Clinical Trial Protocol

Document Number:		**c09063095-08**
EudraCT No.:	2017-005043-33	
BI Trial No.:	1381.1	
BI Investigational Product:	BI 754091 (ezabenlimab)	
Title:	An open-label, Phase I trial to determine the maximum-tolerated dose and investigate safety, pharmacokinetics, and efficacy of BI 754091 in patients with advanced solid tumours	
Lay Title:	A trial to find and investigate a safe dose of a new substance (BI 754091) for patients with solid tumours	
Clinical Phase:	Phase I	
[redacted] **Physician** [redacted]	[redacted]	
Trial Clinical Monitor:	[redacted] Phone: [redacted] Fax: [redacted]	
Coordinating Investigator	[redacted]	
Status:	Final protocol (revised protocol [based on global amendment 7])	
Version and Date:	**Version: 8.0**	**Date: 07 Mar 2023**
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CLINICAL TRIAL PROTOCOL SYNOPSIS

Name of company:		**Boehringer Ingelheim**	
Name of finished product:		N.A.	
Name of active ingredient:		BI 754091	
Protocol date: 22 Sep 2016	**Trial number:** 1381.1		**Revision date:** 07 March 2023

Title of trial:	An open-label, Phase I trial to determine the maximum-tolerated dose and investigate safety, pharmacokinetics, and efficacy of BI 754091 in patients with advanced solid tumours
[redacted] **Investigator**	[redacted]
Clinical phase:	I
Objectives:	Phase Ia Dose Escalation: To determine the maximum-tolerated dose (MTD) and the recommended Phase 2 dose (RP2D) and investigate the safety, pharmacokinetics (PK), biomarkers, and efficacy of BI 754091 in patients with advanced and/or metastatic solid tumours Phase Ib Dose Expansion: To further evaluate the safety, the PK profile, biomarkers, and efficacy of the RP2D in 4 cohorts of patients with selected advanced and/or metastatic cancers
Methodology:	Phase Ia Dose Escalation: Open-label, single arm, dose escalation (consecutive cohorts of escalating doses of BI 754091), Bayesian Logistic Regression Model (BLRM) with overdose control Phase Ib Dose Expansion: Open-label, 4 dose-expansion cohorts
No. of patients:	Approximately 145 patients, depending on dose-escalation results
Total entered:	Phase Ia Dose Escalation: approximately 15 patients Phase Ib Dose Expansion at the RP2D: 4 cohorts of approximately 30-40 patients each
Each treatment:	All patients participating in any part of this trial will receive BI 754091.

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Diagnosis:	Phase Ia Dose Escalation: Patients with a confirmed diagnosis of advanced, unresectable, and/or metastatic solid tumours. Phase Ib Dose Expansion: advanced and/or metastatic cancers including tumours with specific histology/tumour types and/or specific genetic profiles as specified in the following cohorts : - Cohort 4: solid tumours including non-small-cell lung cancer (NSCLC), bladder cancer, melanoma, gastric cancer, ovarian cancer, triple-negative breast cancer (TNBC), and renal-cell cancer (RCC) - Cohort 5: Tumours with high tumour-mutational burden (TMB), excluding those with high microsatellite instability (MSI-high) - Cohort 6: Refractory squamous cell cervical, anal, and skin tumours. - Cohort 7: Recurrent human papillomavirus (HPV)-positive, or HPV-negative (per local testing), vaginal or vulvar squamous cell carcinoma (VSCC), not amenable to surgery.
Main criteria for inclusion:	Phase Ia Dose Escalation – adult patients with a confirmed diagnosis of advanced, unresectable, and/or metastatic solid tumours (any type) who have received all therapy known to confer clinical benefit (including anti-PD-1 therapies, if relevant and if the last dose of the prior anti-PD-1 was received more than 60 days prior to starting study drug), or for whom no therapy of proven efficacy exists, or who are not amenable to standard therapies Phase Ib Dose Expansion – adult patients with a confirmed diagnosis of select advanced, unresectable, and/or metastatic solid tumours who are anti-PD-1/PD-L1 naïve but have failed conventional treatment (excluding anti-PD-1/PD-L1 treatment), or for whom no therapy of proven efficacy exists, or who are not amenable to standard therapies. All patients must have measurable lesions according to Response Evaluation Criteria in Solid Tumours (RECIST) v1.1 and/or Immune-Related Response Evaluation Criteria in Solid Tumours (iRECIST). Additional specific criteria for the individual expansion cohorts include: - Cohort 4: Advanced and/or metastatic solid tumours including NSCLC, bladder cancer, melanoma, gastric cancer, ovarian cancer, TNBC, and RCC - Cohort 5: Patients with tumours that are TMB-high: any tumour with TMB-high status (>10 mutations/Mb), excluding those that are MSI-high (TMB and MSI status based on any validated test) - Cohort 6: Patients with squamous cell cervical, anal, and skin tumours that are refractory to standard therapies. - Cohort 7: Patients with recurrent HPV-positive, or HPV-negative, vaginal or VSCC

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Test product:	BI 754091
Dose:	Phase Ia Dose Escalation: starting dose is 80 mg (1 mg/kg for a 80-kg person) once every 3 weeks (q3w) Phase Ib Dose Expansion: the RP2D established in Phase Ia
Mode of administration:	Intravenous infusion
Duration of treatment:	BI 754091 will be given on Day 1 of 21-day cycles for up to 1 year, or until progressive disease (PD) or unacceptable toxicity in the absence of other withdrawal criteria. If the patient is benefiting clinically at 1 year, he/she may continue after a case by case review with the sponsor, but no longer than 31 August 2023.
Endpoints	**Endpoints for the Phase Ia Dose Escalation:** Primary: − Number of patients experiencing dose-limiting toxicities (DLTs) graded according to the Common Terminology Criteria for Adverse Events (CTCAE Version 4.03/5.0), observed in the first cycle (3 weeks) in order to meet the objective of assessment of the MTD of BI 754091. Secondary: − The following PK parameters will be calculated: C_{max} and AUC_{0-504}, after single and multiple dose of BI 754091, as measured during the first and subsequent cycles (administration q3w) (if data permits) − Number of patients experiencing DLTs from start of treatment until end of treatment (in all cycles) − Confirmed Objective Response (OR) according to RECIST v1.1 assessed by the Investigator. **Endpoints for the Phase Ib Dose Expansion:** Primary: − Number of patients with DLTs observed during the entire treatment period − Confirmed OR according to RECIST v1.1 as assessed by the Investigator Secondary: − Progression-free survival (PFS) according to RECIST 1.1 as assessed by the Investigator Safety will continue to be assessed by the recording of AEs, SAEs (including DLTs), physical examinations, laboratory evaluations, vital signs, and ECGs as: − Percentage of subjects with AEs − Percentage of subject with SAEs

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Safety criteria:	– Percentage of subjects with clinical relevant abnormalities in vital signs, laboratory evaluations or ECG parameters (note that clinically relevant abnormalities are those which have to be reported by the investigator as AEs). Adverse events (AEs) according to CTCAE v. 4.03 / 5.0, incidence of DLTs for determination of the MTD (Phase Ia dose escalation only), results of physical examinations, laboratory evaluations, vital signs, and electrocardiograms (ECGs).
Statistical methods:	Phase Ia: Dose escalation is guided by a BLRM with overdose control that will be fitted to binary toxicity outcomes. The estimate of parameters will be updated as data are accumulated using the BLRM. At the end of dose escalation, the toxicity probability at each dose level will be calculated to determine an estimate of the MTD. If there are too few or no DLTs for BLRM guided dose selection, PK and/or biomarker data will be taken into consideration for RPIID determination. Phase Ib: data collected during this phase will be recorded and presented in a descriptive fashion. No hypothesis testing is planned in either phase.

FLOW CHART 1: BI 1381.1 (REFMAL 473) PHASE IA (DOSE ESCALATION) TRIAL ASSESSMENTS

Flow Chart 1	**Trial Treatment Days[a,b] Cycle = 21 Days**						**Post-Treatment Days[b]**		
	Screening	**Cycles 1, 2, and 4**					**Cycles 3, 5, and 6+**	**End-of-Treatment[o] (EOT) Visit**	**30-Day[b] Safety Follow-up**	**PFS Follow-up[q]**
Assessments	**-28 to -1**	**1 (±2 C3+)**	**2 (±2 C3+)**	**4 (±2 C3+)**	**8 (±1 C1) (±2 C3+)**	**15 (±1 C1) (±2 C3+)**	**1 (±2)**	**(within 7 days of EOT)**	**(+2)**	
Informed Consent[c]	X									
Inclusion/Exclusion Criteria	X									
Medical History and Demographics[d]	X									
Physical Examination[d, e]	X	X				X[e,m]	X	X	X	X
ECOG Performance Status[d, e]	X	X					X (C3,5,7,9,etc)	X	X	X
Vital Signs[d]	X	X	X	X	X	X	X	X	X	X
12-Lead Digital Electrocardiogram[d, f]	X	X					X[f]	X	(X)	
Hematology and Clinical Chemistry Labs[d]	X	X			X[m]	X[m]	X		X	
Urinalysis[d]	X							X		
Pregnancy Test for Women of Child-Bearing Potential[d, g]	X	X					X	X		X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X
Survival[q]										X[q]
Blood Samples for Biomarkers [redacted][h]		X	X		X		X	X		
Blood Samples for [redacted][i, p]		X					X[q]	X	X	
Blood Samples for Pharmacokinetics[j, p]		X	X	X	X	X	X	X[j, p]	X[j]	
Biopsy[k]	(X)						(X) (end C2)	(X)		
Tumour Assessments[d, l]	X	Every 6 weeks (then every 9 weeks after 6 months of treatment)								
BI 754091 infusion		X					X			
DLT Assessment (report required at Phase Ia Cycle 1)[n]		X	X	X	X[m]	X[m]	X	X		

Flow Chart 1 Footnotes (Dose-Escalation)

a All cycles are 3 weeks (21 days) in duration. Patients will continue treatment with BI 754091 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 signs an informed consent describing this circumstance. In addition, patients without PD may stay on trial after 1 year on a case-by-case basis after discussion with the Medical Monitor and the sponsor but no longer than 31 August 2023. Day 1 of Cycle 1 is defined as the day when BI 754091 is first administered. During Phase Ia (dose escalation), Cycle 2 cannot begin without Safety Review Committee approval.

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, serum biochemistry, and urinalysis will be performed locally. The screening medical history and demographics, physical examination and Eastern Cooperative Oncology Group (ECOG) performance status, vital signs, electrocardiogram (ECG), haematology, clinical chemistry (sodium, potassium, phosphate, chloride, creatinine, calcium, venous bicarbonate HCO_3, albumin, total protein, AST, ALT, alkaline phosphatase, bilirubin, lactate dehydrogenase, serum glucose, c-peptide, serum cholesterol [baseline only], serum triglycerides [baseline only], serum creatinine, serum urea nitrogen [or urea], serum uric acid, and TSH, free T4, and free T3), urinalysis, and screening pregnancy test should be done ≤14 days prior to initiation of treatment. Additionally, amylase and lipase should be analysed in case of symptoms of pancreatitis. If these assessments are performed within 72 hours of initiation of treatment, they do not need to be repeated on Cycle 1 Day 1 with the exception of the ECOG performance status, an abbreviated physical examination, vital signs (pre- and post-infusion), and a single ECG required prior to first trial dose. Tumour assessments (scans) should be performed ≤28 days prior to initiation of treatment and copies may be collected by the sponsor or designee. Refer to Section 5.3 for additional details.

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. ECOG performance status will be done at screening, on Day 1 of Cycles 1 and 2, on Day 1 of every other cycle beginning with Cycle 3, at the EOT visit, and at the 30-day follow-up visit.

f Single digitalised ECGs must be done before blood work or other procedures after 5 minutes of rest at screening, Cycle 1 Day 1, Cycle 3 Day 1, Day 1 of every third cycle thereafter (Cycles 6, 9, 12, etc), 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 5.3.3).

g Women of child-bearing potential must have a serum βHCG pregnancy test at screening, on Day 1 of each cycle, and at the EOT visit. Beginning with Cycle 3, urine dipstick tests can be done on Day 1 of odd-numbered cycles (Cycles 3, 5, 7, etc).

h [redacted] on Days 1 (pre-treatment), 2, and 8 of Cycles 1, 2, and 4, on Day 1 (pre-treatment) of Cycles 3, 5 through 12, 14, and 17, and at the 30-day follow-up visit. (see Section 5.5.2.1 and Appendix 10.4.1).

i Blood samples for [redacted] will be collected from all patients as presented in the tables in Appendix 10.4.1.

j Pharmacokinetic (PK) blood sampling: there is extensive PK sampling in Cycles 1, 2, and 4 and it is strongly recommended to follow the visit days and sampling time points as outlined in the Appendix 10.4.1 tables. The permitted visit windows should only be used if medically indicated.

k Patients in the dose-escalation cohorts may consent to optional paired biopsies:
- The equivalent of 2 fine needle biopsies (archival) from the most recent relapse (if within 6 months of trial start with no subsequent therapy); otherwise, a minimum of 2 fine needle biopsies must be freshly taken between screening and the day before first treatment with BI 754091.
- The equivalent of 2 fine needle biopsies on treatment at the end of Cycle 2 (6 weeks).
- Another biopsy (optional) should be taken upon PD (according to RECIST v1.1 and iRECIST), if possible. An optional biopsy should also be taken if a patient has stable disease over 3 subsequent disease assessment periods.

l Tumour assessments should be done according to RECIST v1.1 and iRECIST and should include 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 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 5.2.1 for more detail). Assessments will be performed by the Investigator at screening and every 2 cycles (6 weeks) for the first 6 months of treatment and once every 3 cycles (9 weeks) thereafter until PD or start of further treatment for disease, and at the discretion of the Investigator.

m Cycle 1 only

n Dose-limiting toxicities (DLTs) will be collected throughout the trial and will be assessed for dose-escalation decisions following Cycle 1. After a first cycle is completed, a BI DLT Assessment report must be sent to the Medical Monitor (see Section 4.1.5). Cycle 2 cannot begin without Safety Review Committee approval.

o If the decision is made to permanently discontinue BI 754091 during a scheduled visit, the EOT visit assessments should be performed instead of the scheduled visit assessments.

p [redacted] PK blood samplings are to be collected during Cycles 1 through 12, Cycle 14, Cycle 17, at the EOT visit, and the 30-day safety follow-up.

q Additional progression-free survival (PFS) follow-up visits after the 30-day safety follow-up visit will only be performed for patients who did not progress on treatment. These will be performed once every 12 weeks at least (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.

FLOW CHART 2: BI 1381.1 (REFMAL 473) PHASE IB (DOSE EXPANSION) TRIAL ASSESSMENTS

Flow Chart 2									Post-Treatment Days[b]		
	Screening	**Cycles 1, 4, and 8**				**Cycles 2, 3, 5-7, & 9**	**Cycles 10, 11, 13, 14, 16, 17, etc**	**Cycles 12, 15, 18, etc**	**End-of-Treatment[n] (EOT) Visit**	**30-Day[b] Safety Follow-up**	**PFS, OS Follow-up[o,q]**
Assessments	**-28 to -1**	**1 (±2 C4+)**	**2[p] (±2 C4+)**	**8 (±1 C1)**	**15[p] (±1 C1) (±2 C4+)**	**1 (±2)**	**1 (±2)**	**1 (±2)**	**(within 7 days of**	**(+2)**	
Informed Consent[c]	X										
Inclusion/Exclusion Criteria	X										
Medical History and Demographics[d]	X										
Physical Examination[d, e]	X	X				X	X		X	X	X
ECOG Performance Status[d, e]	X	X				X (C3,5,7,9)	X (C11, 13,17 etc)	X (C15, 21 etc)	X	X	X
Vital Signs[d]	X	X	X (C1)	X	X (C1)	X	X	X	X	X	X
12-Lead Digital Electrocardiogram[d, f]	X	X (C1)				X[f]		X	X	(X)	
Hematology and Clinical Chemistry	X	X				X		X		X	
Urinalysis[d]	X								X		
Pregnancy Test for Women of Child-Bearing Potential[d, g]	X	X				X	X	X	X		X
Concomitant Medications	X	X	X (C1)	X	X (C1)	X	X	X	X	X	X
Adverse Events	X	X	X (C1)	X	X (C1)	X	X	X	X	X	X
Survival[o]											X[o]
Blood Samples for [redacted][h]		X (C1)		X (C1)	X (C1)	X (C2)			X[q]		
[redacted]		X (C1)	X (C1)	X (C1)	X (C1)	X (C2)			X[q]		
Blood Samples [redacted]		X				X		X	X[q]	X[q]	
Blood Samples for Pharmacokinetics[k]		X		X		X		X	X[k,q]	X[k,q]	
Biopsy[l]	X					X (end C2)			(X)[q]		
Tumour Assessments[d, m]	X	Every 6 weeks (then every 9 weeks after 6 months of treatment)									

Flow Chart 2									Post-Treatment Days[b]		
	Screening	Cycles 1, 4, and 8				Cycles 2, 3, 5-7, & 9	Cycles 10, 11, 13, 14, 16, 17, etc	Cycles 12, 15, 18, etc	End-of-Treatment[a] (EOT) Visit	30-Day[b] Safety Follow-up	PFS, OS Follow-up[o,q]
Assessments	**-28 to -1**	**1 (±2 C4+)**	**2[p] (±2 C4+)**	**8 (±1 C1)**	**15[p] (±1 C1) (±2 C4+)**	**1 (±2)**	**1 (±2)**	**1 (±2)**	**(within 7 days of**	**(+2)**	
BI 754091 infusion		X				X	X	X			

Flow Chart 2 Footnotes (Dose Expansion)

a All cycles are 3 weeks (21 days) in duration. Patients will continue treatment with BI 754091 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 signs an informed consent describing this circumstance. In addition, patients without PD may stay on trial after 1 year on a case-by-case basis after discussion with the Medical Monitor and the sponsor, but no longer than 31 August 2023. Day 1 of Cycle 1 is defined as the day when BI 754091 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, serum biochemistry, and urinalysis will be performed locally. The screening medical history and demographics, physical examination and Eastern Cooperative Oncology Group (ECOG) performance status, vital signs, electrocardiogram (ECG), haematology, clinical chemistry (sodium, potassium, phosphate, chloride, creatinine, calcium, venous bicarbonate HCO_3, albumin, total protein, AST, ALT, alkaline phosphatase, bilirubin, lactate dehydrogenase, serum glucose, c-peptide, serum cholesterol [baseline only], serum triglycerides [baseline only], serum creatinine, serum urea nitrogen [or urea], serum uric acid, and TSH, free T4, and free T3), urinalysis, and screening pregnancy test should be done ≤14 days prior to initiation of treatment. Additionally, amylase and lipase should be analysed in case of symptoms of pancreatitis. If these assessments are performed within 72 hours of initiation of treatment, they do not need to be repeated on Cycle 1 Day 1 with the exception of the ECOG performance status, an abbreviated physical examination, vital signs (pre- and post-infusion), and a single ECG required prior to first trial dose. Tumour assessments (scans) should be performed ≤28 days prior to initiation of treatment and copies may be collected by the sponsor or designee. Refer to Section 5.3 for additional details.

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. ECOG performance status will be done at screening, on Day 1 of Cycles 1 and 2, on Day 1 of every other cycle beginning with Cycle 3, at the EOT visit, and at the 30-day follow-up visit.

f Single digitalised ECGs must be done before blood work or other procedures after 5 minutes of rest at screening, Cycle 1 Day 1, Cycle 3 Day 1, Day 1 of every third cycle thereafter (Cycles 6, 9, 12, etc), 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 5.3.3).

g Women of child-bearing potential must have a serum βHCG pregnancy test at screening, on Day 1 of each cycle, and at the EOT visit. Beginning with Cycle 3, urine dipstick tests can be done on Day 1 of odd-numbered cycles (Cycles 3, 5, 7, etc).

h Blood samples for [redacted] for flow analysis will be collected (if feasible) during Cycle 1 on Day 1 (pre-treatment), Day 8, and Day 15, on Cycle 2 Day 1 (pre-treatment), and at EOT (see Section 5.5.2.1 and Table 10.4.2: 1).

i Blood samples for cytokines will be collected (if feasible) during Cycle 1 on Day 1 (pre-treatment), Day 2, Day 8, and Day 15, on Cycle 2 Day 1 (pre-treatment), and at EOT (see Section 5.5.2.1 and Table 10.4.2: 1).

j Blood samples for [redacted] will be collected from all patients as presented in Table 10.4.2: 1.

k Pharmacokinetic (PK) blood sampling will be collected from all patients as presented in Table 10.4.2: 1.

l The following fresh tumour biopsies will be mandatory for all patients in the Phase Ib dose-expansion cohorts of the trial (refer to Section 6.2.1.1):
- 2 core needle biopsies or 1 punch biopsy (refer to lab manual for specifications) from the most recent relapse (if within 6 months of trial start with no subsequent therapy); otherwise, a minimum of 2 core needle biopsies or 1 punch biopsy must be taken between the start of screening and the day before first treatment with BI 754091.
- 2 core needle biopsies or 1 punch biopsy on treatment at the end of Cycle 2 (6 weeks), preferably from the same lesion.
- Another biopsy (optional) should be taken upon PD (according to RECIST v1.1 and iRECIST), if possible. An optional biopsy should also be taken if a patient has stable disease over 3 subsequent disease assessment periods.

m Tumour assessments should be done according to RECIST v1.1 and iRECIST and should include 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 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 5.2.1 for more detail). Assessments will be performed by the Investigator at screening and every 2 cycles (6 weeks) for the first 6 months of treatment and once every 3 cycles (9 weeks) thereafter until PD or start of further treatment for disease, and at the discretion of the Investigator.

n If the decision is made to permanently discontinue BI 754091 during a scheduled visit, the EOT visit assessments should be performed instead of the scheduled visit.

o **Patients enrolled in Protocol Version 4.0 (expansion Cohort 4 and higher):** 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 (by telephone) until death, loss to follow-up, withdrawal of consent, or end of the whole trial. **Patients enrolled in Protocol Version 3.0 and earlier (expansion Cohort 1,2,3):** Additional PFS follow-up visits after the 30-day safety follow-up visit will only be performed for patients who did not progress on treatment. These will be performed once every 12 weeks at least (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.

p The patients will not be required to go to the clinic on Cycle 4 Days 2 and 15 and Cycle 8 Days 2 and 15.

q Only patients completed the activity up to until the cut of date for the primary report. All remaining patients will undergo EOT and 30 days visits safety procedures only.

