-3 mAb) has recently been shown to have antitumour activity and an acceptable safety profile in multiple solid tumours and hematological malignancies (R16-5204; R16-5218).

1.2 DRUG PROFILE

1.2.1 BI 754091

BI 754091 is a humanised IgG4Pro isotype mAb against PD-1 that is being developed as an intravenous (i.v.) infusion for the treatment of cancer. BI 754091 has highly human frameworks and a low predicted immunogenicity score. The BI 754091 molecule has a molecular weight of approximately 148 kilodaltons. The antibody is composed of 2 heavy chains (446 amino acids each) and 2 light chains (218 amino acids each). The 4 polypeptide chains of the antibody are linked together by disulfide bonds. Each heavy chain contains one consensus sequence for N-linked glycosylation.

In pre-clinical studies, repeat-dose administrations of BI 754091 at 0, 3, 30, or 100 mg/kg (via i.v. injection) once per week for 13 weeks in the cynomolgus monkey were well tolerated. No test article related adverse changes in body weight, food consumption, respiratory rate, electrocardiograms (ECGs), or clinical observations were noted at any doses. There was no BI 754091-related mortality during that study. No BI 754091-related neurologic or ophthalmic physical examination findings, or changes in any haematology, coagulation, clinical chemistry, or urinalysis parameters were observed. BI 754091 was not associated with any gross or organ weight findings. BI 754091 related microscopic findings included marginal increases in mononuclear cell infiltrates considered non-adverse and related to expected pharmacology.

BI 754091 is currently being tested in patients in the BI 1381-0001 and 1381-0002 clinical trials. In trial 1381-0001 dose escalation cohorts, 80 mg, 240 mg, and 400 mg dose levels were investigated and 3 patients were dosed at each dose level. No dose limiting toxicities (DLTs) or immune-related AEs were reported and the maximum tolerated dose MTD was not reached in the dose escalation cohorts. Recommended dose for further investigation was determined to be 240 mg.

1.2.2 BI 754111

BI 754111 is a humanised IgG4Pro mAb against LAG-3 that is being developed as an i.v. infusion for the treatment of cancer. BI 754111 has highly human frameworks and a low predicted immunogenicity score. The BI 754111 molecule has a molecular weight of approximately 149 kilodaltons. The antibody is composed of 2 heavy chains (448 amino acids each) and 2 light chains (214 amino acids each). The 4 polypeptide chains of the antibody are linked together by disulfide bonds. Each heavy chain contains one consensus sequence for N-linked glycosylation.

In a 13-week repeat-dose toxicity study in cynomolgus monkeys, which included a BI 754111/BI 754091 combination arm, animals were given 0, 3, 30, or 100 mg/kg/doses of BI

754111 monotherapy or a 30 mg/kg/dose of both BI 754111 and BI 754091 via i.v. infusion once per week for 13 weeks. BI 754111 monotherapy and the combination of BI 754111/BI 754091 were well tolerated and did not cause mortality or changes to body weight, food consumption, respiratory rate, or ECGs. There were no neurologic, ophthalmic, or physical examination findings directly related to BI 754111 treatment or combined treatment with BI 754111/BI 754091, and no gross pathology or organ weight findings. BI 754111 and the BI 754111/BI 754091 combination increased T-lymphocyte IFN-γ secretion in response to ex vivo tetanus toxoid challenge. There were no changes in haematology, coagulation, clinical chemistry, or urinalysis parameters except for non-adverse, reversible low-grade changes in serum triglycerides, albumin, globulin, and albumin/globulin ratio. At the end of the 13-week dosing phase, BI 754111-monotherapy-related and combination-therapy-related microscopic findings included marginal increases in mononuclear cell infiltrates considered non-adverse and related to expected pharmacology.
BI 754111 is currently being tested in patients in the BI 1381-0002 trial. BI 754111 was administered at dose range from 4 mg to 600 mg in combination with BI 754091 240 mg. No DLTs were reported in these dose levels from patients who were eligible for DLT evaluation (see section 4.1.2.2).

The residual effect period of BI 754091 monotherapy and BI 754091/BI 754111 combination therapy is 30 days.

For more detailed descriptions of the BI 754091 and BI 754111profiles please refer to the respective Investigator's Brochures (IBs).

1.3 RATIONALE FOR PERFORMING THE TRIAL

Most patients with locally advanced or metastatic tumours will succumb to their disease, justifying the substantial need for novel therapeutic strategies to improve the outcome for patients with advanced or metastatic malignancies.

The currently available data clearly demonstrate the clinical benefits that patients with many tumour types gain from checkpoint-inhibitor monotherapy. It is also clear that combination checkpoint-inhibitor treatment has resulted in improved efficacy compared to checkpoint-inhibitor monotherapy. There is now sufficient evidence that blockage of the PD-1 pathway leads to over-expression of other checkpoint inhibitors, including LAG3. 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; R16-0852; R16-0868, R16-0881; R16-2707; R16-5335; R16-5545).

New, more tolerable, combinations of immune-therapy treatments are needed to continue to improve the outcome for patients. BI 754091 in combination with BI 754111 has the potential to be such a combination.
Clinical trials to of BI 754091 monotherapy and combination of BI 754091 and BI 754111 are being conducted in North America, and Asian countries are not included in those trials.

This trial is intended to assess the safety, efficacy and pharmacokinetics (PK) of BI 754091 monotherapy and combination of BI 754091 and BI 754111 in Asian patients to establish a safe combination dose that can be explored further in later development.

Multiple immune checkpoint inhibitors have been approved for the treatment of patients metastatic NSCLC including pembrolizumab, nivolumab and atazolizumab. In second line NSCLC, blockade of the PD-1 pathway with an anti-PD-1 or anti-PD-L1 mAbs results in significant improvement in response rate (approximately 20 % Vs. 9%) and a significant improvement in overall survival (approximately 3 months) compared to standard of care chemotherapy (R16-0878; R15-3715; R16-1875; R16-5828).

It is postulated that treating patients with immune checkpoint inhibitor early in their treatment continuum, while their immune system is still relatively intact, may maximize the chance of response and prolonged survival. To this end, immune checkpoint inhibitors have made remarkable changes to the standard of care for previously untreated patients with advanced NSCLC. Pembrolizumab monotherapy resulted in significant improvement in response rates, progression free survival and overall survival in previously untreated patients with NSCLC whose tumors express high level expression of PD-L1 of (to ≥50%) when compared to standard of care chemotherapy (R16-4803). As a result, pembrolizumab monotherapy is a now well-established treatment of choice as the replacement for cytotoxic chemotherapy in the first-line (R16-4803). However, approximately half the patients treated with pembrolizumab in this setting do not respond (response rate of 44.8%) and will require other immune therapy combination to achieve clinical benefit. Indeed, recent data have demonstrated that response rates in previously untreated NSCLC by combining pembrolizumab with chemotherapy can be improved (approximately 61% and 48%-55%) in patients with ≥50% and ≥1% PD-L1 expression, respectively, by combination pembrolizumab with chemotherapy (R16-4804; P18-03589). However, the combination of pembrolizumab with chemotherapy is associated with a significant increase in toxicity, owing to the chemotherapy component, compared to checkpoint inhibitor monotherapy (R16-4804; P18-03589). Therefore, finding more tolerable, less toxic checkpoint inhibitor combination to treat previously untreated NSCLC patients is of immense interest. As such, this trial aims to test the safety and efficacy of chemotherapy-sparing combination of BI 754091 with BI 754111 in patients with previously untreated NSCLC. The combination of BI 754091 with BI 754111 has the potential to be less toxic than chemotherapy containing regimens and would reserve chemotherapy as a subsequent line of treatment for patients whose disease progresses.

The therapeutic benefit or specific adverse events in patients cannot always be anticipated during the trial setup. Later on there may be new scientific knowledge about biomarkers and other factors contributing to diseases or the action of a drug. In order to address future scientific questions, patients will be asked to voluntarily donate biospecimens for banking. If the patient agrees, banked samples may be used for future drug development projects, e.g., to identify patients that are more likely to benefit from a treatment or experience an adverse event, and thereby better match patients with therapies.

1.4 BENEFIT - RISK ASSESSMENT

The role of the immune-checkpoint inhibitors within a normal immune response is to dampen the immune response after the trigger (antigen) is resolved, minimizing collateral-immune-mediated damage to healthy tissue. Immune-checkpoint inhibitors also play a major role in promoting and maintaining self-tolerance by inactivating auto-reactive T-cells. Therefore, manipulation of immune-checkpoint-inhibitor 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 (R16-2362; R16-2364; R16-2968; R16-2969; R16-2970).

Data from immune-checkpoint clinical trials show that irAEs occur frequently in patients treated with anti-CTLA-4 (90%) and anti-PD-1 or anti-PD-Ll (70%) mAbs. However, the majority of these AEs are mild in severity (R12-5176; R15-3588; R15-3715) and commonly occur within the first 4 months of initiating therapy (R15-3780; R16-0864; R16-0899). Immune-related AEs affect mainly the gastrointestinal tract (including diarrhoea and, less frequently colitis), skin (including rash/erythema and less frequently vitiligo), endocrine glands (including hypothyroidism, hyperthyroidism, and hypophysitis), liver (frequently asymptomatic elevated transaminases), and lung (pneumonitis), but could also potentially affect other tissues. Rare fatal cases of colitis, pneumonitis and myocarditis have been reported with use of immune-checkpoint inhibitors. The main treatment of irAEs is the administration of steroids for 2 to 4 weeks; other immunosuppressive agents (such as infliximab, mycophenolate mofetil and cyclosporine) can be used in case of steroid-refractory irAE (R16-0763; R16-0899).

As previously mentioned, 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 754091 and BI 754111 is anticipated to be associated with a similar pattern of AEs. Immune-related AE management guidance will be provided in the trial documentation. 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.

Based on the 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 754091 and BI 754111 may

translate into a clinical benefit in cancer patients. The dose-escalation scheme is guided by a Bayesian Logistic Regression Model (BLRM) (de-escalation of dose is possible in case of insufficient tolerability of a dose level) and is designed to escalate the dose quickly and minimise the risk of safety issues.

In addition, dose levels which are higher than the ones investigated in preceding trials 1381-0001 and 1381-0002 will not be investigated in this trial.

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

By the end of June 2018, 48 patients were treated with the combination therapy of BI 754091 and BI 754111 (BI 754111 dose range: 4mg to 600mg, all in combination with BI 754091 240mg) and the risk benefit profile from the observed data was considered positive.

The trial safety will be monitored by the Safety Monitoring Committee (SMC, see Section 8.7) established in this trial to safeguard the patient safety.

Even so, patients should be advised of the potential risks of side effects from investigational trial treatments. 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, a 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, see also Section 5.2.7.5, adverse events of special interest.

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

2.1.1 Main objectives

The main objectives of the BI 754091 monotherapy dose-finding part (Part I) of the trial are to investigate the following items in advanced solid tumours:
- Safety, tolerability, and pharmacokinetics (PK) of BI 754091 as monotherapy.
- Maximum tolerated dose (MTD) and/or recommended dose (RD) of BI 754091 monotherapy.

The main objectives of the Combination dose-finding part (Part II) of the trial are to investigate the following items in advanced solid tumours:
- Safety, tolerability, and PK of the combination treatment of BI 754091 and BI 754111.
- MTD and/or RD of the combination treatment of BI 754091 and BI 754111.

The main objectives of the expansion part (Part III) of the trial are:
- To further investigate the safety, tolerability, and PK of the RD of BI 754091 and BI 754111 combination in patients with gastric/esophagogastric junction cancer, esophageal cancer, hepatocellular cancer, or non-small cell lung cancer (NSCLC)
- To explore the efficacy of the RD of the combination of BI 754091 and BI 754111 in patients with gastric/esophagogastric junction cancer, esophageal cancer, hepatocellular cancer, or NSCLC

2.1.2 Primary endpoints

The primary endpoints of Part I (BI 754091 monotherapy dose-finding) are:
- Maximum tolerated dose (MTD) of BI 754091
- Number of patients experiencing dose limiting toxicities (DLTs) during the MTD evaluation period (first cycle of treatment)

The primary endpoints of Part II (combination dose finding) are:
- MTD of the BI 754091 plus BI 754111 combination
- Number of patients experiencing DLTs during the MTD evaluation period (first cycle of treatment)

The definition of MTD is described in Section 4.1.6. For definition of DLTs, refer to Section 4.1.5.

The primary endpoint of Part III (expansion) is:
- Objective response (OR) - confirmed complete response (CR) or partial response (PR) according to response evaluation criteria in solid tumours (RECIST) Version 1.1 (R09-0262) as assessed by the Investigator.

2.1.3 Secondary endpoints

The secondary endpoints of Part I are the following:

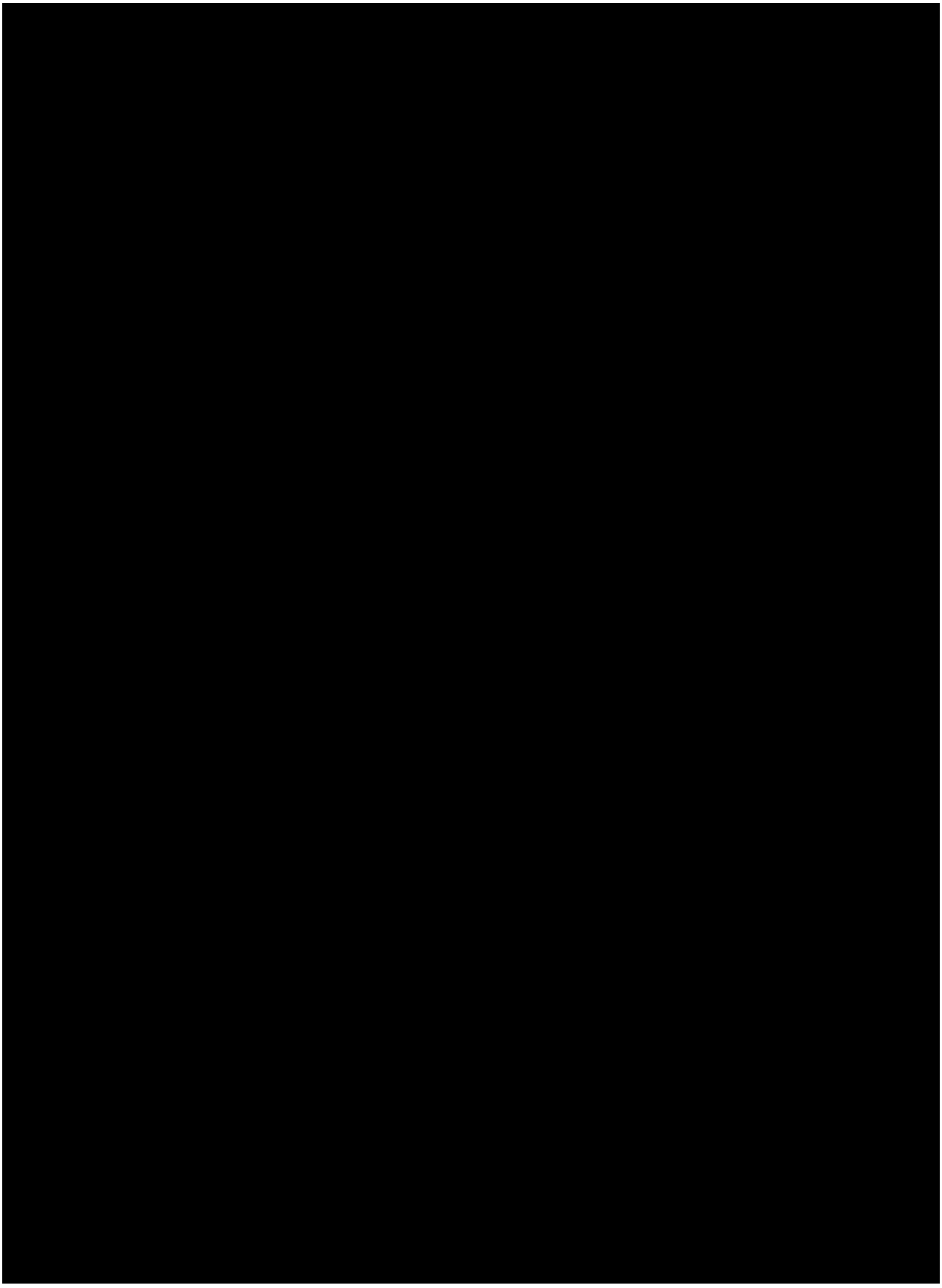
- The following pharmacokinetics (PK) parameters of BI 754091 will be measured after single administration:
  - C_{max}: maximum measured concentration of BI 754091 in plasma
  - AUC_{0-504}: area under the concentration-time curve of BI 754091 in plasma over the time interval from 0 to 504 hours
- Objective response (OR): confirmed CR or PR according to RECIST v1.1 as assessed by the Investigator.

The secondary endpoints of Part II are the following:

- The following PK parameters of BI 754091 and BI 754111 will be measured after single administration:
  - C_{max}: maximum measured concentration of BI 754091 and BI 754111 in plasma
  - AUC_{0-504}: area under the concentration-time curve of BI 754091 and BI 754111 in plasma over the time interval from 0 to 504 hours
- Objective response (OR): confirmed CR or PR according to RECIST v1.1 as assessed by the Investigator.

The secondary endpoints of Part III are the following:

- Duration of response: defined as the duration from the date of first documented PR or CR according to RECIST Version 1.1 as assessed by the Investigator to the date of progressive disease (PD) or death.
- Disease control: CR, PR, or stable disease (SD) according to RECIST Version 1.1 as assessed by the Investigator.



3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

This is a Phase I, open-label, non-randomised, multicentre trial of BI 754091 and BI 754111 that will be conducted in 3 parts. The data obtained from the trial will determine the MTD estimate based on a Bayesian logistic regression model with overdose control (R13-4803). The BLRM estimates the MTD by updating estimates of the probability of observing a DLT in the MTD evaluation period for each dose level in the trial as patient information becomes available. At any time in the trial, it will not be permitted to escalate to a dose which does not fulfil the escalation with overdose control (EWOC) principle.

It is planned that approximately 6 to 12 patients with advanced solid tumour will be enrolled in the first part of the trial, which is for dose-finding of BI 754091 administered as monotherapy. A cohort or successive cohorts of patients will receive doses of BI 754091 until the MTD is reached, or RD determined in 1381-0001 is confirmed in this trial.

Following determination of the MTD and/or RD of BI 754091 in Part I, approximately 6 to 12 patients with advanced solid tumour will be enrolled in Part II of the trial and will receive BI 754091 at RD determined in Part I and escalating doses of BI 754111. Successive cohorts of patients will receive doses of BI 754091 and BI 754111 until MTD is reached, or RD determined in 1381-0002 is confirmed in this trial.

The DLT information collected in trials 1381-0001 and 1381-0002 will be used to construct the priors for the BLRM, and therefore will be included in the dose escalation decision-making process. In general, it will be permitted to escalate to a dose that fulfils the EWOC principle (see section 7).

At the starting dose level of Part I, patient recruitment will continue until 6 evaluable patients are enrolled for the review of this dose level by the SMC. The SMC may determine to stop the recruitment and perform a safety evaluation if necessary. A cohort size of 3 patients will be treated at each subsequent dose level. Additional patients may be added to some previously evaluated cohorts to expand the safety and PK evaluation.

After all patients in a cohort have either experienced a DLT or have been observed for at least the MTD evaluation period (cycle 1, 21 days) without experiencing a DLT, the Bayesian model will be updated with the newly accumulated data. The overdose risk will then be calculated for each dose, and escalation will be permitted to all doses/dose combinations which fulfil the EWOC criterion. Hypothetical data scenarios (examples in section 10.5) will be calculated with potential cohort sizes and provided to the SMC. Based on the model and on additional information (e.g. PK, PD, patient profiles), the SMC will reach a joint decision on the next dose level to be investigated and the size of the next cohort.

If DLTs are observed in the first two consecutive patients of a previously untested dose level, subsequent enrolment to that cohort will be stopped. The BLRM will be re-run to confirm that the dose level still fulfils the EWOC principle. Based on this information, the SMC will

evaluate whether the next patients will be enrolled at the same dose level, or if they will be enrolled at a lower dose level.

The SMC may recommend stopping the dose finding phase after the criterion for MTD (Section 7.1) is fulfilled. Further patients may be included to confirm this MTD estimate, i.e., to confirm that the EWOC criterion is still fulfilled. If the criterion for MTD is not fulfilled at the RD determined in the corresponding trial of the Parts (i.e. RD in 1381-0001 for Part I, RP2D in 1381-0002 for Part II), the SMC may decide to include an additional number of patients at the same dose level or to declare this dose as the RD from this trial. The SMC can declare any dose that fulfils the EWOC criterion as RD, independent of the MTD estimate.

Following determination of the MTD and/or the RD from the dose-finding parts, Part III will commence and approximately 155 patients with gastric/esophagogastric junction cancer, esophageal cancer, hepatocellular cancer, or NSCLC will be enrolled to explore the efficacy and further evaluate the safety, tolerability, PK profile, biomarkers of the combination of BI 754091 and BI 754111 at RD determined in Part II. Part II may still continue for further safety and/or PK evaluation at any dose levels, after the start of recruitment in Part III at the recommended dose.

In Part III, patient will be enrolled in cohorts of approximately 35 patients, designated for different patient populations as follows:

Cohort A: Patients with gastric/esophagogastric junction cancer, with no prior treatment with anti-PD-1/PD-L1 antibody, and who received at least one line of systemic medical treatment excluding adjuvant therapy

Cohort B: Patients with esophageal cancer with no prior treatment with anti-PD-1/PD-L1 antibody, and who received at least one line of systemic medical treatment excluding adjuvant therapy

Cohort C: Patients with hepatocellular cancer with no prior treatment with anti-PD-1/PD-L1 antibody, who received at least one line of systemic medical treatment excluding adjuvant therapy, and whose Child-Pugh score is 7 or less

Cohort D: Patients with gastric/esophagogastric junction cancer, esophageal cancer, or hepatocellular cancer with a prior treatment with anti-PD-1/PD-L1 antibody

Cohort E: First line NSCLC patients with wildtype (wt) epidermal growth factor receptor [EGFR] and anaplastic lymphoma kinase [ALK] tumours of squamous or non-squamous origin.

In Part I and Part II, only Japanese patients will be enrolled. From Part III, Asian patients will be included.

In December 2019, BI decided to close the recruitment of new patients into Cohort C, based on an analysis of the available data from patients enrolled in this cohort. The data showed less than expected clinical efficacy for the patient population studied in this indication, and the likelihood that the cohort will meet the protocol defined criteria to continue at the planned futility analysis was considered very low. This decision did not affect the recruitment of other cohorts, the treatment of patients who were already receiving study treatment in Cohort C, or the overall benefit risk assessment of the combination therapy of BI 754091 and BI 754111.

3.2 DISCUSSION OF TRIAL DESIGN, INCLUDING THE CHOICE OF CONTROL GROUP(S)

Dose-finding and cohort size will be determined based on the recommendation of the SMC, guided by a BLRM with overdose control. An EWOC design will increase the chance of treating patients at efficacious doses while reducing the risk of overdosing. This design is based on practical experience and is an efficient method due to its ability to identify the dose with a desired toxicity rate and its allocation of a greater proportion of patients to doses at or close to that desired dose (R13-4802; R13-4804; R13-4805). The use of Bayesian models for Phase I studies has also been advocated by the European Medicines Agency (EMA) guideline on small populations (R07-4856) and by the United States Food and Drug Administration (FDA) (R13-4881).

For the expansion part, cancer types which are more common in Asia than Western countries, or whose epidemiology is different between Asia and Western countries, will be included, to explore the possibilities of further clinical development in these patient populations. Data from clinical trials of other anti-PD-1 antibodies suggest that anti-PD-1 treatment have clinical activities in these cancer types.