TABLE OF CONTENTS

ABBREVIATIONS

ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the curve
BI	Boehringer Ingelheim
BLRM	Bayesian Logistic Regression Model
CI	Confidence Interval
CKD-EPI	Chronic Kidney Disease Epidemiology
CL	Drug clearance
CR	Complete response
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTP	Clinical Trial Protocol
DILI	Drug-Induced Liver Injury
DLT	Dose-limiting toxicity
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EF	Ejection fraction
EMA	European Medicines Agency
EOT	End-of-treatment visit
EWOC	Escalation with overdose control
FFPE	Formalin fixed and paraffin embedded
FM	Foundation Medicine
GCP	Good Clinical Practice
GEP	Gene-expression profile
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Committee on Harmonisation
[redacted]	
irAE	Immune-related adverse events
IRB	Institutional review board
iRECIST	Immune Response Evaluation Criteria in Solid Tumours
IRT	Interactive Response Technology
ISF	Investigator Site File
i.v.	Intravenous
mAB	Monoclonal antibody
MDSC	Myeloid-deprived suppressor cell
MedDRA	Medical Dictionary for Drug Regulatory Activities
MRI	Magnetic resonance imaging
MSI	Microsatellite instability
MSS	Microsatellite stability
MTD	Maximum-tolerated dose

NSCLC	Non-small cell lung cancer
OR	Objective response
ORR	Objective response rate
PBMC	Peripheral blood mononuclear cell
PD	Progression of disease
PD-1	Programmed cell death 1 (receptor)
PDc	Pharmacodynamics
PD-L1	Programmed cell death ligand 1
PET	Positron emission tomography
PFS	Progression-free survival
PK	Pharmacokinetics
POLE	Polymerase epsilon (ε) catalytic subunit
PR	Partial response
q3w	Once every 3 weeks
RCC	Renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumours
REP	Residual-effect period
RO	Receptor occupancy (assay)
RP2D	Recommended Phase 2 dose
SAE	Serious adverse event
SOP	Standard operating procedure
SRC	Safety Review Committee
TMB	Tumour mutational burden
TNBC	Triple negative breast cancer
TSAP	Trial Statistical Analysis Plan
ULN	Upper limit of normal

1. INTRODUCTION

This trial is sponsored by Boehringer Ingelheim (BI).

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). The American Cancer Society estimated that there will be approximately 595,000 deaths due to cancer in the United States during 2016. In the majority of cases, the disease is diagnosed in late stages and the vast majority of patients progress on available treatment and succumb to their disease. These statistics clearly highlight the urgent need for novel therapeutic agents and treatment strategies to improve the treatment outcome for cancer patients.

The normal role of the immune system is to protect the body against the invasion of foreign antigens such as bacteria, viruses, and parasites as well as the body's own malfunctioning cells. Once a mounted immune response (adaptive or innate) completes its task of eliminating the threat, the immune system deploys the immune checkpoint program to dampen the immune response and minimise collateral immune-mediated damage to healthy tissue. The programmed-cell-death 1 (PD-1; CD279) receptor and its ligands, programmed-cell-death ligand 1 (PD-L1; B7-H1; CD274) and programmed-cell-death ligand 2 (PD-L2; B7-DC; CD273) are the major immune checkpoint master switches. The expression of PD-1 on immune cells, including T and B lymphocytes, natural killer (NK) cells and antigen presenting cells is upregulated in response to inflammation in peripheral tissue (R16-2360). While PD-L2 expression is limited, PD-L1 is expressed broadly and constitutively on many immune cells including T lymphocytes (T-cells), B lymphocytes, dendritic cells (DCs) and macrophages. As with PD-1 levels, the expression of PD-L1 is also induced as a result of peripheral tissue inflammation. The interaction between PD1 and PD-L1 results in an inhibitory signal that interferes with antigen receptor signaling, marked changes in the cytokine profile, decreased T-cell activation, increased activation of regulatory T-cells, and an increase in cytotoxic T-cell apoptosis. Collectively, these events lead to an immune suppressive environment and a dampening of the immune response. Many tumours usurp immune checkpoint pathways to evade immune response mediated destruction. PD-L1 expression is induced on tumour cells, tumour stromal cells, and antigen-presenting cells in response to IFN-gamma produced by activated T-helper cells, cytotoxic T-cells and natural killer cells initially responding to tumour neoantigens in many cancer types. Tumour immune evasion is achieved when PD-L1 within the tumour microenvironment engages PD-1 expressed on activated tumour infiltration T-cells and initiates the immune suppressive tumour microenvironment in which activated cytotoxic T-cells are inactivated and, some are sent down an apoptotic pathway (R16-2371).

Therefore, it stands to reason that blocking of immune checkpoint pathways may result in the reactivation of the suppressed tumour-specific cytotoxic T-cells capable of killing tumour cells leading to tumour elimination. To this end, preclinical data have clearly demonstrated that blockade of the PD-1/PD-L1 checkpoint pathway results in restoration of anti-tumour immune response. More importantly, clinical data have clearly demonstrated remarkable

survival benefits for treatment with anti-PD-1 monoclonal antibodies (mAb) (nivolumab and pembrolizumab) compared to standard of care in many tumour types including non-small cell lung cancer (NSCLC) (R15-3588; R16-0876; R15-3715; R15-6023), melanoma (R16-0864; R15-3780; R15-3778; R15-3777), renal cell carcinoma (RCC) (R16-2809), gastric cancer and squamous cell carcinoma of head and neck among others. Nivolumab is currently FDA-approved for the treatment of NSCLC, melanoma, Hodgkin's lymphoma, and RCC. Pembrolizumab is currently approved for the treatment of NSCLC, head and neck carcinomas, and melanoma. Results from anti-PD-1 studies in cervical carcinoma, an HPV-linked gynecological cancer, provide rationale for studying immunotherapy in vulvar squamous cell carcinoma (VSCC). Preliminary data from the phase I/II CheckMate358 study (NCT 02488759), which evaluates nivolumab in virus-associated, recurrent or metastatic cervical, vaginal and vulvar carcinoma, showed that in the nivolumab-treated cohort, the ORR and the disease control rate (ORR + SD) were 20.8% and 70.8%, respectively.

Despite these encouraging clinical results with nivolumab and pembrolizumab, up to 80% of treated patients do not respond to current checkpoint inhibitors (R15-3588; R15-3778). The limited success achieved by checkpoint inhibitor monotherapy is likely due to multiple factors including the inherent complexity of the immune response, possible redundancy of checkpoint inhibitor pathways, the complexity of mechanisms of tumour immune evasion and the exclusion of effector T-cell from some tumours. These findings demonstrate the need for the development of new checkpoint inhibitors and checkpoint inhibitor combinations to improve response rates and outcomes for cancer patients.

1.2 DRUG PROFILE

BI 754091 is a humanized IgG4Pro isotype mAb 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 dosing frequency is expected to be once every 3 weeks (q3w) based on the pharmacokinetic (PK) properties of BI 754091 and similarities to the pharmacology, chemical and pharmaceutical properties, and PK of nivolumab and pembrolizumab.

For a more detailed description of the BI 754091 profile please refer to the current Investigator's Brochure (IB).

2. RATIONALE, OBJECTIVES, AND BENEFIT-RISK ASSESSMENT

2.1 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.

Immune checkpoint inhibition has been shown to be a promising therapeutic strategy. Programmed death receptor 1 (PD-1) represents one of the immune checkpoints used by tumours to suppress antitumour immunity. The safety and durable efficacy of anti-PD-1 mAbs has been clearly established in multiple tumour types as indicated previously.

BI 754091 is an anti-PD-1 mAb that has been shown to have anti-tumour activity in several preclinical *in vitro* and *in vivo* studies (n00250946; n00250933; n00252624; n00252631).

This trial is the first study with BI 754091 in humans and will be conducted in 2 parts. The first part will include dose-escalation cohorts to determine the maximum-tolerated dose (MTD) and/or the recommended Phase 2 dose (RP2D). The second part consists of 4 expansion cohorts at the RP2D that will also further evaluate the safety, tolerability, efficacy, PK, and biomarkers of BI 754091. The dose-escalation portion of the trial will enrol patients with advanced and/or metastatic solid tumours, while the dose-expansion portion will enrol patients with advanced and/or metastatic solid tumours with select types of cancer and/or specific genetic mutations. Recent evidence has shown that several tumour types with high TMB have better response rates with immune checkpoint inhibitors (R17-0923; R16-1497). Therefore, patients with tumours with high mutation rates will be included in the expansion phase of this trial. More recent data have demonstrated that the combination of nivolumab and ipilimumab had better efficacy in NSCLC patients with a tumour mutational burden of at least 10 mutations per megabase than those with <10 mutations per megabase (R18-1492). As such, a ≥10 mutation per megabase threshold was selected to define patients with high TMB for this trial.

Please see Section 3.3.2 for a list of target tumour types for the dose-expansion portion.

2.2 TRIAL OBJECTIVES

The main objective of the dose-escalation part of the trial is to determine the safety and tolerability, and to determine the MTD and/or the RP2D of BI 754091 on the basis of patients with dose-limiting toxicities (DLTs) in patients with selected advanced solid malignancies. Safety and tolerability will be evaluated by monitoring the occurrence of adverse events (AEs), serious AEs (SAE), and laboratory parameter abnormalities, as well as changes to vital signs (see Section 5.3).

Secondary objectives are the determination of the PK profile of BI 754091 after single and multiple doses of BI 754091 (see Section 5.4.1), and the preliminary assessment of anti-tumour activity (see Section 5.2).

In the dose-expansion part of the trial, the main objectives are to further assess the safety, efficacy, PK profile, and biomarkers of BI 754091 in tumours with specific tumour types and/or genetic mutations at the RP2D.

2.3 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 minimising 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 event (irAEs). Indeed, mice deficient in PD-1 or its ligands (PD-L1 and PD-L2) were found

to be highly prone to development of autoimmune diseases (R16-2968; R16-2362; R16-2364; 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-L1 (70%) mAbs. However, the majority of these AEs are mild in severity (R12-5176; R15-3588; R15-3715) and occur within the first 4 months of initiating therapy (R16-0899; R15-3780; R16-0864). 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 and pneumonitis 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, mycophenylate mofetil and cyclosporine) can be used in case of steroid-refractory irAE (R16-0899; R16-0870; R16-0763). Treatment with BI 754091 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 treatment. These reactions occur infrequently and are typically managed based on symptoms using treatments ranging from treatment with histamine antagonists in mild cases to administration of epinephrine when symptoms of anaphylaxis are detected.

BI 754091 has not been tested in humans thus far, however, it is expected that BI 754091 will have a comparable safety profile to marketed anti-PD-1 mAbs. Repeat-dose administrations of BI 754091 at 0, 3, 30 or 100 mg/kg/dose of BI 754091 (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. Administration of BI 754091 had no adverse effects on clinical pathology parameters including haematology, immunophenotyping, and clinical chemistry. 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.

Based on these pre-clinical data, as well as clinical data obtained with other anti-PD-1 inhibitor mAbs, the inhibitory effects of BI 754091 on PD-1 may translate into a clinical benefit in cancer patients. All doses planned to be tested are expected to have some level of efficacy. Efficacy is expected for patients with tumours that have a high rate of mutations, such as high levels of TMB and squamous cell skin cancers, which have about the highest mutation rate among cancers.

The dose-escalation scheme is guided by a Bayesian 2-parameter 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 undue tolerability issues. Therefore, treatment with BI 754091 is expected to provide patients with clinical benefit at an acceptable risk.

Even so, patients should be advised of the potential risks of side effects from investigational trial treatments. 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 Section 5.3.6.5.4).

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

This is a Phase I, open-label, multi-centre trial of BI 754091 administered as a single agent. The trial design allows an escalation of dose with intensive safety monitoring to ensure the safety of the patients.

It is planned that approximately 15 patients with advanced solid malignancies will be enrolled in the Phase Ia portion of the trial, which will include dose-escalation of BI 754091 administered as monotherapy. The total number of patients will depend on the number of dose escalations necessary. Dose escalation will be guided by a BLRM with overdose control (EWOC). The BLRM estimates the MTD by updating estimates of the probability of observing a DLT in the MTD evaluation period (first 3 weeks) for each dose level in the trial as patient information becomes available. At no time in the trial, will it be permitted to escalate to a dose which does not fulfil the EWOC principle (refer to Section 7).

Successive cohorts of patients will receive doses of BI 754091 until the MTD is reached. A cohort size of 3 patients will be treated at each dose level. Additional patients (up to 6 more) could 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 (first 3 weeks) 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 which fulfil the EWOC criterion. Hypothetical data scenarios (see example in Section 10.5.1) will be calculated with potential cohort sizes and presented at the meetings with the Safety Review Committee (SRC, see Section 3.1.2). Based on the model and on additional information (PK, pharmacodynamics [PDc], patient profiles), the members of the SRC will reach a joint recommendation on the next dose level to be investigated and the size for the next dose-escalation cohort. However, the final decision on the next dose level and cohort size will be made mutually between the BI Clinical Program Leader and the SRC.

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 SRC 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 SRC 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 no DLT is observed at a dose at which the efficacy is considered sufficient, the SRC may decide to include an additional number of patients at the same dose level and to declare this dose as the recommended dose for further development (RP2D). The SRC can declare any dose that fulfils the EWOC criterion as RP2D, independent of the MTD estimate.

Following determination of the MTD and/or RP2D from the Phase Ia portion, separate cohorts of approximately 30-40 patients each will be conducted in patients with select advanced solid malignancies including tumours with specific histology/tumour types and/or specific genetic profiles as specified in the following cohorts:

- Cohort 4: Solid tumours including NSCLC, bladder cancer, melanoma, gastric cancer, ovarian cancer, triple-negative breast cancer, and renal-cell cancer
- Cohort 5: Tumours with high TMB excluding those with high microsatellite instability (MSI-high)
- Cohort 6: Refractory squamous cell cervical, anal, and skin tumours
- Cohort 7: Recurrent human papillomavirus (HPV)-positive, or HPV-negative, vaginal or vulvar squamous cell carcinoma (VSCC)

The Phase Ib portion of the trial will further evaluate the safety, tolerability, efficacy, PK profile, and biomarkers of BI 754091.

The analysis of the squamous cell tumour cohort (Cohort 6) and the VSCC cohort (Cohort 7) will follow a two-stage approach.

The interim analysis for Cohort 6:

- Squamous cervical and/or anal cancer, Stage 1 will include 10 treated patients.
- Squamous skin tumours, Stage 1 will include 10 treated patients.

The interim analysis for Cohort 7:

- Vaginal or VSCC, Stage 1 will include 20 treated patients.

Based on the interim analyses results, the sponsor will determine if recruitment into these tumour groups will continue or be terminated (recruitment does not have to pause while interim analysis is conducted). More details on the interim analyses are specified in Section 7.4. The sponsor reserves the right to terminate recruitment in any of the tumour groups if the recruitment target is not met. Patients who are already enrolled may continue in the trial regardless of recruitment termination of their cohort.

Patients will continue treatment with BI 754091 until disease progression (PD) according to the Response Evaluation Criteria in Solid Tumours (RECIST) and the Guidelines for Response criteria for use in trials testing immunotherapeutics (iRECIST) (R17-0923, withdrawal of patient consent, an unacceptable toxicity occurs, or 1 year of treatment is completed, whichever occurs first but no longer than 31 August 2023. Patients will be allowed to stay on treatment in the case of initial radiological PD, if the Investigator feels that

it is in the patient's best interest. In addition, patients without PD may stay on trial after 1 year on a case-by-case basis after discussion with the Medical Monitor and the sponsor, but no longer than 31 August 2023. After this date treatment with the ezabenlimab will no longer be available.

3.1.1 Administrative structure of the trial

A contract research organisation, [redacted], is responsible for project management, medical management, site management, data management, site regulatory document management, some aspects of safety management and reporting, medical writing, and medical monitoring.

The Global Study [redacted] from [redacted] and the Coordinating Investigator, [redacted], are responsible for coordinating Investigators at different centres participating in this multicentre trial. Tasks and responsibilities are defined in contracts.

An SRC (see Section 3.1.2) including representatives from clinical sites, sponsor representatives, and [redacted] members, will be established to assess the progress of the clinical trial, including making safety and efficacy assessments at specified intervals, making dose-escalation decisions, and recommending to the sponsor whether to continue, modify, or stop the trial. The tasks and responsibilities of the SRC will be documented. The SRC will maintain written records of all its meetings.

Relevant documentation on the participating (Principal) Investigators and other important participants, including their curricula vitae, will be filed in Investigator Site File (ISF).

The Statistical analysis will be done by BI according to BI Standard Operating Procedures (SOPs).

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

An Interactive Response Technology (IRT) vendor will be used in this trial. Details will be provided in an IRT Manual available in the ISF.

3.1.2 Safety Review Committee

Members of the SRC will include:
- [redacted] Medical Monitor for the trial
- Principal Investigators, or delegates, from each investigational site.

In addition, one other physician from the following will be invited:
- BI Safety Physician, or delegate
- BI Clinical Program Leader responsible for the project.

The BI Safety Physician, BI Clinical Program Leader, or delegate, should always attend the SRC, if there are safety issues for discussion.

The [redacted] Medical Monitor, or delegate, should always be present at the SRC.

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

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

Dose escalation and cohort size will be determined based on the recommendation of the SRC, guided by a Bayesian model 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 FDA (R13-4881).

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

3.3 SELECTION OF TRIAL POPULATION

A log of all patients enrolled into the trial (i.e., who have signed an informed consent form [ICF]) will be maintained in the ISF at the investigational site irrespective of whether or not they have been treated with investigational drug or not.

3.3.1 Main diagnosis for trial entry

Patients with selected advanced, unresectable, and/or metastatic solid tumours, who are anti-PD-1 naïve but have failed conventional treatment or for whom no therapy of proven efficacy exists, or who are not amenable to standard therapies are eligible for either portion of this trial.

Patients included in the dose-escalation phase are not eligible to enter the dose-expansion phase.

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

3.3.2 Inclusion criteria

For inclusion in the trial, patients must fulfil all of the following criteria:

1. Provision of signed and dated, written ICF prior to any trial-specific procedures, sampling, or analyses. If a patient declines to participate in the voluntary pharmacogenetics component of the trial, he/she will not be excluded from other aspects of the trial.
2. Patients ≥18 years of age at the time of signature of the ICF
3. Phase Ia (dose escalation):
   - Patients with a histologically confirmed diagnosis of advanced, unresectable, and/or metastatic solid tumours (any type)
   - Patients who have received all therapy known to confer clinical benefit (including anti-PD-1 or anti-PD-L1 therapies, if relevant), or for whom no therapy of proven efficacy exists, or who are not amenable to standard therapies. Patients with anti-PD-1 or anti-PD-L1 experience must have a minimum of 60 days between the last dose of the previous anti-PD-1/PD-L1 and Cycle 1 Day 1 of BI 754091 treatment.
   - Patients may agree to provide optional paired biopsies.
4. Phase Ib (dose expansion):
   - Patients with a histologically confirmed diagnosis of select advanced, unresectable, and/or metastatic solid tumours with specific histology/tumour types and/or specific genetic profiles as specified in the following cohorts:
     - Cohort 4: solid tumours including NSCLC, bladder cancer, melanoma, gastric cancer, ovarian cancer, triple-negative breast cancer, and renal-cell cancer
     - Cohort 5: Tumours with high TMB (showing ≥10 mutations/mega base) excluding those with high microsatellite instability (MSI-high) (TMB and MS status based on any validated test). Refer to Section 6.2.1.1 for details.
     - Cohort 6: Refractory squamous cell cervical, anal, and skin tumours.
     - Cohort 7: Recurrent HPV-positive, or HPV-negative (per local testing), vaginal or VSCC, not amenable to surgery.
   - All patients must have measurable lesions according to RECIST v1.1 criteria, must have at least 1 tumour lesion amenable to biopsy, and must be medically fit and willing to undergo a biopsy before first treatment and, unless clinically contraindicated, after 6 weeks on therapy.
   - Patients who are anti-PD-1 and anti-PD-L1 naïve but have failed conventional treatment (excluding anti-PD-1 treatment), or for whom no therapy of proven efficacy exists, or who are not amenable to standard therapies.
5. Eastern Cooperative Oncology Group (ECOG, R01-0787) score: 0 to 1
6. Life expectancy of at least 12 weeks after the start of the treatment according to the Investigator's judgement
7. Females of child-bearing potential willing to use adequate contraceptive measures from the time of screening until 6 months after trial discontinuation, who are not or will not be breast feeding, and agree to have pregnancy tests prior to the start of dosing and at regular visits during the trial. Females not of childbearing potential must have evidence of such by fulfilling one of the following criteria at screening:

- Post-menopausal: defined as more than 50 years-of-age and amenorrhoeic for at least 12 months following cessation of all exogenous hormonal treatments
- Documentation of irreversible surgical sterilization by hysterectomy, bilateral oophorectomy, or bilateral salpingectomy
- Women under 50 years-of-age would be considered postmenopausal if they have been amenorrhoeic for at least 12 months following the cessation of exogenous hormonal treatments, and have serum follicle-stimulating hormone and luteinizing hormone levels in the postmenopausal range for the institution.
- For women of childbearing potential using a contraceptive pill, an additional barrier method is necessary.. Acceptable highly effective methods of contraception include total sexual abstinence when this is in line with the preferred and usual lifestyle of the study participant **(**periodic abstinence such as calendar, ovulation, symptothermal, post-ovulation methods and withdrawal are not acceptable methods of contraception), an intrauterine device or intrauterine hormone-releasing system, bilateral tubal ligation, and vasectomised partner (with post-vasectomy proof of absence of sperm)

8. Male patients must be willing to use barrier contraception (i.e., condoms) for the duration of the trial and for 6 months after trial treatment discontinuation.

3.3.3 Exclusion criteria

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

1. Major surgery (major according to the Investigator's assessment) performed within 12 weeks prior to first trial treatment 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 enrolment in this trial
4. Any investigational or antitumour treatment within 4 weeks or 5 half-life period (whichever is shorter) prior to the initial administration of BI 754091.
5. Presence of other active invasive cancers other than the one treated in this trial within 5 years prior to screening, with the exception of appropriately treated basal-cell carcinoma of the skin, *in situ* carcinoma of the uterine cervix, or other local tumours considered cured by local treatment.
6. 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
7. 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

- Haemoglobin <90 g/L (<9 g/dL)
- Alanine aminotransferase (ALT) >2.5 times the upper limit of normal (ULN) if no demonstrable liver metastases or >5 times ULN in the presence of liver metastases
- Aspartate aminotransferase (AST) >2.5 times ULN if no demonstrable liver metastases or >5 times ULN in the presence of liver metastases
- 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
- Creatinine >1.5 times ULN or creatinine clearance <50 mL/min (measured or calculated by Chronic Kidney Disease Epidemiology (CKD-EPI) Collaboration equation); confirmation of creatinine clearance is only required when creatinine is >1.5 times ULN.