The results from this trial will form the basis for decisions for future studies.

3.3 SELECTION OF TRIAL POPULATION

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 has been entered.
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) at the investigational site irrespective of whether they have been treated with investigational drug or not.

3.3.1 Main diagnosis for trial entry

Part I and II: Patients with a confirmed diagnosis of advanced, unresectable, and/or metastatic solid tumours
Part III: Patients with advanced and/or metastatic disease of following tumour types:

Cohort A: Patients with gastric/esophagogastric junction cancer, with no prior treatment with anti-PD-1/PD-L1 antibody, and who received at least one line of systemic medical treatment excluding adjuvant therapy

Cohort B: Patients with esophageal cancer with no prior treatment with anti-PD-1/PD-L1 antibody, and who received at least one line of systemic medical treatment excluding adjuvant therapy

Cohort C: Patients with hepatocellular cancer with no prior treatment with anti-PD-1/PD-L1 antibody, who received at least one line of systemic medical treatment excluding adjuvant therapy, and whose Child-Pugh score is 7 or less

Cohort D: Patients with gastric/esophagogastric junction cancer, esophageal cancer, or hepatocellular cancer with a prior treatment with anti-PD-1/PD-L1 antibody

Cohort E: First line NSCLC patients with wt EGFR and ALK tumours of squamous or non-squamous origin.

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

3.3.2 Inclusion criteria

1. Of full age (according to local legislation) at the time of signing of the informed consent form (ICF)
2. Women of childbearing potential (WOCBP)[1] with negative serum pregnancy test at screening and men able to father a child, who agree to 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 in the patient information. The requirement of contraception does not apply to women of no childbearing potential but they must have an evidence of such at screening
3. Signed and dated written informed consent in accordance with ICH-GCP and local legislation prior to admission to the trial
4. Patients with measurable lesions according to RECIST v1.1
5. Conditions specific to respective part of the trial:
    - Part I (BI 754091 dose-finding part):
        - Patients with a confirmed diagnosis of advanced, unresectable, and/or metastatic solid tumours (any type)
        - For whom no therapy of proven efficacy exists, or who are not amenable to standard therapies.
        - Previous treatment with an anti-PD-1 mAb is allowed as long as the last administration of the anti-PD-1 mAb on the previous treatment is a minimum of 28 days prior to the first BI 754091 treatment.
    - Part II (Combination dose-finding part):
        - Patients with a confirmed diagnosis of advanced, unresectable, and/or metastatic solid tumours (any type)
        - For whom no therapy of proven efficacy exists, or who are not amenable to standard therapies.
        - Previous treatment with an anti-PD-1 mAb is allowed as long as the last administration of the anti-PD-1 mAb on the previous treatment is a minimum of 28 days prior to the first BI 754091 treatment.
    - Part III (Expansion part):
        - Cohort A: Patients with gastric/esophagogastric junction cancer, with no prior treatment with anti-PD-1/PD-L1 antibody, and who received at least one line of systemic medical treatment excluding adjuvant therapy

[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.

- Cohort B: Patients with esophageal cancer with no prior treatment with anti-PD-1/PD-L1 antibody, and who received at least one line of systemic medical treatment excluding adjuvant therapy
- Cohort C: Patients with hepatocellular cancer with no prior treatment with anti-PD-1/PD-L1 antibody, who received at least one line of systemic medical treatment excluding adjuvant therapy, and whose Child-Pugh score is 7 or less
- Cohort D: Patients with gastric/esophagogastric junction cancer, esophageal cancer, or hepatocellular cancer with a prior treatment with anti-PD-1/PD-L1 antibody
- Cohort E: First line squamous or non-squamous NSCLC patients:
  - Without EGFR mutations or ALK rearrangements
  - PD-L1 expression level <50%
- All cohorts: Patients with advanced and/or metastatic disease, with at least 1 tumour lesion amenable to biopsy, and must be medically fit for biopsy at screening as determined by investigator and willing to undergo a biopsy before first treatment (if adequate archival tissue is not available) and, unless clinically contraindicated, after 6 weeks on therapy.

6. Eastern Cooperative Oncology Group (ECOG, R01-0787) performance status (PS): 0 to 1 at screening

3.3.3 Exclusion criteria

1. Major surgery (major according to the investigator's assessment) performed within 12 weeks prior to study entry or planned within 12 months after screening, e.g. hip replacement
2. Patients who must or wish to continue the intake of restricted medications (see Section 4.2.2.2) or any drug considered likely to interfere with the safe conduct of the trial
3. Previous treatment with study medications in this trial
4. Any investigational or anti-tumour treatment within 4 weeks or 5 half-life periods (whichever is shorter) prior to the initiation of trial treatment
5. Any unresolved toxicities from prior therapy greater than Common Terminology Criteria for Adverse Events (CTCAE) Grade 1 at the time of starting study treatment with the exception of alopecia and Grade 2 neuropathy due to chemotherapy
6. (Part II and III only) Prior treatment with anti-LAG-3 agents
7. Patients with lung cancer that have epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) rearrangements, unless disease has progressed following available EGFR or ALK targeted therapy
8. 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 or in situ carcinoma of the uterine cervix, or other local tumours considered cured by local treatment
9. Untreated brain metastasis(es) that may be considered active. Patients with previously treated brain metastases may participate provided they are stable (i.e., without evidence of PD by imaging for at least 4 weeks prior to the first dose of trial treatment, and any

neurologic symptoms have returned to baseline), and there is no evidence of new or enlarging brain metastases

10. Inadequate organ function or bone marrow reserve as demonstrated by the following laboratory values:
    - Absolute neutrophil count <1.5 x 10^9/L (<1500/mm^3)
    - Platelet count <100 x 10^9/L (<100,000/mm^3)
    - Haemoglobin <9.0 g/dL
    - Alanine aminotransferase (ALT) >2.5 times the upper limit of normal (ULN) if no demonstrable liver lesion(s) (primary or metastases) or >5 times ULN in the presence of liver lesion(s)
    - Aspartate aminotransferase (AST) >2.5 times ULN if no demonstrable liver lesion(s) or >5 times ULN in the presence of liver lesion(s)
    - Total bilirubin >1.5 times ULN, except for patients with Gilbert's syndrome who are excluded if total bilirubin >3.0 times ULN or direct bilirubin >1.5 times ULN
    - Serum creatinine (measured by enzymatic assay, Isotope dilution mass spectroscopy [IDMS] standardized Jaffe assay, or non-IDMS Jaffe assay) >1.5 times ULN or estimated glomerular filtration rate (eGFR) <30 mL/min/1.73m^2 (Chronic Kidney Disease Epidemiology [CKD-EPI] Collaboration equation); confirmation of eGFR is only required when creatinine is >1.5 X ULN
    - International normalized ratio (INR) (only tested if clinically indicated) >1.5 times ULN (if treated with anticoagulants, prolonged INR is acceptable)
11. 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 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 [ECHO], multi-gated acquisition scan [MUGA]). A historic measurement of EF no older than 6 months prior to first administration of study 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.
12. History (including current) of interstitial lung disease or pneumonitis within the last 5 years
13. History of severe hypersensitivity reactions to other mAbs
14. History of severe hypersensitivity reactions to the ingredients of study drug
15. Immunosuppressive corticosteroid doses (>10 mg prednisone daily or equivalent) within 4 weeks prior to the first dose of study treatment
16. Active autoimmune disease or a documented history of autoimmune disease, except vitiligo or resolved childhood asthma/atopy, or asthma well controlled with steroids

17. Active infection requiring systemic treatment (antibacterial, antiviral, or antifungal therapy) at start of treatment in this trial
18. Known history of human immunodeficiency virus (HIV) infection. Test results obtained in routine diagnostics are acceptable if done within 14 days before the informed consent date
19. Any of the following laboratory evidence of hepatitis virus infection. Test results obtained in routine diagnostics are acceptable if done within 14 days before the informed consent date
    - Positive results of hepatitis B surface (HBs) antigen
    - Presence of HBc antibody together with HBV-DNA
    - Presence of hepatitis C RNA

    However, for patients with hepatocellular cancer in Part III Cohorts C and D, patients with HBV and/or HCV infection are allowed. Hepatocellular cancer patients in Part III Cohorts C and D with HBV infection must be receiving effective antiviral therapy (viral load <100 IU/mL)
20. Chronic alcohol or drug abuse or any condition that, in the investigator's opinion, makes him/her an unreliable trial patient, unlikely to complete the trial, or unable to comply with the protocol procedures. However, for patients with hepatocellular cancer in Part III Cohorts C and D, past chronic alcohol abuse are allowed
21. Women who are pregnant, nursing, or who plan to become pregnant during the trial. Women who are nursing can be enrolled if they stop nursing. In this case, the patient cannot resume nursing even after discontinuation of study treatment.

3.3.4 Withdrawal of patients from therapy or assessments

Patients may potentially be withdrawn from trial treatment or from the trial as a whole ("withdrawal of consent") with very different implications, please see Sections 3.3.4.1 and 3.3.4.2 below.
Every effort should be made to keep the entered patients in the trial: if possible on tretament, or at least to collect important trial data.
Measures to control the withdrawal rate include careful patient selection, appropriate explanation of the trial requirements and procedures prior to enrolment, as well as the explanation of the consequences of withdrawal.
The decision to withdraw from trial treatment or from the whole trial as well as the reason must be documented in the patient files and case report form (CRF).

3.3.4.1 Withdrawal from trial treatment

An individual patient is to be withdrawn from trial treatment if:

- The patient wants to withdraw from trial treatment, without the need to justify the decision.
- The patient needs to take concomitant drugs that interfere with the investigational product. Refer to Section 4.2.2.2 for permitted and prohibited concomitant medications.
- The patient can no longer be treated with trial medication for other medical reasons (such as surgery, AEs, other diseases, or pregnancy). Refer to Section 4.1.4 for AEs that require treatment discontinuation.

- 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 stick to the trial requirements in the future.
- The patient experiences unequivocal PD by RECIST v1.1 and/or iRECIST.
- The patient completes 1 year of treatment. If the patient is benefiting clinically at 1 year, he/she may continue after a case-by-case review with the sponsor.

Given the patient's agreement, the patient will undergo the procedures for the end-of-treatment (EOT) visit and follow up as outlined in the Flow Chart and Section 6.2.3. For all patients the reason for withdrawal from trial treatment (e.g. AEs) must be recorded in the CRF. These data will be included in the trial database and reported.
During the dose finding part, patients withdrawn for a reason other than having a DLT or patients who miss more than one visit during MTD evaluation period may be replaced after discussion in the SMC if the information that needed to be collected during that visit is not available and makes the patient non-evaluable for the PK analyses or safety parameters (including evaluation for DLTs).

Patients who come off trial due to a DLT will not be replaced.

If a patient should become pregnant during the trial, the treatment with BI 754091 and BI 754111 must immediately be stopped. The patient will be followed up until delivery or termination of pregnancy (see Section 5.2.7.9 for information on pregnancy forms). The data of the patient will be collected and reported in the eCRF until the last patient's last visit and any events occurring thereafter will be reported in the BI drug safety database.

3.3.4.2 Withdrawal of consent for trial participation

Patients may withdraw their consent for trial participation at any time without the need to justify the decision.
This will however mean that no further information may be collected for the purpose of the trial and negative implications for the scientific value may be the consequence. Furthermore, it may mean that further patient follow up on safety cannot occur.
If a patient wants to withdraw consent, the investigator should explain the difference between treatment withdrawal and withdrawal of consent for trial participation and explain the options for continued follow up after withdrawal from trial treatment, please see Section 3.3.4.1 above.

3.3.4.3 Discontinuation of the trial by the sponsor

Boehringer Ingelheim reserves the right to discontinue the trial overall 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 survival data has been collected.

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

3.3.4.3.1 Enrolment stopping rules in case of unacceptable toxicities

All AEs, including serious adverse events (SAEs) and deaths will be carefully analysed by the sponsor. Unacceptable toxicity will be defined as:

- Clinically relevant adverse events that are:
  - unexpected considering the mode of action, and are not manifestations of underlying disease or background events typical of the trial population
  - and/or are debilitating, non-reversible, not manageable
  - or lead to a fatal outcome

  where evidence suggests that there was a reasonable possibility that the drug caused the adverse event.
- Higher than expected frequency or severity of adverse events (such as irAEs) that indicates those events occur more frequently or with higher severity in the drug treatment group than would be expected in the trial population.

If one or both of the above criteria are met the enrolment to the trial will be stopped to allow for in-depth analysis of the safety profile of the study medications. The benefit-risk profile of BI 754091 and/or BI 754111 will be re-assessed by the SMC. The outcome of the analysis and the recommendations will be shared with all involved regulatory health authorities prior to a possible re-start of enrolment. In case the benefit-risk assessment is no longer considered to be positive, the trial will be discontinued.

4. TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

4.1.1 Identity of the Investigational Medicinal Products

4.1.1.1 BI 754091

Details of the drug product, BI 754091 are presented in Table 4.1.1.1: 1. Additional details are presented in the BI 754091 IB and Pharmacy Manual.

Table 4.1.1.1: 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

4.1.1.2 BI 754111

Details of the drug product, BI 754111 are presented in Table 4.1.1.2: 1. Additional details are presented in the BI 754111 IB and Pharmacy Manual.

Table 4.1.1.2: 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

4.1.2 Selection of doses in the trial

4.1.2.1 Starting dose of BI 754091

BI 754091 will be tested at a flat starting dose of 240 mg to be administered via infusion q3w. In case of DLTs, lower doses may also be explored. The dose-finding will be guided by the BLRM, and the final decision will be made by the SMC (see Section 8.7).

The starting dose was selected based on the data obtained in 1381-0001 dose-escalation cohorts, where 3 patients each received BI 754091 monotherapy at dose levels of 80, 240, and 400 mg and none of them experienced DLT or AESI and MTD was considered not reached and the RD was determined to be 240 mg.

The results of in vitro binding experiments suggest that BI 754091 has at least similar affinity to PD-1 as pembrolizumab (n00250922). Therefore, determining the dose based on the similarity of pharmacokinetic properties between BI 754091 and pembrolizumab is considered appropriate. The dose of pembrolizumab for PD-L1 positive, unresectable, advanced or recurrent NSCLC is 200 mg per dose at intervals of 3 weeks, which is similar to the starting dose of BI 754091 for Part I of this trial (240 mg). A comparison of the simulated pembrolizumab blood concentrations over time under 240 mg q3w dosing based on the population PK model (R17-2460) and the actual BI 754091 blood concentrations observed in the trial 1381-0001 (under the same dosing schedule) showed observed concentration of BI 754091 is mostly within the 90% prediction interval of simulated gMean of pembrolizumab. Hence BI 754091 240 mg appears to be appropriate and is expected to be effective in Asian patients. The preliminary results from trial 1381-0001 further showed that the binding of BI 754091 to the PD-1 receptors was saturated also support that the selected dose of 240mg q3w should be adequate.

Generally, antibody drugs, which are intravenously administered, are not metabolised via CYPs, and are not substrate of the transporter. Therefore, no differences in PK due to race and ethnicity are expected. Notable PK differences between Asian and Western patients have not been reported for similar drugs (anti-PD-1 antibodies including nivolumab and pembrolizumab). In fact, the dose and administration of similar drugs are comparable in Asian and non-Asian patients, which suggests that notable racial difference in PK is not expected with BI 754091 and justifies the determination of the starting dose in Asian patients by extrapolating the results in Western patients.

The exposure in a 13-week repeated dose toxicity study NOAEL (100 mg/kg) in cynomolgus monkeys (C_{max}: 6210 µg/mL, AUC_{0-168}: 710000 µg/mL h or AUC_{0-504}: 2130000 µg/mL h) and the simulated steady state BI 754091 exposure following dosing of 240 mg q3w i.v. in humans (C_{max}: 110 µg/mL, AUC_{0-504}: 29700 µg/mL h based on predictions of the exploratory population pharmacokinetic BI 754091 model) showed the safety margin based on C_{max} and AUC_{0-504} to be 56-fold and 72-fold, respectively.

4.1.2.2 Starting dose of BI 754111

BI 754111 will be tested at a starting dose of 400 mg to be administered via infusion q3w. In case of DLTs in 400 mg cohort, lower doses may also be explored.

The starting dose was selected based on the data obtained in 1381-0002 dose-escalation cohorts. By the end of June 2018, BI 754111 was administered at dose range from 4 mg to 600 mg in combination with BI 754091 240 mg. DLTs were not reported at any dose level and the MTD was not reached.

Table 4.1.2.2: 1 Number of evaluable patients and DLTs in trial 1381-0002 (as of Jun 2018)

Dose level	BI 754091 dose	BI 754111 dose	Number of evaluable patients	Number of DLTs
1	240 mg	4 mg	3	0
2	240 mg	20 mg	9	0
3	240 mg	80 mg	9	0
4	240 mg	200 mg	9	0
5	240 mg	400 mg	9	0
6	240 mg	600 mg	9	0
Total	-	-	48	0

4.1.3 Dose-finding scheme

The dose is planned to be tested in cohorts at pre-defined provisional dose levels. The provisional dose levels to be assigned to separate cohorts of patients are listed in Table 4.1.3: 1 and 4.1.3: 2. Intermediate or lower dose levels may be investigated if agreed in the SMC, depending on the number of DLTs observed in the trial.

In Part II, increasing doses of BI 754111 will be administered in combination with BI 754091 at the RD determined in Part I. The dose of BI 754091 may also be titrated based on DLTs and the overall safety profile of the combination.

Table 4.1.3: 1 Example of dose titration in BI 754091 monotherapy dose finding part*

Dose level	Increment from previous dose	Proposed dose of BI 754091
-1	-66.6%	80 mg*
0	Starting dose	240 mg

Table 4.1.3: 2 Example of dose titration in combination dose finding part*

Dose level	Increment from previous dose	Proposed dose of BI 754111
-1	-50%	200 mg*
0	Starting dose	400 mg
1	50%	600 mg*
2	33.3%	800 mg*

*Actual dose assignments for individual patients will be communicated separately as determined by the SMC.

When the last patient in each cohort completes Cycle 1, the SMC will evaluate the available data. The SMC will review all safety data including, but not limited to, DLTs and all CTCAE Version 4.03 Grade ≥2 toxicity data during cycle 1. Updated safety data on other ongoing patients, including data beyond cycle 1, will be discussed as well. Based on that, a decision on the next dose level to be tested will be made.

4.1.4 Dose modifications and premedications

There will be no dose reductions or escalations of BI 754091 or BI 754111 in any one patient. The dose may be delayed for up to 6 weeks because of AEs, following discussion with the sponsor.

During combination therapy, 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 or baseline – exceptions should be discussed and agreed with the sponsor) of the AE, both BI 754091 and BI 754111 must be started together.

The study drug(s) should be permanently discontinued for Grade 3 to 4 pneumonitis, 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 irAEs, 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 (unless unequivocally attributed to another cause) 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 permanently discontinued if ≥ Grade 4 drug-related AEs are reported. Please see Appendix 10.2 for guidelines for management of immune-related adverse events.

Infusion related reactions have been reported in approximately 7% of patients treated with the combination of BI 754091 and BI 754111, none 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 of CTCAE Grade 2. Two events were Grade 3 events and led to treatment discontinuation. The reported infusion related reactions occurred during the infusion mostly at cycle 2 or cycle 3. Symptoms of infusion related reactions may include, but not limited to, flushing, rigors, chills, dyspnea, nausea, vomiting, hypotension, hypertension, syncope, pruritus, tachycardia, and back pain.

To reduce the risk of IRRs, patients are to be premedicated with an antihistamine and acetaminophen or paracetamol. Premedications 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, permanently discontinue study drug(s) (see Section 5.2.7.5.3).

4.1.5 Definition of dose-limiting toxicity

DLTs will be recorded throughout the trial. This report should be submitted to the sponsor within 24 hours of first knowledge. Only DLTs occurring during cycle 1 will be used for MTD determination. All relevant safety information (including DLTs) will be considered when selecting the RD.

Previous anti-PD-l mAbs have been associated in the clinical setting with inflammatory adverse reactions resulting from increased or excessive immune activity (irAEs), likely to be related to the mechanism of action. These adverse reactions, which can be severe, may involve the gastrointestinal, skin, liver, endocrine, respiratory, renal, or other organ systems.

Severity of AEs will be graded according to CTCAE (Version 4.03 in Parts I and II, Version 5 in Part III). Any of the following AEs will be classified as DLTs following review by the Investigators and the sponsor, unless unequivocally due to underlying malignancy or an extraneous cause.

Haematologic toxicities:

- Any Grade 5 toxicity
- Neutropenia ≥ Grade 4 lasting for >5 days
- Febrile neutropenia of any duration (absolute neutrophil count <1.0 X 10^9 cells/L and fever ≥38.5°C)
- Grade 4 thrombocytopenia, or Grade 3 thrombocytopenia with bleeding
- Thrombocytopenia of any Grade which requires platelet transfusions
- Grade 4 anaemia unexplained by underlying disease
- Anaemia of any Grade which requires blood transfusions

Non-haematological toxicities:
- AST or ALT >3 times ULN and concurrent total bilirubin >2 times ULN without initial findings of cholestasis (findings consistent with Hy's law or the FDA definition of potential DILI)
- ≥ Grade 4 AST or ALT of any duration
- Any ≥ Grade 3 non-haematologic toxicity with the following exceptions:
    - Grade 3 irAE that resolves to ≤ Grade 1 or to baseline with immunosuppressive therapy within 2 weeks
    - Grade 3 fatigue that persists <7 days
    - Grade 3 rash that resolves to ≤ Grade 1 within 2 weeks
    - Grade 3 or 4 elevation in serum amylase and/or lipase that is not associated with clinical or radiographic evidence of pancreatitis
    - Grade 3 electrolyte abnormality that lasts <72 hours, is not clinically complicated, and resolves spontaneously or responds to conventional medical intervention
    - Grade 3 nausea or vomiting that lasts <48 hours, and resolves to ≤ Grade 1 either spontaneously or with conventional medical intervention
    - Alopecia
    - Grade 3 endocrine disorders (thyroid, pituitary, and/or adrenal insufficiency) that are sufficiently managed with or without systemic corticosteroid therapy and/or hormone replacement therapy, and the patient is asymptomatic.
    - Grade 3 tumour flare.
- Any Grade 4 or 5 AE
- Any Grade 2 pneumonitis of any duration
- Any Grade 2 uveitis, eye pain, or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within 2 weeks or requires systemic treatment
- Any ≥ Grade 2 toxicity that persists and results in an inability to administer study medication (BI 754091 in Part I, BI 754091 and BI 754111 in Part II and III) on Cycle 2 Day 1.

Late immune-related DLTs are irAEs that meet the same grading criteria as DLT criteria but occur after the MTD evaluation period. These, as well as all toxicities, will be monitored throughout the trial. If any late immune-related DLT is reported during dose-finding, the BLRM will be rerun including the late immune-related DLT, and updated results will be reviewed in the SMC meeting to recommend the next dose level and cohort size.

4.1.6 Definition of maximum-tolerated dose

The MTD may be considered reached if one of the following criteria is fulfilled:
1. The posterior probability of the true DLT rate in the target interval [0.16, 0.33) of the MTD is above 0.5, OR
2. At least 6 patients have been treated at the MTD in each part

4.1.7 Definition of evaluable patient

For decisions on dose escalation, an evaluable patient is defined as a patient who has received BI 754091 or BI 754091 plus BI 754111 and either:
- has completed cycle 1 without experiencing DLT

OR
- has experienced DLT during cycle 1

4.1.8 Method of assigning patients to treatment groups

There will be no randomisation in this trial, as it is a single-arm open-label trial. After assessment of all inclusion and exclusion criteria, each eligible patient will be assigned a dose of medication available at the time of enrolment.

To determine the dose or doses for subsequent cohorts, the available safety data (including DLTs, AEs that are not DLTs, and AE information), as well as the recommendations from the BLRM, will be evaluated by the SMC members.

The SMC must reach a consensus on whether to declare the MTD, escalate the dose any further, or de-escalate and/or expand recruitment into particular cohorts. Dose-finding of BI 754091 monotherapy in Part I will continue until the MTD is reached, or RD determined in 1381-0001 is confirmed. Similarly, dose-finding of BI 754091 and BI 754111 combination in Part II will continue until the MTD is reached, or RD determined in 1381-0002 is confirmed. Part II may still continue for further safety and/or PK evaluation at any dose levels, after the start of recruitment in Part III at the recommended dose.

To further characterise the safety (e.g., specific suspected treatment-related AEs) or PK profiles of BI 754091 monotheraply or BI 754091 plus BI 754111 combination, one or several doses may be expanded. Dose-finding may be terminated at any time based on emerging safety concerns without establishing the RD or the MTD.

In the expansion part, all patients will be treated with the schedule and dose determined by the assessment of DLTs, available PK, and available biomarker results from the dose finding parts of this trial and the data from 1381-0001 and 1381-0002.

Patient numbers will be assigned as enrolment (screening) occurs.

4.1.9 Drug assignment and administration of doses for each patient

Patients will be assigned to their doses based on the available toxicity information (including DLTs, AEs that are not DLTs, and AE information post MTD evaluation period), PK, and anti-tumour activity information, as well as the recommendations from the SMC members following the dose decision meeting, please see Section 4.1.2.

BI 754091 and BI 754111 will be assigned to subjects via interactive response technology (IRT). BI 754091 and BI 754111 will be diluted and administered via i.v. infusion according to the details in the Pharmacy Manual.

Dosing will be sequential when the dose of BI 754111 is less than 80 mg, with BI 754091 infused first followed by infusion of BI 754111. The infusion duration for each will be specified in the pharmacy manual. It is anticipated that the entire infusion time will take ~1 hour. When the dose of BI 754111 is 80 mg or more, the infusion will be simultaneously (infusion duration ~1 hour).

4.1.10 Blinding and procedures for unblinding

Not applicable as this is an open-label trial.

4.1.11 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 (GMP).
Each site will be provided with an initial shipment of trial drug supply. Re-supply to the sites will be managed via an IRT system, which will also monitor expiry dates of supplies available at the sites.

For details of packaging and the description of the label, refer to the ISF.

4.1.12 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 clinical monitor local (as provided in the list of contacts) must be contacted immediately.

4.1.13 Drug accountability

The investigator and/or pharmacist and/or investigational drug storage manager will receive the investigational drugs delivered by the sponsor when the following requirements are fulfilled:

- Approval of the clinical trial protocol by the institutional review board (IRB) / ethics committee,
- Availability of a signed and dated clinical trial contract between the sponsor and the investigational site,
- Approval/notification of the regulatory authority, e.g. competent authority,
- Availability of the curriculum vitae of the Principal Investigator,
- Availability of a signed and dated clinical trial protocol

Investigational drugs are not allowed to be used outside the context of this protocol. They must not be forwarded to other investigators or clinics. The investigator and/or pharmacist and/or investigational drug storage manager must maintain records of the product's delivery to the trial site, the inventory at the site, the use by each patient, and the return to the sponsor or warehouse / drug distribution centre or alternative disposal of unused products. If applicable, the sponsor or warehouse / drug distribution centre will maintain records of the disposal.

These records will include dates, quantities, batch / serial numbers, expiry ('use- by') dates, and the unique code numbers assigned to the investigational product and trial patients. The investigator / pharmacist / investigational drug storage manager will maintain records that document adequately that the patients were provided the doses specified by the CTP and reconcile all investigational products received from the sponsor. At the time of return to the sponsor, the investigator / pharmacist / investigational drug storage manager must verify that all unused drug supplies have been returned to sponsor or destroyed on site, and partially used drug supplies have been destroyed on site, and that no remaining supplies are in the investigator's possession.

4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

4.2.1 Other treatments and emergency procedures

There are no other mandatory treatments to be used or special emergency procedures to be followed in this trial.

4.2.2 Concomitant medications

Rescue medications to reverse the action of BI 754091 or BI 754111 are not available. Therefore, potential side effects of the study drugs have to be treated symptomatically.

Concomitant therapy, with reasons for taking each treatment, must be recorded in the eCRF during the screening and treatment periods, starting at the date of signature of the 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 must be documented in the eCRF.

4.2.2.1 Permitted concomitant medications

- If medically feasible, patients taking regular medication for their coexisting disease should be maintained on it throughout the trial.
- To reduce the risk of IRRs, patients are to be premedicated with an antihistamine and acetaminophen or paracetamol. Premedications should be administered at sufficient time prior to initiation of infusion to allow the agents to exert their effect. This applies to all cycles and all patients except for cycle 1 in the dose-finding part. The patients in the dose-finding part should not be treated prior to cycle 1 to avoid masking the emergence of DLTs.
- 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.
  <for Japan> No erythropoietin product is approved in Japan for anaemia associated with cancer chemotherapy.
- Granulocyte colony stimulating factors should not be used prophylactically during the first 3 weeks of any cohort. Thereafter, prophylactic colony stimulating factors may be used according to institutional standards.
- For symptom control, palliative radiotherapy is permitted for any lesion in the dose-finding part of the trial, except during the first cycle as it could interfere with the DLT evaluation for MTD/RD determination. In the expansion phase (Part III), palliative radiotherapy is allowed only for non-target lesions, following discussion with the sponsor, provided that the reason for radiotherapy does not reflect PD and does not interfere with response assessment. 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. These lesions may also not be used for a trial biopsy. Unless in emergency situations, the sponsor should be contacted prior to the administration of palliative radiotherapy in the expansion phase.
- Hepatocellular cancer patients in Part III Cohorts C and D with HBV infection must be receiving effective antiviral therapy (viral load <100 IU/mL)

4.2.2.2 Prohibited concomitant medications

- 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.

- 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.
- 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.
- Prophylactic erythropoietin, prophylactic granulocyte colony stimulating factors, are not allowed during the first 3 weeks. Palliative radiotherapy is not allowed during the first 3 weeks of the dose finding parts.

4.2.3 Restrictions

4.2.3.1 Restrictions on diet and life style

The usual restrictions on diet and life style that were already applicable for a given patient before entry into the trial, according to his/her medical condition, have to be continued.

4.2.3.2 Restrictions regarding women of childbearing potential

Due to the advanced stage of disease of Phase I trial patient populations and the high medical need, women of childbearing potential can be included in this trial provided that they agree to use a highly-effective contraception method. These are methods of birth control per the International Conference on Harmonisation (ICH) M3 (R2) that result in a low failure rate of less than 1% per year when used consistently and correctly.

Examples of highly-effective methods of contraception are provided in the patient information in the ICF.

Women of childbearing potential must follow these methods during the trial and for at least 6 months after the end of the trial treatment. Although use of a contraceptive pill is considered a highly-effective method of birth control, women of childbearing potential taking a contraceptive pill must use an additional barrier method for the entire duration of the trial treatment intake and for 6 months after the end of the trial treatment intake.

Male patients with partners of childbearing potential must agree to use condoms and ensure their partner is 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.

4.3 TREATMENT COMPLIANCE

BI 754091 and BI 754111 will be administered by i.v. infusion 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. 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

5.1.1 Tumour assessments

The tumour response will be evaluated according to RECIST Version 1.1 (R09-0262) and iRECIST (R17-0923). The overview of iRECIST will be found in Appendix 10.6.

The assessment by the Investigator and/or the local radiologist will be the basis for continuation or discontinuation of the trial 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 2 cycles (6 weeks ±5 days) for the first 6 months, then every 3 cycles (9 weeks ±5 days) thereafter, and at the EOT visit (if not performed within the previous 4 weeks).

If a patient discontinues trial medication for a reason other than PD, 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 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, and the patient provides an additional consent. If a patient is considered to be confirmed progressive disease according to iRECIST (iCPD), the patient may still continue to receive treatment if the Investigator and sponsor agree that the patient is deriving clinical benefit, and the patient provides an additional consent.

Copies of CT/MRI/PET scan data will be collected by the sponsor 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 BI 754091 and BI 754111 will be assessed by a descriptive analysis of incidence and severity of AEs graded according to CTCAE (Version 4.03 in Parts I and II, Version 5 in Part III), the incidence of DLTs, laboratory data, and results of physical examinations. Safety will be assessed in a descriptive way without confirmatory analysis.

DLTs observed during the MTD evaluation period will be considered for MTD determination. However, all DLTs observed in all treatment cycles will be collected and will be considered for determining a RD. The BLRM will be re-run including the DLT information from all

cycles. Based on both estimates, the recommended dose for further development will be selected. At regular intervals, all available safety data including AEs qualifying as DLTs will be submitted to the SMC. The SMC will assess this information and provide recommendations for trial conduct and dose escalation. If there are too few or no DLTs for BLRM guided dose selection, other data including PK will be taken into consideration for RD determination.

5.2.1 Physical examination

Physical examinations will be performed at screening, prior to trial medication administration on Day 1 of each 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.

The physical examination will include measurement of height (screening only) and of body weight. Weight will be measured during screening and at each full physical examination (not during abbreviated physical examinations).

5.2.2 ECOG performance status

The ECOG PS will be assessed at the times indicated in the Flow Chart.

5.2.3 Vital signs

Vital signs (blood pressure, body temperature, pulse rate, and arterial oxygen saturation [SpO_2] after 2 minutes of supine rest) will be recorded at the screening visit, before and after infusion during the first treatment, at every visit of treatment cycles (pre-infusion) including PK sampling days, at the EOT visit, and at the 30-day safety follow-up visit. Measurement of SpO_2 is included in the vital signs check for early detection of pneumonitis.

5.2.4 Safety laboratory parameters

Blood (venous) samples will be collected at the times indicated in the Flow Chart and will be analysed by the sites' local safety laboratories. For Free T3, Troponin I, and venous HCO_3, these will be measured at a central laboratory if study site cannot measure it locally. With the protocol amendment to version 4, Troponin I can be substituted by Troponin T, and HCO_3 does not have to be measured if not available at the study site (the central lab will not be used for Troponin I and HCO_3 after the approval of protocol version 4). Screening laboratory assessments performed within 72 hours of the first trial treatment administration are not required to be repeated on Cycle 1 Day 1. In cases where screening laboratory investigations have been performed >72 hours prior to the first trial treatment intake, the results of the new laboratory investigations performed within 72 hours of the first trial treatment administration must be available to confirm eligibility.

5.2.4.1 Haematology

Red blood cell count, haemoglobin, haematocrit, mean corpuscular volume, platelets, and white blood cell count with differential (neutrophils, lymphocytes, monocytes, eosinophils, and basophils) will be measured. White blood cell differentials should be expressed in absolute values.

5.2.4.2 Biochemistry

The standard biochemistry panel will consist of glucose, sodium, potassium, chloride, calcium, phosphate, venous bicarbonate HCO_3 (if the local lab test is available at the study site), urea (or blood urea nitrogen [BUN]), creatinine, CPK, AST, ALT, alkaline phosphatase, lactate dehydrogenase (LDH), bilirubin (total and direct), total protein, albumin, and uric acid. Troponin will be tested according to the times listed in the Flow Chart. The troponin measurement should be quantitative analysis and can be either Troponin I or T, according to the institutional standard as long as the testing method is consistent. In case of pathological CPK, then CPK-MB, additional tropoinin (either I or T), and myoglobin should be reactively tested and the findings documented.

A thyroid panel (TSH, free T4, and free T3) will be done at the time of each standard biochemistry panel.

HBV, HCV, and HIV testing should be performed at screening unless test results obtained in routine diagnostics within 14 days before the informed consent date are available (For patients with hepatocellular cancer in Part III Cohorts C and D, if a patient is known to have HBV and/or HCV infection, the diagnostic testing for that item does not need to be repeated).

Additionally, amylase and lipase should be analysed in case of symptoms of pancreatitis.

5.2.4.3 Urinalysis

Urine (pH, glucose, erythrocytes, leukocytes, protein, and nitrite) will be analysed by dipstick (semi-quantitative measurements) during the screening visit, on Day 1 of each cycle, at the EOT visit, and as clinically indicated. In case of pathological findings, further evaluation must be performed and the findings documented.

5.2.4.4 Pregnancy test

Beta human chorionic gonadotropin (β-HCG) pregnancy test in serum will be performed for women of childbearing potential at screening, within 14 days prior to first trial treatment. If done within 72 hours of Cycle 1 Day 1, this test does not need to be repeated on the first day of treatment. Thereafter, this test can be done in either serum or urine on Day 1 of each cycle, and at the EOT visit.

5.2.5 Electrocardiogram

Local ECGs will be done throughout the trial. The ECG should be assessed by a physician (cardiologist if available). There will not be a centralised analysis. Single digitalised ECGs must be done after 5 minutes of rest at the time points specified in the Flow Chart, 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.

When the ECG time point is concomitant with a blood sampling (or any other procedure), the ECG must always be performed prior to the blood sampling (or other procedure) to allow the recording in reproducible resting conditions. In case of drug-related ECG changes, additional ECG monitoring will be performed in later cycles of treatment, as deemed necessary by the Investigator. Dated and signed printouts of ECG with findings should be documented in patient's source document.

Following assessment of safety data at the timepoint of interim database lock, it was determined that continued ECG monitoring would not be required (see section 6.2.3.5)

Clinically relevant abnormal findings will be reported either as a baseline condition (if identified at the screening visit) or as AEs and will be followed up and/or treated as medically appropriate.

5.2.6 Other safety parameters

No assessment planned.

5.2.7 Assessment of adverse events

5.2.7.1 Definitions of adverse event

An adverse event (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.

5.2.7.2 Definition of adverse reaction

An adverse reaction is defined as a response to a medicinal product which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility. Adverse reactions may arise from use of the product within or outside the terms of the marketing authorisation or from occupational

exposure. Conditions of use outside the marketing authorisation include off-label use, overdose, misuse, abuse and medication errors.

5.2.7.3 Definition of 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 or
- requires prolongation of existing hospitalisation,
- results in persistent or significant disability or incapacity, or
- is a congenital anomaly / birth defect,
  or
- 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.

For Japan only: the following events will be handled as “deemed serious for any other reason”. AEs which possibly lead to disability will be reported as SAEs.

Patients may be hospitalized for administrative reasons during the trial, including hospitalization for respite care. These as well as hospitalizations/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 hospitalization/surgical procedure has not changed/worsened after signing informed consent)

5.2.7.4 Adverse events considered “Always Serious”

Every new occurrence of cancer of new histology must be classified as a serious event regardless of the duration between discontinuation of the trial medication and must be reported as described in 5.2.7.8, 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 eDC system. These events should always be reported as SAEs as described above.

5.2.7.5 Adverse events of special interest (AESIs)

The term 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 as described in Section 5.2.7.8, subsections "AE Collection" and **AE reporting to sponsor and timelines**.

In this trial, DLTs, irAEs as defined in Appendix 10.1, infusion-related AEs, potential DILI events, and hepatic injury are AESIs.

5.2.7.5.1 Dose-limiting toxicities (DLTs)

All DLTs are considered to be AESIs, and must be reported as such. The definition of DLT is presented in Section 4.1.5.

5.2.7.5.2 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. The sponsor has defined a list of irAEs in Table 10.1: 1 that must be reported as AESIs. 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 Table 10.1: 1. If an Investigator determines a Grade 3 event (not on the list) to be immune-related, the Investigator should also report that event as an AESI.

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

5.2.7.5.3 Infusion-related reactions

In the event of an infusion-related reaction ≤ Grade 2, 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 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 BI 754091 and/or BI 754111 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 sponsor within 24 hours:

- Allergic reaction
- Anaphylaxis
- Cytokine-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.

5.2.7.5.4 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 at any point during the trial.

Hepatic injury definition

In patient with normal baseline hepatic function, a hepatic injury is defined by the following alterations of hepatic laboratory parameters:

- an elevation of AST and/or ALT $\geq$ 3 fold ULN combined with an elevation of total bilirubin $\geq$2 fold ULN measured in the same blood draw sample, and/or
- aminotransferase (ALT, and/or AST) elevations $\geq$10 fold ULN

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.

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 eDC system.

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 should be followed.

5.2.7.6 Severity of adverse events

Part I and II:
The severity of AEs should be classified and recorded in the eCRF according to the CTCAE Version 4.03.

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

5.2.7.7 Causal relationship of adverse events

The definition of an adverse reaction implies at least a reasonable possibility of a causal relationship between a medicinal product and an AE. An adverse reaction, in contrast to an AE, is characterised by the fact that a causal relationship between a medicinal product and an occurrence is suspected.

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.

Examples of 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).
- An indication of dose-response (i.e. greater effect size if the dose is increased, smaller effect size if dose is diminished).

Examples of 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)
- Continuation of the event 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.
- Disappearance of the event even though the trial drug treatment continues or remains unchanged.
- 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).

5.2.7.8 Adverse event collection and reporting

5.2.7.8.1 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 informed consent onwards until the end of the 30-day safety follow-up visit
  - all AEs (non-serious and serious) and all AESIs.
- After the 30-day safety follow-up visit until the individual patient's end of trial:
  - all related SAEs and all related AESIs.
- After the individual patient's end of the trial:
  the investigator does not need to actively monitor the patient for AEs but should report related SAEs and related AESIs 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 Adverse Event Reporting exemptions still apply.

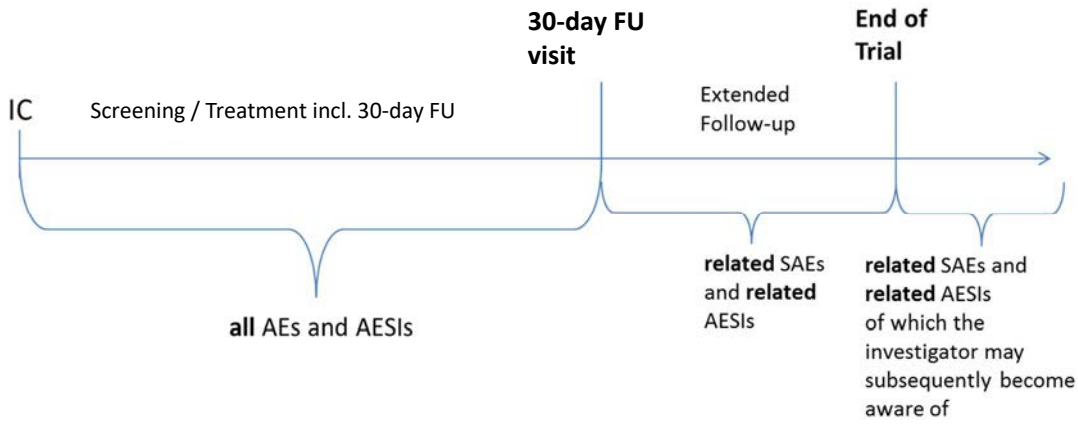


Figure 5.2.7.8.1: 1 Safety follow-up schema

AE reporting to sponsor and timelines
The investigator must report SAEs, AESIs, and non-serious AEs which are relevant for the reported SAE or AESI, on the BI SAE form via fax immediately (within 24 hours) to the sponsor's unique entry point (country specific contact details will be provided in the ISF). The same timeline applies if follow-up information becomes available. In specific occasions the investigator could inform the sponsor upfront via telephone. This does not replace the requirement to complete and fax the BI SAE form.

With receipt of any further information to 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.

Information required
For each AE, the investigator should provide the information requested on the appropriate eCRF pages and the BI SAE form, if applicable. The investigator should determine the causal relationship to the trial medication.

The following should also be recorded as an (S)AE in the CRF and BI SAE form (if applicable):

- Worsening of pre-existing conditions other than the underlying disease
- Changes in vital signs, ECG, physical examination and laboratory test results, if they are judged clinically relevant by the investigator

If such abnormalities already pre-exist prior to trial inclusion they will be considered as baseline conditions and should be collected in the eCRF only. All (S)AEs, including those persisting after individual patient's end of trial must be followed up until they have resolved, have been assessed as "chronic" or "stable" , or no further information can be obtained.

5.2.7.9 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.
<for Japan only> Pregnancy until 6 months after the last dose of study medication should be reported as a drug exposure during pregnancy.

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 Studies (Part B). The ISF will contain the Pregnancy Monitoring Form for Studies (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 Studies 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.

5.2.7.10 Exemptions from 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 (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 reviewed at appropriate intervals.

Lab values meeting the hepatic injury definition as defined in section 5.2.7.5.4 will need to be reported as AESI. PD reporting exemption does not apply to hepatic injury. Please follow the flowchart below for reporting hepatic injury / potential DILI cases.

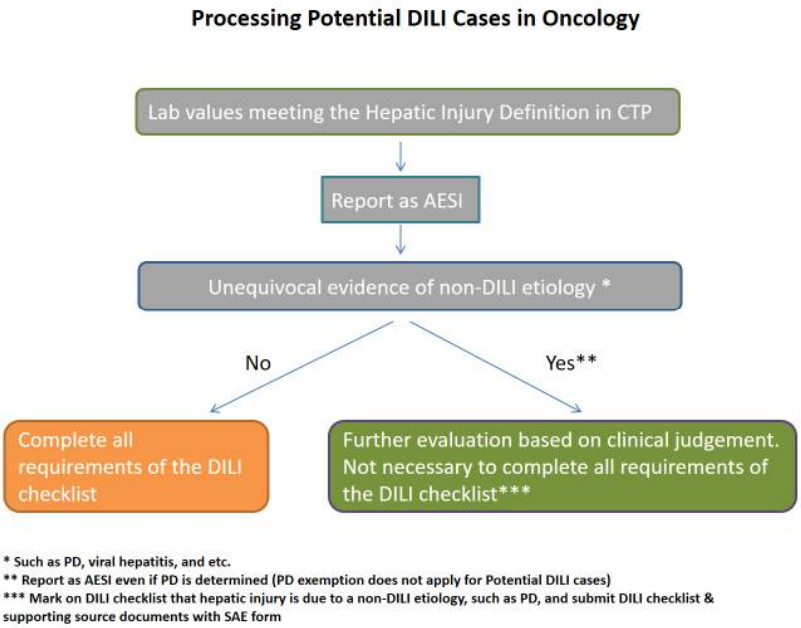


Figure 5.2.7.10: 1 Processing potential DILI cases

5.3 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

5.3.1 Assessment of pharmacokinetics

If data allow, PK parameters of BI 754091 after single and multiple doses of BI 754091 monotherapy in Part I, and PK parameters of BI 754091 and BI 754111 after single and multiple doses of combination of BI 754091 and BI 754111 in Part II and III will be evaluated as secondary [redacted] endpoints using non-compartmental analysis methods according to BI internal SOP (001-MCS-36-472).

If deemed necessary, further PK parameters (other than those defined see Sections 2.1.3 and 2.1.4) might be calculated. Exact date and clock time of drug administration and pharmacokinetic sampling will be recorded in the CRFs by the medical personnel. The actual sampling times will be used for determination of pharmacokinetic parameters.

5.3.2 Methods of sample collection

For quantification of analyte plasma concentrations, blood will be drawn for BI 754091 (Part I) and for both BI 754091 and BI 754111 (Part II and Part III) at the time points listed in Flow Chart under PK sampling and specified in PK time schedules in Tables 10.4: 1 and 10.4: 2 in Appendix 10.4.

Details on sample characteristics, collection, processing, handling, and shipment are provided in the Laboratory Manual.

After completion of the trial, plasma samples may be used for further methodological investigations, e.g., stability testing. However, only data related to the analyte or bioanalytical assay will be generated by these additional investigations. 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.