8. Any of the following cardiac criteria:
   - Mean resting corrected QT interval (QTc) >470 msec
   - Any clinically important abnormalities (as assessed by the Investigator) in rhythm, conduction, or morphology of resting ECGs, e.g., complete left bundle branch block, third degree heart block
   - Any factors that increase the risk of QTc prolongation or risk of arrhythmic events such as heart failure, hypokalaemia, congenital long QT syndrome, family history of long QT syndrome or unexplained sudden death under 40 years-of-age, or any concomitant medication known to prolong the QT interval
   - 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.
9. History of pneumonitis within the last 5 years
10. History of severe hypersensitivity reactions to other mAbs
11. Immunosuppressive corticosteroid doses (>10 mg prednisone daily or equivalent) within 4 weeks prior to the first dose of BI 754091
12. Active autoimmune disease or a documented history of autoimmune disease, except vitiligo or resolved childhood asthma/atopy
13. Known history of human immunodeficiency virus infection or an active hepatitis B or C virus infection. HIV infection is allowed for patients in cohort 6 (cervical/anal squamous) and cohort 7 (vulvar).
14. Interstitial lung disease
15. Chronic alcohol or drug abuse or any condition that, in the Investigator’s opinion, makes him/her an unreliable trial subject, unlikely to complete the trial, or unable to comply with the protocol procedures.

3.3.4 Removal of patients from therapy or assessments

3.3.4.1 Removal of individual patients

An excessive withdrawal rate can have a severe negative impact on the scientific value of the trial. Every effort should be made to keep patients in the trial as scheduled. This includes careful patient selection and appropriate explanation of the trial requirements and procedures prior to enrolment as well as an explanation of the consequences of premature withdrawal.

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

- The patient withdraws consent for trial treatment or trial participation, without the need to justify the decision.
- The patient needs to take concomitant drugs that interfere with the investigational product other than those listed under 'Permitted concomitant medications' (see Section 4.2.2.1).
- The patient can no longer be treated with trial medication for other medical reasons (such as surgery, AEs, other diseases, or pregnancy)
- 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.

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 1, Flow Chart 2, and Section 6.2.3.

For all patients the reason for withdrawal (e.g., AEs) must be recorded in the electronic case report form (eCRF). These data will be included in the trial database and reported.

During their first treatment cycle, patients withdrawn for a reason other than having a DLT or patients who miss more than one visit will be replaced after discussion between the sponsor and the Investigator 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 must immediately be stopped. The patient will be followed up until delivery or termination of pregnancy (see Section 5.3.6.9 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 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 Good Clinical Practice (GCP), the clinical trial protocol (CTP), or the contract disturbing the appropriate conduct of the trial.
4. Completion of treatment by all patients and the sponsor determines that sufficient survival data has been collected.
5. Termination of the development program by the sponsor .

In case the trial is ended by the sponsor, the available clinical trial data will be analyzed and reported approximately one year after the last patient has been enrolled. Patients who are still being treated with BI 754091 when the primary report of the trial is being prepared, will be kept on treatment in this trial and finalize the clinical observation period by 31 August 2023 at the latest. Data of those patients will then be reported in a revised report and it will be noted in the primary report that such a revised report will be written.

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

4. TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

4.1.1 Identity of the Investigational Medicinal Product

Details of the drug product, BI 754091, are presented in Table 4.1.1: 1. Additional details are presented in the BI 754091 IB and Pharmacy Manual.

Table 4.1.1: 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.

4.1.2 Selection of doses in the trial

Given that the patients to be enrolled in this trial will have advanced/metastatic cancer, it is preferable to set the starting dose at a level that is anticipated to bring them clinical benefit. Research by Bai et al (R13-4749) found that the fixed-dosing approach (flat dosing) is the recommended first option for administration of mAbs in first-in-human studies. Hence, we

plan to test BI 754091 at a flat starting dose of 80 mg (equivalent to 1 mg/kg for an 80-kg person) to be administered via infusion q3w. A sample dose-escalation scheme is shown in Section 4.1.3. The actual dose escalation will be guided by the BLRM, and the final decision will be made by the SRC (see Section 3.1.2).

The starting dose was selected based on the well-established positive safety profile of approved anti-PD-1 mAbs and the observation that maximum serum target engagement is reached with doses of 1 mg/kg administered q3w. Therefore, the selected starting dose is expected to be in the therapeutic range providing participating patients with a reasonable chance of clinical benefit while reducing the risk of toxicities. The estimated exposures for the planned starting dose are 94 x AUC and 173 x C_{max} lower than the exposures at the no-observable-adverse-effect level of 100 mg/kg/dose in the 13-week toxicity study in cynomolgus monkeys. The predicted efficacious human dose is 2 mg/kg (160 mg for an 80-kg person) q3w.

4.1.3 Dose-escalation scheme

The dose is planned to be escalated in cohorts. The sample dose levels to be assigned to separate cohorts of patients are listed in Table 4.1.3: 1. Intermediate or lower dose levels, depending on the number of DLTs observed in the trial, and dose levels higher than 400 mg (as long as they fulfil the EWOC criterion) may be investigated if agreed upon between Investigator and sponsor.

Table 4.1.3: 1 Example of dose escalation*

Dose Escalation Rules		Example Dose Levels
Dose level	Increment from previous dose	Proposed dose
first	Starting dose	80 mg
second	200%	240 mg*
third	67%	400 mg*

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

At the end of each treatment cohort, BI will convene a meeting with the SRC members. At the dose-escalation meeting the clinical course (safety information including but not limited to both DLTs and all Common Terminology Criteria for Adverse Events (CTCAE) Grade ≥2 toxicity data during Cycle 1) for each patient in the current dose cohort will be described in detail. Updated safety data on other ongoing patients, including data in later cycles, 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

There will be no dose reductions or escalations of BI 754091. The dose may be delayed for up to 6 weeks because of AEs, following discussion with the Medical Monitor.

4.1.5 Definition of dose-limiting toxicity

Dose-limiting toxicities (DLTs) will be recorded throughout the trial. The BI DLT Assessment report is required to be completed and submitted by the Investigator after Phase I Cycle 1 only. This report should be submitted to the Medical Monitor and a copy kept in the ISF. Only DLTs occurring during Phase I Cycle 1 will be used for dose-escalation decisions. All relevant safety information (including DLTs) will be considered when selecting the RP2D.

Previous anti-PD-1 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 / 5.0. For the purpose of a dose-finding decision, any of the following AEs occurring during the first cycle of treatment (21 days) will be classified as DLTs following review by the Investigators and the sponsor.

Haematologic toxicities:
- Neutropenia ≥ Grade 4 present for >7 days
- Febrile neutropenia
- Neutropenia Grade 3 with documented infection
- Any Grade 3 thrombocytopenia with bleeding or a requirement for platelet transfusions
- ≥ Grade 4 thrombocytopenia (platelets <25,000/μL).

Non-haematological toxicities:
- AST or ALT >3 times ULN and concurrent total bilirubin >2 times ULN without initial findings of cholestasis (e.g., 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 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 drug-related uveitis or 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 treatment-related ≥ Grade 2 toxicity that persists and results in an inability to administer BI 754091 on Cycle 2 Day 1.

The frequency, time to onset, and severity of toxicities, as well as the success of standard medical management and dosing interruptions/delays, will be analysed to determine if a given toxicity should be considered a DLT for dose escalation purposes.

Late immune-related DLTs are irAEs that meet the same grading criteria as DLT criteria but occur after the initial 21-day DLT period and during the first 90-day assessment period. These, as well as all toxicities, will be monitored throughout the trial. If any late immune-related DLT is reported during dose-escalation, the BLRM will be rerun including the late immune-related DLT, and updated results will be reviewed in the SRC 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 at least one DLT is observed in the trial and one of the following criteria is fulfilled:

- The posterior probability of the true DLT rate in the target interval [0.16 – 0.33) of the MTD is above 0.50

OR

- At least 15 patients have been treated in the trial, of which at least 6 have been treated at the MTD.

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 and either:

- has completed the minimum safety evaluation requirements during the first cycle (first 3 weeks)

OR

- has experienced a DLT during the first cycle (first 3 weeks).

4.1.8 Method of assigning patients to treatment groups

After assessment of all inclusion and exclusion criteria, each eligible patient in the Phase Ia (dose escalation) portion of the trial will be assigned the lowest medication dose available at the time of enrolment.

To determine the dose regimen for the next cohort, the available toxicity information (including DLTs, AEs that are not DLTs, and AE information post-Cycle 1), PK, and PDc information, as well as the recommendations from the BLRM will be evaluated by the SRC members at the dose decision meeting. The parties must reach a consensus on whether to declare MTD, escalate the dose any further, or whether to de-escalate and/or expand recruitment into particular cohorts. Minutes from these meetings will be prepared and circulated to the trial team and each Investigator for comment prior to finalization. Dose escalation will continue until identification of the MTD estimate is encountered or until the trial is terminated for other reasons.

To further characterise the safety (e.g. specific suspected treatment-related AEs) or PK/PDc of BI 754091, one or several doses that are considered acceptably safe (i.e., shown to be lower than or equal to any potential MTD) may be expanded. Dose escalation may be terminated at any time based on emerging safety concerns without establishing the MTD.

In the second part (Phase Ib Dose Expansion), all patients will be treated with the schedule and dose determined by the assessment of DLTs and PK and biomarker results from the Phase Ia portion of the trial. Patient numbers will be assigned as enrolment (screening) occurs.

4.1.9 Administration of doses for each patient

Vials of BI 754091 will be diluted and administered via infusion according to the details in the Pharmacy Manual. Sites will provide normal saline (sodium chloride 0.9%) for the dilution of study drug. For sites in the UK, the saline must be an EU licensed product.

4.1.10 Blinding and procedures for unblinding

Not applicable in this open-label trial.

4.1.11 Packaging, labelling, and re-supply

The investigational product will be provided by BI. It will be packaged and labelled in accordance with the principles of Good Manufacturing Practice. Each site will be provided with an initial shipment of trial drug supply. It will be the responsibility of the Investigator or designee to monitor that supply to ensure the site has enough for current and potential patients. [redacted] will monitor expiry dates of trial drug to trigger replacement supplies as needed. As needed, sites will request additional re-supply from [redacted] by using the Drug Request and Shipment form, which is available in the ISF. Upon receipt of the request, [redacted] will trigger drug supply for the site using an IRT ‘light’ system. No re-supply will be possible after 31 August 2023.

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.

4.1.13 Drug accountability

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

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

The Investigator, or designee, 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 alternative disposal of unused products.

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

4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, CONCOMITANT MEDICATIONS, AND RESTRICTIONS

4.2.1 Other treatments and emergency procedures

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

4.2.2 Concomitant medications

Rescue medication to reverse the action of BI 754091 is not available. Therefore, potential side effects of BI 754091 have to be treated symptomatically.

Concomitant therapy, with reasons for the 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 will be documented in the eCRF, on a separate page of follow-up therapy, different from the concomitant therapies pages.

4.2.2.1 Permitted concomitant medications

- If medically feasible, patients taking regular medication should be maintained on it throughout the trial.
- Pre-medication will not be required, but may be utilised following the first dose of BI 754091. This includes medications for the management of nausea, diarrhoea, and vomiting for which the patient must be treated according to institutional standards.
- Supportive care and other medications that are considered necessary for the patient's well-being may be given at the discretion of the Investigator.
- Blood transfusions are allowed at any time during the trial, except to meet inclusion criteria. There must be at least 4 weeks between a patient's last transfusion and the 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.
- 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-escalation part of the trial, except during the first cycle as it could interfere with the DLT evaluation for MTD determination. Following the first cycle of the dose-expansion phase (Phase Ib), palliative radiotherapy is allowed only for non-target lesions, following discussion with the Medical Monitor, 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. 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 anymore for a trial biopsy. Unless in emergency situations, the Medical Monitor should be contacted prior to the administration of palliative radiotherapy in the expansion phase.

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, CT scan contrast hypersensitivity) are acceptable upon discussion with the Medical Monitor.
- Live attenuated vaccines during the trial through 30 days after the last dose of investigational product are prohibited.
- 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 BI 754091.

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, females of childbearing potential can be included into this trial provided that they agree to use a highly-effective contraception method. These are 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.

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

Details of these contraception methods are also described 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 will be administered intravenously 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.

5. VARIABLES AND THEIR ASSESSMENT

5.1 TRIAL ENDPOINTS

5.1.1 Primary endpoints

The primary endpoint of the Phase Ia dose-escalation portion of the trial is:

- Number of patients experiencing DLTs graded according to CTCAE Version 4.03 / 5.0 observed in the first cycle (3 weeks) in order to meet the objective of assessment of the MTD of BI 754091.

The MTD is defined as the highest dose with less than 25% risk of the true DLT rate being above 33%. For definition of DLTs, refer to Section 4.1.5.

A BLRM employing the EWOC principle will be used during the escalation phase for selection of doses to investigate and for estimation of the MTD. Cohorts of patients will receive escalating doses of BI 754091 until the MTD is reached. Each cohort will consist of newly enrolled patients. Estimation of the MTD during the escalation phase of the trial will be based upon the estimation of the probability of a DLT in Cycle 1 in the set of evaluable patients for MTD. The corresponding methodology is described in Section 7 and Appendix 10.5. The MTD estimate established during the dose escalation phase will be re-investigated after the expansion phase by re-running the BLRM including all data from escalation and expansion phase, in particular also considering the DLT information from all treatment cycles.

The primary endpoints of the Phase Ib dose-expansion portion of the trial are:

- Number of patients with DLTs observed during the entire treatment period.
- Confirmed Objective Response (OR), defined as the best overall response of confirmed complete response (CR) or partial response (PR) according to RECIST v1.1 as assessed by the Investigator

5.1.2 Secondary endpoints

5.1.2.1 Secondary endpoints of the Phase Ia (dose escalation) portion of the trial

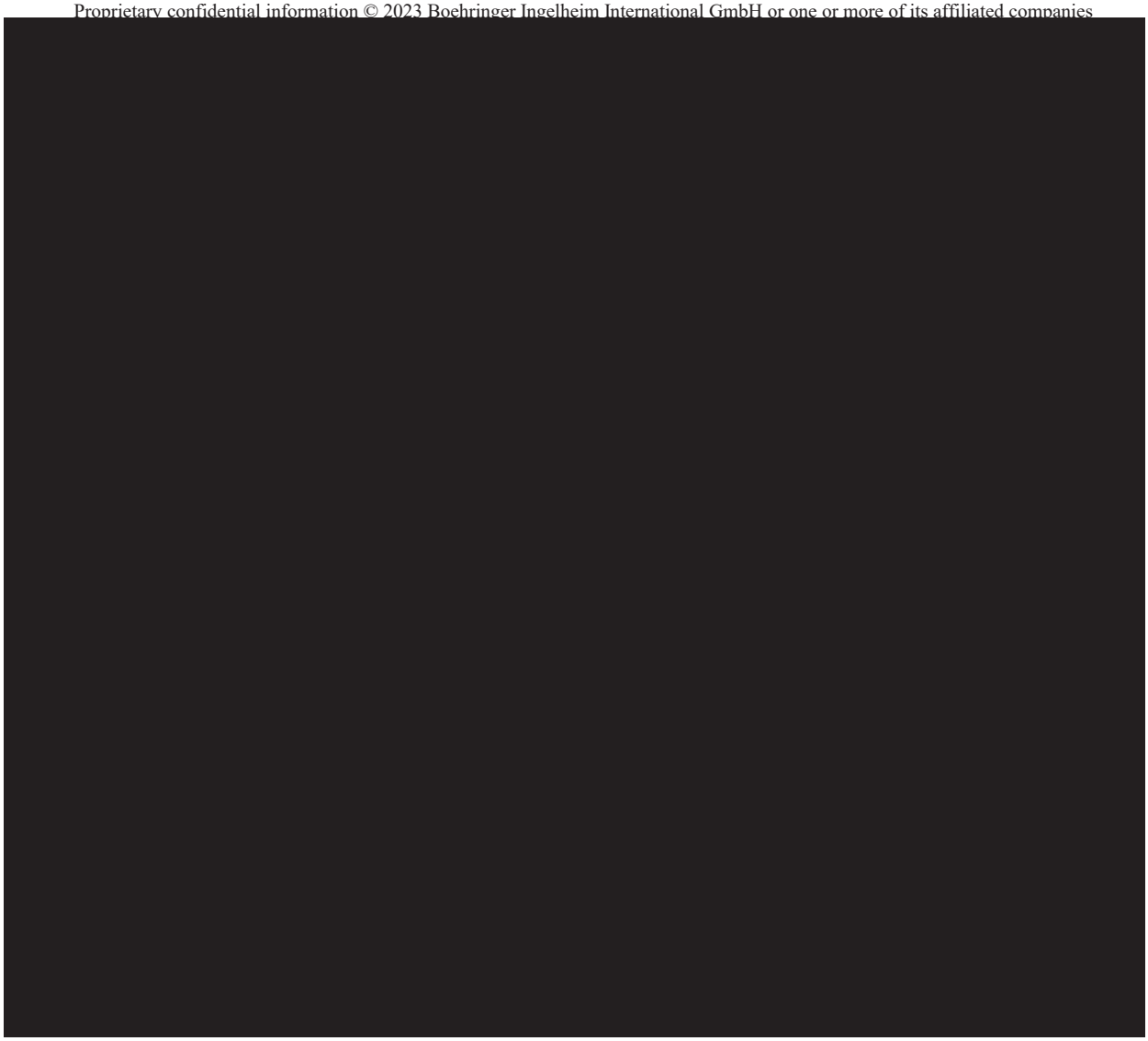
The secondary endpoints of the Phase Ia dose-escalation portion of the trial are:

- The following PK parameters of BI 754091 (if feasible) will be evaluated after the first and after multiple administrations of BI 754091:
  - 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
- Confirmed OR according to RECIST v1.1 as assessed by the Investigator
- Number of patients experiencing DLTs from the start of treatment until end of treatment (in all cycles) as assessed approximately every 3 weeks.

5.1.2.2 Secondary endpoints of the Phase Ib (dose expansion) portion of the trial

The secondary endpoints of the Phase Ib dose-expansion portion of the trial are:
- Progression-free survival (PFS) defined from date of start of BI 754091 to the date of disease progression or death, whichever is earlier, according to RECIST v1.1 as assessed by the Investigator
- Safety will continue to be assessed by the recording of AEs, SAEs (including DLTs), laboratory evaluations, vital signs, and ECGs as:
  - Percentage of subjects with AEs
  - Percentage of subject with SAEs
  - Percentage of subjects with clinical relevant abnormalities in vital signs, laboratory evaluations or ECG parameters (note that clinically relevant abnormalities are those which have to be reported by the investigator as AEs).

[redacted]



5.2 ASSESSMENT OF EFFICACY

5.2.1 Tumour assessments

The tumour response will be evaluated according to RECIST Version 1.1 (R09-0262) and iRECIST (R17-0923). 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 considered measurable at baseline unless the lesions occurred after irradiation. Tumour assessment will be performed at screening (as close as possible to the treatment start and no more than 28 days before the start of BI 754091), every 2 cycles during the first 6 months, and at the EOT visit (if not performed within the last 4 weeks). Following 6 months of treatment, tumour assessments can be done once every 3 cycles, and at the discretion of the Investigator.

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

Following PD, a patient may continue to receive treatment for a year if the Investigator, Medical Monitor, and sponsor agree that the patient is deriving clinical benefit.

Copies of scans are to be collected by the sponsor upon request 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.

5.3 ASSESSMENT OF SAFETY

The safety of BI 754091 will be assessed by a descriptive analysis of incidence and severity of AEs graded according to CTCAE (Version 4.03/5.0), the incidence of DLTs, laboratory data, and results of physical examination. Safety will be assessed in a descriptive way without confirmatory analysis.

Dose-limiting toxicities observed during the MTD evaluation period (first 3 weeks) will be considered for MTD determination. However, all DLTs observed in all treatment cycles will be considered for determining a RP2D. The BLRM model 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 SRC. The SRC will independently 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, PK and/or biomarker data will be taken into consideration for RPIID determination.

5.3.1 Physical examinations and ECOG performance status

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, and the evaluation of the ECOG performance score. Weight will be measured during screening and at each full physical examination (not during abbreviated physical examinations).

The ECOG score will be assessed at screening, on Day 1 of Cycles 1 and 2, on Day 1 of every other cycle beginning with Cycle 3 prior to trial medication intake, at the EOT visit, and at the 30-day safety follow-up visit.

5.3.2 Vital signs

Vital signs (blood pressure, body temperature, and pulse rate after 2 minutes 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.

5.3.3 Electrocardiogram

Local ECGs will be done throughout the trial. There will not be a centralised analysis. Single digitalized ECGs must be done at screening, Cycle 1 Day 1, Cycle 3 Day 1, Day 1 of every third cycle thereafter (Cycles 6, 9, 12, etc.), 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.

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. Detailed instructions for correct ECG recording are provided in the ISF. In case of drug-related ECG changes, additional ECG monitoring will be performed in the respective and later cycles of treatment, as deemed necessary by the Investigator.

The recordings will be checked for pathological results (to be recorded as AEs) by the Investigator.

5.3.4 Safety laboratory parameters

Blood (venous) samples will be collected at the times indicated in Flow Chart 1 and Flow Chart 2 and will be analysed by the sites' local safety laboratories. 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.

5.3.4.1 Haematology

Red blood cell count, haemoglobin, haematocrit, mean corpuscular volume, white blood cell count, and differential blood count will be expressed in absolute values, and platelets will be measured.

5.3.4.2 Biochemistry

The standard biochemistry panel will consist of glucose, sodium, potassium, chloride, calcium, phosphate, venous bicarbonate HCO_3, creatinine, AST, ALT, alkaline phosphatase, lactate dehydrogenase (LDH), bilirubin, total protein, albumin, urea nitrogen (or urea), and uric acid. In addition, cholesterol, triglycerides, c-peptide, and creatine phosphokinase will be done at baseline and when clinically indicated. In case of pathological creatine

phosphokinase, further evaluation (e.g., by troponin assays) must be performed and the findings documented.

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

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

5.3.4.3 Urinalysis

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

5.3.4.4 Pregnancy test

Beta human chorionic gonadotropin (β-HCG) pregnancy test in urine or serum will be performed for women of childbearing potential at screening, within 14 days prior to first trial treatment, on Day 1 of each cycle prior to administration of BI 754091, before the start of each repeated cycle, and at the EOT visit.

5.3.5 Other safety parameters

None

5.3.6 Assessment of adverse events

5.3.6.1 Definition of adverse event

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

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

5.3.6.2 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.

5.3.6.3 Definition of serious adverse events

An SAE is defined as any AE that:
- results in death,
- is life-threatening. This refers to an AE 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
- prolongation of existing hospitalisation,
- results in persistent or significant disability or incapacity, or
- is a congenital anomaly / birth defect, or
- is to be deemed serious for any other reason if it is an important medical event when based upon appropriate medical judgment 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.
- Any suspected transmission via a medicinal product of an infectious agent is also considered an SAE.

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

5.3.6.4 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 Section 5.3.6.8, subsections “AE Collection” and AE reporting to sponsor and timelines”.

In accordance with the EMA initiative on Important Medical Events, BI 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 given above. The latest list of ‘Always

Serious AEs' can be found in the electronic document system. These events should always be reported as SAEs as described above.

5.3.6.5 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. AESI need to be reported within the same timeframe that applies to SAEs and according to the information in Section 5.3.6.8.