5.3.4 Pharmacokinetic – pharmacodynamic relationship

No formal analysis of a PK/pharmacodynamics (PDc) relationship is planned.

Data may be used to develop PK/PDc models by using nonlinear mixed effect modelling techniques, if feasible. For this purpose, data may also be combined with data from other trials. Modelling activities will be planned and documented separately according to internal and external guidelines and SOPs.

5.4 ASSESSMENT OF BIOMARKERS

The study of biomarkers will be mostly hypothesis-generating and will be used to expand our understanding of the disease and trial drug. The following exploratory biomarkers are planned to be examined in this trial:

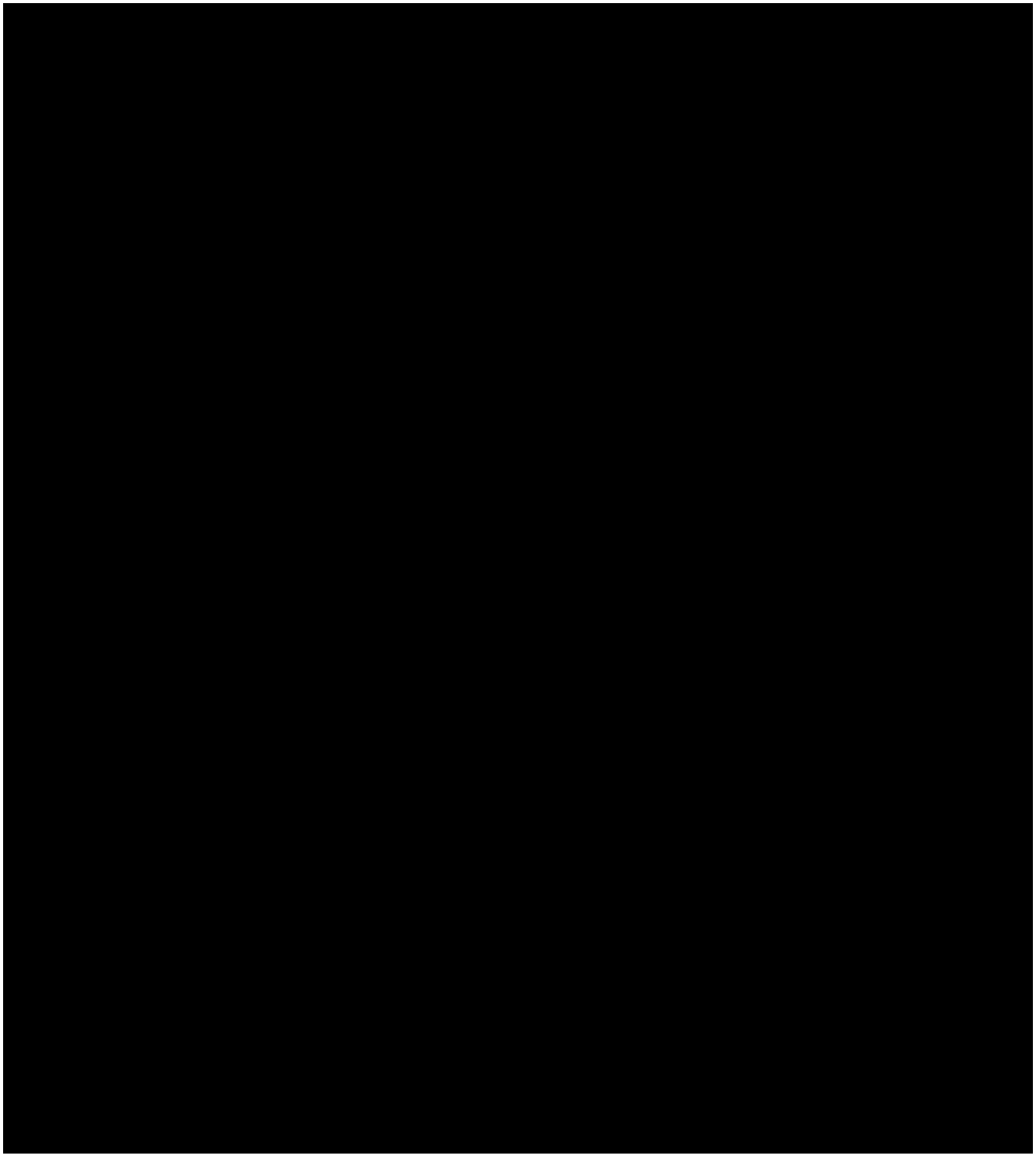
- Mechanism-related cytokines (e.g., IL-2, IFN-γ), as well as exploratory immune-related cytokines during expansion cohorts (see Section 5.4.2.2)
- PD-L1, PD-1, LAG-3, MHC-II, CD-8 positive cells in tumour biopsies taken before and on treatment, if feasible (see Section 5.4.2.3). If enough formalin-fixed and paraffinembedded (FFPE) material is available, a gene-expression profile analysis will be performed. Also, genomic profiling may be performed on pre-treatment biopsies in order to define mutational load (unless a similar analysis has been performed beforehand).
- Peripheral blood mononuclear cells (PBMC) will be characterized for the presence of individual cell lineages, and subsets of T cells will be further analysed for the expression of activation and checkpoint marker expression (PBMC [extract]).

- In a complementary analysis to the above, PBMC (blood), myeloid-derived suppressor cells (MDSC), PD1+ and LAG3+ T-cells, PD-L1+ monocytes, as well as regulatory T-cells and activated T-effector memory cells and activated dendritic cells will be measured (see Section 5.4.2.1)

As medical knowledge in this field is constantly evolving, other tissue/blood biomarkers that may become relevant as predictive markers of treatment response may also be explored via available tissues/blood or acquisition of additional tumour tissues/blood. The list of biomarkers planned to be studied during the trial may change based on new information in the literature or early analyses. The results of biomarker analysis will not be disclosed to patients because they are exploratory analysis which is not validated for diagnostic use.

5.4.1 Methods of sample collection

Pre- and on-treatment tumour biopsy collections for biomarker and PDc analyses will be mandatory from all patients in the Part III dose-expansion portion of the trial. In addition, optional biopsies could be taken after treatment discontinuation, if possible. 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.



5.4.3 Biobanking

Participation in biobanking is voluntary and not a prerequisite for participation in the trial. Biobanking will be realized only after a separate 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 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, including an 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.

The leftovers of the following biomarker samples as specified in Section 5.4 ('Assessment of Biomarkers') will be banked:

- FFPE blocks of pre- and on-treatment biopsies.

The samples for biobanking will be stored at Boehringer Ingelheim at room temperature for maximum 30 years after the end of the clinical trial. If a patient withdraws the consent for biobanking, the samples will be destroyed. However, the results that have been obtained before the withdraw of consent will not be discarded.

5.5 OTHER ASSESSMENTS

5.5.1 Plasma sampling for anti-drug antibodies (ADAs)

All patients: for ADA assessments, the specified blood volume will be drawn into blood-drawing tubes at the time points listed in Flow Chart, and Tables 10.4: 1 and 10.4: 2 in Appendix 10.4.

Details on sample characteristics, processing, handling, and shipment are provided in the Laboratory Manual.

After completion of the trial, plasma samples may be used for further methodological investigations, e.g., stability testing. However, only data related to the ADAs will be generated by these additional investigations. 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.

Note that for some disease indications, it may be necessary to use plasma samples collected prior to administration of study treatments in order to assess the performance of the ADA assay.

5.6 APPROPRIATENESS OF MEASUREMENTS

All assessments except for iRECIST have been planned in accordance with traditional oncology Phase I trial methodology.
iRECIST is a new guideline for response assessment and still to be validated, so this guideline will be used as an exploratory efficacy assessment in this trial.

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

Patients that have met the inclusion and exclusion criteria for the part they are participating in and who have signed a written ICF, are eligible for participation in the trial. Patients will visit the clinical site at the time points specified in the 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. The next visit must then take place at the scheduled time after the first administration of the trial drug in the respective treatment cycle.

Once the decision for any reason is made for a patient to stop the treatment with BI 754091 or the combination of BI 754091 plus BI 754111, 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 EOT.

Additional follow-up visits for progression after the 30-day safety follow-up visit will only be performed in Part III for patients who did not progress on treatment. The follow-up visits for progression will be performed once every 12 weeks at least (in person or by telephone) 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 all portions of the trial are presented in the Flow Chart of this protocol. The key procedures required include:

- PK samples throughout the trial
- Reporting of all AEs occurring after the ICF has been signed
- Baseline and on-treatment blood samplings for biomarker and immunogenicity assessments
- Tumour biopsy biomarker assessments
- Tumour assessments (based on CT/positron emission tomography [PET] and/or magnetic resonance imaging [MRI] scan) according to RECIST Version 1.1 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 study medications for the first 6 months, and then every 3 cycles (9 weeks) thereafter.

6.2.1 Screening period

The screening period may occur a period of 28 days (period within the trial and before the first administration of study medication). For the detailed description of the tests to be performed during this period and their timing, please refer to the Flow Chart.

6.2.1.1 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.

6.2.1.2 Medical History

6.2.1.2.1 Medical history of cancer

History of the patient's cancer 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 information relevant to the disease history such as PD-L1 expression level, microsatellite instability (MSI), and tumour mutation burden (TMB) information will be collected in eCRF where available.

6.2.1.2.2 Other medical history

Past diseases and/or concomitant diagnoses relevant to patient's safety during the trial as judged by the Investigator will be recorded in eCRF.

6.2.1.3 Concomitant medications

Past medications relevant to patient's safety during the trial as judged by the Investigator will be recorded in eCRF. From the date of signature of the ICF, all concomitant medications will be recorded (see Section 4.2.2 for details on concomitant medications).

6.2.2 Treatment period(s)

Please refer to the 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 as soon as possible but no later than 7 days after permanent discontinuation of the trial medication for any reason or e.g. 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 EOT, unless it has been done within the past 4 weeks.

6.2.3.2 30-day safety follow-up visit

The safety follow-up visit is performed 30 (+7) days after the EOT visit. 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 Follow up visits for PFS (extended follow-up period)

Additional follow-up visits for PFS after the 30-day safety follow-up visit will only be performed for patients in Part III who did not progress on treatment. These will be performed once every 12 weeks at least (by telephone or in person) until PD.

The follow-up period for PFS will end at the earliest if one of the following events is met:

- Disease progression
- Start of a new anti–cancer therapy
- Death
- Withdrawal of consent
- Lost to follow-up
- End of whole trial as specified in Section 8.6

The following will be obtained and/or performed during the follow-up visits for PFS.

- Date of contact
- For each reportable serious adverse event / AESI, the investigator should provide the information with regard to concomitant medication and the medication administered to treat the adverse events on the appropriate CRF pages and the SAE form including trade name, indication and dates of administration
- Treatment and date with any subsequent anti-cancer therapy (including surgery and radiotherapy) including the name and type of the anti-cancer drug and/or best supportive care (if applicable)
- Outcome (date of and reason for death [if applicable], in case the patient had PD the actual date of PD shall be recorded)

6.2.3.4 Follow up visits for overall survival (OS)

Additional follow-up visits after the 30-day safety follow-up visit will be performed for patients in Part III Cohort E. These will be performed once every 12 weeks at least (by telephone or in person) on the same schedule as PFS follow-up visits until death, loss to follow-up, or end of the whole trial as specified in Section 3.3.4.3. 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.

6.2.3.5 Study procedures modification after an interim database lock

After an interim database lock (planned in year 2021), the following study procedures do not need to be performed:

- 12-lead ECG (could be performed if clinically indicated with significant abnormalities recorded as AEs)
- Blood samples for Anti-Drug Antibodies
- PK blood samples
- Blood samples and extraction of PBMC for biomarkers (PBMC [extract])
- Plasma samples for biomarkers, and biopsy

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN - MODEL

7.1.1 Statistical design – Part I (BI 754091 monotherapy dose finding part)

Part I of the trial will be designed as an open label study. The objective of the design is to determine the MTD defined as the highest dose with less than 25% risk of the true DLT rate being equal or above 0.33 (EWOC criterion). The part I dose-finding will be guided by a Bayesian 2-parameter logistic regression model with overdose control (R13-4806; R13-4803).

The model is given as follows:

$\text{logit}(\pi_d) = \log(\alpha) + \beta * \log(d/d^*)$,

where $\text{logit}(\pi) = \log(\pi/(1-\pi))$.

π_d represents the probability of having a DLT in the MTD evaluation period at dose d, d* = 400 mg is the reference dose, allowing for the interpretation of α as the odds of a DLT at dose d*, and $\theta = (\log(\alpha), \log(\beta))$ with $\alpha, \beta > 0$ is the parameter vector of the model.

The estimated probability of a DLT at each dose level from the model will be summarized using the following intervals:

Underdosing: [0.00, 0.16)
Targeted toxicity: [0.16, 0.33)
Over toxicity: [0.33, 1.00]

The BLRM-recommended dose for the next cohort is the level with the highest posterior probability of the DLT rate falling in the target interval [0.16, 0.33) among the doses fulfilling EWOC. Applying the EWOC criterion it should be unlikely (<25% posterior probability) that the DLT rate at that dose will exceed 0.33.

The MTD may be considered reached if one of the following criteria is fulfilled:
1. The posterior probability of the true DLT rate in the target interval [0.16 – 0.33) of the MTD is above 0.5, OR
2. At least 6 patients have been treated at the MTD in each part

The SMC may recommend stopping the dose finding phase after the criterion for MTD is fulfilled. Further patients may be included to confirm this MTD estimate. If no DLT is observed at a dose of which the efficacy is considered sufficient, the SMC may decide to include additional number of patients at this dose level and to declare this dose as the dose recommended for further testing.

Since a Bayesian approach is applied, a prior distribution $f(\theta)$ for the unknown parameter vector θ needs to be specified.

The prior distribution for θ will be specified as a mixture of two bivariate normal distributions,
$f(\theta) = a_1 f_1(\theta) + a_2 f_2(\theta)$
with
a_i, i = 1, 2 the prior mixture weights ($a_1 + a_2 = 1$)
and
$f_i(\theta) = MVN(\mu_i, \Sigma_i)$
the multivariate normal distribution of the i-th component with mean vector μ_i and covariance matrix Σ_i, where

$$\Sigma_i = \begin{pmatrix} \sigma^2_{i,11} & \sigma_{i,11}\sigma_{i,22}\rho_i \\ \sigma_{i,11}\sigma_{i,22}\rho_i & \sigma^2_{i,22} \end{pmatrix}$$

Mixture prior distributions have the advantage that they allow for specification of different logistic dose-toxicity curves, therefore making the prior more robust.

Prior derivation:
To determine the prior distribution for θ, a meta-analytic predictive (MAP) approach will be used. Toxicity information on BI 754091 from the 1381-0001 dose-finding part is available. Exact details on the derivation of the prior distributions and on the evaluation of the model using hypothetical data scenarios and operating characteristics are provided in the statistical appendix, a brief description is given here.
The historical data for 1381-0001 phase Ia as of 01 Jun 2017 can be found in Table 7.1.1: 1.

Table 7.1.1: 1 Historical data for BI 754091

Study	Dose	N of patients with DLTs during MTD evaluation period / N of patients
1381-0001(phase Ia)	80 mg	0/3
	240 mg	0/3
	400 mg	0/3

The following steps were performed to derive the prior distribution for θ:

- The MAP prior was derived using the information in Table 7.1.1: 1 allowing for moderate to substantial between-trial heterogeneity. This mixture component was assigned 90% mixture weight.
- A second, weakly informative component was added with 10% mixture weight.

The prior distributions are given in Table 7.1.1: 2. The corresponding prior probabilities of a DLT at different doses and the corresponding probability of underdosing, targeted dosing, and overdosing are shown in Table 7.1.1: 3.

Table 7.1.1: 2 Prior distribution

Parameter	Means, standard deviations, correlation	Mixture weight
θ: component 1	(-1.553, 0.269), (1.002, 1.025), 0.1107	0.9
θ: component 2	(0.1, 0.6), (2,1), 0	0.1

Table 7.1.1: 3 Prior probabilities of DLTs

Dose	Probability of true DLT rate in					Quantiles		
	[0,0.16)	[0.16,0.33)	[0.33,1]	Mean	StD	2.5%	50%	97.5%
80 mg	0.848	0.076	0.076	0.096	0.185	0.000	0.026	0.809
240 mg	0.687	0.182	0.132	0.164	0.206	0.002	0.090	0.883
400 mg	0.424	0.319	0.257	0.257	0.216	0.031	0.190	0.916

The prior may be updated once the trial has started in case new data that can be used will be available. The prior that is used for each BLRM analysis for the SMC meetings will be documented in the SMC minutes, the prior used for the final analysis will be documented in the Trial Statistical Analysis Plan (TSAP).

7.1.2 Statistical design – Part II (BI 754091 and BI 754111 combination dose finding)

Part II of the trial will be performed as an open label single arm study. The primary objective of the design is also to determine the MTD in Japanese patients of BI 754091 in combination with BI 754111. To determine the MTD, patients are entered sequentially into escalating dose cohorts. The dose-finding will be guided by a Bayesian 5-parameter logistic regression model with overdose control. The model is defined as follows. Let $\pi_{1,d1}$ be the probability of having a DLT when giving dose d_1 of BI 754091 as monotherapy, and $\pi_{2,d2}$ the probability of having a DLT when giving dose d_2 of the combination partner BI 754111 as monotherapy, respectively. A logistic regression model is used to model the dose-toxicity relationship for each component individually:
BI 754091 part:
$\text{logit}(\pi_{1,d1}) = \log(\alpha_1) + \beta_1 \log(d_1/d_1^*)$

BI 754111 part:
$\text{logit}(\pi_{2,d2}) = \log(\alpha_2) + \beta_2 \log(d_2/d_2^*)$

where $\text{logit}(\pi) = \log(\pi/(1-\pi))$, the reference doses d_1^* and d_2^* are set for BI 754091 and BI 754111, respectively.

Assuming no toxicity interaction between the two compounds, the probability of a DLT when giving the combination of dose d_1, d_2 is obtained as

$\pi^0_{12,d1,d2} = \pi_{1,d1} + \pi_{2,d2} - \pi_{1,d1}\pi_{2,d2}$
with corresponding odds
$odds(\pi^0_{12,d1,d2}) = \pi^0_{12,d1,d2} / (1 - \pi^0_{12,d1,d2})$

In order to account for a potential positive (higher toxicity than expected under independence) or negative (lower toxicity than expected under independence) interaction between BI 754091 and BI 754111, a dose-dependent interaction term $-\infty<\eta<\infty$ is introduced to the model by the following definition:

$odds(\pi_{12,d1,d2}) = odds(\pi^0_{12,d1,d2}) \exp(\eta\, d_1/d_1^* \, d_2/d_2^*)$
and $\pi_{12,d1,d2}$ is used in the likelihood
$r_{d1,d2} \sim Binomial(n_{d1,d2}, \pi_{12,d1,d2})$

where $r_{d1,d2}$ denotes the variable describing the observed number of DLTs from $n_{d1,d2}$ patients at the dose combination d_1, d_2.

Since a Bayesian approach is applied, prior distributions f for each of the parameter vectors $\theta_1=(\log(\alpha_1),\log(\beta_1))$, $\theta_2=(\log(\alpha_2),\log(\beta_2))$ and for the interaction term η need to be specified.

The prior distributions for θ_1 and θ_2 will be specified as mixtures of three multivariate normal distributions, i.e.
$f(\theta_k) = a_{1,k}\, f_1(\theta_k) + a_{2,k}\, f_2(\theta_k) + a_{3,k}\, f_3(\theta_k)$
with
$a_{1,k}$, $a_{2,k}$ the prior mixture weights, k=1,2,3 and
$f_i(\theta_k) = MVN(\mu_{ik}, \Sigma_{ik})$ (k=1,2,3),
the multivariate normal distribution of the i-th component with mean vector μ_{ik} and covariance matrix Σ_{ik}, where

$$\Sigma_{ik} = \begin{pmatrix} \sigma^2_{ik,11} & \sigma_{ik,11}\sigma_{ik,22}\rho_{ik} \\ \sigma_{ik,11}\sigma_{ik,22}\rho_{ik} & \sigma^2_{ik,22} \end{pmatrix}$$

Mixture prior distributions have the advantage that they allow for specification of different logistic dose-toxicity curves, therefore making the prior more robust.
A weakly informative normal prior distribution will be used for η.

The estimated probability $\pi_{12,d1,d2}$ of a DLT at each dose combination d_1, d_2 from the model will be summarised using the following intervals:
Under dosing: [0.00, 0.16)
Targeted toxicity: [0.16, 0.33)
Over dosing: [0.33, 1.00]

The BLRM-recommended dose for the next cohort is the level with the highest posterior probability of the DLT rate falling in the target interval [0.16, 0.33) among the doses fulfilling EWOC. Applying the EWOC criterion it should be unlikely (<25% posterior probability) that the DLT rate at that dose will exceed 0.33.

As described The MTD may be considered to be reached if one of the following criteria is fulfilled:

1. The posterior probability of the true DLT rate in the target interval [0.16 – 0.33) of the MTD is above 0.5, OR
2. At least 6 patients have been treated in the study, of which at least 6 at the MTD.

The prior distributions for θ_1 and θ_2 are modelled as mixtures of three multivariate normal distributions.
Prior for combination in 1381-0004 to be derived is a mixture with 3 components. One is a weakly-informative one with a weight of 10%. Second one uses only the mono data from PD1 with a weight of 30% (based on MAP). Third one uses all available data based on the posterior of this approach (weight of 60%, mono is used via MAP, combo is actual data).

The following information is currently available.
- Updated mono data for PD1 from 1381-0001
- Updated mono data for PD1 from part I of 1381-0004
- Updated combo data for PD1/LAG3 from 1381-0002

Table 7.1.2: 1 Historical data from 1381-0001 and part I of 1381-0004 as of 06 Jul 2018

Dose BI 754091 (mg)	N of patients treated	N of patients with DLTs during MTD evaluation period
80	3	0
240	40	0
400	3	0

Table 7.1.2: 2 Historical data from 1381-0002 as of 06 Jul 2018

Dose BI 754091 (mg) / BI 754111 (mg)	N of patients treated	N of patients with DLTs during MTD evaluation period
240 / 4	3	0
240 / 20	9	0
240 / 80	9	0
240 / 200	9	0
240 / 400	9	0
240 / 600	9	0

Prior probability is calculated based on the Table 7.1.2: 1 and Table 7.1.2: 2.

Table 7.1.2: 3 Derivation of weakly informative prior distributions both PD-1 and LAG-3

Parameter	Prior distributions Means, standard deviations, correlation	Mixture weight
$\log(\alpha_1)$, $\log(\beta_1)$: component 1	-4.855, 1.062, 2, 1, 0	0.90
$\log(\alpha_1)$, $\log(\beta_1)$: component 2	-0.578, 0.028, 2, 1, 0	0.10
$\log(\alpha_2)$, $\log(\beta_2)$: component 1	-1.386, -0.921, 2, 1, 0	0.90
$\log(\alpha_2)$, $\log(\beta_2)$: component 2	-1.895, 0.545, 2, 1, 0	0.10
η	0.1, 0.707, n/a	n/a

Table 7.1.2: 4 Derivation of prior distributions based on PD-1 mono data (1381-0001) for component 1 + weakly informative for the others

Parameter	Prior distributions Means, standard deviations, correlation	Mixture weight
$\log(\alpha_1)$, $\log(\beta_1)$: component 1	-3.749, -0.13, 0.758, 0.819, -0.129	0.90
$\log(\alpha_1)$, $\log(\beta_1)$: component 2	-1.895, 0.545, 2, 1, 0	0.10
$\log(\alpha_2)$, $\log(\beta_2)$: component 1	-1.386, -0.921, 2, 1, 0	0.90
$\log(\alpha_2)$, $\log(\beta_2)$: component 2	-1.895, 0.545, 2, 1, 0	0.10
η	0.1, 0.707, n/a	n/a

Table 7.1.2: 5 Derivation of posterior distributions based on PD-1/LAG-3 combo data (1381-0002) + prior distribution obtained in step 2

Parameter	Posterior distributions Means, standard deviations, correlation
$\log(\alpha_1)$, $\log(\beta_1)$	-4.148, -0.145, 0.707, 0.781, -0.171
$\log(\alpha_2)$, $\log(\beta_2)$	-4.023, -0.812, 1.292, 0.984, 0.043
η	-0.665, 0.523, n/a

Table 7.1.2: 6 Summary of components of mixture prior distribution with their corresponding weights

Parameter	Obtained from	Prior distributions Means, standard deviations, correlation	Mixture weight
$\log(\alpha_1)$, $\log(\beta_1)$: component 1	Step1	-4.439, 0.983, 2.383, 1.050, -0.182	0.10
$\log(\alpha_1)$, $\log(\beta_1)$: component 2	Step2	-3.565, -0.047, 1.119, 0.863, 0.024	0.30
$\log(\alpha_1)$, $\log(\beta_1)$: component 3	Step3	-4.148, -0.145, 0.707, 0.781, -0.171	0.60
$\log(\alpha_2)$, $\log(\beta_2)$: component 1	Step1	-1.431,-0.774, 2.003,1.099,-0.037	0.10
$\log(\alpha_2)$, $\log(\beta_2)$: component 2	Step2	-1.431, -0.774, 2.003, 1.099, -0.037	0.30
$\log(\alpha_2)$, $\log(\beta_2)$: component 3	Step3	-4.023, -0.812, 1.292, 0.984, 0.043	0.60
η: component 1	Step1	-0.011, 1.125, n/a	0.10
η: component 2	Step2	0.093, 0.71, n/a	0.30
η: component 3	Step3	-0.665, 0.523, n/a	0.60

The corresponding prior probabilities of a DLT at different doses and the corresponding probability of underdosing, targeted dosing, and overdosing are shown in Table 7.1.2: 7.

Table 7.1.2: 7 Prior probabilities of DLTs

Dose (mg)	Dose (mg)	Probability of true DLT rate in			Descriptive statistics	
BI 754091	BI 754111	[0,0.16)	[0.16,0.33)	[0.33,1]	Mean	SD
240	4	0.858	0.074	0.068	0.092	0.152
240	20	0.827	0.087	0.086	0.108	0.169
240	80	0.787	0.101	0.112	0.126	0.188
240	200	0.743	0.116	0.141	0.146	0.21
240	400	0.695	0.115	0.19	0.175	0.252
240	600	0.677	0.102	0.221	0.198	0.289
240	800	0.671	0.087	0.242	0.214	0.316

7.1.3 Statistical design – Part III (expansion)

Part III (dose expansion) of the trial will be designed as open-label. 155 patients with advanced disease of selected tumour types (Section 3.3.2) will be enrolled.

The analyses of the safety and efficacy for part III will be descriptive and exploratory in nature.

7.2 NULL AND ALTERNATIVE HYPOTHESES

The analyses in this trial are descriptive and exploratory. No formal statistical test will be performed.

7.3 PLANNED ANALYSES

No per protocol set will be used in the analysis. However, important protocol violations will be summarised. The TSAP will specify the important protocol violations in detail.

For the determination of the MTD, only MTD evaluable patients will be considered. For the analysis of secondary and further endpoints, all patients in the treated set (i.e. patients treated with at least one dose of trial medication) will be included in the analysis. Any other analysis sets will be defined in the TSAP.

7.3.1 Primary endpoint analyses

7.3.1.1 Primary endpoint analyses for Part I and Part II

In order to identify the MTD, the number of patients with DLTs during the MTD evaluation period of Part I and Part II at each dose level must be presented. Patients who discontinue during the first treatment course for reasons other than DLTs will be excluded from the determination of MTD.

In addition, the number of patients with DLTs that occurred during the entire treatment period will be also summarised.

7.3.1.2 Primary endpoint analyses for Part III

The primary endpoint for Part III of the trial is OR defined by confirmed CR or PR according to RECIST 1.1 as assessed by the Investigator. Overall response will be analysed in terms of OR rate (ORR), defined as the proportion of patients with best overall response of CR or PR determined and confirmed by RECIST 1.1. The ORR will be calculated and presented with 95% two-sided confidence intervals using the exact Clopper-Pearson method.

7.3.2 Secondary endpoint analyses

7.3.2.1 Secondary endpoint analyses for Part I and Part II

Objective response will be analysed in terms of ORR, defined as the proportion of patients with best overall response of CR or PR. The ORR will be calculated and presented with 95% two-sided confidence intervals using the exact Clopper-Peason method.

Detailes on the statistical inference for PK parameters, e.g., dose proportionality using C_{max} and AUC_{0-504} of BI 754111 in Part II in case of more than 3 dose level tested, will be specified in the TSAP.

Analyses of PK parameters, i.e., C_{max} and AUC_{0-504} will be described in Section 7.3.5. More detail will be provided in TSAP.

7.3.2.2 Secondary endpoint analyses for Part III

Duration of response – for all patients with an OR, the duration of OR will be calculated as follows:
For patients with PD or death:

- Duration of response [days] = date of outcome – date of first assessment indicating OR + 1

For patients without disease progression or death:

- Duration of response (censored) [days] = date of outcome – date of first assessment indicating OR + 1

The consoring rules for OR (i.e., outcome and date of outcome) are described in the TSAP.
The outcome will be assessed according to RECIST 1.1.
Kaplan-Meier estimates will be used to calculate median duration of OR.

Disease control (DC) will be analysed in terms of DC rate (DCR), defined as the proportion of patients with best overall response of CR, PR, or SD according to RECIST 1.1.
Proportions will be presented with 95% two-sided confidence interval using the exact Clopper-Pearson method.
7.3.5

[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 adverse events with an onset between start of treatment and end of the residual effect period (REP), a period of 30 days after the last dose of trial medication, will be assigned to the on-treatment period for evaluation. Statistical analysis and reporting of adverse events will concentrate on

treatment-emergent adverse events, i.e. all adverse events occurring between start of treatment and end of the residual effect period. Adverse events that start before first drug intake and deteriorate under treatment will also be considered as 'treatment-emergent'.

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.

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 Medical Dictionary for Drug Regulatory Activities (MedDRA).

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

The pharmacokinetic parameters listed in Sections 2.1.3 and 2.1.4 will be calculated according to the relevant SOP (001-MCS-36-472). Pharmacokinetic analyses will be performed using validated software programs, normally. Phoenix Winnonlin (Pharsight®) with applications validated will be used for the respective purpose. Graphs and tables will be generated using validated customised SAS® macros or appropriate graphic software. A reference to the software used, e.g., name, will be indicated in the Clinical Trial Report (CTR).

The subject set for the evaluation [redacted] will include all treated patients (Treated set).

Only concentration values within the validated concentration range and actual sampling times will be used for the calculation of pharmacokinetic parameters. Concentrations used in the pharmacokinetic calculations will be in the same format provided in the bioanalytical report, (that is, to the same number of decimal places provided in the bioanalytical report).

Further details on analysis will be described in the TSAP

7.4 INTERIM ANALYSES

The sponsor will continuously monitor the safety. The dose escalation design foresees that the sponsor and the SMC perform regular safety evaluations. These evaluations will be unblinded to dose.

No formal interim analysis of PK data is planned. However, exploratory analyses of PK will be done during the dose finding part (Part I and Part II) and may also be done during the expansion part (Part III), if considered reasonable exploratory PK analyses will be based on planned sampling times. The results of these evaluations will be preliminary and may be subject to change, as these do not involve a formal database lock. No interim report will be written for exploratory PK analyses.

If deemed appropriate, an interim futility analysis will be performed for each cohort in part III. 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 patient if the defined efficacy boundary (see Table 7.7.2: 1) is not met at the first stage.

The interim analyses for part III will be conducted when:

- After the 17th patients has completed the third on-treatment imaging assessment (i.e. end of cycle 6).
- If the 17th patient discontinues earlier than the third on-treatment imaging, the interim futility analysis will be triggered at approximately 4 months after the first administration of the 17th patient.

For cohort E, data from 1381-0002 will be pooled for the interim futility decision making, if applicable. If considered necessary, an evaluation of the efficacy and safety aspects will be performed. Results of this evaluation will be documented and archived. If applicable, such an analysis will be defined in more detail in the 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, with particular emphasis on potential DLTs. For partial or missing AE onset and/or end dates, BI internal rules will be followed (see Reference Document 001-MCG-156 “Handling of missing and incomplete AE dates”)

7.5.1 Plasma drug concentration - time profiles

Handling of missing PK data will be performed according to the relevant SOP (001-MCS-36-472).

Drug concentration data identified with no sample available (NOS), no valid result (NOR), not analysed (NOA), or below the limit of quantification (BLQ) will be displayed as such and not replaced by zero at any time point (this rule also applies also to the lag phase, including the predose values).

7.5.2 Pharmacokinetic parameters

Handling of missing PK data will be performed according to the relevant SOP of the Sponsor (001-MCS-36-472).

For the non-compartmental analysis, concentration data identified with NOS, NOR or NOA will generally not be considered. Concentration values in the lag phase identified as BLQ will be set to zero. All other BLQ values of the profile will be ignored. The lag phase is defined as the period between time zero and the first time point with a concentration above the quantification limit.

7.6 RANDOMISATION

No randomisation will be performed. Patients will be assigned to escalating dose groups by order of admission into the trial.

7.7 DETERMINATION OF SAMPLE SIZE

7.7.1 Determination of sample size for Part I and Part II

For Part I and Part II, no formal statistical power calculations of sample size were performed. A minimum of 6 and up to approximately 12 paients for Part I are expected. A minimum of approximately 12 and up to approximately 18 patients for Part II are expected. Fewer or more patients might be needed based on the recommendation of the SMC and the actual number of cohorts tested.

7.7.2 Determination of sample size for Part III

For Part III, below cohorts are assumed.

Cohort A: Patients with gastric/esophagogastric junction cancer, with no prior treatment with anti-PD-1/PD-L1 antibody, and who received at least one line of systemic medical treatment excluding adjuvant therapy

Cohort B: Patients with esophageal cancer with no prior treatment with anti-PD-1/PD-L1 antibody, and who received at least one line of systemic medical treatment excluding adjuvant therapy

Cohort C: Patients with hepatocellular cancer with no prior treatment with anti-PD-1/PD-L1 antibody, who received at least one line of systemic medical treatment excluding adjuvant therapy, and whose Child-Pugh score is 7 or less

Cohort D: Patients with gastric/esophagogastric junction cancer, esophageal cancer, or hepatocellular cancer with a prior treatment with anti-PD-1/PD-L1 antibody
Cohort E: Patients with first-line squamous or non-squamous NSCLC patients without EGFR mutations or ALK rearrangements and PD-L1 expression level < 50%

For cohort A, around 10% ORR with anti-PD-1 antibody monotherapy is assumed. In ONO-4538-12 (R17-3846) which is a randomized phase III trial of Nivolumab in Asian patients with advanced gastric or esophagogastric junction cancer who failed second or later line chemotherapy, the ORR in Nivolmab group was 11.2% [95%CI, 7.7-15.6] (N=330). In KEYNOTE-059 (R17-3847) which is a phase II trial with Pembrolizumab in patients with advanced gastric or esophagogastric junction adenocarcinoma, the ORR in cohort 1 (Pembrolizumab monotherapy in previously treated patients) was 11.2% [95%CI, 7.6-15.7] (N=259).
Based on above result, the futility boundary was set for cohort A as 15% at planned interim futility analysis timing. Assuming the underlying ORR of 35%, the probability of observing <3 responders out of 17 and stopping at interim is 3%, and the probability of observing >=25% ORR at final analysis 90%. If the underlying ORR is 10%, the probability of stopping early is 77%, and the false positive probability of observing >=25% ORR at final analysis is 1%.

For cohort B, around 15% ORR with anti-PD-1 antibody monotherapy is assumed. In ONO-4538-07 (R17-3828) which is an open label phase II trial of Nivolumab in Japanese patients with esophageal squamous-cell carcinoma, the ORR by central review was 17% [95%CI, 10-28] (N=64) and the ORR by investigator assessment was 22% [95%CI, 14-33] (N=64). In KEYNOTE-028 (R17-3849) which is a phase Ib study of Pembrolizumab in PD-L1 positive advanced solid tumour, the ORR result in esophageal cancer cohort was 30.4% [95%CI, 13.2-52.9] (N=23). In KEYNOTE-180 (R19-0167) which is a phase II study of Pembrolizumab in patients with metastatic esophageal cancer progressing after at least 2 lines of prior therapy was 9.9% [95%CI, 5.2-16.7] (N=121).
Based on above result, the futility boundary was set for cohort B as 20% at planned interim futility analysis timing. Assuming the underlying ORR of 45%, the probability of observing <4 responders out of 17 and stopping at interim is 2%, and the probability of observing >=40% ORR at final analysis 77%. If the underlying ORR is 15%, the probability of stopping early is 76%, and the false positive probability of observing >=40% ORR at final analysis is 0%.

For cohort C, around 20% ORR with anti-PD-1 andibody monotherapy is assumed. In Checkmate-040 (R17-3829) which is an open label phase I/II trial of Nivolumab in patients with advanced hepatocellular carcinoma, the ORR was 20% [95%CI, 15-26] (N=50) in dose expansion phase and 15% [95% CI, 6-28] (N=10) in the dose escalation phase. In KEYNOTE-224 (R19-0168) which is a phase 2 study of Pembrolizumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib , the ORR was 17% [95% CI, 11-26] (N=104).
Based on above result, the futility boundary was for cohort C as 20% at planned interim futility analysis timing. Assuming the underlying ORR of 40%, the probability of observing <4 responders out of 17 and stopping at interim is 5%, and the probability of observing >=30% ORR at final analysis 87%. If the underlying ORR is 15%, the probability of stopping

early is 76%, and the false positive probability of observing >=30% ORR at final analysis is 1%.

For cohort D, there is no literature available for the target patients. As there are no treatments of proven efficacy for this population, it is assumed around 5% ORR.
Based on above result, the futility boundary was for cohort D as 10% at planned interim futility analysis timing. Assuming the underlying ORR of 30%, the probability of observing <2 responders out of 17 and stopping at interim is 2%, and the probability of observing >=20% ORR at final analysis 93%. If the underlying ORR is 5%, the probability of stopping early is 80%, and the false positive probability of observing >=20% ORR at final analysis is 0%.

For cohort E, around 20% ORR with antibody monotherapy is assumed. In Keynote-042 (R20-0754) which is randomised, open-label phase 3 trial of Pembrolizumab in patients with previously untreated locally advanced or metastatic non-small cell lung cancer without a sensitising EGFR mutation or ALK translocation, the ORR in the Pembrolizumab group was 118 pts, 39%[95%CI, 34-45](N=299) in the PD-L1 tumour proportion score of 50% or greater and 174 pts, 27%[95%CI, 24-31](N=637) in the PD-L1 tumour proportion score of 1% or greater. Based on the results, the ORR in the pembrolizumab group in the PD-L1 tumour proportion score of 1% to 50% was 17% (56 pts/338 pts).

In part III, a total of around 155 patients will be enrolled and allocated to 5 cohorts. The sample size of each cohort is planned around 35 patients for cohort A to D. For cohort E, the 30 patients is the maximum target sample size.

Table 7.7.2: 1 shows the early stopping criterion and probability for the two-stage approach. It has been calculated that with an earlier interim point, the probabilities of false early stopping or observing a false positive/negative result at the final analysis will be too high. With a later interim point, the false positive, false negative and false early stopping probabilities will be improved, but the scale of improvement is not that meaningful.

Table 7.7.2: 1 Early stopping criteria and probabilities for the two-stage approach for part III

Assumed underlying ORR	Total sample size	Stage 1 sample size	Early stopping criterion (observed ORR)	Early stopping prob.*	Observed ORR at final	Probability of observed ORR at final**
Cohort A						
10%	35	17	<15%(< 3 out of 17)	77%	>=25%(>= 9 out of 35)	1%
15%	35	17	<15%(< 3 out of 17)	53%	>=25%(>= 9 out of 35)	6%

20%	35	17	<15%(< 3 out of 17)	31%	>=25%(>= 9 out of 35)	24%
25%	35	17	<15%(< 3 out of 17)	17%	>=25%(>= 9 out of 35)	50%
30%	35	17	<15%(< 3 out of 17)	8%	>=25%(>= 9 out of 35)	74%
35%	35	17	<15%(< 3 out of 17)	3%	>=25%(>= 9 out of 35)	90%
Cohort B						
15%	35	17	<20%(< 4 out of 17)	76%	>=40%(>= 14 out of 35)	0%
20%	35	17	<20%(< 4 out of 17)	56%	>=40%(>= 14 out of 35)	1%
25%	35	17	<20%(< 4 out of 17)	36%	>=40%(>= 14 out of 35)	3%
30%	35	17	<20%(< 4 out of 17)	20%	>=40%(>= 14 out of 35)	13%
35%	35	17	<20%(< 4 out of 17)	11%	>=40%(>= 14 out of 35)	32%
40%	35	17	<20%(< 4 out of 17)	5%	>=40%(>= 14 out of 35)	55%
45%	35	17	<20%(< 4 out of 17)	2%	>=40%(>= 14 out of 35)	77%
Cohort C						
15%	35	17	<20%(< 4 out of 17)	76%	>=30%(>= 11 out of 35)	1%
20%	35	17	<20%(< 4 out of 17)	56%	>=30%(>= 11 out of	7%

					35)	
25%	35	17	<20%(< 4 out of 17)	36%	>=30%(>= 11 out of 35)	23%
30%	35	17	<20%(< 4 out of 17)	20%	>=30%(>= 11 out of 35)	46%
35%	35	17	<20%(< 4 out of 17)	11%	>=30%(>= 11 out of 35)	70%
40%	35	17	<20%(< 4 out of 17)	5%	>=30%(>= 11 out of 35)	87%
Cohort D						
5%	35	17	<10%(< 2 out of 17)	80%	>=20%(>= 7 out of 35)	0%
10%	35	17	<10%(< 2 out of 17)	49%	>=20%(>= 7 out of 35)	5%
15%	35	17	<10%(< 2 out of 17)	25%	>=20%(>= 7 out of 35)	25%
20%	35	17	<10%(< 2 out of 17)	12%	>=20%(>= 7 out of 35)	55%
25%	35	17	<10%(< 2 out of 17)	5%	>=20%(>= 7 out of 35)	79%
30%	35	17	<10%(< 2 out of 17)	2%	>=20%(>= 7 out of 35)	93%
Cohort E[#]						
15%	30	17	<20%(< 4 out of 17)	76%	>=35%(>= 11 out of 30)	0%
20%	30	17	<20%(< 4 out of 17)	56%	>=35%(>= 11 out of 30)	2%

25%	30	17	<20%(< 4 out of 17)	36%	>=35%(>= 11 out of 30)	10%
30%	30	17	<20%(< 4 out of 17)	20%	>=35%(>= 11 out of 30)	26%
35%	30	17	<20%(< 4 out of 17)	11%	>=35%(>= 11 out of 30)	48%
40%	30	17	<20%(< 4 out of 17)	5%	>=35%(>= 11 out of 30)	70%

*the probability is stopping due to meeting the futility boundary at interim analysis.
**the probability is not meeting the futility boundary at interim analysis and meeting the observed ORR specified at final analysis.
#the futility analysis will be done with 1381.2 data, if conduct.

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 Harmonised Tripartite Guideline for Good Clinical Practice (GCP), relevant BI Standard Operating Procedures (SOPs), the Japanese GCP regulations (Ministry of Health and Welfare Ordinance No. 28, March 27, 1997) and other relevant regulations.

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. In exceptional cases, data may be published before the clinical trial report as long as this is discussed and agreed to by the investigators and the sponsor

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

8.1 TRIAL APPROVAL, PATIENT INFORMATION, INFORMED CONSENT

This trial will be initiated only after all required legal documentation has been reviewed and approved by the respective Institutional Review Board (IRB) / Independent Ethics Committee (IEC) and competent authority (CA) according to national and international regulations. The same applies for the implementation of changes introduced by amendments.

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 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 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 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

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 4.1.13.

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 good documentation practices and be attributable, legible, contemporaneous, original and accurate. 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 documented attempts to retrieve previous medical records. If this fails a verbal history from the patient, documented in their medical records, would be acceptable.

During the site visit the sponsor's Clinical Research Associate (CRA) or auditor must be granted access to the original patient file (see Section 8.3.2). 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 before sending them to the sponsor.

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, date or 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.
- Technical information collected on PK sampling days (e.g., PK sampling times, repeated vital signs linked with PK) may be collected on specific paper PK logs, which will be considered as source data for related entries in eCRF and are considered part of the ISF.

8.3.2 Direct access to source data and documents

The sponsor will monitor the conduct of the trial by regular on-site monitoring visits and in-house data quality review. The frequency of site monitoring will be determined by assessing all characteristics of the trial, including its nature, objective, methodology and the degree of any deviations of the intervention from normal clinical practice.

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 sites:
The trial sites 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 5.2.7.10, 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 below. Patient privacy will be ensured by using patient identification code numbers.
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.
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 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, storage and future use of biological samples from clinical trial participants and the corresponding data, in particular

- A Quality Management System has been implemented to ensure the adherence with the Principles of Good Clinical Practice as outlined in 'Note For Guidance On Good Clinical Practice' (CPMP/ICH/135/95)
- The BI-internal facilities storing and analysing biological samples and data from clinical trial participants as well as the laboratories' activities for clinical trials sponsored by Boehringer Ingelheim are regularly audited. The analytical groups and the banking facility are therefore assessed to be qualified for the storage and use of biological samples and data collected in clinical trials.
- Samples and data are used only if an appropriate informed consent is available.

8.6 TRIAL MILESTONES

The **start of the trial** is defined as the date when the first patient in the whole trial signs informed consent.
The end of the trial is defined as the date of the last visit of the last patient in the whole trial ("Last Patient Out").
The "**Last Patient Drug Discontinuation"** (LPDD) date is defined as the date on which the last patient at an individual trial site ends trial medication (as scheduled per protocol or prematurely). Individual investigators will be notified of Suspected Unexpected Serious Adverse Reactions (SUSARs) occurring with the trial medication until 30 days after LPDD 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.

The target group of Principal Investigators will be oncologists who have experiences in clinical trials of immune-oncology products and working at centres where physicians who are experts of oncology phase 1 trials are available. Tasks and responsibilities will be defined in a contract. Relevant documentation on the participating (Principal) Investigators (e.g. their curricula vitae) will be filed in the ISF. The investigators will have access to the BI clinical trial portal (Clinergize) to facilitate document exchange and maintain electronic ISF.

A Safety Monitoring Committee (SMC) will be established in this trial.
Members of the SMC will include:
- An investigator representative or delegate
- BI safety physician or delegate
- BI Team Member Medicine
- BI Project or Trial Statistician
- BI Clinical Trial Leader (CTL)

Other BI and non-BI subject matter experts may also be invited, as appropriate. The SMC documentation for this trial will define the exact membership and who should be present for decisions to be made.

The SMC will be responsible for making dose-selection decisions for BI 754091 and BI 754111, making decisions on the next cohort size, and recommending to the sponsor whether to continue, modify, or stop the trial.

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

BI has appointed a Trial Clinical Monitor, responsible for coordinating all required activities, in order to

- manage the trial in accordance with applicable regulations and internal SOPs,
- direct the clinical trial team in the preparation, conduct, and reporting of the trial,
- ensure appropriate training and information of Local Clinical Monitors (CML), Clinical Research Associates (CRAs), and investigators of participating countries.