For this trial, DLTs, infusion-related AEs, DILI events, hepatic injury and qualifying irAEs, as defined in Appendix 10.1, are AESIs (see Section 5.3.6.5.2 and Section 5.3.6.5.3, respectively).

5.3.6.5.1 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.

5.3.6.5.2 Immune-related adverse events (irAE)

Immune-related AEs are AEs associated with immunotherapy treatments that appear to be associated with the immune therapy's mechanism of action. These adverse reactions, which can be severe, may involve the gastrointestinal, skin, liver, endocrine, respiratory, renal, or other organ systems. All immune-related events are to be reported as AEs. Some irAEs also need to be reported as AESIs as defined 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.

5.3.6.5.3 Infusion-related reactions

In the event of an infusion-related reaction ≤ Grade 2, the infusion rate of BI 754091 may be decreased by 50% or interrupted until resolution of the event and re-initiated at 50% of the initial rate until completion of the infusion. In patients experiencing infusion-related reactions ≤ Grade 2, subsequent infusions may be administered at 50% of the initial rate.

If 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 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 recognize and treat anaphylaxis. The trial site must have immediate access to emergency resuscitation teams and equipment in addition to the ability to admit patients to an intensive care unit if necessary.

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

- 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.

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

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

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

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

Hepatic injury definition:
In patient with normal baseline hepatic function, hepatic injury is defined by the following alterations in hepatic laboratory parameters:

- An elevation of AST and/or ALT ≥3 times the ULN combined with an elevation of total bilirubin ≥2 times the ULN measured in the same blood draw sample. And/or
- Marked peak AST and/or ALT elevation ≥10 times the ULN.

Hy's Law cases have the following 3 components:

- The drug causes hepatocellular injury, generally shown by a higher incidence of 3-fold or greater elevations above the ULN of ALT or AST
- Among trial subjects showing such aminotransferase elevations, often with elevations much greater than 3 times ULN, one or more also show elevation of serum total bilirubin to >2 times ULN, without initial findings of cholestasis (elevated serum ALP)

- No other reason can be found to explain the combination of increased aminotransferase and total bilirubin, such as viral hepatitis A, B, or C; pre-existing or acute liver disease; or another drug capable of causing the observed injury.

5.3.6.6 Severity of adverse events

The severity of AEs should be classified and recorded in the eCRF according to the CTCAE Version 4.03/5.0.

5.3.6.7 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 was evident.
- There is 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) exist.
- The event is typically drug-related and infrequent in the general population not exposed to drugs (e.g., Stevens-Johnson syndrome).
- There was an indication of dose-response (i.e., greater effect size if the dose is increased, smaller effect size if dose is 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).
- The event continued despite the withdrawal of the medication, taking into account the pharmacological properties of the compound (e.g., after 5 half-lives).
  Of note, this criterion may not be applicable to events whose time course is prolonged despite removing the original trigger.
- There may be additional arguments amongst those stated before, like alternative explanation (e.g., situations where other drugs or underlying diseases appear to provide a more likely explanation for the observed event than the drug concerned).

- The event disappeared even though the trial drug treatment continued or remained unchanged.

5.3.6.8 Adverse event collection and reporting

5.3.6.8.1 Adverse event collection

The Investigator shall maintain and keep detailed records of all AEs in their patient files.

A schema of the safety follow-up period is presented in Figure 5.3.6.8.1: 1. The following must be collected and documented on the appropriate eCRF by the Investigator:

- From signing the ICF onwards until the end of treatment (including the Residual Effect Period [REP]; a period of 30 days after the last dose of trial medication):
  -all AEs (non-serious and serious) and all AESIs.
- After the EOT (including the REP) 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 only report relevant SAEs and relevant AESIs of which the Investigator may become aware of.

The rules for Adverse Event Reporting exemptions still apply.

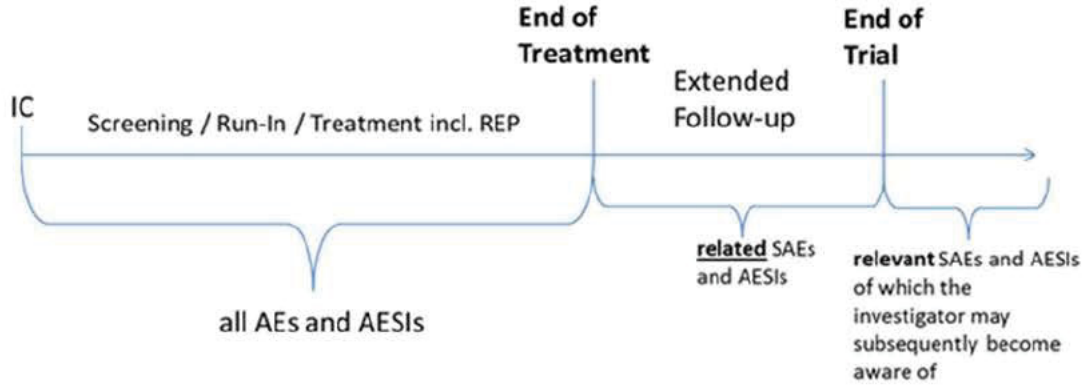


Figure 5.3.6.8.1: 1 Safety follow-up schema

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

Adverse event reporting to the sponsor and timelines

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

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

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

The same timeline applies if follow-up information becomes available. On specific occasions, the Investigator could inform the [redacted] upfront via telephone by calling the [redacted] SAE reporting phone number ([redacted]). 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 on the BI SAE Report form. The Investigator should determine the causal relationship to the trial medication.

The following should also be recorded as (S)AEs in the eCRF and SAE form (if applicable):
- Worsening of pre-existing conditions
- Changes in vital signs, ECGs, physical examinations, and laboratory test results, if they are judged clinically relevant by the Investigator.

If such abnormalities already pre-exist prior trial inclusion they will be considered as baseline conditions.

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

5.3.6.9 Pregnancy

In rare cases pregnancy may occur in a clinical trial. Once a patient has been enrolled into this clinical trial and has taken trial medication, the Investigator must report immediately (within 24 hours) a potential drug exposure during pregnancy to the [redacted] The Pregnancy Monitoring Form for Clinical Trials (Part A) should be used.

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

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

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

5.3.6.10 Exemptions to SAE Reporting

Disease progression is a trial endpoint for analysis of efficacy and as such is exempted from reporting as an AE or an 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(s) and the progression of the underlying malignancy, the event must be reported as an SAE on the SAE Form and on the eCRF.

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

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

5.4 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

5.4.1 Assessment of pharmacokinetics

If data allow, the PK parameters of BI 754091 mentioned as secondary and further endpoints (see Section 5.1.2 and Section 5.1.3, respectively) will be evaluated using non-compartmental analysis methods according to BI internal SOP.

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5.4.2 Methods of sample collection for pharmacokinetic analyses

For quantification of analyte plasma concentrations, samples will be drawn at the time points listed in Flow Chart 1 and Flow Chart 2 under PK sampling and specified in PK time schedules in Appendix 10.4 (Phase Ia dose escalation: Table 10.4.1: 1 and Table 10.4.1: 2, and all cohorts in Phase Ib dose expansion: Table 10.4.2: 1).

If collected from an arm, it is essential to collect blood from the arm that is opposite to the arm used for infusion in order to avoid artificially high or low drug concentration determinations. Further 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 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.

[redacted]

5.4.4 Pharmacokinetic/pharmacodynamic (PK/PDc) relationship

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

If data suggest a PK/PDc relationship of special parameters [redacted] an analysis may be performed. Further assessments might be done, if feasible.

[redacted], but if BI 754091 behaves similarly to pembrolizumab, a maximum RO of 80% will be measured already at the starting dose of 80 mg (1 mg/kg for an 80-kg person) (R16-2024). Most other potential PDc markers (e.g., CD8 infiltration) occur at the tumour site and are dependent on efficacy, and are therefore not suited to establish a PK/PDc relationship.

Data may also 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.

5.5 [redacted]

[redacted]

[redacted]

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.

5.5.1 Methods of sample collection

Pre- and on-treatment tumour biopsy collections for biomarker and PDc analyses will be mandatory from all patients in the Phase Ib dose-expansion portion of the trial. In addition, biopsies should be taken according to the flowchart and Section 5.5.2.3. Patients in the dose-escalation cohorts may consent to optional paired biopsies. 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.

[redacted]

[redacted]

5.5.3 Biobanking

Any leftover samples (including tissue, plasma, serum, DNA, RNA, etc.) from the trial may be stored at the sponsor or an external biobanking facility on behalf of the sponsor for up to 30 years. These samples may be used to further address scientific questions that evolve during and after the trial.
Note: Participation in the long-term storage and use of leftover samples is voluntary and not a prerequisite for participation in the trial. The biological samples will be stored after the appropriate separate boxes are checked on the ICF by consenting patients in accordance with local ethical and regulatory requirements.

5.6 OTHER ASSESSMENTS

[redacted]

Details on sample collection, characteristics, processing, handling, and shipment are provided in the Laboratory Manual. 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 test article in order to assess the performance of the ADA assay. Such use of pre-dose samples will not compromise the collection of valid ADA data for those pre-dose samples.

5.7 APPROPRIATENESS OF MEASUREMENTS

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

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

The trial consists of 2 parts. The first part is a dose-escalation phase (Phase Ia) to determine the MTD and the recommended dose for the Phase Ib dose expansion. The schedule shown to have a more favourable safety, PK, and biomarker profile will be chosen to be further investigated in the expansion phase. The second part (Phase Ib) is an expansion phase to further evaluate safety, efficacy and PK profile of BI 754091, as well as biomarker values as a result of treatment.

Patients meeting the inclusion and exclusion criteria for the part they are participating in and who have given their written ICF, are eligible for participation in the trial. Patients will visit the clinical site at the time points specified in Flow Chart 1 (dose escalation) and Flow Chart 2 (dose expansion). 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. For the biopsies and PK sampling procedures of Cycle 1, the patient must however still be under treatment and not in a treatment break period in order to perform the evaluations planned for the missed 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, an EOT visit must occur as soon as possible (preferably within 7 days). After the EOT visit, the patient must undergo a follow-up evaluation 30 (+2) days after the last BI 754091 administration.

The trial will be conducted according to the principles of Good Clinical Practice (GCP).

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

The procedures required at each trial visit in both portions of the trial are presented in Flow Chart 1 (dose escalation) and Flow Chart 2 (dose expansion) 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 biomarker and immunogenicity assessments
- Tumour biopsy biomarker assessments
- Tumour assessments (based on CT/PET and/or 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 BI 754091.

6.2.1 Screening period

The screening period may run over a period of 28 days (period within the trial and before the first intake of BI 754091). For the detailed description of the tests to be performed during this period and their timing, please refer to Flow Chart 1 (dose escalation) and Flow Chart 2 (dose expansion).

6.2.1.1 Screening for tumour mutational burden (TMB) and MSI-high cohort

For Cohort 5, the TMB, as well as the microsatellite stability (MS) status have to be assessed. Patients that have high TMB (defined as ≥10 mutations/Mb) and are MS stable (MSS) will be included. Any validated assay may be used to determine the MS status and TMB.

If polymerase epsilon (ε) catalytic subunit (POLE) mutation status is known for any patient in the TMB-high cohort, this information should be collected.

6.2.1.2 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.

6.2.1.3 Medical history

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, 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 line 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.

Exclusion Criterion #13 (see Section 3.3.3) does not apply to the patients with cervical/anal and vulvovaginal cancer enrolling into Cohorts 6 and 7. However, virology testing should still be done and the status of HIV and hepatitis B or C virus should be collected on the eCRF.

6.2.1.4 Concomitant therapies

Relevant concomitant diagnoses and/or therapies present at trial entry and/or during screening and relevant to the patient's safety during the trial as judged by the Investigator will be recorded in the eCRF (see Section 4.2.2 for details on concomitant medications). Post-trial therapy for advanced or metastatic disease will also be documented.

6.2.2 Treatment period

Please refer to Flow Chart 1 (dose escalation) and Flow Chart 2 (dose expansion) for a detailed presentation of each visit during the treatment period.

6.2.3 Follow-up period and trial completion

6.2.3.1 End-of-treatment visit

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

The assessments of the EOT visit will then be performed instead of at the next planned visit. If the patient finishes active treatment without having PD, tumour assessment/imaging must be performed at the time of treatment discontinuation, unless it has been done within the past 4 weeks.
For patients still on treatment with ezabenlimab at the time point of this protocol amendment, the investigators are asked to prepare for discontinuation of patients from the current investigational treatment with ezabenlimab and to switch them to alternative available treatment options outside of the current protocol no later than by the final availability of ezabenlimab in August 2023 the latest. After this date treatment with the ezabenlimab will no longer be available.
For these patients only EOT visit will be performed. 30-day post-treatment safety visit as well as Progression-free survival visits are not applicable.

6.2.3.2 30-day post-treatment safety visit

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

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

6.2.3.3 Progression-free survival visits

Additional follow-up visits after the 30-day safety follow-up visit will only be performed for patients who did not progress on treatment. These will be performed once every 12 weeks at least (by telephone) until PD, introduction of a new anti-cancer treatment, death, loss to follow-up, or end of the whole trial as specified in Section 3.3.4.2.

6.2.3.4 Overall survival visits

Additional follow-up visits after the 30-day safety follow-up visit will be performed for patients that enrolled in Protocol Version 4.0 and beyond. These will be performed once every 12 weeks at least (by telephone) on the same schedule as PFS survival visits until death, loss to follow-up, or end of the whole trial as specified in Section 3.3.4.2. 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.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN - MODEL

This is a Phase I, open-label, dose-escalating trial to determine the MTD and the RP2D for BI 754091 in patients with solid tumours. In addition, the safety and PK profiles, biomarkers, and efficacy of BI 754091 will also be assessed.

7.1.1 Statistical design – Phase Ia (dose escalation)

The objective of the Phase Ia portion of the trial is to determine the MTD and the RP2D. The MTD is defined as the highest dose with less than 25% risk of the true DLT rate being above 0.33 (EWOC criterion) under the condition of at least one DLT observed in this trial. The Phase Ia dose-finding will be guided by a BLRM with overdose control (R13-4803).

The model is given as follows:

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

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

p(d) represents the probability of having a DLT in the first cycle at dose d, d* = 800 mg is the reference dose, allowing for the interpretation of α as the odds of a DLT at dose d*, and θ = (log(α), log(β)) with α, β > 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:

Under dosing:	[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:
- At least one DLT observed in the trial, and either
- The posterior probability of the true DLT rate in the target interval [0.16 – 0.33) of the MTD is above 0.50, OR
- At least 15 patients have been treated in the trial, of which at least 6 at the MTD.

The SRC may recommend stopping the dose-finding phase after the criteria for MTD are fulfilled. If no DLTs are observed during the Phase Ia dose-escalation phase, the SRC may conclude that the MTD was not found and decide to include an additional number of patients at a dose of which the efficacy is considered sufficient as the dose recommended for further testing. This dose level may be equal or below the highest tested dose level.

Since a Bayesian approach is applied, a prior distribution $\pi(\theta)$ for the unknown parameter vector θ needs to be specified. This prior distribution will be specified as a mixture of two multivariate normal distributions, i.e.

$$\pi(\theta) = \varphi_1\pi_1(\theta) + \varphi_2\pi_2(\theta)$$

with

φ_i, i = 1, 2 the prior mixture weights ($\varphi_1 + \varphi_2 = 1$)

and

$$\pi_i(\theta) = MVN(\mu_i, \Sigma_i)$$

the multivariate normal distribution of the i-th component with mean vector μ_i and covariance matrix Σ_i, where

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

Mixtures of prior distributions have the advantage of allowing for specification of different logistic dose-toxicity curves, therefore making the prior more robust.

7.1.1.1 Prior derivation

For the current trial, limited information about PD-1 from human data was available (Phase I Study of Pembrolizumab [MK-3475; Anti–PD-1 Monoclonal Antibody] in Patients with Advanced Solid Tumours [R16-2024]). PD-1 is considered as a well-tolerated treatment with low DLT rate. Therefore, the 2 mixture components were established as follows:

1. A weakly informative prior was derived to reflect a priori assumption that the median DLT rate at the starting dose of 80 mg would equal 0.001%, and the median DLT rate at 3200 mg would equal 30%. This yields $\mu_1 = (-4.855, 1.062)$. The standard deviations were set such that large uncertainty about the parameter means is reflected, and the correlation was set to 0, thus yielding $\sigma_{1,11} = 2$, $\sigma_{1,22} = 1$ and $\rho_1 = 0$, respectively. The prior weight φ_1 for the first component was chosen as 0.9.

2. A high-toxicity weakly informative prior was derived to reflect the case that the compound would be much more toxic than expected. For this prior component, it was assumed that the median DLT rate at 80 mg would equal 5%, and the median DLT at 3200 mg would equal 70%. These assumptions yield $\mu_2 = (-0.578, 0.028)$. The standard deviations and correlations were set identical to the weakly informative prior, i.e. $\sigma_{2,11} = 2$, $\sigma_{2,22} = 1$ and $\rho_2 = 0$, respectively. The prior weight φ_2 for the second component was chosen as 0.1.

A summary of the prior distribution is provided in Table 7.1.1.1: 1. Additionally, the prior probabilities of DLT at different doses, as well as the corresponding probability of under-, targeted and overdosing, are shown in Table 7.1.1.1: 2. Graphically, the prior medians with accompanying 95% credible intervals are shown in Figure 7.1.1.1: 1. As can be seen from both the table and the figure, the prior medians of the DLT probabilities are all quite low for the selected doses in the range of 80 mg to 800 mg which is in-line with the prior medians derived from the weakly informative prior, and the uncertainty around the medians is large, showing the low amount of information this prior provides. This is also supported by the prior sample size, i.e., the information contained in the prior. This is approximately equal to 1.35 patients. A detailed evaluation of the model using hypothetical data scenarios and operating characteristics is provided in the statistical appendix (see Appendix 10.5).

Table 7.1.1.1: 1 Summary of prior distribution

Prior Component	Mixture Weight	Mean vector	Std Dev vector	Correlation
1: Weakly Informative Prior	**0.9**	**(-4.855, 1.062)**	**(2.000, 1.000)**	**0.000**
2: High Tox	**0.1**	**(-0.578, 0.028)**	**(2.000, 1.000)**	**0.000**

Table 7.1.1.1: 2 Prior probabilities of DLTs at selected doses

Dose	Probability of true DLT rate in					Quantiles		
Mg	[0–0.16)	[0.16–0.33)	[0.33–1]	Mean	Std Dev	2.5%	50%	97.5%
80	0.970	0.012	0.019	0.018	0.090	0	0	0.218
160	0.961	0.015	0.024	0.023	0.103	0	0	0.319
240	0.953	0.017	0.029	0.028	0.113	0	0	0.398
320	0.946	0.020	0.034	0.033	0.122	0	0.001	0.456
480	0.930	0.026	0.044	0.043	0.139	0	0.002	0.56
640	0.912	0.034	0.054	0.055	0.154	0	0.004	0.645
800	0.881	0.049	0.070	0.075	0.172	0	0.01	0.727

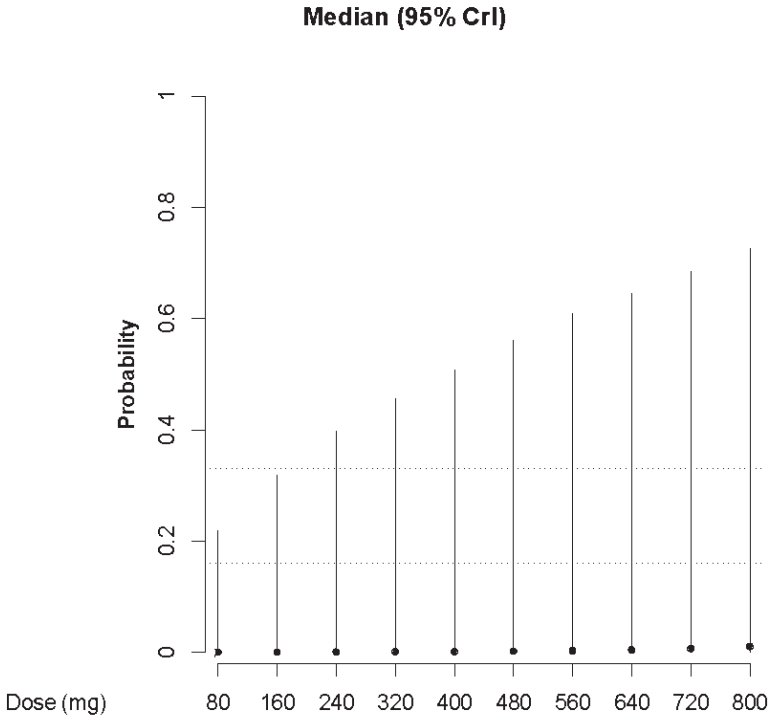

Figure 7.1.1.1: 1 Prior medians and 95% credible intervals

7.1.1.2 Statistical model assessment

The model was assessed using 2 different metrics:
1. Hypothetical data scenarios: for various potential data constellations as they could occur in the actual trial, the maximal doses allowed in the next cohort by the model are investigated. Data scenarios thus provide a way to assess the 'on-study' behaviour of the model.
2. Simulated operating characteristics: these illustrate for different assumed true dose-toxicity relationships, how often a correct dose would be declared as MTD by the model. They are a way to assess the 'long-run' behaviour of the model.

In summary, the model showed very good behaviour as assessed by these metrics. More details can be found in Appendix 10.5. The simulations for scenarios and operating characteristics were produced using RStudio version 0.98.507.

7.1.2 Statistical design – Phase Ib (dose expansion)

The Phase Ib (dose-expansion) portion of the trial will recruit approximately 130 patients with selected locally advanced or metastatic cancers at the dose and schedule recommended by the SRC.

The analyses of the safety and efficacy for this portion of the trial will be descriptive and exploratory in nature. Additional analysis may be applied to evaluate the robustness of the efficacy results. More details will be specified in the TSAP.

7.2 NULL AND ALTERNATIVE HYPOTHESES

No formal hypothesis testing is planned in this trial.

7.3 PLANNED ANALYSES

For the determination of the MTD, only MTD-evaluable patients will be considered. For other analysis of efficacy and safety 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 Trial Statistical Analysis Plan (TSAP).

No per protocol set will be used in the analysis. However, important protocol violations will be summarised with details specified in the TSAP.

7.3.1 Primary endpoint analyses

In order to identify the MTD of the trial, the number of patients with DLTs at each dose level during the Phase Ia MTD evaluation period (first three weeks) must be presented. Patients who discontinue during the first treatment course for reasons other than a DLT will be excluded from the determination of the MTD.

In addition, the number of patients with DLTs that occurred during the entire treatment period, including Phase Ia and Phase Ib, will be summarised at each dose level. The BLRM will be rerun to re-evaluate the MTD and RP2D together with all relevant data collected during Phase Ib.