The organisation of the trial in the participating countries will be performed by the respective local or regional BI-organisation (Operating Unit, OPU) in accordance with applicable regulations and BI SOPs, or by a Contract Research Organisation (CRO) with which the responsibilities and tasks will have been agreed and a written contract filed before initiation of the clinical trial.

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.
Central laboratory services, a central imaging archiving service, and an IRT vendor will be used in this trial. Details will be provided in the Central Laboratory Manual, the imaging manual, and the IRT manual available in the ISF.

9. REFERENCES

9.1 PUBLISHED REFERENCES

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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 (report as AESI if an irAE is ≥ Grade 2)
• Acute interstitial pneumonitis • Interstitial lung disease • Pneumonitis
Colitis (report as AESI if an irAE is ≥ 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 • Diarrhea
Endocrine (report as AESI if an irAE is ≥ 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 (report as AESI for any grade)
• Type 1 diabetes mellitus (if new onset)

Immune-related adverse events of special interest
Hematologic (report as AESI if an irAE is ≥ 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 (report as AESI if an irAE is ≥ 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 (report as AESI for any grade)
• Allergic reaction • Anaphylaxis • Cytokine release syndrome • Serum sickness • Infusion reactions • Infusion-like reactions
Neurologic (report as AESI for any grade)
• Autoimmune neuropathy • Guillain-Barre syndrome • Demyelinating polyneuropathy • Myasthenic syndrome
Ocular (report as AESI if an irAE is ≥ Grade 2 or any grade resulting in dose modification or use of systemic steroids to treat the AE)
• Uveitis • Iritis

Immune-related adverse events of special interest
Renal (report as AESI if an irAE is ≥ 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)
Skin (report as AESI for any grade)
• Dermatitis exfoliative • Erythema multiforme • Stevens-Johnson syndrome • Toxic epidermal necrolysis
Skin (report as AESI if an irAE is ≥ Grade 3)
• Pruritus • Rash • Rash generalized • Rash maculopapular • Any rash considered clinically significant in the physician's judgment
Other (report as AESI for any grade)
• 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. **BI 754091 and BI 754111 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 increased >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.
    - BI 754091 and BI 754111 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 BI 754091 and BI 754111, 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.
- BI 754091 and BI 754111 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.

  - BI 754091 and BI 754111 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 BI 754091 and BI 754111, 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.
  - BI 754091 and BI 754111 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.
  - BI 754091 and BI 754111 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.
- BI 754091 and BI 754111 should be permanently discontinued for any recurrent Grade 3-4 AE, transaminase increases >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.
  - BI 754091 and BI 754111 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:
  - BI 754091 and BI 754111 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:
  - BI 754091 and BI 754111 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:
  - BI 754091 and BI 754111 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.

10.3 HANDLING PROCEDURES FOR BLOOD SAMPLES FOR PLASMA CONCENTRATION-TIME MEASUREMENTS

Handling procedures for blood samples are presented in the Laboratory Manual.

10.4 TIME SCHEDULE FOR PHARMACOKINETIC (PK), ADA, AND BIOMARKER BLOOD SAMPLING

Table 10.4: 1 Time schedule for PK, ADA, and biomarker blood sampling during treatment (Parts I and II)

Treatment Cycle	Visit	Day	CRF Time /PTM	Event	PK	ADA	PBMC[2)] (frozen)
1, 2, 4	1	1	-0:05 (Just before drug admin)	Blood	X	X	X (C1&2)
			0:00	Drug admin			
			1:00 (Immediately before end of infusion)	Blood	X		
			1:30	Blood	X		
			2:00	Blood	X		
			4:00	Blood	X		
			7:00	Blood	X		
	2	2	24:00	Blood	X		X (C1)
	3	3	48:00	Blood	X		
	4	4	72:00	Blood	X		
	5	8 ±1	168:00	Blood	X		X (C1)
	6	15±1	336:00	Blood	X		
3, 5-12, 14, 17[1)]	1	1	-0:05 (Just before drug admin)	Blood	X	X	X (C3&5)
			0:00	Drug admin			
EOT				Blood	X	X	
FU				Blood	X	X	X

1) every 3 cycles after Cycle 17
2) PBMC sample will be taken in Part II (only if feasible)

Table 10.4: 2 Time schedule for PK, ADA, and biomarker blood sampling during treatment (Part III)

Treatment Cycle	**Visit**	**Day**	**CRF Time /PTM[hh:min]**	**Event**	**PK**	**ADA**	**PBMC (extract)**	**PBMC (blood)**	**Cytokine**
1, 4	1	1	-0:05 (Just before drug admin)	Blood	X	X	X (C1)	X (C1)	X
			0:00	Drug admin					
			1:00 (Immediately before end of infusion)	Blood	X				
	2	2	24:00	Blood	X		X (C1)		X
	3	8 ±1	168:00	Blood	X		X (C1)	X (C1)	X
	4	15±1	336:00	Blood	X			X (C1)	
2, 3, 5-12, 14, 17[1)]	1	1	-0:05 (Just before drug admin)	Blood	X	X	X (C2, 3, and 5)	X (C2)	X (C2, C3)
			0:00	Drug admin					
EOT[2)]				Blood	X	X		X	
FU[2)]				Blood	X	X	X		X

1) every 3 cycles after Cycle 17
2) blood samples for PK, ADA, PBMC and cytokines are not required after the interim database lock

10.5 STATISTICAL APPENDIX INCLUDING MODEL PERFORMANCE AND DATA SCENARIOS

A Bayesian logistic regression model with overdose control will be used to guide dose-finding in this study. The BLRM is introduced in Section 7.1, which also specifies the prior for the model. After patients in each cohort have completed at least one cycle of treatment, the prior distribution will be updated through Gibbs sampling procedures with the accumulated DLT data from the MTD evaluation period. Posterior probabilities for the rate of DLTs will be summarised from BLRM. Selection of the next dose will be based on these probabilities as well as on other safety and laboratory data.

The purpose of this statistical appendix is to present performance metrics (operating characteristics) that illustrate the precision of the design in estimating the MTD under various dose-toxicity relationships through computer simulation. These results are summarized in Table 10.5: 3. In addition, recommendations of the next dose level by the BLRM with overdose control principle are also provided under various hypothetical outcome scenarios in early cohorts to show how it facilitates on-study dose-finding decisions (see Table 10.5: 1). At 1st SMC, 6 patients will be evaluated in part 1. After that, a cohort size of 3 patients who are all evaluable is assumed. Though the simulation results are showed, the next dose level decision will be done by the SMC. The simulations for scenarios and operating characteristics were produced using RStudio version 3.3.2 in conjunction with WinBUGS 1.4.3.

Hypothetical data scenarios

Hypothetical data scenarios are shown in Table 10.5: 1. These scenarios reflect potential on-study data constellations and related escalation as allowed by the model. For each scenario, the probability of overdose for the current dose, as well as the next potential dose and related probabilities of under-dosing, target dose, and over-dosing are shown.

For example, scenario 1 represents the case that no DLT is observed in the first 6 patients at the starting dose of 240 mg. In this case, the next dose recommended by BLRM is 240 mg. And the SMC may conclude the completion of part 1.

Scenario 2 and 3 represents that the case that 1 or 2 DLTs are observed in the first 6 patients at the starting dose of 240 mg. In this case, the next dose level recommended by BLRM is 240 mg.

Scenario 4 and 5 represents that the case that 1 DLT is observed in the first 6 patients at the starting dose of 240 mg, and the next dose level is kept the same where 0 or 1 DLT occurred.

Scenario 6 and 7 represents that the case that 2 DLTs are observed in the first 6 patients at the starting dose of 240 mg and the next dose level is different based on the SMC decision.

Table 10.5: 1 Hypothetical data scenarios

Scenario	Dose (mg)	# Patients	# DLT	Current Dose : P(OD)	Next recommended dose (mg)	Next dose:		
						P(UD)	P(TD)	P(OD)
1	240	6	0	0.005	240	0.926	0.069	0.005
2	240	6	1	0.043	240	0.686	0.271	0.043
3	240	6	2	0.173	240	0.367	0.460	0.173
4	240 240	6 3	1 0	0.015	240	0.795	0.195	0.015
5	240 240	6 3	1 1	0.071	240	0.519	0.410	0.071
6	240 80	6 3	2 0	0.010	240	0.452	0.435	0.112
7	240 240	6 3	2 1	0.207	240	0.255	0.537	0.207

Operating characteristics

Operating characteristics are a way to assess the long-run behaviour of a model by illustrating the precision of the design in estimating the MTD. Under an assumed true dose-toxicity curve, metrics such as the probability of recommending a dose with true DLT rate in the target interval can be approximated via simulation. Table 10.5: 2 describes 4 assumed true dose-toxicity scenarios which were used to assess the operating characteristics of the model. The scenario setting was referred to 1381-0001 trial assumptions. These scenarios reflect a wide range of possible cases as follows:

- Scenario 1: aligned with prior means
- Scenario 2: low-toxicity scenario
- Scenario 3: high-toxicity scenario
- Scenario 4: low-toxicity followed by high-toxicity

Table 10.5: 2 Assumed true dose-toxicity scenarios

Scenario		Dose (mg)		
		80	240	400
1: Prior	P(DLT)	0.096	0.164	0.257
2: Low Tox		0.001	0.009	0.028
3: High Tox		0.100	0.200	0.300

4: Low-High		0.001	0.180	0.360

For each of these scenarios, 1000 trials were simulated. The each cohort consisted of 3 patients and the MTD was considered reached if at least 6 patients have been evaluated at a dose level which is the model's recommendation for the next dose cohort and for which the posterior probability of targeted toxicity was at least 50%.
It was then assessed how often a dose was declared as MTD with true DLT rate in the under-, targeted-, or over-dose range. Furthermore, the average, minimum and maximum number of patients per trial and the average number of DLTs per trial are reported. Results are shown in Table 10.5: 3.

Table 10.5: 3 Simulated operating characteristics

Scenario	% of trials declaring a MTD with true DLT rate in				# Patients	# DLTs
	Underdose	Target dose	Overdose	Stopped Before MTD	Mean (Min-Max)	Mean (Min-Max)
1: Prior	44.2	53.4	0	2.4	10.1 (3-33)	1.59 (1-6)
2: Low Tox	76.9	0	0	23.1	34.8 (6-60)	0.8 (0-2)
3: High Tox	50.7	45.5	0	3.8	9.56 (3-33)	1.67 (1-6)
4: Low-High	48.9	42.3	8.0	0.8	9.78 (3-30)	1.39 (1-6)

In scenario 1 (Prior), which reflects the case that the true dose-toxicity is aligned with prior means, 53.4% of the simulated trials that have found a MTD declared the MTD with true toxicity rate in the target interval. Few simulated trials (2.4%) have been stopped before declaring a MTD.
In scenario 2 (Low-toxicity scenario), since none of the assumed true dose-toxicity scenarios were beyond 16%, 76.9% of the simulated trials declared a dose as MTD with true DLT rate in the under dose range. 23.1% of the trials stopped before MTD was reached.

In scenario 3 (High-toxicity scenario) illustrate a behaviour similar to scenario 1 because of the similar setting dose toxicity scenarios.

In scenario 4 (Low-High scenario) shows 42.3% of the simulated trials declared a dose as MTD with true DLT rate in the targeted dose range. 8.0% of the simulated trials declared a dose as MTD in the overdose range. This is because the assumed true dose-toxicity rate at 400 mg was above 33%.

The mean patients numbers range from 9 to 10 patients except for scenario 2 (Low-toxicity scenario). The mean patients number was around 35 patients at scenario 2. But in case low toxicity and no safety concern at RD level (i.e. 240 mg), the SMC may recommend stopping the dose finding phase.

In summary, the considered data scenarios show a reasonable behaviour of the model and the operating characteristics demonstrate a good precision of MTD determination.

Part II

The purpose of this statistical appendix is to present performance metrics (operating characteristics) that illustrate the precision of the design in estimating the MTD under various dose-toxicity relationships through computer simulation. These results are summarized in Table 10.5: 6. In addition, recommendations of the next dose level by the BLRM with overdose control principle are also provided under various hypothetical outcome scenarios in early cohorts to show how it facilitates on-study dose-finding decisions (see Table 10.5: 4).

Hypothetical data scenarios
Hypothetical data scenarios are shown in Table 10.5: 4. These scenarios reflect potential on-study data constellations and related escalation as allowed by the model. For each scenario, the probability of overdose for the current dose, as well as the next potential dose and related probabilities of under-dosing, target dose, and over-dosing are shown.

For example, scenario 1 represents the case that no DLT is observed in the first 3 patients at the starting dose of 240/400 mg. In this case, the next dose recommended by BLRM is 240/600 mg.

Scenario 2 represents that the case that 1 DLT is observed in the first 3 patients at the starting dose of 240/400 mg. In this case, the next dose level is 240/400 mg.

Scenario 3 represents that the case that 1 DLT is observed in the first 3 patients at the starting dose of 240/400 mg. And no DLTs is observed at next dose level 240/400 mg. In this case, the next dose level is 240/600 mg.

Scenario 4 represents that the case that 1 DLT is observed in the first 3 patients at the starting dose of 240/400 mg. And 1 DLT is observed at next dose level 240/400 mg. In this case, the next dose level is 240/200 mg.

Scenario 5 represents the case that no DLT is observed in the first 3 patients and next 3 patients. In this case, the next dose recommended by BLRM is 240/800 mg.

Table 10.5: 4 Hypothetical data scenarios

Scenario	Dose comb. BI754091/ BI754111 (mg/mg)	# Patients	# DLT	Current Dose : P(OD)	Next dose comb. BI754091/ BI754111 (mg/mg)	Next dose:		
						P(UD)	P(TD)	P(OD)
1	240/400	3	0	0.024	240/600	0.874	0.077	0.048
2	240/400	3	1	0.279	240/200	0.562	0.251	0.186
3	240/400 240/400	3 3	1 0	0.084	240/600	0.631	0.203	0.166
4	240/400 240/400	3 3	1 1	0.333	240/200	0.214	0.219	0.163
5	240/400 240/600	3 3	0 0	0.008	240/800	0.934	0.044	0.022

Operating characteristics

Operating characteristics are a way to assess the long-run behaviour of a model by illustrating the precision of the design in estimating the MTD. Under an assumed true dose-toxicity curve, metrics such as the probability of recommending a dose with true DLT rate in the target interval can be approximated via simulation. Table 10.5: 5 describes 4 assumed true dose-toxicity scenarios which were used to assess the operating characteristics of the model. These scenarios reflect a wide range of possible cases as follows:

- Scenario 1: aligned with prior means
- Scenario 2: low-toxicity scenario
- Scenario 3: high-toxicity scenario
- Scenario 4: low-toxicity followed by high-toxicity

Table 10.5: 5 Assumed true dose-toxicity scenarios

Scenario		BI 754091 / BI 754111 (mg / mg)			
		240 / 200	240 / 400	240 / 600	240 / 800
1: Prior	P(DLT)	0.146	0.175	0.198	0.214
2: Low Tox		0.001	0.009	0.028	0.160
3: High Tox		0.100	0.200	0.300	0.600
4: Low-High		0.001	0.180	0.360	0.720

For each of these scenarios, 1000 trials were simulated. The each cohort consisted of 3 patients and the MTD was considered reached if at least 6 patients have been evaluated at a dose level which is the model's recommendation for the next dose cohort and for which the posterior probability of targeted toxicity was at least 50%.
It was then assessed how often a dose was declared as MTD with true DLT rate in the under-, targeted-, or over-dose range. Furthermore, the average, minimum and maximum number of patients per trial and the average number of DLTs per trial are reported. Results are shown in Table 10.5: 6.

Table 10.5: 6 Simulated operating characteristics

Scenario	% of trials declaring a MTD with true DLT rate in				# Patients	# DLTs
	Underdose	Target dose	Overdose	Stopped Before MTD	Mean (Min-Max)	Mean (Min-Max)
1: Prior	14.0	69.3	0	16.7	27.41 (9-60)	1.24 (0-4)
2: Low Tox	21.0	72.8	0	6.2	11.97 (3-42)	2.161 (1-7)
3: High Tox	8.6	75.4	1.5	14.5	11.5 (3-30)	2.5 (1-9)
4: Low-High	5.5	66.9	18.2	9.4	11.7 (3-42)	2.57 (1-9)

In scenario 1 (Prior), which reflects the case that the true dose-toxicity is aligned with prior means, 69.3% of the simulated trials that have found a MTD declared the MTD with true toxicity rate in the target interval.

In scenario 2 (Low-toxicity scenario), almost all simulated trials (93.8%) are declared as MTD in underdose or target dose. The resut is similar to scenario 1.

In scenario 3 (High-toxicity scenario), 75.4 % of the simulated trials are declared te MTD with true toxicity rate in the target intervals. Though overdose toxicity is assumed but the only 1.5% is declared as MTD in overdose.

In scenario 4 (Low-High scenario) shows 66.9% of the simulated trials declared a dose as MTD with true DLT rate in the targeted dose range. 18.2% of the simulated trials declared a dose as MTD in the overdose range. This is because the assumed true dose-toxicity rate at 240/600 mg and 240/800 mg was above 33%.

The mean patients numbers range is from 3 to 60 patients and the DLT numbers range is from 0 to 9.

In summary, the considered data scenarios show a reasonable behaviour of the model and the operating characteristics demonstrate a good precision of MTD determination.

10.6 iRECIST

Immunotherapeutics may result in infiltration of immune cells leading to transient increase in the size in malignant lesions, or undetectable lesions becoming detectable. The criteria are identical to those of RECIST 1.1 in many respects but have been adapted to account for instances where an increase in tumour burden, or the appearance of new lesions, does not reflect true tumour progression. Key differences are described below. All responses defined using iRECIST criteria are designated with a prefix. iRECIST time-point and best overall responses will be recorded separately.

Confirming progression

Unlike RECIST 1.1, iRECIST requires the confirmation of progression and uses the terms iUPD (unconfirmed progression) and iCPD (confirmed progression). Confirmatory scans should be performed at least 4 weeks, but no longer than 8 weeks after iUPD.
iCPD is confirmed if further increase in tumour burden, compared to the last assessment, is seen as evidenced by one or more of the following:

- Continued increase in tumour burden (from iUPD) where RECIST 1.1 definitions of progression had been met (from nadir) in target, non-target disease or new lesions
  - Progression in target disease worsens with an increase of at least 5 mm in the absolute value of the sum
  - Continued unequivocal progression in non-target disease with an increase in tumour burden
  - Increase in size of previously identified new lesion(s) (an increase of at least 5 mm in the absolute value of the sum of those considered to be target new lesions) or additional new lesions
- RECIST 1.1 criteria are met in lesions types (target or non-target or new lesions) where progression was not previously identified, including the appearance of additional new lesions.

If iUPD is not confirmed at the next assessment, then the appropriate response will be assigned (iUPD if the criteria are still met, but no worsening, or iSD, iPR or iCR if those criteria are met compared to baseline). The prior documentation of iUPD does not preclude assigning iCR, iPR, or iSD in subsequent time-point assessments or as best overall response (BOR) providing that iCPD is not documented at the next assessment after iUPD.

New lesions

New lesions should be assessed and measured as they appear using RECIST 1.1 criteria (maximum of 5 lesions, no more than 2 per site, at least 10 mm in long axis (or 15 mm in short axis for nodal lesions), and recorded as New Lesions-Target (NLT) and New

Lesion-Non-Target (NLNT) to allow clear differentiation from baseline target and non-target lesions.
New lesions may either meet the criteria of NLT or NLNT to drive iUPD (or iCPD).
However, the measurements of target lesions should NOT be included in the sum of measures of original target lesions identified at baseline. Rather, these measurements will be collected on a separate table in the case record form.
PD is confirmed in the New Lesion category if the next imaging assessment, conducted at least 4 weeks (but not more than 8 weeks) after iUPD confirms further progression from iUPD with either an increase of at least 5 mm in the absolute value of the sum of NLT OR an increase (but not necessarily unequivocal increase) in the size of NLNT lesions OR the appearance of additional new lesions

Table 10.6: 1 Time-point (TP) iResponse

Target Lesions*	Non-Target Lesions*	New Lesions *	Time Point Response	
			No prior iUPD**	Prior iUPD**; ***
iCR	iCR	No	iCR	iCR
iCR	Non-iCR/Non-iUPD	No	iPR	iPR
iPR	Non-iCR/Non-iUPD	No	iPR	iPR
iSD	Non-iCR/Non-iUPD	No	iSD	iSD
iUPD with no change OR decrease from last TP	iUPD with no change OR decrease from last TP	Yes	NA	NLs confirms iCPD if NLs were previously identified and increase in size (≥5 mm in SOM for NLT or any increase for NLNT) or number.
iSD	iUPD	No	iUPD	Remains iUPD unless iCPD confirmed based in further increase in size of NT disease (need not meet RECIST 1.1 criteria for unequivocal PD)
iUPD	Non-iCR/Non-iUPD	No	iUPD	Remains iUPD unless iCPD confirmed based on: o further increase in SOM of at least 5 mm, otherwise remains iUPD
iUPD	iUPD	No	iUPD	Remains iUPD unless iCPD confirmed based on further increase in: o previously identified T lesion iUPD SOM ≥5 mm and / or o NT lesion iUPD (prior assessment - need not be unequivocal PD)

iUPD	iUPD	Yes	iUPD	Remains iUPD unless iCPD confirmed based on further increase in: o previously identified T lesion iUPD ≥5 mm and / or o previously identified NT lesion iUPD (need not be unequivocal) and /or o size or number of new lesions previously identified
Non-iUPD/PD	Non-iUPD/PD	Yes	iUPD	Remains iUPD unless iCPD confirmed based on o increase in size or number of new lesions previously identified
* Using RECIST 1.1 principles. If no PSPD occurs, RECIST 1.1 and iRECIST categories for CR, PR and SD would be the same. ** in any lesion category. *** previously identified in assessment immediately prior to this TP.				

All patients will have their iBOR from the start of study treatment until the end of treatment classified as outlined below.

Table 10.6: 2 iRECIST Best Overall Response (iBOR)

TPR1	TPR2	TPR3	TPR4	TPR5	iBOR
iCR	iCR	iCR, iPR, iUPD, NE	iUPD	iCPD	iCR
iUPD	iPR, iSD, NE	iCR	iCR	iCR, iPR, iSD, iUPD, NE	iCR
iUPD	iPR	iPR	iPR, iSD, iUPD, NE	iPR, iSD, iUPD, NE, iCPD	iPR
iUPD	iSD, NE	iPR	iPR	iPR, iSD, iUPD, NE	iPR
iUPD	iSD	iSD, iUPD, NE	iSD, iUPD, iCPD, NE	iSD, iUPD, iCPD, NE	iSD
iUPD	iCPD	Anything	Anything	Anything	iCPD
iUPD	iUPD	iCPD	Anything	Anything	iCPD
iUPD	NE	NE	NE	NE	iUPD
• NE = not evaluable that cycle. • Designation “I” for BOR can be used to indicate prior iUPD to aid in data interpretation. • For patients with non-target disease only at baseline, only CR or non-CR/non-PD can be					

assigned at each TPR but is not shown in the table for ease of presentation.

10.7 RELATIONSHIP BETWEEN VISIT NUMBER AND DATE

Table 10.7: 1 Relationship between visit number and date in Part I and II

Cycle	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6
1, 2, 4	Day 1	Day 2	Day 3	Day 4	Day 8	Day 15
3	Day 1	Day 15				
5 onward	Day 1					

Table 10.7: 2 Relationship between visit number and date in Part III

Cycle	Visit 1	Visit 2	Visit 3	Visit 4
1, 4	Day 1	Day 2	Day 8	Day 15
2	Day 1	Day 8	Day 15	
3	Day 1	Day 15		
5 onward	Day 1			

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

11.1 GLOBAL AMENDMENT 1

Number of global amendment		1
Date of CTP revision		14 Aug 2018
EudraCT number		Not applicable
BI Trial number		1381-0004
BI Investigational Product(s)		BI 754091 and BI 754111
Title of protocol (previous - see below for title update)		An open label, Phase I study of BI 754091 monotherapy and combination therapy of BI 754091 and BI 754111 in Asian patients with advanced solid tumours
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		Cover page and Synopsis – Coordinating investigator
Description of change		Added: [redacted] **Telephone:** [redacted]
Rationale for change		Coordinating investigator was appointed for the expansion of the trial from single-centre to multi-centre.

Section to be changed		General
Description of change		The term "recommended phase 2 dose (RP2D)" was replaced with "recommended dose (RD)".

Rationale for change		The recommended dose for phase 2 trials may change based on the data from the expansion part.
Section to be changed		Synopsis - dose
Description of change		Part II: The starting dose of BI 754111 will be ~~80~~ **400** mg, based on the safety information from another ongoing trial, 1381-0002. BI 754111 will be administered once every 3 weeks in combination with BI 754091 at the ~~RP2D~~ **RD** (Part I).
Rationale for change		Starting dose of BI 754111 was changed based on the latest safety data from a preceding trial 1381-0002
Section to be changed		Flow chart footnote d and section 5.2.4.2
Description of change		Added: **Heaptitis B virus (HBV), hepatitis C virus (HCV), and human immunodeficiency virus (HIV) testing should be performed at screening unless test results obtained in routine diagnostics within 14 days before the informed consent date are available (In Part III Cohort C, if a patient is known to have HBV and/or HCV infection, the diagnostic testing for that item does not need to be repeated).**
Rationale for change		To clarify these tests are required at the screening to check the eligibility
Section to be changed		1.2.2 BI 754111
Description of change		BI 754111 is currently being tested in patients in the BI 1381-0002 trial. BI 754111 ~~4 mg and 20 mg were~~ **was** administered **at dose range from 4 mg to 600 mg** in combination with BI 754091 240 mg ~~at the first and second dose levels of this trial~~. No DLTs were reported in these dose levels from patients who were eligible for DLT evaluation (**see section 4.1.2.2**~~3 patients at each dose level~~).
Rationale for change		Update based on the latest safety data from a preceding trial 1381-0002
Section to be changed		1.2.2 BI 754111
Description of change		Added: **The residual effect period of BI 754091 monotherapy and BI 754091/BI 754111 combination therapy is 30 days.**
Rationale for change		Clarification
Section to be changed		1.4 Benefit – Risk assessment
Description of change		In addition, dose levels which are higher than the ~~recommended phase II doses (RP2Ds) determined~~ **ones investigated** in preceding trials 1381-0001 and 1381-0002 will not be investigated in this trial.
Rationale for change		Clarification, as a dose level higher than RD may be investigated in 1381-0002 and that dose level may also be investigated in 1381-0004.
Section to be changed		3.1 Overall trial design and plan
Description of change		Following determination of the MTD and/or the ~~RP2D~~ **RD** from the dose-finding parts, Part III will commence and approximately 140 patients with gastric/esophagogastric

		junction cancer, esophageal cancer, or hepatocellular cancer will be enrolled to explore the efficacy and further evaluate the safety, tolerability, PK profile, biomarkers of the combination of BI 754091 and BI 754111 at ~~RP2D~~ **RD** determined in Part II. **Part II may still continue for further safety and/or PK evaluation at any dose levels, after the start of recruitment in Part III at the recommended dose.**
Rationale for change		Clarification
Section to be changed		3.3.3 Exclusion criteria
Description of change		2. Patients who must or wish to continue the intake of restricted medications (see Section ~~4.2.2.1~~**4.2.2.2**) or any drug considered likely to interfere with the safe conduct of the trial
Rationale for change		Correction of error
Section to be changed		4.1.2.2 Starting dose of BI 754111
Description of change		BI 754111 will be tested at a starting dose of ~~80~~**400** mg to be administered via infusion q3w. In case of DLTs in ~~80~~**400** mg cohort, lower doses may also be explored. The starting dose was selected based on the data obtained in 1381-0002 dose-escalation cohorts. By the end of ~~November 2017~~**June 2018**, BI 754111 ~~4 mg, 20 mg, and 80 mg were~~ **was** administered **at dose range from 4 mg to 600 mg** in combination with BI 754091 240 mg. ~~In these dose levels, three patients were evaluable for DLT in each dose level and none of them experienced DLT.~~**DLTs were not reported at any dose level and the MTD was not reached.**
Rationale for change		Starting dose of BI 754111 was changed based on the latest safety data from a preceding trial 1381-0002
Section to be changed		4.1.2.2 Starting dose of BI 754111
Description of change		Table 4.1.2.2: 1 was added
Rationale for change		To summarise the number of evaluable patients and DLTs in trial 1381-0002 as a rationale for the change in the starting dose.
Section to be changed		4.1.3 Dose-finding scheme
Description of change		Table 4.1.3.2 Example of dose titration in combination dose finding part*:

Dose level	Increment from previous dose	Proposed dose of BI 754111
-1	**-50%**	**200 mg***
0	Starting dose	~~80~~ **400** mg
1	~~150~~ **50**%	~~200~~ **600** mg*
2	~~100~~ **33.3**%	~~400~~ **800** mg*
~~3~~	~~50%~~	~~600 mg*~~

Rationale for change		Starting dose of BI 754111 was changed based on the latest safety data from a preceding trial 1381-0002. The example of dose levels was updated accordingly.
Section to be changed		4.1.8 Method of assigning patients to treatment groups

Description of change		Added: **Part II may still continue for further safety and/or PK evaluation at any dose levels, after the start of recruitment in Part III at the recommended dose.**
Rationale for change		Clarification
Section to be changed		4.2.2.1 Permitted concomitant medications
Description of change		Added: **Patients in Part III Cohort C with HBV infection must be receiving effective antiviral therapy (viral load <100 IU/mL)**
Rationale for change		Clarification
Section to be changed		5.1.1 Tumour assessments
Description of change		**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, and the patient provides an additional consent.** ~~Following PD, a~~ **If a patient is considered to be confirmed progressive disease according to iRECIST (iCPD), the** patient may **still** continue to receive treatment ~~for a maximum of a year~~ if the Investigator and sponsor agree that the patient is deriving clinical benefit**, and the patient provides an additional consent**.
Rationale for change		Clarification
Section to be changed		5.1.1 Tumour assessments
Description of change		Added: **Copies of CT/MRI/PET scan data will be collected by the sponsor 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.**
Rationale for change		Clarification
Section to be changed		5.2.7.8.1 AE collection
Description of change		The following must be collected and documented on the appropriate CRF(s) by the investigator: • From signing the informed consent onwards until the end of treatment (including ~~the Residual Effect Period [REP]; a period of 30 days after the last dose of trial medication~~ **period between EOT visit and the 30-day follow up visit**) ➢ all AEs (non-serious and serious) and all AESIs. • After the ~~end of treatment (including the REP)~~ **30-day safety follow-up visit** until the individual patient's end of trial: ➢ all related SAEs and all related AESIs.
Rationale for change		Clarification
Section to be changed		7.1.2 Statistical design – Part II (BI 754091 and BI 754111 combination dose finding)
Description of change		The following information is currently available. • Updated mono data for PD1 from 1381-0001 • **Updated mono data for PD1 from part I of 1381-0004**

		• Updated combo data for PD1/LAG3 from 1381-0002 Table 7.1.2: 1 Historical data from 1381-0001 as of ~~06 Dec 2017~~ **06 Jul 2018 and part I of 1381-0004 as of 20 Jun 2018** Dose BI 754091 (mg) / N of patients treated / N of patients with DLTs during MTD evaluation period 80 / 3 / 0 240 / ~~25~~ **40** / 0 400 / 3 / 0 Table 7.1.2: 2 Historical data from 1381-0002 as of 06 ~~Dec 2017~~ **Jul 2018** Dose BI 754091 (mg) / BI 754111 (mg) / N of patients treated / N of patients with DLTs during MTD evaluation period 240 / 4 / 3 / 0 240 / 20 / ~~3~~**9** / 0 240 / 80 / ~~3~~**9** / 0 **240 / 200** / **9** / **0** **240 / 400** / **9** / **0** **240 / 600** / **9** / **0**
Rationale for change		Prior information to be used for DLT rate estimate was updated based on the latest data.
Section to be changed		7.1.2 Statistical design – Part II (BI 754091 and BI 754111 combination dose finding)
Description of change		Table 7.1.2: 4 Derivation of prior distributions based on PD-1 mono data (1381-0001) for component 1 + weakly informative for the others Parameter / Prior distributions Means, standard deviations, correlation / Mixture weight $\log(\alpha_1)$, $\log(\beta_1)$: component 1 / ~~-3.541, 0.123, 0.778, 0.816, 0.126~~ **3.749, -0.13, 0.758, 0.819, -0.129** / 0.90 $\log(\alpha_1)$, $\log(\beta_1)$: component 2 / -1.895, 0.545, 2, 1, 0 / 0.10 $\log(\alpha_2)$, $\log(\beta_2)$: component 1 / -1.386, -0.921, 2, 1, 0 / 0.90 $\log(\alpha_2)$, $\log(\beta_2)$: component 2 / -1.895, 0.545, 2, 1, 0 / 0.10 η / 0.1, 0.707, n/a / n/a

Table 7.1.2: 5 Derivation of posterior distributions based on PD-1/LAG-3 combo data (1381-0002) + prior distribution obtained in step 2

Parameter	Posterior distributions Means, standard deviations, correlation
$\log(\alpha_1)$, $\log(\beta_1)$	~~-3.730, -0.115, 0.752, 0.796, -0.140~~ **-4.148, -0.145, 0.707, 0.781, -0.171**
$\log(\alpha_2)$, $\log(\beta_2)$	~~-2.745, 0.406, 1.578, 1.154, 0.265~~ **-4.023, -0.812, 1.292, 0.984, 0.043**
η	~~-0.032, 0.698~~ **-0.665, 0.523, n/a**

Table 7.1.2: 6 Summary of components of mixture prior distribution with their corresponding weights

Parameter	Obtained from	Prior distributions Means, standard deviations, correlation	Mixture weight
$\log(\alpha_1)$, $\log(\beta_1)$: component 1	Step1	-4.439, 0.983, 2.383, 1.050, -0.182	0.10
$\log(\alpha_1)$, $\log(\beta_1)$: component 2	Step2	~~-3.378, 0.040, 1.100,0.859, 0.010~~ **-3.565, -0.047, 1.119, 0.863, 0.024**	0.30
$\log(\alpha_1)$, $\log(\beta_1)$: component 3	Step3	~~-3.730, 0.115, 0.752, 0.796, 0.140~~ **-4.148, -0.145, 0.707, 0.781, -0.171**	0.60
$\log(\alpha_2)$, $\log(\beta_2)$: component 1	Step1	-1.431,-0.774, 2.003,1.099,-0.037	0.10
$\log(\alpha_2)$, $\log(\beta_2)$: component 2	Step2	~~-1.431, 0.774, 2.003,1.099, 0.037~~ **-1.431, -0.774, 2.003, 1.099, -0.037**	0.30
$\log(\alpha_2)$, $\log(\beta_2)$: component 3	Step3	~~-2.745, 0.406, 1.578, 1.154, 0.265~~ **-4.023, -0.812, 1.292, 0.984, 0.043**	0.60
η: component 1	Step1	-0.011, 1.125, n/a	0.10
η: component	Step2	0.093, 0.71~~0~~, n/a	0.30

2				
η: component 3	Step3	~~0.032, 0.698~~ **-0.665, 0.523**, n/a	0.60	

The corresponding prior probabilities of a DLT at different doses and the corresponding probability of underdosing, targeted dosing, and overdosing are shown in Table 7.1.2: 7.

Table 7.1.2: 7 Prior probabilities of DLTs

Dose (mg)	Dose (mg)	Probability of true DLT rate in			Descriptive statistics	
BI 754091	BI 754111	[0,0.16)	[0.16,0.33)	[0.33,1]	Mean	SD
~~80~~	~~4~~	~~0.884~~	~~0.059~~	~~0.057~~	~~0.074~~	~~0.142~~
~~80~~	~~20~~	~~0.837~~	~~0.082~~	~~0.081~~	~~0.098~~	~~0.164~~
~~80~~	~~80~~	~~0.750~~	~~0.124~~	~~0.125~~	~~0.139~~	~~0.193~~
~~80~~	~~200~~	~~0.599~~	~~0.184~~	~~0.217~~	~~0.207~~	~~0.229~~
~~80~~	~~400~~	~~0.459~~	~~0.180~~	~~0.360~~	~~0.307~~	~~0.295~~
~~80~~	~~600~~	~~0.401~~	~~0.166~~	~~0.433~~	~~0.364~~	~~0.326~~
~~240~~	~~4~~	~~0.824~~	~~0.100~~	~~0.076~~	~~0.109~~	~~0.154~~
~~240~~	~~20~~	~~0.773~~	~~0.125~~	~~0.102~~	~~0.132~~	~~0.173~~
~~240~~	~~80~~	~~0.668~~	~~0.174~~	~~0.158~~	~~0.175~~	~~0.202~~
~~240~~	~~200~~	~~0.503~~	~~0.205~~	~~0.292~~	~~0.256~~	~~0.251~~
~~240~~	~~400~~	~~0.400~~	~~0.150~~	~~0.450~~	~~0.375~~	~~0.336~~
~~240~~	~~600~~	~~0.376~~	~~0.115~~	~~0.509~~	~~0.438~~	~~0.378~~
~~400~~	~~4~~	~~0.700~~	~~0.155~~	~~0.145~~	~~0.168~~	~~0.209~~
~~400~~	~~20~~	~~0.647~~	~~0.180~~	~~0.174~~	~~0.191~~	~~0.219~~
~~400~~	~~80~~	~~0.543~~	~~0.208~~	~~0.249~~	~~0.238~~	~~0.243~~
~~400~~	~~200~~	~~0.418~~	~~0.179~~	~~0.403~~	~~0.333~~	~~0.303~~
~~400~~	~~400~~	~~0.374~~	~~0.110~~	~~0.516~~	~~0.445~~	~~0.383~~
~~400~~	~~600~~	~~0.376~~	~~0.076~~	~~0.548~~	~~0.492~~	~~0.417~~
240	**4**	**0.858**	**0.074**	**0.068**	**0.092**	**0.152**
240	**20**	**0.827**	**0.087**	**0.086**	**0.108**	**0.169**
240	**80**	**0.787**	**0.101**	**0.112**	**0.126**	**0.188**
240	**200**	**0.743**	**0.116**	**0.141**	**0.146**	**0.21**
240	**400**	**0.695**	**0.115**	**0.19**	**0.175**	**0.252**
240	**600**	**0.677**	**0.102**	**0.221**	**0.198**	**0.289**
240	**800**	**0.671**	**0.087**	**0.242**	**0.214**	**0.316**

Rationale for change		Prior probability of DLT rate was updated based on the latest data.
Section to be changed		8.7 Administrative structure of the trial
Description of change		Added:

		A Coordinating Investigator is responsible to coordinate investigators at the different sites participating in this trial. Tasks and responsibilities are defined in a contract.
Rationale for change		Coordinating investigator was appointed for the expansion of the trial from single-centre to multi-centre.
Section to be changed		10.5 Statistical appendix including model performance and data scenarios
Description of change		Hypothetical data scenarios, assumed true dose-toxicity scenarios, and operating characteristics were added.
Rationale for change		To present performance metrics that illustrate the precision of the design in estimating the MTD under various dose-toxicity relationships through computer simulation.

11.2 GLOBAL AMENDMENT 2

Date of amendment		28 Sep 2018
EudraCT number **EU number**		Not applicable
BI Trial number		1381-0004
BI Investigational Medicinal Product(s)		BI 754091 and BI 754111
Title of protocol		An open label, Phase I study of BI 754091 monotherapy and combination therapy of BI 754091 and BI 754111 in Asian patients with advanced solid tumours
Global Amendment due to urgent safety reasons		☐
Global Amendment		☒
Section to be changed		Synopsis – Objective(s)
Description of change		The main objectives of the dose-finding parts (Parts I and II) of the trial are to investigate the following in patients with advanced solid tumours: • **Part I:** Safety, tolerability, and pharmacokinetics (PK) of BI 754091 as monotherapy. • **Part II:** Safety, tolerability, and PK of escalating doses of BI 754111 when administered with BI 754091, and PK of BI 754091 when administered with escalating doses of BI 754111. • **Parts I and II:** Maximum tolerated dose (MTD) and/or recommended dose (RD) of BI 754091 monotherapy and the combination of BI 754091 and BI 754111.
Rationale for change		Clarification
Section to be changed		Synopsis – safety criteria, 4.1.5 Definition of dose limiting toxicities, 5.2 Assessment of safety, and 5.2.7.6 Severity of adverse events
Description of change		The version of CTCAE to be used for the safety assessment in Part III was changed from 4.03 to 5. The criteria in Parts I and II were not changed.
Rationale for change		Boehringer Ingelheim decided to use the most updated criteria for the safety assessment.
Section to be changed		Flow chart and section 5.2.4.2 Biochemistry
Description of change		HBV, HCV, and HIV testing should be performed at screening unless test results obtained in routine diagnostics within 14 days before the informed consent date are available (**For patients with hepatocellular cancer in ~~In~~** Part III Cohort**s** C **and D**, if a patient is known to have HBV and/or HCV infection, the diagnostic testing for that item does not need to be repeated).
Rationale for change		Clarification
Section to be changed		Section 1.4 Benefit risk assessment
Description of change		Added: **By the end of June 2018, 48 patients were treated with the**

		combination therapy of BI 754091 and BI 754111 (BI 754111 dose range: 4mg to 600mg, all in combination with BI 754091 240mg) and the risk benefit profile from the observed data was considered positive.
Rationale for change		Update
Section to be changed		Section 3.3.3 Exclusion criteria
Description of change		19. *snip* However, **for patients with hepatocellular cancer in** ~~in~~ Part III Cohort**s** C **and D**, patients with HBV and/or HCV infection are allowed. **Hepatocellular cancer patients** ~~Patients~~ in Part III Cohort**s** C **and D** with HBV infection must be receiving effective antiviral therapy (viral load <100 IU/mL)
Rationale for change		Clarification
Section to be changed		Section 4.2.2.1 Permitted concomitant medications
Description of change		• If medically feasible, patients taking regular medication **for their coexisting disease** should be maintained on it throughout the trial. *snip* • **Hepatocellular cancer patients** ~~Patients~~ in Part III Cohort**s** C **and D** with HBV infection must be receiving effective antiviral therapy (viral load <100 IU/mL)
Rationale for change		Clarification
Section to be changed		Section 5.2.4.2 Biochemistry
Description of change		Added: **The regular troponin measurement should be quantitative analysis and can be either Troponin I or T, according to the institutional standard as long as the testing method is consistent.**
Rationale for change		Clarification
Section to be changed		Section 5.2.7.8.1 AE collection
Description of change		The following must be collected and documented on the appropriate CRF(s) by the investigator: • From signing the informed consent onwards until the **end of the 30-day safety follow-up visit** ~~end of treatment (including period between EOT visit and the 30-day follow-up visit)~~ - all AEs (non-serious and serious) and all AESIs.
Rationale for change		
Section to be changed		Figure 5.2.7.8.1: 1
Description of change		The time point "end of treatment" was updated to "30-day FU visit".
Rationale for change		Clarification
Section to be changed		6.2.1.2.1 Medical history of cancer
Description of change		Added: **Baseline information relevant to the disease history such as PD-L1 expression level, microsatellite instability (MSI), and tumour mutation burden (TMB) information will be**

		collected in eCRF where available.
Rationale for change		To collect the information which is considered relevant for the response to the study medications.

11.3 GLOBAL AMENDMENT 3

Date of amendment		21 Feb 2019
EudraCT number **EU number**		Not applicable
BI Trial number		1381-0004
BI Investigational Medicinal Product(s)		BI 754091 and BI 754111
Title of protocol		An open label, Phase I study of BI 754091 monotherapy and combination therapy of BI 754091 and BI 754111 in Asian patients with advanced solid tumours
Global Amendment due to urgent safety reasons		☐
Global Amendment		☒
Section to be changed		Flow Chart
Description of change		d. Safety laboratory assessments including haematology, clinical biochemistry, and urinalysis will be performed locally **(Free T3, Troponin I, and venous HCO_3 will be measured at a central laboratory if study site cannot measure it locally)**. The screening medical history and demographics, physical examination and Eastern Cooperative Oncology Group (ECOG) performance status (PS), vital signs, ECG, haematology, clinical chemistry (sodium, potassium, phosphate, chloride, creatinine, calcium, venous bicarbonate HCO_3 **(if the local lab test is available at the study site)**, albumin, total protein, aspartate aminotransferase [AST], alanine aminotransferase [ALT], alkaline phosphatase, bilirubin, lactate dehydrogenase, glucose, c-peptide [baseline only], serum cholesterol [baseline only], serum triglycerides [baseline only], creatine phosphokinase [CPK: if CPK is elevated, then CPK-MB, troponin **(either** I **or T)**, and myoglobin should be reactively tested], urea [or blood urea nitrogen (BUN)], 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.
Rationale for change		Clarification
Section to be changed		Flow Chart and section 5.4.2.3
Description of change		The conditions to allow archival tumor tissue was updated as follows: - If available and taken within 6 months of study start **and no anti-tumour treatment has been given after the sample is taken**, at least 20 (4-5 µm) sections from an archival FFPE block should be collected. If adequate archival tissue is not available, 2 fine-needle biopsies must be taken between screening and the day before the first study drug treatment.
Rationale for change		Clarification