For the primary efficacy endpoint of Phase Ib, objective response rate (ORR) will be summarised and presented with 95% two-sided confidence intervals using the Clopper-Pearson method.

7.3.2 Secondary endpoint analyses

For PFS, the Kaplan-Meier curve and estimates will be displayed with 95% confidence intervals, using Greenwood's variance formula. The detailed censoring rules are specified in the TSAP.

Details on statistical inference for PK parameters, e.g. dose proportionality using C_{max} and AUC etc., and all other secondary endpoints analysis will be specified in the TSAP.

[redacted]

7.3.4 Safety analyses

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary. Standard BI summary tables and listings will be produced. Statistical analysis and reporting of AEs will concentrate on treatment-emergent AEs. All AEs with an onset between start of treatment and end of the REP, a period of 30 days after the last dose of trial medication, will be considered 'treatment-emergent' and assigned to the treatment period for evaluation. 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 AEs will be tabulated by system organ class and preferred term after coding according to the current version of MedDRA.

Laboratory data will be analysed 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 highlighted in the listings.

Treatment groups will be compared descriptively with regard to distribution parameters as well as 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

Pharmacokinetic parameters as described in Section 5.4.1 will be calculated by means of non-compartmental analysis. The derivation of PK parameters is described in BI internal SOP.

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 dictates that the sponsor and the SRC perform regular safety evaluations. These evaluations will be unblinded to dose.

If considered necessary, as soon as the MTD is determined, an evaluation of the 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, an exploratory analysis of PK will be done after patients in Cohort 1 complete Cycle 1 and once patients in Cohort 2 complete Cycle 1. Further exploratory analyses of PK might be performed if considered reasonable.
Exploratory PK analyses will be based on planned sampling times, if information on actual times should not be available. 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 medically justified, further or fewer exploratory PK analyses may be performed.

Interim efficacy analyses are planned for selected groups of patients (defined in Section 3.1) in the Phase Ib portion of the trial. Because of the expected challenge in recruiting these patients, the two-stage design is planned to stop further recruitment of the specific patient group if the defined efficacy boundary (see Table 7.4: 1) is not met at the first stage. Interim efficacy analyses were not deemed necessary for the TMB high cohort 5 as recent literature already demonstrates an association between high TMB and better response rates for patients taking immune checkpoint inhibitors (R18-1492).

The interim analyses for Cohort 6 will be conducted when:

- 10 patients with squamous cervical and/or anal cancer have been treated, and the 10th patient has been on treatment for ~3 months.
- 10 patients with squamous skin tumours have been treated, and the 10th patient has been on treatment for ~3 months.

The interim analysis for Cohort 7 will be conducted when 20 patients with vaginal or VSCC have been treated, and the 20th patient has been on treatment for ~3 months.

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.

- Literature on preliminary data of nivolumab and pembrolizumab (R17-3902; R17-3903; R17-3822) showed ORR ranges from 13% to 24% in patients with squamous cervical and anal tumours. Therefore, an underlying ORR of 25% is assumed. The probability of observing zero responders out of 10 and stopping at interim is 6%, and the probability of observing ≥20% ORR at final analysis is 77%. If the underlying ORR is 5%, the probability of stopping early is 61%, and the false positive probability of observing ≥20% ORR at final analysis is almost 0.
- It was shown in Chalmers ZR et al, 2017 (R17-3824) that the population with squamous skin cancer had very high proportion of patients with high TMB (~70%). Therefore, the clinical benefit is expected to be similar to patients with high TMB (R17-3768). Assume the underlying ORR is 50%, the probability of observing <3 responders out of 10 and stopping at interim is 5%, and the probability of observing ≥40% ORR at final analysis is 87%. If the underlying ORR is 20%, the probability of stopping early is 67%, and the false positive probability of observing ≥40% ORR at final analysis is 1%.
- Literature on preliminary data from older chemotherapy/targeted agent trials (R18-2645; R18-2646; R18-2647) and early phase immunotherapy trials (R18-2650; R18-2651) showed ORR ranges from 13% to 29% in patients with recurrent, inoperable VSCC. Therefore, an underlying ORR of 25% is assumed. The probability of observing 0 or 1 responder out of 20 and stopping at interim is 2%, and the probability of observing ≥20% ORR at final analysis is 82%. If the underlying ORR is 5%, the probability of stopping early is 74%, and the false positive probability of observing ≥20% ORR at final analysis is almost 0.

Table 7.4: 1 Early stopping criterion and probabilities for the two-stage approach – selected patient groups

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
Squamous cervical or anal tumour patients						
5%	30	10	<10% (< 1 out of 10)	61%	>=20% (>= 6 out of 30)	0%
10%	30	10	<10% (< 1 out of 10)	35%	>=20% (>= 6 out of 30)	7%
15%	30	10	<10% (< 1 out of 10)	19%	>=20% (>= 6 out of 30)	29%
20%	30	10	<10% (< 1 out of 10)	11%	>=20% (>= 6 out of 30)	55%
25%	30	10	<10% (< 1 out of 10)	6%	>=20% (>= 6 out of 30)	77%
30%	30	10	<10% (< 1 out of 10)	3%	>=20% (>= 6 out of 30)	91%
Squamous skin cancer patients						
20%	30	10	<30% (< 3 out of 10)	67%	>=40% (>= 12 out of 30)	1%
25%	30	10	<30% (< 3 out of 10)	52%	>=40% (>= 12 out of 30)	5%
30%	30	10	<30% (< 3 out of 10)	39%	>=40% (>= 12 out of 30)	14%
35%	30	10	<30% (< 3 out of 10)	26%	>=40% (>= 12 out of 30)	33%
40%	30	10	<30% (< 3 out of 10)	17%	>=40% (>= 12 out of 30)	54%
45%	30	10	<30% (< 3 out of 10)	10%	>=40% (>= 12 out of 30)	73%
50%	30	10	<30% (< 3 out of 10)	5%	>=40% (>= 12 out of 30)	87%
Vaginal or VSCC patients						
5%	40	20	<10% (< 2 out of 20)	74%	>=20% (>= 8 out of 40)	0%
10%	40	20	<10% (< 2 out of 20)	39%	>=20% (>= 8 out of 40)	4%
15%	40	20	<10% (< 2 out of 20)	18%	>=20% (>= 8 out of 40)	25%

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
20%	40	20	<10% (< 2 out of 20)	7%	>=20% (>= 8 out of 40)	56%
25%	40	20	<10% (< 2 out of 20)	2%	>=20% (>= 8 out of 40)	82%
30%	40	20	<10% (< 2 out of 20)	1%	>=20% (>= 8 out of 40)	94%

7.5 HANDLING OF MISSING DATA

No imputation will be performed on missing efficacy data. 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.

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 Phase Ia

No formal statistical power calculations to determine sample size were performed. Approximately 15 patients are expected; fewer or more patients might be needed based on the recommendation of the SRC and the actual number of dose cohorts tested.

7.7.2 Determination of sample size for Phase Ib

For the cohort of 7 solid tumours (Cohort 4), no formal statistical sample size calculations were performed. Some efficacy signals are expected to be observed from ~30 treated patients.

Several papers demonstrated the association between high TMB and better response rates, progression-free survival, and overall clinical benefit. In Hellmann et al., 2018 (R18-1492) response rates were 45.3% (63/139) in patients with ≥10 mutations/mega base. Therefore, in the planning of the TMB-high-tumour cohort (Cohort 5), it is deemed clinically meaningful if BI 754091 will have an underlying ORR of 35%. With 30 patients, an ORR of 30% or more would be observed with a probability of 78% assuming a true response rate of 35%. The probability of observing a false positive signal, e.g., to observe at least an ORR of 30% if the underlying true ORR is 15%, is around 3%. Table 7.7.2: 1 summarises the probability of observing certain ORRs based on different assumptions of the underlying ORR.

Table 7.7.2: 1 Probabilities of observing certain objective response rates

Assumed underlying ORR	Sample size	Probability to observe at least		
		ORR >= 25% (>=8 responders)	ORR >= 30% (>=9 responders)	ORR >= 35% (>= 11 responders)
15%	30	7%	3%	0%
20%	30	24%	13%	3%
25%	30	49%	33%	11%
30%	30	72%	57%	27%
35%	30	88%	78%	49%
40%	30	96%	91%	71%
45%	30	99%	97%	86%

For the selected squamous tumours cohort (Cohort 6), probability calculations are provided in Table 7.4: 1 using the two-stage approach. Depending on the Stage 1 result for the squamous cohort, sample size may vary between 20 and 60 patients.

For the vaginal or VSCC cohort (Cohort 7), probability calculations are provided in Table 7.4: 1 using the two-stage approach. If the stage 1 result is positive (i.e., at least 2 responders out of 20 patients), sample size for this cohort will be increased to 40 patients; otherwise, recruitment will be stopped in case of negative interim analysis.

8. INFORMED CONSENT, TRIAL RECORDS, DATA PROTECTION, PUBLICATION POLICY

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 GCP, relevant BI SOPs, and other relevant regulations.

Standard medical care (prophylactic, diagnostic and therapeutic procedures) remains in 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 subjects against any immediate hazard, and also of any serious breaches of the protocol or of ICH GCP.

The BI 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.

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 IRB and competent authority 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 signed ICF 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 ICF and any additional patient-information form retained by the Investigator as part of the trial records. A signed copy of the ICF 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 ICF information. 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 ICF after confirming that the patient understands the contents. The Investigator must sign (or place a seal on) and date the ICF. If a trial collaborator has given a supplementary explanation, the trial collaborator also signs (or places a seal on) and dates the ICF.

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 the IRB or regulatory authorities. The quality assurance auditor will have access to all medical records, the Investigator's trial-related files and correspondence, and the ICF documentation of this clinical trial.

8.3 RECORDS

Electronic CRFs for individual patients will be provided by [redacted]

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 subject. 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 eCRF must be consistent with the source data or the discrepancies must be explained.
The current medical history of the subject 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 3 documented attempts to retrieve previous medical records. If this fails a verbal history from the patient, documented in the medical records, will be acceptable.

Before providing any copy of patients' source documents to the sponsor, 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 to ensure patient confidentiality.

Copies of tumour assessments scans may be collected by the sponsor upon request. This could include CT/PET scans of the chest and abdomen and/or imaging of any other known or suspected sites of disease (e.g., pelvis, brain) using an appropriate method (CT/PET scan or MRI).

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 eCRF, 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 AEs (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 properly 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 makes the patient ineligible 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

[redacted] will monitor the conduct of the trial by regular on-site monitoring visits and in-house data quality reviews. The frequency of on-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 on-site trial-related monitoring, audits, IRB review and regulatory inspections. Direct access must be provided to the eCRF 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 monitor, auditor, and regulatory inspector (e.g., FDA). The monitor and auditor may review all CRFs and ICFs. 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 ICH GCP.

8.3.3 Storage period of records

Trial sites:
The trial sites must retain the source and essential documents (including ISF) according to the national or local requirements (whichever are is longer) valid at the time of the end of the trial.

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

[redacted] will retain trial documents according to contractual agreements with the sponsor.

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 5.3.6.10, 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 World Health Organization 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, the IRB, 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 GCP as outlined in 'Note For Guidance On Good Clinical Practice' (CPMP/ICH/13 5/95)
- 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 BI 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 ICF is available.

8.6 TRIAL MILESTONES

The **start of the trial** is defined as the date of the enrolment of the first patient in the trial. **The end of the trial** is defined as the date of the last visit of the last patient in the 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 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.

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

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

Immune-related adverse events of special interest
Renal (reported as an AESI if ≥ Grade 2)
• Nephritis • Nephritis autoimmune • Renal failure • Renal failure acute • Creatinine elevations (report as an irAE if ≥Grade 3 or any grade resulting in dose modification or use of systemic steroids to treat the AE)
Skin (reported as an AESI for any grade)
• Dermatitis exfoliative • Erythema multiforme • Stevens-Johnson syndrome • Toxic epidermal necrolysis
Skin (reported as an AESI if ≥ Grade 3)
• Pruritus • Rash • Rash generalized • Rash maculopapular • Any rash considered clinically significant in the physician's judgment
Other (reported as an AESI 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 event toxicities associated with anti-PD-1 mAbs are presented below. BI 754091 should be permanently discontinued for Grade 3-4 pneumonitis, Grade 3-4 adrenal insufficiency, Grade 4 diabetes mellitus, any grade encephalitis, Grade 4 hypophysitis, Grade 4 rash, Grade 3-4 or recurrent colitis of any grade, any recurrent Grade 3-4 AE, transaminase >5 times ULN or total bilirubin >3 times ULN, 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 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 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 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 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 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 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 liothyroinine, 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 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 should be permanently discontinued for any recurrent Grade 3-4 AE, transaminase >5 times ULN or total bilirubin >3 times ULN, inability to taper steroids to 10 mg or less prednisone or equivalent within 12 weeks, or persistent Grade 2-3 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 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 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 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 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 SCHEDULES FOR PHARMACOKINETIC, BIOMARKER, AND IMMUNOGENICITY BLOOD SAMPLING

10.4.1 Schedules for PK, biomarker, and immunogenicity blood sampling – Phase Ia (dose escalation) cohorts

Table 10.4.1: 1 Time schedule for PK, biomarker [redacted] blood sampling during Cycles 1, 2, and 4 - Phase Ia dose-escalation cohorts

Treatment Cycles	Day	Time Point [hh:min]	CRF Time	Event	PK	[redacted]	[redacted]
1, 2, 4	1	Just before start of infusion	-0:05	Blood sampling	X	X	X
		0:00	0:00	Start of BI 754091 infusion	---		
		Sampling during infusion	0:30	Blood sampling	X		
		Immediately before end of infusion*	1:00	Blood sampling	X		
		1.5 hours post SOI	1:30	Blood sampling	X		
		2 hours post SOI	2:00	Blood sampling	X		
		4 hours post SOI	4:00	Blood sampling	X		
		7 hours post SOI	7:00	Blood sampling	X		
	2	24 hours post SOI	24:00	Blood sampling	X		X
	4	72 hours post SOI	72:00	Blood sampling	X		
	8	168 hours post SOI	168:00	Blood sampling	X		X
	15	336 hours post SOI	336:00	Blood sampling	X		
EOT		Within 7 days of treatment discontinuation		Blood sampling	X	X	
30-Day FU		30 days after last drug administration		Blood sampling	X	X	X

ADA = anti-drug antibodies; BI = Boehringer Ingelheim; CRF = Case Report Form; EOT = end of treatment; FU = follow up; PK = pharmacokinetics; [redacted]
*In the event that infusion duration is >15 minutes longer than planned, the subsequent time points for PK blood collection on the day of drug infusion should be adjusted accordingly.

Table 10.4.1: 2 Time schedule for PK, biomarker [redacted] blood sampling during Cycles 3, 5 through 12, 14, 17, EOT (end-of-treatment visit) and 30-day FU (follow-up visit) - Phase Ia dose-escalation cohorts

Treatment Cycles	Day	Time Point [hh:min]	CRF Time	Event	PK	[redacted]	[redacted]
3, 5 to 12, 14, and 17	1	Just before start of infusion	-0:05	Blood sampling	X	X	X
		0:00	0:00	Start of BI 754091 infusion	---		
		Immediately before end of infusion	1:00	Blood sampling	X		
EOT				Blood sampling	X	X	
30-day FU				Blood sampling	X	X	X

ADA = anti-drug antibodies; BI = Boehringer Ingelheim; CRF = Case Report Form; EOT = end of treatment; FU = follow up; PK = pharmacokinetics; [redacted]; only done during dose escalation, if feasible)

10.4.2 Schedules for PK, biomarker, and immunogenicity blood sampling – Phase Ib (dose expansion) - All Cohorts

Table 10.4.2: 1 Time schedule for PK, biomarkers [redacted] blood sampling in all Phase Ib dose-expansion cohorts

Treatment Cycles	Day	Time Point [hh:min]	CRF Time	Event	PK**	[redacted]	Cytokines*	[redacted]*
1, 4, 8	1	Just before start of infusion	-0:05	Blood sampling	X	X	X (C1)	X (C1)
		0:00	0:00	Start of BI 754091 infusion	---			
		Shortly after end of infusion	1:00	Blood sampling	X			
	2	24 hours post SOI	24:00	Blood sampling			X (C1)	
	8	168 hours post SOI	168:00	Blood sampling	X		X (C1)	X (C1)
	15	336 hours post SOI	336:00				X (C1)	X (C1)
2, 3, 5-7, 9	1	Just before start of infusion	-0:05	Blood sampling	X	X	X (C2)	X (C2)
		0:00	0:00	Start of BI 754091 infusion	---			
Thereafter every 3rd cycle (12, 15, 18, etc)	1	Just before start of infusion	-0:05	Blood sampling	X	X		
		0:00	0:00	Start of BI 754091 infusion	---			
EOT				Blood sampling	X[1]	X[1]	X[1]	X[1]
30-day FU				Blood sampling	X[1]	X[1]		

ADA = anti-drug antibodies; BI = Boehringer Ingelheim; CRF = Case Report Form; EOT = end of treatment; FU = follow up; [redacted]; PK = pharmacokinetics

* [redacted] for flow analysis are only collected during the dose expansion phase on Cycle 1 Day 1 (pre-dose), Day 2 (cytokines only), Day 8, Day 15, Cycle 2 Day 1 (pre-dose), and end of treatment

**The following windows of time are allowed for PK sampling:
Predose (PTM -0:05): within 1 hour before next drug infusion
Shortly after end of infusion (PTM 1:00): within 5 min after the end of infusion
24 through 336 hours post SOI (PTM 24:00 to 336:00): ±1 hour.
Note: Time windows have been specified for procedural reasons; deviations do not automatically lead to exclusion of samples from data evaluation.

[1] Only patients completed this activity up to until the cut of date for the primary report.

10.5 STATISTICAL APPENDIX INCLUDING MODEL PERFORMANCE AND DATA SCENARIOS

A BLRM with overdose control will be used to guide dose escalation in this study. The BLRM is introduced in Section 7.1.1, 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 (first three weeks). 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 10.5.2: 1. In addition, recommendations for 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 EWOC facilitates on-trial dose-escalation decisions (see Table 10.5.2: 2). For simplicity reasons, a cohort size of 3 patients who are all evaluable is assumed. The simulations for scenarios and operating characteristics were produced using RStudio version 0.98.507.

10.5.1 Hypothetical data scenarios

Hypothetical data scenarios are shown in Table 10.5.1: 1. These scenarios reflect potential on-study data constellations and related escalation as allowed by the model. It is assumed that each cohort has exactly 3 patients who are all evaluable. 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 80 mg. In this case, the next optimal dose, i.e., the dose with the highest probability of being in the target interval, is 800 mg. However, to have the next dose level at 800 mg seems too aggressive and thus the recommended dose for next level should be provided by the SRC.

Scenario 2 represents the case that no DLTs are observed in both the 80 mg and the 240 mg cohorts with 3 patients in each cohort. The probabilities of each dose level under both target-dose and over-dose range are lower than the probabilities in Scenario 1 as expected.

Scenario 3 represents the case that no DLTs are observed in the first 3 patients at the starting dose of 80 mg but there is one DLT in the next dose level, 240 mg. In this case, the next optimal dose is 320 mg which has the highest probability in the target dose level. However, it will be SRC's decision whether to have another cohort tested at dose 240 mg or to increase the dose level to 320 mg, since one DLT was observed at the dose level of 240 mg.

Table 10.5.1: 1 Hypothetical data scenarios

Scenario	Dose (mg)	# DLT	# Pat	Current Dose: P(OD)	Next Recommended Dose (mg)	Next optimal dose		
						P(under dose)	P(target dose)	P(over dose)
1	80	0	3	0.001	800	0.898	0.054	**0.047**
2	80 240	0 0	3 3	0	800	0.919	0.047	**0.034**
3	80 240	0 1	3 3	0.186	320	0.506	0.247	**0.247**
4	80 240	0 1	3 6	0.031	560	0.541	0.247	**0.212**
5	80 240 400	0 1 0	3 6 3	0.033	800	0.613	0.217	**0.170**
6	80 240 400	0 1 1	3 6 3	0.195	400	0.406	0.399	**0.195**

*non-DLT drug-related AE of CTCAE grade ≥2
**Overdose-probability of the next optimal dose is too high (violates EWOC criterion), therefore the maximal allowed dose would be chosen as next dose by the model.

10.5.2 Operating Characteristics

Operating characteristics are a way to assess the long-run behaviour of a model. 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: 1 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. Scenarios 1 and 2 reflect the extremes of very low and very high toxicity probabilities, respectively. Scenario 3 covers a true dose-toxicity relationship that does not have a logistic form. Finally, Scenario 4 reflects the possibility of having very low DLT rates at the lower dose levels and high DLT rates at the upper dose levels. Scenario 1 is more similar to the prior distribution of this trial. The stopping rule is the same as the MTD criteria mentioned in Section 7.1.1.

Table 10.5.2: 1 Assumed True Dose-Toxicity Scenarios

Scenario	Dose (mg)						
	80	160	240	320	400	480	3200
1: Low Tox	0.00001	0.0005	0.009	0.013	0.028	0.050	0.160
2: High Tox	0.050	0.097	0.140	**0.180**	**0.249**	**0.309**	0.359
3: Non-Logistic	0.001	0.0102	0.0397	**0.1795**	**0.220**	**0.269**	0.339
4: Low-High	0.001	0.040	**0.180**	**0.280**	0.360	0.380	0.500

Bold numbers indicate true DLT rates in the target interval [0.16, 0.33].

For each of these scenarios, 1000 trials were simulated. 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 10.5.2: 2.

Table 10.5.2: 2 Simulated Operating Characteristics

Scenario	**% of Trials Declaring an MTD with True DLT Rate in**				**# Patients**	**# DLT**
	Underdose	**Target dose**	**Overdose**	**Stopped Before MTD**	**Mean (Min-Max)**	**Mean (Min-Max)**
1: Low Tox	**94.0**	**0**	**0**	**6.0**	**25.36 (12-60)**	**1.011 (0-4)**
2: High Tox	**16.7**	**83.3**	**0**	**0**	**17.18 (3-42)**	**3.152 (1-11)**
3: Non-Logistic	**4.5**	**95.5**	**0**	**0**	**16.03 (12-39)**	**2.48 (1-9)**
4: Low-High Tox	**6.7**	**46.0**	**47.3**	**0**	**17.83 (6-42)**	**3.78 (1-11)**

In Scenario 1 (low-toxicity scenario), since none of the assumed true dose-toxicity scenarios were beyond 16%, 94% of the simulated trials declared a dose as MTD with true DLT rate in the under dose range. 6% of the trials stopped before MTD was reached and this is because the very low-toxicity level to allow a trial stop before reaching an MTD. For Scenario 2 (high-toxicity scenario), 83.3% of the simulated trials declared an MTD with true DLT rate in the target dose range. This is an expected situation as assumed dose-toxicity scenarios at 320 mg, 400 mg, and 480 mg lie within the target dose level. Results of Scenario 3 (high-toxicity scenario) are very close to the results of Scenario 2 as the setting for the high-dose

level is similar between these two scenarios. Results of Scenario 4 (Low-High scenario) show ~50% of the simulated trials declared a dose as MTD with true DLT rate in both the targeted dose range and also overdose range. This is because in the setup, assumed true dose-toxicity rates at 400 mg, 480 mg, and 320 mg were above 33%.

The mean patient numbers range from 16.03 (Scenario 3) to 25.36 (Scenario 1) and only Scenario 1 had the maximum of 60 patients. The patient numbers are as expected and decrease when moving away from the low-toxicity scenario. In summary, the considered data scenarios show a reasonable behaviour of the model and the operating characteristics demonstrate a good precision of MTD determination.

11. DESCRIPTION OF GLOBAL AMENDMENTS

Number of global amendment		1
Date of CTP revision		01 November 2016
EudraCT number		Not applicable
BI Trial number		1381.1
BI Investigational Product		BI 754091
Title of protocol		An open-label, Phase I trial to determine the maximum-tolerated dose and investigate safety, pharmacokinetics, and efficacy of BI 754091 in 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~~. Please note that formatting changes and minor changes to punctuation or spelling that do not affect meaning are not noted in this summary.		
Section to be changed		Synopsis: Main criteria for inclusion
Description of change		Phase Ia (dose escalation) – adult patients with a confirmed diagnosis of advanced, unresectable, and/or metastatic solid tumours (any type) **who have received all therapy known to confer clinical benefit (including anti-PD-1 therapies, if relevant and if last dose of the prior anti-PD-1 received more than 60 days prior to starting study drug), or for whom no therapy of proven efficacy exists, or who are not amenable to standard therapies**
Rationale for change		In response to the FDA review, the decision was made to allow patients who had received previous treatment with an anti-PD-1 therapy to enter the dose-escalation phase (Part 1a) of the trial.
Section to be changed		Synopsis: Main criteria for inclusion

Description of change		Phase Ib (dose expansion) – adult patients with a confirmed diagnosis of select advanced, unresectable, and/or metastatic solid tumours (non-small cell lung cancer, bladder cancer, melanoma, gastric cancer, ovarian cancer, triple-negative breast cancer [TNBC], or renal cell carcinoma) ~~Patients~~ who are anti-PD-1 naïve, but **have failed conventional treatment (excluding anti-PD-1 treatment)**, or for whom no therapy of proven efficacy exists, or who are not amenable to standard therapies
Rationale for change		Clarification that patients in the dose-expansion portion (Part 1b) of the trial still must be naïve to anti-PD-1 therapy.
Section to be changed		Flow Chart Footnote d (third sentence)
Description of change		If these assessments are performed within 72 hours of initiation of treatment, they do not need to be repeated on Cycle 1 Day 1 with the exception of the ECOG performance status, an abbreviated physical examination, vital signs **(pre- and post-infusion)**, and a single ECG required prior to first trial dose.
Rationale for change		To clarify this requirement for the sites.
Section to be changed		Flow Chart and Footnote k
Description of change		The collection of optional DNA banking samples was removed from the protocol. All footnotes following Footnote k were reordered.
Rationale for change		Optional DNA banking has been removed as the number of samples is not anticipated to be enough to provide significant benefit to the patients or the sponsor.
Section to be changed		Flow Chart Footnote i, Section 5.5.2.1, and footnotes of Tables 10.4.1: 1 and 10.4.1: 2
Description of change		Blood samples for biomarkers [redacted] will be collected **(if feasible)**
Rationale for change		To clarify that this test may not be done.
Section to be changed		Flow Chart 1 Footnote k, Flow Chart 2 Footnote l, Section 5.5.2.3
Description of change		~~Stable disease over 3 subsequent measurements would also be qualified as a response, and a biopsy (optional) would be taken at that time point~~ **An optional biopsy should also be taken if a patient has stable disease over 3 subsequent disease assessment periods.**
Rationale for change		Clarification
Section to be changed		Section 3.1 Overall trial design and plan
Description of change		Successive cohorts of patients will receive doses of BI 754091 until the MTD is reached. **A cohort size of 3 patients will be treated at each dose level. Additional patients (up to 6 more) could be added to some previously evaluated cohorts to expand the safety and PK evaluation.** ~~At least 3 patients will be required for any dose-escalation cohort (refer to Section 7).~~

		~~A Safety Review Committee (SRC, see Section 3.1.2) may also recommend the size for the next dose escalation cohort. However, the final decision on the next cohort size will be made mutually between the BI Clinical Program Leader and the SRC.~~ After all patients in a cohort have either experienced a DLT or have been observed for at least the MTD evaluation period (first 3 weeks) 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 which fulfil the EWOC criterion. **Hypothetical data scenarios (example in Section 10.5.1) will be calculated with potential cohort sizes and presented at the meetings with the Safety Review Committee (SRC, see Section 3.1.2).** Based on the model and on additional information (PK, pharmacodynamics [PDc], patient profiles), the members of the SRC will reach a joint ~~decision~~ **recommendation** on the next dose level to be investigated **and the size for the next dose-escalation cohort. However, the final decision on the next dose level and cohort size will be made mutually between the BI Clinical Program Leader and the SRC**.
Rationale for change		In response to the FDA review, clarification was added on how the number of patients per dose level will be determined during dose escalation.
Section to be changed		Section 3.3.2 Inclusion Criterion #4
Description of change		**Phase 1a (dose escalation) – patients who have received all therapy known to confer clinical benefit (including PD-1 therapies, if relevant), or for whom no therapy of proven efficacy exists, or who are not amenable to standard therapies. Patients with PD-1 experience must have a minimum of 60 days between the last dose of the previous PD-1 and Cycle 1 Day 1 of BI 754091 treatment. Phase 1b (dose expansion) -** ~~P~~patients who are anti-PD-1 naïve but have failed conventional treatment (excluding anti-PD-1 treatment), or for whom no therapy of proven efficacy exists, or who are not amenable to standard therapies.
Rationale for change		In response to the FDA review, the decision was made to allow patients who had received previous treatment with an anti-PD-1 therapy to enter the dose-escalation phase (Part 1a) of the trial. Patients must still be naïve to anti-PD-1 therapies in order to enter the dose-expansion phase.
Section to be changed		Section 3.3.2 Inclusion Criterion #8
Description of change		Females of child-bearing potential willing to use adequate contraceptive measures from the time of screening until 6 months after trial discontinuation, who are not or will not be breast feeding, and agree to have pregnancy tests prior to the start of dosing and at regular visits during the trial. Females not of childbearing potential must have evidence of such by fulfilling one of the following criteria at screening:

		- Post-menopausal: defined as more than 50 years-of-age and amenorrhoeic for at least 12 months following cessation of all exogenous hormonal treatments - Documentation of irreversible surgical sterilization by hysterectomy, bilateral oophorectomy, or bilateral salpingectomy~~, but not tubal ligation~~.
Rationale for change		The sponsor considers tubal ligation as a highly effective form of birth control and the current ICF text reflects this.
Section to be changed		Section 4.1.5 Definition of dose-limiting toxicity
Description of change		• 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**~~3~~ weeks - Grade 3 rash that resolves to ≤ Grade 1 within **2**~~3~~ weeks - ~~Grade 3 infusion reaction that resolves within 6 hours to ≤ Grade 1 with the appropriate clinical management~~
Rationale for change		Exceptions were updated to reflect FDA feedback.
Section to be changed		Section 4.1.5 Definition of dose-limiting toxicity
Description of change		Late immune-related DLTs are irAEs that meet the same grading criteria as DLT criteria but occur after the initial 21-day DLT period and during the first 90-day assessment period. These, as well as all toxicities, will be monitored throughout the trial. **If any late immune-related DLT is reported during dose-escalation, the BLRM will be rerun including the late immune-related DLT, and updated results will be reviewed in the SRC meeting to recommend the next dose level and cohort size.**
Rationale for change		In response to the FDA review, text was added to clarify how information on late immune-related DLTs will be used in making dosing (or other) decisions during the trial.
Section to be changed		Section 5.3.1 Physical examinations and ECOG performance status
Description of change		The ECOG score will be assessed at screening, on Day 1 of Cycles 1 and 2, on Day 1 of every other cycle **beginning with Cycle 3**~~treatment cycle~~ prior to trial medication intake, at the EOT visit, and at the 30-day safety follow-up visit.
Rationale for change		To clarify this statement for the sites and to align with the Study Flow Footnote e.
Section to be changed		Section 5.3.6.3 Definition of serious adverse events
Description of change		is to be deemed serious for any other reason if it is an important medical event when based upon appropriate medical judgment which may jeopardise the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions.

		~~Medical and scientific judgement should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalisation, but might jeopardise the patient or might require intervention to prevent one of the other outcomes listed above.~~ 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. Any suspected transmission via a medicinal product of an infectious agent is also considered an SAE.
Rationale for change		Corrected to align with the sponsor's accepted safety language.
Section to be changed		Section 5.3.6.5.3 Infusion-related reactions
Description of change		If **an**~~the~~ infusion-related reaction is Grade 3 or higher in severity **at any point during the study**, treatment with BI 754091 will be permanently discontinued.
Rationale for change		In response to the FDA review, this statement was clarified.
Section to be changed		Section 5.3.6.5.4 **Hepatic injury and** ~~D~~drug-induced liver injury (DILI)
Description of change		During the course of the trial the Investigator will remain vigilant for increases in liver biochemistry. The Investigator is responsible for determining whether a patient meets the **hepatic injury definition or** potential Hy's Law criteria at any point during the trial. The Investigator participates, together with the Medical Monitor and BI clinical project representatives, in review and assessment of cases meeting potential **hepatic injury and** Hy's Law criteria. Hy's Law criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than a DILI caused by the investigational product. **Hepatic injury definition:** **In patients with normal baseline hepatic function, hepatic injury is defined by the following alterations in hepatic laboratory parameters:** **• An elevation of AST and/or ALT ≥3 times the ULN combined with an elevation of total bilirubin ≥2 times the ULN measured in the same blood draw sample. And/or** **• Marked peak AST and/or ALT elevation ≥10 times the ULN.**
Rationale for change		To clarify potential liver injury by including hepatic injury definitions in addition to the definition of Hy's Law criteria.
Section to be changed		[redacted]

Description of change		[redacted]
Rationale for change		
Section to be changed		Section 5.5.3 Biobanking
Description of change		~~At the Cycle 1 Day 1 visit, one 8.5 mL blood sample for DNA banking will be collected in a PAXgene Blood DNA tube for those patients in either portion of the trial who agree by checking the appropriate box in the ICF. The DNA Banking sample, derived from the original blood sample, will be stored at the sponsor. The stored DNA may retrospectively be analysed, e.g., to identify whether there are other genetic factors that could contribute to a better therapeutic outcome or a higher risk of developing treatment-related adverse drug reactions.~~ Note: Participation in the ~~DNA banking sampling and the~~ long-term storage and use **of** leftover samples is voluntary and not a prerequisite for participation in the trial. The biological samples ~~to be banked~~ will be stored after the appropriate separate boxes are checked on the ICF by consenting patients in accordance with local ethical and regulatory requirements.
Rationale for change		Optional DNA banking has been removed as the number of samples is not anticipated to be enough to provide significant benefit to the patients or the sponsor.
Section to be changed		Section 5.5.3 Biobanking
Description of change		Any leftover samples (including tissue, plasma, serum, ~~ADA,~~ DNA, RNA, etc.) from the trial may be stored at the sponsor or an external biobanking facility on behalf of the sponsor for up to 30 years.
Rationale for change		ADA samples will be stored as per Section 5.6.1
Section to be changed		Section 8.4 Expedited reporting of adverse events
Description of change		BI is responsible to fulfil their legal and regulatory reporting obligation in accordance with **regulatory** requirements.
Rationale for change		For clarification purposes.

Section to be changed		Section 10.2 Management of immune-related (only parts that changed are presented)
Description of change		Management of immune-related event toxicities associated with anti-PD-1 mAbs **are presented below. BI 754091 should be permanently discontinued for Grade 3-4 pneumonitis, Grade 3-4 adrenal insufficiency, Grade 4 diabetes mellitus, any grade encephalitis, Grade 4 hypophysitis, Grade 4 rash, Grade 3-4 or recurrent colitis of any grade, any recurrent Grade 3-4 AE, transaminase >5 times ULN or total bilirubin >3 times ULN, 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.**
Description of change		• Pneumonitis: - **BI 754091 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 does not recover to Grade 1 or less within 12 weeks.**
Description of change		• Diarrhoea/Colitis: - For Grade 3 or 4 diarrhoea~~/colitis~~ 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 immediately treat with i.v. steroids followed by high-dose oral steroids.** **- BI 754091 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.**
Description of change		• Type 1 diabetes mellitus (if new onset, including diabetic ketoacidosis) **Grade 3-4**, 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. **- BI 754091 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.**
Description of change		• Hypophysitis: - For Grade 3~~-4~~ 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 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 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.**
		• Hepatic: - **BI 754091 should be permanently discontinued for any recurrent Grade 3-4 AE, transaminase >5 times ULN or total bilirubin >3 times ULN, inability to taper steroids to 10 mg or less prednisone or equivalent within 12 weeks, or persistent Grade 2-3 AEs that do not recover to Grade 1 or less within 12 weeks.**
		• Renal failure or nephritis: **- BI 754091 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.**
Description of change		**• Adrenal insufficiency** **- BI 754091 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.**
Description of change		**• Rash** **- BI 754091 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.**
Description of change		**• Encephalitis** **- BI 754091 should be permanently discontinued for any grade encephalitis.**
Rationale for change		In response to the FDA review, the information in Section 10.2 was updated to clarify that BI 754091 should be permanently discontinued for the recommended irAEs.

Number of global amendment		2
Date of CTP revision		02 March 2017
EudraCT number		Not applicable
BI Trial number		1381.1
BI Investigational Product		BI 754091
Title of protocol		An open-label, Phase I trial to determine the maximum-tolerated dose and investigate safety, pharmacokinetics, and efficacy of BI 754091 in patients with advanced solid tumours
To be implemented only after approval of the IRB / IEC / Competent Authorities		X
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		
Section to be changed		Synopsis and Section 5.3 Assessment of safety
Description of change		Phase Ia: Dose escalation is guided by a BLRM with overdose control that will be fitted to binary toxicity outcomes. The estimate of parameters will be updated as data are accumulated using the BLRM. At the end of dose escalation, the toxicity probability at each dose level will be calculated to determine an estimate of the MTD. **If there are too few or no DLTs for BLRM guided dose selection, PK and/or biomarker data will be taken into consideration for RPIID determination.**
Rationale for change		Clarification of the RPIID determination
Section to be changed		Flow chart Footnote d and Section 5.2.1 Tumour Assessments
Description of change		Tumour assessments (scans) should be performed ≤28 days prior to initiation of treatment **and copies may be collected by the sponsor or designee**.
Rationale for change		Clarification of the process to be followed.
Section to be changed		Flow chart and Footnote i (second part)and table in Appendix 10.4.
Description of change		Phase Ib (dose expansion) only – samples for [redacted] will be collected ~~during~~ **on** Cycle 1 on Day 1 (pre-treatment), **Day 8, and Day 15, on Cycle 2**

		Day 1 (pre-treatment), and at the 30-day follow-up visit (see Section 5.5.2.1 and Appendix 10.4).
Rationale for change		A mechanism-of-action-related PD effect of anti-PD-1 treatment may be detected in the periphery, and may also be independent of whether the tumour responds.
Section to be changed		Flow chart - Adverse event row
Description of change		The superscript 'o' (Phase Ia Cycle 1 only) was removed from Days 8 and 15 check boxes for Cycles 1, 2, and 4.
Rationale for change		These superscripts were in error, since adverse events will be collected at every visit.
Section to be changed		Abbreviations
Description of change		Added CKD-EPI: Chronic Kidney Disease Epidemiology
Rationale for change		New criterion added to the protocol
Section to be changed		Section 3.3.3 Exclusion Criterion #7
Description of change		Creatinine >1.5 times ULN or creatinine clearance <50 mL/min (measured or calculated by ~~Cockcroft Gault~~ **Chronic Kidney Disease Epidemiology (CKD-EPI) Collaboration** equation); confirmation of creatinine clearance is only required when creatinine is >1.5 times ULN.
Rationale for change		To comply with comment from regulatory authority and align with sponsor's latest approach for estimating kidney function.
Section to be changed		Section 5.3.6.3
Description of change		**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).**
Rationale for change		Updated to align with the sponsor's latest safety language.
Section to be changed		Section 5.3.6.4
Description of change		~~Cancers of new histology and exacerbations of existing cancer must be reported as serious events regardless of the amount of time between discontinuation of the drug and the occurrence of the cancer.~~ **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 Section 5.3.6.8, subsections " AE Collection" and AE reporting to sponsor and timelines".**
Rationale for change		This change will clarify the exempting of progressive disease from expedited SAE reporting.
Section to be changed		Section 5.3.6.8.1

Description of change		**The rules for Adverse Event Reporting exemptions still apply.**
Rationale for change		This change will clarify the exempting of progressive disease from expedited SAE reporting.
Section to be changed		Section 5.3.6.8.1
Description of change		The following should also be recorded as SAEs/AEs in the eCRF and SAE form (if applicable): •Worsening of ~~the underlying disease or of other~~ pre-existing conditions • Changes in vital signs, ECGs, physical examinations, and laboratory test results, if they are judged clinically relevant by the Investigator. If such abnormalities already exist prior trial inclusion they will be considered as baseline conditions.
Rationale for change		This change will clarify the exempting of progressive disease from expedited SAE reporting.
Section to be changed		Section 5.3.6.10
Description of change		**5.3.6.10 Exemptions to SAE Reporting** **Disease Progression is a trial endpoint for analysis of efficacy and as such is exempted from reporting as an AE or an 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 (e)CRF page and not on the SAE Form. However, when there is evidence suggesting a causal relationship between the study drug(s) and the progression of the underlying malignancy, the event must be reported as an SAE on the SAE Form and on the (e)CRF.** **Examples of exempted events of PD may be:** **• Progression of underlying malignancy (Progressive disease [PD]): if PD is clearly consistent with the suspected progression of the underlying malignancy as defined by the respective response criteria.** **• Hospitalization/Procedures due solely to the progression of underlying malignancy (PD)** **• Clinical symptoms and/or signs of progression (without confirmation by objective criteria e.g. imaging, clinical measurement): if the symptom can exclusively be determined to be due to the progression/relapse of the underlying malignancy and does meet the expected pattern of progression for the disease under study.**

		Exempted events are collected and tracked following a protocol specified monitoring plan. Exempted events are monitored at appropriate intervals throughout the study at quarterly Program Safety Management Team Meetings.
Rationale for change		This change will clarify the exempting of progressive disease from expedited SAE reporting
Section to be changed		Section 5.4.2 Methods of sample collection for pharmacokinetic analyses
Description of change		[redacted]
Rationale for change		These are unnecessary details that can be specified in the Laboratory Manual.
Section to be changed		[redacted]
Description of change		

		[redacted]
Rationale for change		
Section to be changed		Section 5.5 First 2 bullets
Description of change		[redacted]
Rationale for change		To clarify the types of assays that may be performed.
Section to be changed		[redacted]
Description of change		

		[redacted]
Rationale for change		
Section to be changed		[redacted]
Description of change		
Rationale for change		
Section to be changed		Section 5.6.1 Plasma sampling for anti-drug antibodies (ADAs)
Description of change		All patients in Phase Ia and Ib: [redacted] **D**etails on sample characteristics, processing, handling, and shipment are provided in the Laboratory Manual. The trial samples will be discarded after completion of the additional investigations but not later than 5 years after the final trial report has been signed.
Rationale for change		These are unnecessary details that can be specified in the Laboratory Manual.
Section to be changed		Section 7.4 Interim analysis - fourth paragraph
Description of change		No formal interim analysis of PK data is planned. However, ~~the first~~ **an** exploratory analysis of PK will be

		done after ~~5 to 6~~ patients **in Cohort 1** complete Cycle 1 **and once patients in Cohort 2 complete Cycle 1**. Furthermore, **exploratory analyses might be performed if considered reasonable, e.g.,** after the last patient of the dose-escalation Phase Ia portion completes Cycle 4, there ~~will~~**might** be an exploratory analysis to further characterise the PK and immunogenicity.
Rationale for change		These edits reflect the latest modifications to the statistical methods.
Section to be changed		Section 8.3.1 Source documentation - new paragraph added
Description of change		**Copies of tumour assessments scans may be collected by the sponsor upon request. This could include CT/PET scans of the chest and abdomen and/or imaging of any other known or suspected sites of disease (e.g., pelvis, brain) using an appropriate method (CT/PET scan or MRI).**
Rationale for change		Clarification that the sponsor may collect tumour assessment scans.
Section to be changed		Section 8.4
Description of change		**Exemptions from expedited reporting are described in Section 5.3.6.10, if applicable.**
Rationale for change		This change will clarify the exempting of progressive disease from expedited SAE reporting
Section to be changed		Appendix 10.4 - Tables 10.4.1:1 and 10.4.2:1
Description of change		The Time Point column was filled for rows that were previously blank. For Table 10.4.2:1, 2 PK sampling time points were removed (1:30 and 2:00 hours post treatment), and updates in PDMC sampling were applied, as previously mentioned.
Rationale for change		To clarify the time point information, harmonise PK sampling with the sampling that will be done in the second protocol with BI 754091, and to clarify the PBMC samplings.

Number of global amendment		3
Date of CTP revision		06 December 2017
EudraCT number		Not applicable
BI Trial number		1381.1
BI Investigational Product		BI 754091
Title of protocol		An open-label, Phase I trial to determine the maximum-tolerated dose and investigate safety, pharmacokinetics, and efficacy of BI 754091 in 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
Description of change		~~Principal~~ **Coordinating** Investigator
Rationale for change		The trial will expand into EU where a Coordinating Investigator is required
Section to be changed		Synopsis page 1 Trial sites
Description of change		~~The entire row was removed:~~ [redacted]
Rationale for change		This detail is removed because study sites are not required to be pre-specified in the protocol and more sites will be identified.
Section to be changed		Flow Chart
Description of change		The single Flow Chart was split into 2 charts separating the dose escalation and dose expansion portions of the study.
Rationale for change		To simplify study conduct at the sites.