Section to be changed		3.3.3 Exclusion criteria
Description of change		10. Inadequate organ function or bone marrow reserve as demonstrated by the following laboratory values: *snip* o Alanine aminotransferase (ALT) >2.5 times the upper limit of normal (ULN) if no demonstrable liver **lesion(s) (primary or** metastases**)** or >5 times ULN in the presence of liver **lesion(s)**~~metastases~~ o Aspartate aminotransferase (AST) >2.5 times ULN if no demonstrable liver **lesion(s)**~~metastases~~ or >5 times ULN in the presence of liver **lesion(s)**~~metastases~~
Rationale for change		Clarification
Section to be changed		3.3.3 Exclusion criteria
Description of change		20. Chronic alcohol or drug abuse or any condition that, in the investigator's opinion, makes him/her an unreliable trial patient, unlikely to complete the trial, or unable to comply with the protocol procedures. However, **for patients with hepatocellular cancer** in Part III Cohort**s** C **and D**, ~~patients with~~ past chronic alcohol abuse are allowed
Rationale for change		Clarification
Section to be changed		4.1.4 Dose modifications **and premedications**
Description of change		Added: **Infusion related reactions have been reported in approximately 7% of patients treated with the combination of BI 754091 and BI 754111, none 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 of CTCAE Grade 2. Two events were Grade 3 events and led to treatment discontinuation. The reported infusion related reactions occurred during the infusion mostly at cycle 2 or cycle 3. Symptoms of infusion related reactions may include, but not limited to, flushing, rigors, chills, dyspnea, nausea, vomiting, hypotension, hypertension, syncope, pruritus, tachycardia, and back pain.** **To reduce the risk of IRRs, patients are to be premedicated with an antihistamine and acetaminophen or paracetamol. Premedications should be administered at sufficient time prior to initiation of infusion to allow the agents to exert their effect.** Updaed: 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~~ **discontinue study drug(s)**
Rationale for change		The pre-treatment is considered warranted to prevent the IRRs for patients' safety.
Section to be changed		4.2.2.1 Permitted concomitant medications
Description of change		• ~~Pre-medication will not be required, but may be utilised following the first dose of study medication. This includes medications for the management of nausea, diarrhoea, and vomiting for which the patient must be treated according to institutional standards.~~ **To reduce the risk of IRRs, patients are to be premedicated with an antihistamine and acetaminophen or paracetamol. Premedications should be administered at sufficient time prior to initiation of infusion to allow the agents to exert their effect. This applies to all cycles and all patients except for cycle 1 in the dose-finding part. The patients in the dose-finding part should not be treated prior to cycle 1 to avoid masking the emergence of DLTs.**
Rationale for change		The pre-treatment is considered warranted to prevent the IRRs for patients' safety.
Section to be changed		4.2.2.1 Permitted concomitant medications
Description of change		• For symptom control, palliative radiotherapy is permitted for any lesion in the dose-finding part of the trial, except during the first cycle as it could interfere with the DLT evaluation for MTD/RD determination. ~~Following the first cycle of the~~ **In the** expansion phase (Part III), palliative radiotherapy is allowed only for non-target lesions, following discussion with the sponsor, provided that the reason for radiotherapy does not reflect PD and does not interfere with response assessment. ~~Palliative radiotherapy is not allowed during the first cycle of in Part III.~~
Rationale for change		It was concluded that the restriction of radiotherapies in the first cycle should be only for dose finding parts and would not be useful in the expansion part.
Section to be changed		4.2.2.2 Prohibited concomitant medications
Description of change		• Prophylactic erythropoietin, prophylactic granulocyte colony stimulating factors, ~~and palliative radiotherapy~~ are not allowed during the first 3 weeks. **Palliative radiotherapy is not allowed during the first 3 weeks of the dose finding parts.**
Rationale for change		It was concluded that the restriction of radiotherapies in the first cycle should be only for dose finding parts and would not be useful in the expansion part.
Section to be changed		5.2.4 Safety laboratory parameters
Description of change		Following description was added: **For Free T3, Troponin I, and venous HCO_3, these will be measured at a central laboratory if study site cannot**

		measure it locally. With the protocol amendment to version 4, Troponin I can be substituted by Troponin T, and HCO_3 does not have to be measured if not available at the study site (the central lab will not be used for Troponin I and HCO_3 after the approval of protocol version 4).
Rationale for change		Clarification on the use of central laboratory was added. HCO_3 was considered to be not mandatory as blood gas tests according to local standard in case of medical need would be sufficient. Troponin T as well as Troponin I was considered valid to detect the cardiac AE.
Section to be changed		5.2.4.2 Biochemistry
Description of change		The standard biochemistry panel will consist of glucose, sodium, potassium, chloride, calcium, phosphate, venous bicarbonate HCO_3 **(if the local lab test is available at the study site)**, urea (or blood urea nitrogen [BUN]), creatinine, CPK, AST, ALT, alkaline phosphatase, lactate dehydrogenase (LDH), bilirubin (total and direct), total protein, albumin, and uric acid. In addition, serum cholesterol, serum triglycerides, and c-peptide will be done at baseline and when clinically indicated. Troponin will be tested according to the times listed in the Flow Chart. The troponin measurement should be quantitative analysis and can be either Troponin I or T, according to the institutional standard as long as the testing method is consistent. In case of pathological CPK, then CPK-MB, additional tropoinin **(either** I **or T)**, and myoglobin should be reactively tested and the findings documented.
Rationale for change		Clarification on the use of central laboratory was added. HCO_3 was considered to be not mandatory as blood gas tests according to local standard in case of medical need would be sufficient. Troponin T as well as Troponin I was considered valid to detect the cardiac AE.
Section to be changed		5.2.7.5 and 5.2.7.5.4
Description of change		A prefix "potential" was added to the term "DILI"
Rationale for change		To indicate that the reporting requirement applies not only confirmed DILI cases but also potential DILI cases.
Section to be changed		5.2.7.10 Exemptions ~~to~~ **from AE**/SAE reporting
Description of change		Section title updated: 5.2.7.10 Exemptions ~~to~~ **from AE**/SAE reporting Updated: Exempted events are reviewed at appropriate intervals ~~by sponsor following a pre-specified review plan~~. **Lab values meeting the hepatic injury definition as defined in section 5.2.7.5.4 will need to be reported as AESI. PD reporting exemption does not apply to hepatic injury. Please follow the flowchart below for reporting hepatic injury / potential DILI cases.** Figure 5.2.7.10: 1 was added

Rationale for change		Clarification
Section to be changed		7.4 INTERIM ANALYSES
Description of change		~~No formal interim analysis is foreseen.~~ The sponsor will continuously monitor the safety. The dose escalation design foresees that the sponsor and the SMC perform regular safety evaluations. These evaluations will be unblinded to dose. ~~If considered necessary, an evaluation of the efficacy and safety aspects will be performed. Results of this evaluation will be documented and archived. If applicable, such an analysis will be defined in more detail in the TSAP.~~ No formal interim analysis of PK data is planned. However, exploratory analyses of PK will be done during the dose finding part (Part I and Part II) and may also be done during the expansion part (Part III), if considered reasonable Exploratory PK analyses will be based on planned sampling times. The results of these evaluations will be preliminary and may be subject to change, as these do not involve a formal database lock. No interim report will be written for exploratory PK analyses. **An interim futility analysis will be performed for each cohort in part III. 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 patient if the defined efficacy boundary (see Table 7.7.2: 1) is not met at the first stage.** **The interim analyses for part III will be conducted when:** • **After the 17th patients has completed the third on-treatment imaging assessment (i.e. end of cycle 6).** • **If the 17th patient discontinues earlier than the third on-treatment imaging, the interim futility analysis will be triggered at approximately 4 months after the first administration of the 17th patient.** **If considered necessary, an evaluation of the efficacy and safety aspects will be performed. Results of this evaluation will be documented and archived. If applicable, such an analysis will be defined in more detail in the TSAP.**
Rationale for change		It was considered beneficial to discontinue the recruitment if the observed response rate is lower than the expected response rate at a prespecified interim time point.
Section to be changed		7.7.2 Determination of sample size for Part III
Description of change		Futility boundaries for each cohort was added. The reference historical data was updated. Table 7.7.2: 1 to summarise the futility boundary and probability to observe the specified ORs by assumed underlying ORRs.

Rationale for change		It was considered beneficial to discontinue the recruitment if the observed response rate is lower than the expected response rate at a prespecified interim time point.
Section to be changed		9.1 Published references
Description of change		Added: **R19-0167 Efficacy and Safety of Pembrolizumab for Heavily Pretreated Patients With Advanced, Metastatic Adenocarcinoma or Squamous Cell Carcinoma of the Esophagus The Phase 2 KEYNOTE-180 Study** **R19-0168 Pembrolizumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib (KEYNOTE-224): a non-randomised, open-label phase 2 trial**
Rationale for change		For further reference of assumed ORs

11.4 GLOBAL AMENDMENT 4

Date of amendment		23 Mar 2020
EudraCT number **EU number**		Not applicable
BI Trial number		1381-0004
BI Investigational Medicinal Product(s)		BI 754091 and BI 754111
Title of protocol		An open label, Phase I study of BI 754091 monotherapy and combination therapy of BI 754091 and BI 754111 in Asian patients with advanced solid tumours
Global Amendment due to urgent safety reasons		
Global Amendment		X
Section to be changed		Cover page and Synopsis – Coordinating investigator
Description of change		Updated: [redacted] **Telephone:** [redacted] ~~Telephone:~~ [redacted]
Rationale for change		Affiliation of the coordinating investigator was changed.
Section to be changed		Synopsis and 2.1.1 Main objectives
Description of change		Main objectives of Part III were updated as follows: • To further investigate the safety, tolerability, and PK of the RD of BI 754091 and BI 754111 combination in patients with gastric/esophagogastric junction cancer, esophageal cancer, ~~or~~ hepatocellular cancer**, or non-small cell lung cancer (NSCLC)** To explore the efficacy of the RD of the combination of BI 754091 and BI 754111 in patients with gastric/esophagogastric junction cancer, esophageal cancer, ~~or~~ hepatocellular cancer**, or NSCLC**
Rationale for change		Updated as the objectives apply to the new cohort for NSCLC.
Section to be changed		Synopsis, 3.1 Overall trial design and plan, and 7.1.3 Statistical design – Part III (expansion)
Description of change		The planned number of patients were updated as follows: Total: approximately 179 patients Part III: approximately 155 patients
Rationale for change		The numbers were adjusted for the following updates: - Part III Cohort C was discontinued with 20 patients Part III Cohort E was added with the planned number of patients of up to 30
Section to be changed		Synopsis and section 3.3.1 Main diagnosis for trial entry

Description of change		Added: **Cohort E: First line NSCLC patients with wildtype (wt) epidermal growth factor receptor [EGFR] and anaplastic lymphoma kinase [ALK] tumours of squamous or non-squamous origin.**
Rationale for change		BI decided to explore the efficacy of study treatment in first line NSCLC patients
Section to be changed		Synopsis and section 3.3.2 Inclusion criteria
Description of change		Added: **Cohort E: First line squamous or non-squamous NSCLC patients:** • **Without EGFR mutations or ALK rearrangements** • **PD-L1 expression level <50%**
Rationale for change		BI decided to explore the efficacy of study treatment in first line NSCLC patients
Section to be changed		Flow chart table
Description of change		The allowance window for 30-day safety follow-up was updated from +2 to +7.
Rationale for change		To allow more flexibility.
Section to be changed		Flow Chart table and footnote h
Description of change		The column "follow-up visit for progression" was updated to "follow-up visit for PFS/OS" Footnote h was updated as follows: **Patients enrolled in Part III Cohort E: Additional overall survival (OS) and progression-free survival (PFS) follow-up visits after the 30-day safety follow-up visit will be performed once every 12 weeks at least (in person or by telephone) until death, loss to follow-up, withdrawal of consent, or end of the whole trial.** **All other patients:** Additional follow-up visits for ~~progression~~ **PFS** after the 30-day safety follow-up visit will only be performed in Part III for patients who did not progress on treatment. The follow-up visits for ~~progression~~ **PFS** will be performed once every 12 weeks at least (in person or by telephone) until PD, introduction of a new anti-cancer treatment, death, loss to follow-up, withdrawal of consent, or end of the whole trial.
Rationale for change		Follow-up visits for OS will be performed in Cohort E to collect OS data.
Section to be changed		Flow Chart table
Description of change		A new row for the blood sampling for biomarkers (PBMC [blood]) was added. The name of another blood sampling for PBMC biomarkers was renamed as "PBMC (extract)" so that it will not be confused with the new "PBMC (blood)" sampling.
Rationale for change		In cohort E, another PBMC flow cytometry analysis with the same panels as in preceding trial 1381-0002 will be implemented, in order to have a comparable set of data for the NSCLC cohort in these two trials.
Section to be changed		Flow Chart table and footnote m, and 5.1.1 Tumour assessments
Description of change		The imaging interval in the flow chart table was updated from 6 weeks to 2 cycles, from 9 weeks to 3 cycles. The allowance windows for tumour assessments were updated from +/- 3 days to +/- 5 days
Rationale for change		Clarification and to allow more flexibility.

Section to be changed		Flow Chart footnote k
Description of change		PBMC related part was updated as follows: - **PBMC (extract): Blood samples will be taken and peripheral blood mononuclear cells (PBMC) will be extracted during Part II and Part III only at study sites in which the sample preparation is possible, on Day 1 (pre-treatment), 2, 8 of Cycle 1, on Day 1 (pre-treatment) of Cycle 2, 3 and 5, and at the 30-day safety follow-up visit.** - **PBMC (blood): Blood samples for biomarker PBMC (blood) will be taken only in Part III cohort E during Cycle 1 on Day 1 (pre-treatment), Day 8, Day 15, during Cycle 2 on Day 1 (pre-treatment), and at the end-of-treatment visit. Kits will be provided from a designated laboratory logistics vendor. If the kits are not ready at study sites at the time of patient recruitment, this blood sampling will not be performed.**
Rationale for change		In cohort E, another PBMC flow cytometry analysis with the same panels as in preceding trial 1381-0002 will be implemented, in order to have a comparable set of data for the NSCLC cohort in these two trials.
Section to be changed		Flow Chart footnote l
Description of change		Updated as follows: […] - If available and taken within 6 months of study start and no anti-tumour treatment has been given after the sample is taken, at least 20 (4-5 µm) sections from an archival FFPE block should be collected. If adequate archival tissue is not available, 2 ~~fine~~ **core**-needle biopsies must be taken between screening and the day before the first study drug treatment. - Two ~~fine~~ **core**-needle biopsies on treatment at the end of Cycle 2 (after 6 weeks of treatment)**, preferably from the same lesion**. […]
Rationale for change		Clarification
Section to be changed		Flow Chart footnote n
Description of change		Following statement was added: **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.**
Rationale for change		Clarification/reminder
Section to be changed		1.3 Rationale for performing the trial
Description of change		Following paragraphs were added: **Multiple immune checkpoint inhibitors […] standard of care chemotherapy (R16-0878; R15-3715; R16-1875; R16-5828).** **It is postulated that treating patients with immune checkpoint inhibitor early in their treatment continuum […], as a subsequent line of treatment for patients whose disease progresses.**
Rationale for change		To provide the rationale to investigate the combination therapy of BI 754091 and BI 754111 in the first line NSCLC.
Section to be changed		[redacted]
Description of change		

		[redacted]
Rationale for change		
Section to be changed		3.1 Overall trial design and plan
Description of change		Following paragraph was added: **In December 2019, BI decided to close the recruitment of new patients into Cohort C, based on an analysis of the available data from patients enrolled in this cohort. The data showed less than expected clinical efficacy for the patient population studied in this indication, and the likelihood that the cohort will meet the protocol defined criteria to continue at the planned futility analysis was considered very low. This decision did not affect the recruitment of other cohorts, the treatment of patients who were already receiving study treatment in Cohort C, or the overall benefit risk assessment of the combination therapy of BI 754091 and BI 754111.**
Rationale for change		To clarify that Cohort C was closed, its reason, and that this did not affect the recruitment other cohorts, treatment of existing patients, or benefit risk assessment of the combination therapy.
Section to be changed		3.3.3 Exclusion criteria
Description of change		8. Presence of other active invasive cancers other than the one treated in this trial **within 5 years prior to screening**, with the exception of ~~resected/ablated~~ **appropriately treated** basal cell carcinoma of the skin or **in situ** carcinoma ~~in situ~~ of the **uterine** cervix, or other local tumours considered cured by local treatment 11. Any of the following cardiac criteria […] o 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 o **Patients with an ejection** ~~Ejection~~ fraction **(EF)** <55% or the lower limit of normal of the institutional standard 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 [ECHO], multi-gated acquisition scan [MUGA]). A historic measurement of EF no older than 6 months prior to first administration of study 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. 16. Active autoimmune disease or a documented history of autoimmune disease, except vitiligo or resolved childhood asthma/atopy**, or asthma well controlled with steroids**
Rationale for change		#8: To clarify exclusion of other active cancers and to align language across current studies with BI 754091. #11: To clarify exclusion due to cardiac criteria and to align language across current studies with BI 754091. #16: To clarify that patients with asthma will not be excluded if it is well controlled with steroids
Section to be changed		3.3.4.3 Discontinuation of the trial by the sponsor

Description of change		Following condition was added: **4. Completion of treatment by all patients and the sponsor determines that sufficient survival data has been collected.**
Rationale for change		Clarification of the sponsor's rights to discontinue the trial in case sufficient survival data has been collected.
Section to be changed		4.1.4 Dose modifications and premedications
Description of change		Updated as follows: […] During combination therapy, 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 or baseline **– exceptions should be discussed and agreed with the sponsor**) of the AE, both BI 754091 and BI 754111 must be started together. The study drug(s) should be permanently discontinued for Grade 3 to 4 pneumonitis, 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 ~~AEs~~ **irAEs**, 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 **(unless unequivocally attributed to another cause)** 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 permanently discontinued if ≥ Grade 4 drug-related AEs are reported. Please see Appendix 10.2 for guidelines for management of immune-related adverse events.
Rationale for change		Clarification
Section to be changed		4.2.2.1 Permitted concomitant medications
Description of change		Following bullet point was updated: • 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.**
Rationale for change		Clarification
Section to be changed		5.2.4.2 Biochemistry
Description of change		The standard biochemistry panel will consist of glucose, sodium, potassium, chloride, calcium, phosphate, venous bicarbonate HCO3 (if the local lab test is available at the study site), urea (or blood urea nitrogen [BUN]), creatinine, CPK, AST, ALT, alkaline phosphatase, lactate dehydrogenase (LDH), bilirubin (total and direct), total protein, albumin, and uric acid. ~~In addition, serum cholesterol, serum triglycerides, and c-peptide will be done at baseline and when clinically indicated.~~ Troponin will be tested according to the times listed in the Flow Chart. The troponin measurement should be quantitative analysis and can be either Troponin I or T, according to the institutional standard as long as the testing method is consistent. In case of pathological CPK, then CPK-MB, additional tropoinin (either I or T), and myoglobin should be reactively tested and the findings documented.

Rationale for change		It has been determined that these tests are not needed.
Section to be changed		5.2.7.5.2 Immune-related adverse events (irAEs)
Description of change		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. The sponsor has defined a list of irAEs in ~~Appendix 10.1~~ **Table 10.1: 1** that must be reported as AESIs. ~~If an Investigator determines another irAE (not on the list) should be an AESI, the Investigator may also report that event as an AESI.~~ **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 Table 10.1: 1. If an Investigator determines a Grade 3 event (not on the list) to be immune-related, the Investigator should also report that event as an AESI.**
Rationale for change		To clarify the reporting of irAEs as AESI.
Section to be changed		5.4 Assessment of biomarkers
Description of change		[…] • Peripheral blood mononuclear cells (PBMC) will be characterized for the presence of individual cell lineages, and subsets of T cells will be further analysed for the expression of activation and checkpoint marker expression **(PBMC [extract])**. • **In a complementary analysis to the above, PBMC (blood), myeloid-derived suppressor cells (MDSC), PD1+ and LAG3+ T-cells, PD-L1+ monocytes, as well as regulatory T-cells and activated T-effector memory cells and activated dendritic cells will be measured (see Section 5.4.2.1)**
Rationale for change		An explanation regarding the complementary PBMC flow cytometry analysis was added.
Section to be changed		[redacted]
Description of change		[redacted]
Rationale for change		
Section to be changed		Follow up visits for progression PFS (extended follow-up period)
Description of change		The name of the visits "follow-up visit for progression" was updated to "follow-up visit for PFS".
Rationale for change		Clarification
Section to be changed		6.2.3.4 Follow up visits for overall survival (OS)
Description of change		The section was added with the following contents: **Additional follow-up visits after the 30-day safety follow-up visit will**

		be performed for patients in Part III Cohort E. These will be performed once every 12 weeks at least (by telephone or in person) on the same schedule as PFS follow-up visits until death, loss to follow-up, or end of the whole trial as specified in Section 3.3.4.3. 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 change		Follow-up visits for OS will be performed in Cohort E to collect OS data.
Section to be changed		7.3.2.1 Secondary endpoint analyses for Part I and Part II
Description of change		Added: **Analyses of PK parameters, i.e., C_{max} and AUC_{0-504} will be described in Section 7.3.5. More detail will be provided in TSAP.**
Rationale for change		This statement was moved from 7.3.2.2 as these PK related parameters were secondary endpoints for Part I/II.
Section to be changed		7.3.2.2 Secondary endpoint analyses for Part III
Description of change		Following content was removed: ~~Progression-free survival (PFS) is defined as time from first drug intake until PD or death from any cause, whichever occurs earlier. The date of PD will be based on the Investigator assessment according to RECIST 1.1.~~ ~~For patients with 'event' as an outcome for PFS:~~ ~~· PFS [days] = date of outcome – date of start of treatment + 1~~ ~~For patients with 'censored' as an outcome for PFS:~~ ~~· PFS (censored) [days] = date of outcome – date of start of treatment + 1~~ ~~The censoring rules for PFS (i.e., outcome and the date of outcome) are described in the TSAP.~~ ~~Kaplan-Meier estimates will be used to display the distribution of PFS with 95% confidence intervals, using Greenwood's variance estimate.~~ ~~Analyses of PK parameters, i.e., Cmax and AUC0-504 will be described in Section 7.3.5. More detail will be provided in TSAP.~~
Rationale for change		[redacted] A statement about the analysis for PK parameters for Part I and II was moved to section 7.3.2.1.
Section to be changed		7.4 Interim Analysis
Description of change		[…] **If deemed appropriate, a**~~A~~n interim futility analysis will be performed for each cohort in part III. 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 patient if the defined efficacy boundary (see Table 7.7.2: 1) is not met at the first stage. […] **For cohort E, data from 1381-0002 will be pooled for the interim futility decision making, if applicable.** If considered necessary, an evaluation of the efficacy and safety aspects will be performed. Results of this evaluation will be documented and archived. If applicable, such an analysis will be defined in more detail in the TSAP.
Rationale for change		The plan for the interim analysis for cohort E was added.
Section to be changed		7.7.2 Determination of sample size for Part III
Description of change		[…]

		Cohort E: Patients with first-line squamous or non-squamous NSCLC patients without EGFR mutations or ALK rearrangements and PD-L1 expression level < 50% […] **For cohort E, around 20% ORR with antibody monotherapy is assumed. In Keynote-042 (R20-0754) which is randomised, open-label phase 3 trial of Pembrolizumab in patients with previously untreated locally advanced or metastatic non-small cell lung cancer without a sensitising EGFR mutation or ALK translocation, the ORR in the Pembrolizumab group was 118 pts, 39%[95%CI, 34-45](N=299) in the PD-L1 tumour proportion score of 50% or greater and 174 pts, 27%[95%CI, 24-31](N=637) in the PD-L1 tumour proportion score of 1% or greater. Based on the results, the ORR in the pembrolizumab group in the PD-L1 tumour proportion score of 1% to 50% was 17% (56 pts/338 pts).** In part III, a total of ~~140~~ **155** patients will be enrolled and allocated to ~~4~~ **5** cohorts. The sample size of each cohort is planned around 35 patients **for cohort A to D. For cohort E, 30 patients is the maximum target sample size.** […] Table 7.7.2: 1 Early stopping criteria and probabilities for the two-stage approach for part III – The information about cohort E was added.
Rationale for change		Information regarding the sample size for Cohort E was added.
Section to be changed		8.7 Administrative structure of the trial
Description of change		The name of a role "Trial Clinical Monitor (TCM)" was updated to "Clinical Trial Leader (CTL)".
Rationale for change		Based on an update in the sponsor's SOP.

11.5 GLOBAL AMENDMENT 5

Date of amendment		21 Apr 2021
EudraCT number **EU number**		Not applicable
BI Trial number		1381-0004
BI Investigational Medicinal Product(s)		BI 754091 and BI 754111
Title of protocol		An open label, Phase I study of BI 754091 monotherapy and combination therapy of BI 754091 and BI 754111 in Asian patients with advanced solid tumours
Global Amendment due to urgent safety reasons		
Global Amendment		X
Section to be changed		Flowchart footnote and sections 5.2.5, 6.2.3.5, and 10.4
Description of change		Descriptions were added to remove some items from the required study procedures after an interim database lock.
Rationale for change		ECG is considered not required based on the safety data obtained so far. PK and biomarker sampling are not required after the interim database lock as sufficient samples/data have been collected.

APPROVAL / SIGNATURE PAGE

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Title: An open label, Phase I study of BI 754091 monotherapy and combination therapy of BI 754091 and BI 754111 in Asian patients with advanced solid tumours

Signatures (obtained electronically)

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Approval-Therapeutic Area [redacted]		27 Apr 2021 19:53 CEST
Approval-Team Member Medicine		27 Apr 2021 20:36 CEST
Verification-Paper Signature Completion		28 Apr 2021 02:42 CEST

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