Section to be changed		Flow chart 1 Footnote d and Section 5.3.4.2 Biochemistry
Description of change		The standard biochemistry panel will consist of glucose, sodium, potassium, chloride, calcium, phosphate, venous bicarbonate HCO3, ~~urea,~~ creatinine, creatine phosphokinase (CPK), AST, ALT, alkaline phosphatase, lactate dehydrogenase (LDH), bilirubin, total protein, albumin, urea nitrogen **(or urea),** and uric acid. **Additionally, amylase and lipase should be analysed in case of symptoms of pancreatitis.**
Rationale for change		To clarify that within the biochemistry panel, either urea nitrogen or urea will be collected (instead of both) depending on local practice. In addition, to clarify that additional safety testing should be added in case of pancreatitis.
Section to be changed		Flow chart 2 Footnote l
Description of change		The following fresh tumour biopsies will be mandatory for all patients in the Phase Ib dose-expansion ~~portion~~ **cohorts** of the trial **(refer to Section 6.2.1.1)**: - ~~The equivalent of~~ 2 ~~fine~~ **core** needle biopsies ~~(archival)~~ **or 1 punch biopsy (refer to lab manual for specifications)** from the most recent relapse (if within 6 months of trial start with no subsequent therapy); otherwise, a minimum of 2 ~~fine~~ **core** needle biopsies **or 1 punch biopsy** must be ~~freshly~~ taken between screening and the day before first treatment with BI 754091. - ~~The equivalent of~~ 2 ~~fine~~ **core** needle biopsies **or 1 punch biopsy** on treatment at the end of Cycle 2 (6 weeks), p**referably from the same lesion**. - Another ~~fresh~~ biopsy (optional) should be taken upon PD (according to RECIST v1.1 and irRECIST), if possible. ~~Stable disease over 3 subsequent measurements would also be qualified as a response, and a biopsy (optional) would be taken at that time point.~~ **An optional biopsy should also be taken if a patient has stable disease over 3 subsequent disease assessment periods.**
Rationale for change		To clarify expectations for biopsy collection.
Section to be changed		Section 2.1 Rationale for performing the trial
Description of change		[…] The second part ~~is primarily a safety~~ **consists of 3** expansion cohort**s** at the RP2D that will also further evaluate the safety, tolerability, **efficacy**, PK, **and** biomarkers ~~and the preliminary efficacy~~ of BI 754091. The dose-escalation portion of the trial will enrol patients with advanced and/or metastatic solid tumours, while the dose-expansion portion will enrol patients with **advanced and/or metastatic solid tumours with select types of cancer and/or specific genetic mutations. Recent evidence has shown that several tumour types with high TMB have better response rates with immune checkpoint inhibitors (R17-3651; R16-1497). Therefore, patients with tumours with high mutation**

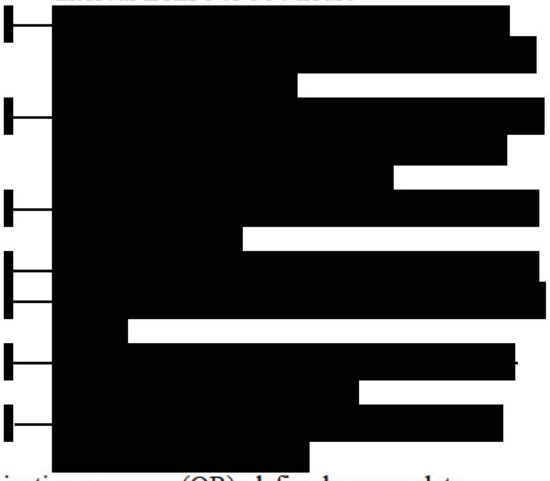
		rates will be included in the expansion phase of this trial. **[…]**
Rationale for change		To describe the details and rationale of the additional expansion cohorts
Section to be changed		Section 2.2 Trial objectives
Description of change		The main objective of the dose-escalation part of the trial is to determine the safety and tolerability, ~~PK, biomarkers, and efficacy~~, and to determine the MTD and/or the RP2D of BI 754091 on the basis of patients with dose-limiting toxicities (DLTs) in patients with selected advanced solid malignancies. Safety and tolerability will be evaluated by monitoring the occurrence of adverse events (AEs), serious AEs (SAE), and laboratory parameter abnormalities, as well as changes to vital signs (see Section 5.3). […] In the dose-expansion part of the trial, the main objectives are to further assess the safety, efficacy, PK profile, and biomarkers of BI 754091 **in tumours with specific tumour types and/or genetic mutations** at the RP2D.
Rationale for change		To clarify the objectives between the 2 parts of the study and to give additional details about the addition expansion cohorts.
Section to be changed		Section 2.3 Benefit – Risk Assessment
Description of change		[…] Based on these pre-clinical data, as well as clinical data obtained with other anti-PD-1 inhibitor mAbs, the inhibitory effects of BI 754091 on PD-1 may translate into a clinical benefit in cancer patients. All doses planned to be tested are expected to have some level of efficacy. **Efficacy is expected for patients with tumours that have a high rate of mutations, such as high levels of TMB and squamous cell skin cancers, which have about the highest mutation rate among cancers.**
Rationale for change		To describe the benefit expected for patients enrolled into the new expansion cohorts.
Section to be changed		Section 3.1 Overall trial design and plan and synopsis
Description of change		[…] Following determination of the MTD and/or RP2D from the Phase Ia portion, ~~a~~ separate cohort**s** of **approximately** 30 patients **each will be conducted in patients** with select~~ed~~ advanced solid malignancies ~~likely to benefit from treatment with **an** anti-PD-1 mAbs~~ including ~~NSCLC, bladder, melanoma, gastric cancer, ovarian cancer, triple negative breast cancer (TNBC), and RCC will be conducted~~ **tumours with specific histology/tumour types and/or specific genetic profiles as specified in the following cohorts:** • **Cohort 4: Solid tumours including NSCLC, bladder cancer, melanoma, gastric cancer, ovarian cancer, triple-negative breast cancer, and renal-cell cancer**

		• **Cohort 5: Tumours with high TMB excluding those with high microsatellite instability (MSI-high)** • **Cohort 6: Refractory squamous cell cervical, anal, and skin tumours** The Phase Ib portion of the trial will further evaluate the safety, tolerability, **efficacy,** PK profile, **and** biomarkers~~, and efficacy~~ of BI 754091. **The analysis of the squamous cell tumour cohort (Cohort 6) will follow a two-stage approach. The interim analysis for:** • **Squamous cervical and/or anal cancer, Stage 1 will include 10 treated patients.** • **Squamous skin tumours, Stage 1 will include 10 treated patients.** **Based on the interim analyses results, the sponsor will determine if recruitment into these tumour groups will continue or be terminated. More details on the interim analyses are specified in Section 7.4. The sponsor reserves the right to terminate recruitment in any of the tumour groups if the recruitment target is not met. Patients who are already enrolled may continue in the trial regardless of recruitment termination of their cohort.** […]
Rationale for change		To describe the additional expansion cohorts in detail and to describe the 2-stage interim analysis of Cohort 6.
Section to be changed		Section 3.3.2 Inclusion Criteria and synopsis
Description of change		3. Phase Ia (dose escalation): • Patients with a histologically confirmed diagnosis of advanced, unresectable, and/or metastatic solid tumours (any type) • Patients who have received all therapy known to confer clinical benefit (including **anti**-PD-1 **or anti-PD-L1** therapies, if relevant), or for whom no therapy of proven efficacy exists, or who are not amenable to standard therapies. Patients with **anti**-PD-1 **or anti-PD-L1** experience must have a minimum of 60 days between the last dose of the previous **anti**-PD-1/**PD-L1** and Cycle 1 Day 1 of BI 754091 treatment. • **[Moved here] Patients may agree to ~~have~~ provide optional paired biopsies.** 4. Phase Ib (dose expansion):

		• **[Moved here] Patients with a histologically confirmed diagnosis of select advanced, unresectable, and/or metastatic solid tumours with specific histology/tumor types and/or specific genetic profiles as specified in the following cohorts:** – **Cohort 4: solid tumours including NSCLC, bladder cancer, melanoma, gastric cancer, ovarian cancer, triple-negative breast cancer, and renal-cell cancer** – **Cohort 5: Tumours with high TMB based on Foundation Medicine's assay (showing ≥20 mutations/mega base) excluding those with high microsatellite instability (MSI-high]) based on Foundation Medicine's assay or another validated test. Refer to Section 6.2.1.1 for details.** – **Cohort 6: Refractory squamous cell cervical, anal, and skin tumours** • **All** patients must have measurable **lesions according to** RECIST v1.1 ~~and irRECIST~~ criteria, must have at least 1 tumour lesion amenable to biopsy, and must be medically fit and willing to undergo a biopsy before first treatment and, unless clinically contraindicated, after 6 weeks on therapy. • **[Moved here] Patients who are anti-PD-1 and anti-PD-L1 naïve but have failed conventional treatment (excluding anti-PD-1 treatment), or for whom no therapy of proven efficacy exists, or who are not amenable to standard therapies.** […]
Rationale for change		To clarify details of the inclusion criteria related to the additional expansion cohorts. This section was rearranged to better organize and group together specific criteria for each of the different phases.
Section to be changed		Section 3.3.3 Exclusion Criteria
Description of change		4. Any investigational or anti-tumour treatment within **4 weeks or 5 half-life period (whichever is shorter)**~~30 days~~ prior to the initial administration of BI 754091.
Rationale for change		To clarify that the wash-out period may be shorter for drugs with a short half-life.
Section to be changed		Section 3.3.3 Exclusion Criteria
Description of change		5. ~~History within the last 5 years~~**Presence** of **other**~~an~~ **active** invasive ~~malignancy~~ **cancers** other than the one treated in this trial **within 5 years prior to screening**, with the exception of **appropriately treated**~~resected/ablated~~ basal ~~or squamous~~-cell carcinoma of the skin, ~~or carcinoma~~ *in situ* **carcinoma** of the **uterine** cervix, or other local tumours considered cured by local treatment.
Rationale for change		To clarify exclusion of other active cancers and to align language across current studies with BI 754091

Section to be changed		Section 3.3.3 Exclusion Criteria
Description of change		9. 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 **- 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.** ~~- Ejection fraction <55% or the lower limit of normal of the institutional standard.~~
Rationale for change		To clarify exclusion of other active cancers and to align language across current studies with BI 754091
Section to be changed		Section 3.3.3 Exclusion Criteria
Description of change		13 Known history of human immunodeficiency virus infection or an active hepatitis B or C virus infection **(exception: this criteria does not apply to patients with cervical/anal tumours enrolling in Cohort 6)**
Rationale for change		Due to the high incidence of HIV in patients with cervical and anal cancers, and no anticipated safety concerns exist for including such patients in the trial, Exclusion Criterion #13 (see Section 3.3.3) does not apply to the patients with cervical/anal cancer enrolling into Cohort 6.
Section to be changed		Section 3.3.4.2 Discontinuation of the trial by the sponsor
Description of change		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 Good Clinical Practice (GCP), the clinical trial protocol (CTP), or the contract disturbing the appropriate conduct of the trial. **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		Section 4.2.2.1 Permitted concomitant medications
Description of change		• 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 the screening laboratory assessment. Exceptions to this will be considered by the sponsor on a case by case basis.**
Rationale for change		This change clarifies the expectations for time since previous transfusions. This time line reflects the half-life of red blood cells.
Section to be changed		Section 4.2.2.2 Prohibited concomitant medications
Description of change		[…] 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,** ~~P~~patients should stop using these herbal medications 7 days prior to first dose of study treatment.
Rationale for change		To clarify that the Principal Investigator can make exceptions for prohibited herbal preparations/medications.
Section to be changed		Section 5.1.1 Primary endpoints and synopsis
Description of change		The primary endpoint**s** of the Phase Ib dose-expansion portion of the trial ~~is~~**are**: • Number of patients with DLTs observed during the entire treatment period. • **Objective response (OR), defined as the best overall response of complete response (CR) or partial response (PR) according to RECIST v1.1 as assessed by the Investigator**
Rationale for change		Objective response has been added as a primary endpoint for the expansion cohorts.
Section to be changed		Section 5.1.2.1 Secondary endpoints of the Phase Ia (dose escalation) portion of the trial And Section 5.1.2.2 Secondary endpoints of the Phase Ib (dose expansion) portion of the trial And Section 5.1.3 Further endpoints

Description of change		The secondary endpoints of the Phase Ia dose-escalation portion of the trial are: • The following PK parameters of BI 754091 (if feasible) will be evaluated after the first and after multiple administrations of BI 754091: - 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~~), defined as complete response (CR) or partial response (PR) with tumour assessments every 2 cycles (every 6 weeks if no delays or as close as possible to the end of the second of the 2 cycles of treatment if there was a delay) during the first 6 months of the treatment period and every 3 cycles thereafter~~ according to RECIST v1.1 ~~Secondary endpoints of the Phase Ia (dose escalation) portion of the trial~~ as assessed by the Investigator • Number of patients experiencing DLTs from the start of treatment until end of treatment (in all cycles) as assessed approximately every 3 weeks.
Section to be changed		Section 5.1.2.2 Secondary endpoints of the Phase Ib (dose expansion) portion of the trial
Description of change		The secondary endpoints of the Phase Ib dose-expansion portion of the trial are: • ~~OR according to RECIST v1.1 and irRECIST as assessed by the Investigator~~ • Progression-free survival (PFS) defined from date of start of BI 754091 to the date of disease progression or death, whichever is earlier, ~~with tumour assessments every 2 cycles (every 6 weeks if no delays or as close as possible to the end of the second of the 2 cycles of treatment if there was a delay) during the first 6 months of the treatment period and every 3 cycles thereafter~~ according to RECIST v1.1 ~~and irRECIST~~ as assessed by the Investigator • ~~Best OR during the entire treatment period~~ • Safety will continue to be assessed by the recording of AEs, SAEs (including DLTs), laboratory evaluations, vital signs, and ECGs.

		• **Depending on available data,** the same PK parameters calculated during the Phase Ia portion of the trial will be calculated for the dose-expansion portion~~, if feasible~~.
Section to be changed		[redacted]
Description of change		

		[redacted]
Rationale for change		[redacted]
Section to be changed		Section 5.3.6.5 Adverse events of special interest (AESIs)
Description of change		[…] For this trial, DLTs, ~~irAEs,~~ infusion-related AEs, DILI events, ~~and~~ hepatic injury, **and qualifying irAEs, as defined in Appendix 10.1,** are AESIs (see Section 5.3.6.5.2 and Section 5.3.6.5.3, respectively).
Rationale for change		To add a link to the appendix defining irAEs.
Section to be changed		Section 5.3.6.5.2 Immune-related adverse events (irAE)
Description of change		[…] **All immune-related events are to be reported as AEs. Some irAEs also need to be reported as AESIs as defined ~~by the sponsor~~ ~~has defined a list of potential~~**

		~~irAEs~~ in Table 10.1: 1 ~~in Appendix 10.1 These irAEs must be reported as AESIs.~~ If an Investigator determines ~~another irAE~~**a Grade 3** event (not on the list) **to be immune related,** ~~should be a potential irAESI,~~ the Investigator ~~may~~ **should** also report that event as an AESI.
Rationale for change		Changes in this section are to clarify that all immune-related AEs are reported as AEs. When they meet the criteria in Table 10.1:1, they also need to be reported as AESIs.
Section to be changed		Section 5.3.6.8.1 Adverse event collection
Description of change		[…] **For sites outside of the US, country-specific fax numbers will be provided in the ISF/Study reference manual.** […] The following should also be recorded as ~~SAEs~~ **(S)AEs** in the eCRF and SAE form (if applicable): • Worsening of pre-existing conditions • Changes in vital signs, ECGs, physical examinations, and laboratory test results, if they are judged clinically relevant by the Investigator. If such abnormalities already pre-exist prior trial inclusion they will be considered as baseline conditions. All ~~SAEs~~ **(S)AEs**, including those persisting after an individual patient's end of trial must be followed up until they have resolved, they have been sufficiently characterised, or no further information can be obtained.
Rationale for change		To clarify country-specific fax numbers will be provided for the reporting of AEs and to clarify that the excerpt is referring to all AEs (serious and non-serious) and not just serious AEs.
Section to be changed		Section 5.4.1 Assessment of pharmacokinetics and Section 7.3.5 Pharmacokinetic and pharmacodynamics analyses
Description of change		If data allow, the PK parameters of BI 754091 mentioned as secondary and further endpoints (see Section 5.1.2 and Section 5.1.3, respectively) will be evaluated using non-compartmental analysis methods according to BI internal SOP (001-MCS-36-472_RD-01 [2.0~~actual version~~] and ~~Kinesis~~ **Venn Life Sciences** SOP 'SOP-1.PKA.03 Non-compartmental PK/PD Analysis'). The parameters are defined as: • 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

		[redacted] If deemed necessary, further PK parameters might be calculated.
Rationale for change		[redacted]

		In addition, the PK parameters that will be determined were clarified.
Section to be changed		[redacted]
Description of change		
Rationale for change		
Section to be changed		Section 5.5 Assessment of Biomarkers
Description of change		• [redacted]
Rationale for change		To clarify that the lab manual will contain details related to biopsy samples
Section to be changed		Section 5.5.1 Methods of Sample Collection
Description of change		Pre- and on-treatment tumour biopsy collections for biomarker and PDc analyses will be mandatory from all patients in the Phase Ib dose-expansion portion of the trial. In addition, ~~an optional biopsy~~ **biopsies** should be taken **according to the flowchart and Section 5.5.2.3** ~~after treatment discontinuation, if possible~~.
Rationale for change		To clarify the expectations regarding biopsy collection.
Section to be changed		[redacted]
Description of change		

		[redacted]
Rationale for change		
Section to be changed		Section 6.2.1.1 Screening for tumour mutational burden (TMB) and MSI-high cohort
Description of change		**For Cohort 5, the TMB, as well as the microsatellite stability (MS) status have to be assessed. Patients that have high TMB (defined as ≥20 mutations/Mb) and are MS stable (MSS) will be included. Whereas for MS status determination any validated assay may be used, the TMB has to be measured by [redacted] (FM). Patients may be included that fulfil the criteria (1) having undergone testing by FM previously; (2) if evidence is available that the criteria may be fulfilled (or with sponsor approval) after providing archival tumour material (as specified in the lab manual) and testing by FM; or (3) if evidence is available that the criteria may be fulfilled, after providing an additional fresh tumour biopsy and testing by FM. Options 2 and/or 3 may be discontinued at the sponsor's discretion.** **If polymerase epsilon (ε) catalytic subunit (POLE) mutation status is known for any patient in the TMB-high cohort, this information should be collected.**
Rationale for change		Details for determining TMB are added and information about collecting available POLE information is added in this new section of the protocol Subsequent sections are renumbered accordingly.
Section to be changed		Section 6.2.1.3 Medical history
Description of change		[…] **Exclusion Criterion #13 (see Section 3.3.3) does not apply to the patients with cervical/anal cancer enrolling into Cohort 6. However, virology testing should still be done and the status of HIV and hepatitis B or C virus should be collected on the eCRF.**
Rationale for change		To clarify that although patients with HIV may be enrolled into Cohort 6, virology testing should still be performed with results recorded in the eCRF.
Section to be changed		Section 6.2.3.4 Overall survival visits (new section added)
Description of change		**Additional follow-up visits after the 30-day safety follow-up visit will be performed for patients that**

		enrolled in Protocol Version 4.0 and beyond. These will be performed once every 12 weeks at least (by telephone) on the same schedule as PFS survival visits until death, loss to follow-up, or end of the whole trial as specified in Section 3.3.4.2. 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		Overall survival is an objective of the dose-expansion part of the study, so this visit has been added to the study plan table for patients going forward.
Section to be changed		Section 7.1 Statistical design model
Description of change		This is **a** Phase I, open-label, dose-escalating trial to determine the MTD **and the RP2D** for BI 754091 in patients with solid tumours ~~and to recommend a dose for Phase Ib dose expansion~~. In addition, the safety and PK profiles, biomarkers, and efficacy of BI 754091 will also be assessed.
Rationale for change		This is to improve consistency in terminology across the text.
Section to be changed		Section 7.1.1 Statistical design – Phase Ia (dose escalation)
Description of change		The objective of the Phase Ia portion of the trial is to determine the MTD and ~~recommend a dose for Phase Ib dose expansion~~ **the RP2D**.
Rationale for change		To present only the objectives of Phase Ia, because the Phase Ib objectives are expanded and in a separate section
Section to be changed		Section 7.1.2 Statistical design – Phase Ib (dose expansion)
Description of change		The Phase Ib (dose-expansion) portion of the trial will recruit approximately ~~30~~ **90** patients with selected locally advanced or metastatic cancers ~~that are likely to benefit from treatment with an anti-PD-1 mAb~~ at the dose and schedule recommended by the SRC. The analyses of the safety and efficacy for this portion of the trial will be descriptive and exploratory in nature. **Additional analyses may be applied to evaluate the robustness of the efficacy results. More details will be specified in the TSAP**.
Rationale for change		Additional cohorts have been added to the expansion phase increasing the total number of patients to be enrolled. New analyses of the additional cohorts are added.
Section to be changed		Section 7.2 Null and Alternative Hypotheses
Description of change		No formal hypothesis testing is planned in this trial. ~~All analyses in this trial are descriptive and exploratory.~~
Rationale for change		To only present a statement about the hypotheses without including a description of analyses.

Section to be changed		Section 7.3 Planned analyses
Description of change		~~The Trial Statistical Analysis Plan (TSAP) will specify the important protocol violations in detail.~~ For the determination of the MTD, only MTD-evaluable patients will be considered. For ~~the~~ **other** analysis of ~~secondary and further~~**efficacy** and **safety** 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 **Trial Statistical Analysis Plan (TSAP)**. [**Moved here**] **No per protocol set will be used in the analysis. However, important protocol violations will be summarised**~~. The Trial Statistical Analysis Plan (~~ with details specified in the TSAP~~) will specify the important protocol violations in detail~~.
Rationale for change		For clarification.
Section to be changed		Sections 7.3.1, 7.3.2, and 7.3.3
Description of change		Primary endpoint analyses In order to identify the MTD ~~and the recommended dose for the Phase Ib portion~~ of the trial, the number of patients with DLTs at each dose level during the Phase Ia MTD evaluation period (first three weeks) must be presented. Patients who discontinue during the first treatment course for reasons other than a DLT will be excluded from the determination of the MTD. […] **For the primary efficacy endpoint of Phase Ib, objective response rate (ORR) will be summarised and presented with 95% two-sided confidence intervals using the Clopper-Pearson method.** Secondary endpoint analyses ~~Efficacy endpoints will be summarised descriptively.~~**For PFS, the Kaplan-Meier curve and estimates will be displayed with 95% confidence intervals, using Greenwood's variance formula. The detailed censoring rules are specified in the TSAP.** **[…]** Further endpoint analyses For further **efficacy** endpoints ~~analyses~~, ~~details will be provided in TSAP~~**similar analysis as specified for OR will be performed for binary endpoints (e.g. disease control), and similar analysis as specified for PFS will be performed for time-to-event endpoints (e.g. duration of response and OS). For tumour shrinkage over time, spider plots will be presented for the percentage changes from baseline in the sum of (1) target lesions and (2) total measured tumour burdens, respectively. Further details and other analyses are specified in the TSAP.**
Rationale for change		To clarify the planned analyses of the efficacy endpoints

Section to be changed		Section 7.4 Interim analyses
Description of change		~~No formal interim analysis of efficacy data is foreseen, although efficacy data when available may be considered as part of the safety evaluations.~~The sponsor will continuously monitor the safety. The dose-escalation design dictates that the sponsor and the SRC perform regular safety evaluations. These evaluations will be unblinded to dose. […] No formal interim analysis of PK data is planned. However, an exploratory analysis of PK will be done after patients in Cohort 1 complete Cycle 1 and once patients in Cohort 2 complete Cycle 1. Further~~more~~ exploratory analyses **of PK** might be performed if considered reasonable.~~, e.g. after the last patient of the dose-escalation Phase Ia portion completes Cycle 4, there might be an exploratory analysis to further characterise the PK and immunogenicity.~~ ~~No pre-specified interim or exploratory PK analysis is planned for the dose-expansion Part II portion of the trial.~~ Exploratory PK analyses will be based on planned sampling times**, if information on actual times should not be available**. 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 medically justified, further or fewer exploratory PK analyses may be performed.** […] **Interim efficacy analyses are planned for selected groups of patients (defined in Section 3.1) in the Phase Ib portion of the trial. Because of the expected challenge in recruiting these patients, the two-stage design is planned to stop further recruitment of the specific patient group if the defined efficacy boundary (see Table 7.4: 1) is not met at the first stage.** **The interim analyses will be conducted when:** **• 10 patients with squamous cervical and/or anal cancer have been treated, and the 10th patient has been on treatment for ~3 months.** **• 10 patients with squamous skin tumours have been treated, and the 10th patient has been on treatment for ~3 months.** **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.** **• Literature on preliminary data of nivolumab and pembrolizumab (R17-3902; R17-3903; R17-3822)**

		showed ORR ranges from 13% to 24% in patients with squamous cervical and anal tumours. Therefore, an underlying ORR of 25% is assumed. The probability of observing zero responders out of 10 and stopping at interim is 6%, and the probability of observing ≥20% ORR at final analysis is 77%. If the underlying ORR is 5%, the probability of stopping early is 61%, and the false positive probability of observing ≥20% ORR at final analysis is almost 0. **• It was shown in Chalmers ZR et al, 2017 (R17-3824) that the population with squamous skin cancer had very high proportion of patients with high TMB (~70%). Therefore, the clinical benefit is expected to be similar to patients with high TMB (R17-3768). Assume the underlying ORR is 50%, the probability of observing <3 responders out of 10 and stopping at interim is 5%, and the probability of observing ≥40% ORR at final analysis is 87%. If the underlying ORR is 20%, the probability of stopping early is 67%, and the false positive probability of observing ≥40% ORR at final analysis is 1%.** **New Table 7.4: 1 was added.**
Rationale for change		To describe the new interim analysis of efficacy for the dose-expansion cohorts.
Section to be changed		**Section 7.7.1 Determination of sample size for Phase Ia**
Description of change		No formal statistical power calculations to determine sample size were performed ~~for this trial~~. ~~A minimum of~~**Approximately** 15 patients ~~for the Phase Ia dose-escalation and approximately 30 patients for the Phase Ib expansion will be~~**are** expected; ~~F~~fewer or more patients might be needed based on the recommendation of the SRC and the actual number of dose cohorts tested.
Rationale for change		To update determination of sample size for Phase Ia portion only.
Section to be changed		**Section 7.7.2 Determination of sample size for Phase Ib**
Description of change		**For the cohort of 7 solid tumours (Cohort 4), no formal statistical sample size calculations were performed. Some efficacy signals are expected to be observed from ~30 treated patients.** **Several papers demonstrated the association between high TMB and better response rates, progression-free survival, and overall clinical benefit. In Goodman et al., 2017 (R17-3768), response rates were 58% (22/38) in patients with ≥20 mutations/mega base compared to 20% (23/113) in patients with low mutational burden. Therefore, in the planning of the TMB-high-tumour cohort (Cohort 5), it is deemed clinically meaningful if BI 754091 will have an underlying ORR of 35%. With 30 patients, an ORR of 30% or more would be**

		observed with a probability of 78% assuming a true response rate of 35%. The probability of observing a false positive signal, e.g., to observe at least an ORR of 30% if the underlying true ORR is 15%, is around 3%. Table 7.7.2: 1 summarises the probability of observing certain ORRs based on different assumptions of the underlying ORR. **New Table 7.7.2: 1 was added.** **For the selected squamous tumours cohort (Cohort 6), probability calculations are provided in Table 7.4: 1 using the two-stage approach. Depending on the Stage I result for the squamous cohort, sample size may vary between 20 and 60 patients.**
Rationale for change		To update determination of sample size for Phase Ib.
Section to be changed		Table 10.1: 1 Immune-related adverse events of special interest
Description of change		**This table defines immune-related AEs that must be reported as AESIs.** Each subsection was updated as for the following example: Pneumonitis (reported as an AE**SI if** ≥ Grade 2)
Rationale for change		To clarify that all immune related AEs are reportable AEs. When they meet the criteria listed in Table 10.1:1, they must also be reported as AESIs.
Section to be changed		Table 10.4.1: 2
Description of change		Footnote removed: ~~*In the event that infusion duration is >15 minutes longer than planned, the subsequent time point for PK blood collection on the day of drug infusion should be adjusted accordingly.~~
Rationale for change		This footnote is no longer necessary since the sample is taken immediately before the end of infusion.
Section to be changed		Table 10.4.2: 1
Description of change		Footnote added for PK sampling: ****The following windows of time are allowed for PK sampling:** **Predose (PTM -0:05): within 1 hour before next drug infusion** **Shortly after end of infusion (PTM 1:00): within 5 min after the end of infusion** **24 through 336 hours post SOI (PTM 24:00 to 336:00): ±1 hour.** **Note: Time windows have been specified for procedural reasons; deviations do not automatically lead to exclusion of samples from data evaluation.**
Rationale for change		To clarify the windows of time allowed for PK sampling.

Number of global amendment		4
Date of CTP revision		15 May 2018
EudraCT number		**Not applicable**
BI Trial number		**1381.1**
BI Investigational Product		**BI 754091**
Title of protocol		**An open-label, Phase I trial to determine the maximum-tolerated dose and investigate safety, pharmacokinetics, and efficacy of BI 754091 in patients with advanced solid tumours**
To be implemented only after approval of the IRB / IEC / Competent Authorities		**X☒X**
To be implemented immediately in order to eliminate hazard – **IRB / IEC / Competent Authority to be notified of change with request for approval**		☐
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		☐
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
Description of change		**EudraCT No. 2017-005043-33**
Rationale for change		The trial will expand into the UK where a EudraCT No is required
Section to be changed		Synopsis Main criteria for inclusion and Section 3,3.2 Inclusion Criteria
Description of change		- Cohort 5: Patients with tumours that are TMB-high: any tumour with TMB-high status (>**10**~~20~~ mutations/Mb) ~~based on the Foundation Medicine assay~~, excluding those that are MSI-high ~~based on the Foundation Medicine assay or another validated test~~ **(TMB and MSI status based on any validated test)**
Rationale for change		The tumor mutational burden has been changed to >10 based on recent research. In addition, to allow for more flexibility, Foundation Medicine assays will no longer be specified in the protocol.
Section to be changed		Section 4.1.5 Definition of dose-limiting toxicity, Section 5.1.1 Primary endpoints (and Synopsis) Section 5.3 Assessment of Safety (and Synopsis) Section 5.3.6.6 Severity of adverse events
Description of change		CTCAE Version **5.0**~~4.03~~
Rationale for change		Adverse events will be graded by the most recent CTCAE version.
Section to be changed		Flow Chart 1 and Flow Chart 2
Description of change		ECOG marked to be assessed on Cycle 3,5,7, 9 etc.
Rationale for change		Added clarification to the footnote stating that ECOG should be assessed every other cycle
Section to be changed		Flow Chart 1 and Flow Chart 2
Description of change		Physical examination ECOG assessment, vital signs, and pregnancy added to the PFS follow up.
Rationale for change		To clarify assessments to be conducted during PFS follow up.
Section to be changed		Flow Chart 1 and Flow Chart 2
Description of change		All cycles are 3 weeks (21 days) in duration. Patients will continue treatment with BI 754091 until disease progression (PD) by RECIST and/or ~~i~~RECIST, 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 signs an informed consent describing this circumstance**. In addition, patients without PD may stay

		on trial after 1 year on a case-by-case basis after discussion with the Medical Monitor and the sponsor. Day 1 of Cycle 1 is defined as the day when BI 754091 is first administered. During Phase Ia (dose escalation), Cycle 2 cannot begin without Safety Review Committee approval.
Rationale for change		With the implementation of iRECIST in this protocol, patients will be re-consented to remain on treatment following PD per RECIST 1.1, until a confirmed progression per iRECIST.
Section to be changed		Flow Chart 2
Description of change		Vital signs, concomitant medications, and adverse events will no longer be assessed on Days 2 and 15 of Cycles 4 and 8.
Rationale for change		Patients will not need to come to the clinic on these days where no blood samples are needed.
Section to be changed		Flow Chart 2
Description of change		Cycles 10, 11, 13, 14, 16, 17, etc. column added
Rationale for change		To clarify that patients should return to the clinic every cycle for a physical assessment, ECOG assessment (every other cycle), vital signs assessment, pregnancy test, concomitant medication review, and adverse events assessment.
Section to be changed		Abbreviations
Description of change		~~ir~~RECIST Immune ~~Related~~ Response Evaluation Criteria in Solid Tumours
Rationale for change		iRECIST will replace irRECIST for response assessments
Section to be changed		Section 2.1 Rationale for Performing the Trial
Description of change		**More recent data have demonstrated that the combination of nivolumab and ipilimumab had better efficacy in NSCLC patients with a tumour mutational burden of at least 10 mutations per megabase than those with < 10 mutations per megabase (R18-1492). As such, a ≥ 10 mutation per megabase threshold was selected to define patients with high TMB for this trial.**
Rationale for change		The research upon which the change in the mutational burden cutoff was provided.
Section to be changed		Section 3.1 Overall Trial Design and Plan
Description of change		Patients will continue treatment with BI 754091 until disease progression (PD) according to the Response Evaluation Criteria in Solid Tumours (RECIST) ~~and/or Immune-Related Response Evaluation Criteria in Solid Tumours (irRECIST) (R16-0342)~~ **and the Guidelines for Response criteria for use in trials testing immunotherapeutics (iRECIST) (R17-0923),** withdrawal of patient consent, an unacceptable toxicity occurs, or 1 year of treatment is completed, whichever occurs first.
Rationale for change		iRECIST will replace irRECIST for response assessments
Section to be changed		[redacted]
Description of change		

		[redacted]
Rationale for change		
Section to be changed		Section 5.2.1 Tumor assessments
Description of change		The tumour response will be evaluated according to RECIST Version 1.1 (R09-0262) and ~~i~~RECIST (R17-0923~~-R16-0342~~).
Rationale for change		iRECIST will replace irRECIST
Section to be changed		Section 5.5 Assessment of Biomarkers
Description of change		• Also, genomic profiling ~~may~~**will** be performed **when possible** on pre-treatment biopsies in order to define **tumour** mutational load (unless a similar analysis has been performed beforehand).
Rationale for change		To clarify that genomic profiling should be performed on pre-treatment tumour biopsies, if possible.
Section to be changed		Section 6.2.1.1
Description of change		For Cohort 5, the TMB, as well as the microsatellite stability (MS) status have to be assessed. Patients that have high TMB (defined as ≥**10**~~20~~ mutations/Mb) and are MS stable (MSS) will be included. ~~Whereas for MS status determination~~**A**~~a~~ny validated assay may be used **to determine the MS status and TMB**~~., the TMB has to be measured by Foundation Medicine (FM). Patients may be included that fulfil the criteria (1) having undergone~~

		~~testing by FM previously; (2) if evidence is available that the criteria may be fulfilled (or with sponsor approval) after providing archival tumour material (as specified in the lab manual) and testing by FM; or (3) if evidence is available that the criteria may be fulfilled, after providing an additional fresh tumour biopsy and testing by FM. Options 2 and/or 3 may be discontinued at the sponsor's discretion.~~
Rationale for change		The tumor mutational burden has been changed to > 10 based on recent research. In addition, to allow for more flexibility, Foundation Medicine assays will no longer be specified in the protocol.
Section to be changed		Section 7.7.2 Determination of sample size for Phase Ib
Description of change		Several papers demonstrated the association between high TMB and better response rates, progression-free survival, and overall clinical benefit. **In Hellmann et al., 2018 (R18-1492) response rates were 45.3% (63/139) in patients with ≥10 mutations/mega base.**~~In Goodman et al., 2017 (R17-3768), response rates were 58% (22/38) in patients with ≥20 mutations/mega base compared to 20% (23/113) in patients with low mutational burden.~~
Rationale for change		The research upon which the change in the mutational burden cutoff was provided.
Section to be changed		Section 9.1 Published references
Description of change		**R17-0923** **Seymour L, Bogaerts J, Perone A, Ford R, Schwartz LH, Mandrekar S, et al. RECIST Working Group iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. Lancet Oncol. 2017;18(3):e143-e152.** **R18-1492** **Hellmann MD, Ciuleanu TE, Pluzanski A, Lee JS, Otterson GA, Audigier-Valette C, et al. Nivolumab plus ipilimumab in lung cancer with a high tumor mutational burden. N Engl J Med. 2018 Apr 16. doi: 10.1056/NEJMoa1801946. [Epub ahead of print]**
Rationale for change		To provide the relevant references for iRECIST assessments and the updated tumour mutational burden cut-off are added.

Number of global amendment		5
Date of CTP revision		14 September 2018
EudraCT number		Not applicable
BI Trial number		1381.1
BI Investigational Product		BI 754091
Title of protocol		An open-label, Phase I trial to determine the maximum-tolerated dose and investigate safety, pharmacokinetics, and efficacy of BI 754091 in 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		Synopsis: Objectives
Description of change		Phase Ib Dose Expansion: To further evaluate the safety, the PK profile, biomarkers, and efficacy of the RP2D in ~~3~~**4** cohorts of patients with selected advanced and/or metastatic cancers
Rationale for change		To include Cohort 7
Section to be changed		Synopsis: Methodology
Description of change		Phase Ib Dose Expansion: Open-label, ~~3~~**4** dose-expansion cohorts
Rationale for change		To include cohort 7
Section to be changed		Synopsis: No. of Patients
Description of change		Approximately 1~~40~~5 patients, depending on dose-escalation results
Rationale for change		To include the patients that will be enrolled in Cohort 7
Section to be changed		Synopsis: Total Entered
Description of change		Phase Ib Dose Expansion at the RP2D: ~~3~~**4** cohorts of approximately 30-**40** patients each
Rationale for change		To include the patients that will be enrolled in Cohort 7
Section to be changed		Synopsis: Diagnosis
Description of change		- **Cohort 7: Recurrent human papillomavirus (HPV)-positive, or HPV-negative (per local testing), vaginal or vulvar squamous cell carcinoma (VSCC) not amenable to surgery.**
Rationale for change		To provide details of Cohort 7 diagnoses
Section to be changed		Synopsis: Main criteria for inclusion
Description of change		- **Cohort 7: Patients with recurrent HPV-positive, or HPV-negative, vaginal or VSCC.**
Rationale for change		To provide inclusion criteria for Cohort 7 patients
Section to be changed		Synopsis: Endponts
Description of change		~~If feasible, the following PK parameters will be calculated: C_{max} and AUC_{0-504} after single and multiple dose of BI 754091, as measured during the first and subsequent cycles (administration q3w).~~

Rationale for change		No PK parameters are needed as a secondary endpoint in the expansion phase.
Section to be changed		Flow Chart 2
Description of change		BI 754091 infusion is marked **X** in the Cycles 10, 11, 13, 14, 16, 17, etc. column
Rationale for change		To correct the flowchart to clarify that BI 754091 will occur on Day 1 of all cycles as noted elsewhere in protocol.
Section to be changed		Flow Chart 2
Description of change		Footnote l: The following fresh tumour biopsies will be mandatory for all patients in the Phase Ib dose-expansion cohorts of the trial (refer to Section 6.2.1.1): - 2 core needle biopsies or 1 punch biopsy (refer to lab manual for specifications) from the most recent relapse (if within 6 months of trial start with no subsequent therapy); otherwise, a minimum of 2 core needle biopsies or 1 punch biopsy must be taken between **the start of** screening and the day before first treatment with BI 754091.
Rationale for change		To clarify when the fresh tumour biopsies will be collected for Phase Ib dose expansion patients
Section to be changed		Section 1.1 Medical Background
Description of change		**Results from anti-PD-1 studies in cervical carcinoma, an HPV- linked gynecological cancer, provide rationale for studying immunotherapy in vulvar squamous cell carcinoma (VSCC). Preliminary data from the phase I/II CheckMate358 study (NCT 02488759), which evaluates nivolumab in virus-associated, recurrent or metastatic cervical, vaginal and vulvar carcinoma, showed that in the nivolumab-treated cohort, the ORR and the disease control rate (ORR + SD) were 20.8% and 70.8%, respectively.**
Rationale for change		To provide background information about patients with VSCC.
Section to be changed		Section 2.1 Rationale for Performing the Trial
Description of change		The second part consists of ~~3~~**4** expansion cohorts at the RP2D that will also further evaluate the safety, tolerability, efficacy, PK, and biomarkers of BI 754091.
Rationale for change		To include Cohort 7.
Section to be changed		Section 3.1 Overall Trial Design and Plan
Description of change		Following determination of the MTD and/or RP2D from the Phase Ia portion, separate cohorts of approximately 30-**40** patients each will be conducted in patients with select advanced solid malignancies including tumours with specific histology/tumour types and/or specific genetic profiles as specified in the following cohorts:

		• **Cohort 7: Recurrent human papillomavirus (HPV)-positive, or HPV-negative, vaginal or vulvar squamous cell carcinoma (VSCC)** The Phase Ib portion of the trial will further evaluate the safety, tolerability, efficacy, PK profile, and biomarkers of BI 754091. The analysis of the squamous cell tumour cohort (Cohort 6) **and the VSCC cohort (Cohort 7)** will follow a two-stage approach. The interim analysis for **Cohort 6**: • Squamous cervical and/or anal cancer, Stage 1 will include 10 treated patients. • Squamous skin tumours, Stage 1 will include 10 treated patients. **The interim analysis for Cohort 7:** • **Vaginal or VSCC, Stage 1 will include 20 treated patients.** Based on the interim analyses results, the sponsor will determine if recruitment into these tumour groups will continue or be terminated **(recruitment does not have to pause while interim analysis is conducted)**.
Rationale for change		To include Cohort 7.
Section to be changed		Section 3.3.2 Inclusion criteria
Description of change		4. Phase 1b (dose expansion): **Cohort 7: Recurrent HPV-positive, or HPV-negative (per local testing), vaginal or VSCC, not amenable to surgery.**
Rationale for change		To provide inclusion criteria for Cohort 7 patients
Section to be changed		Section 3.3.2 Inclusion criteria
Description of change		7. Females of childbearing potential willing to use adequate contraceptive measures from the time of screening until 6 months after trial discontinuation, who are not or will not be breast feeding, and agree to have pregnancy tests prior to the start of dosing and at regular visits during the trial. Females not of childbearing potential must have evidence of such by fulfilling one of the following criteria at screening: - For women of childbearing potential using a contraceptive pill, an additional barrier method is necessary. ~~A list of adequate contraception methods is provided in the patient information.~~ **Acceptable highly effective methods of contraception include total sexual abstinence when this is in line with the preferred and usual lifestyle of the study participant (periodic abstinence such as calendar, ovulation, symptothermal, post-ovulation methods and withdrawal are not acceptable methods of contraception), an intrauterine device or intrauterine hormone-releasing system, bilateral tubal ligation, and vasectomised partner (with post-vasectomy proof of absence of sperm)**
Rationale for change		Appropriate contraception methods are defined.
Section to be changed		Section 3.3.3 Exclusion criteria

Description of change		13. Known history of human immunodeficiency virus infection or an active hepatitis B or C virus infection. **HIV infection is allowed for patients in cohort 6 (cervical/anal squamous) and cohort 7 (vulvar)**.~~(exception: this criteria does not apply to patients with cervical/anal tumours enrolling in Cohort 6)~~
Rationale for change		To clarify that patients with HIV may enroll on Cohort 6 and Cohort 7.
Section to be changed		Section 4.1.9 Administration of doses for each patient
Description of change		**Sites will provide normal saline (sodium chloride 0.9%) for the dilution of study drug. For sites in the UK, the saline must be an EU licensed product.**
Rationale for change		To provide further details about drug dilution
Section to be changed		Section 4.2.3.2 Restrictions regarding women of childbearing potential
Description of change		Highly-effective methods of contraception include: • **Total sexual abstinence when this is in line with the preferred and usual lifestyle of the study participant, OR** • **Bilateral tubal ligation, OR** • **Vasectomised partner (with appropriate post-vasectomy documentation of the absence of sperm in the ejaculate and provided that partner is the sole sexual partner of the woman of childbearing potential study participant), OR** • ~~Oral, injected, or implanted hormonal methods of contraception, OR~~Intrauterine device or intrauterine **hormone-releasing** system ~~OR~~ • ~~"Double Barrier" methods of contraception: Male condom in combination with female diaphragm/cervical cap plus spermicidal foam/gel/film/cream.~~ Details of these contraception methods are **also** described in the patient information in the ICF.
Rationale for change		To define highly-effective contraception methods.
Section to be changed		Section 5.1.2.1 Secondary endpoints of the Phase Ia (dose escalation) portion of the trial
Description of change		• Depending on available data, the same PK parameters calculated during the Phase Ia portion of the trial will be calculated for the dose-expansion portion.
Rationale for change		No PK parameters are needed as a secondary endpoint in the expansion phase.
Section to be changed		[redacted]
Description of change		

		[redacted]
Rationale for change		
Section to be changed		[redacted]
Description of change		
Rationale for change		
Section to be changed		Section 5.2.1 Tumour assessments
Description of change		Copies of scans **are to**~~may~~ be collected by the sponsor upon request **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		To allow for collection of scans for later radiometric assessments.
Section to be changed		Section 5.4.1 Assessment of pharmacokinetics
Description of change		~~The parameters are defined as:~~ • ~~C_{max}: maximum measured concentration of BI 754091 in plasma~~ • ~~$AUC_{0\text{-}504}$: area under the concentration-time curve of BI 754091 in plasma over the time interval from 0 to 504 hours~~ [redacted]

		[redacted] ~~If feasible, the following additional PK parameters may be determined for BI 754091 after single and multiple doses of BI 754091, as measured during the first and subsequent cycles (administration q3w) and evaluated as further endpoints:~~ [redacted] ~~If deemed necessary, further PK parameters might be calculated.~~
Rationale for change		Duplicate text removed.
Section to be changed		Section 6.2.1.3 Medical History
Description of change		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 clarify that relevant disease history will be collected in the eCRF.
Section to be changed		Section 6.2.1.3 Medical History
Description of change		Exclusion criteria #13 (see Section 3.3.3) does not apply to the patients with cervical/anal **and vulvovaginal** cancer enrolling into Cohorts 6 **and 7**.
Rationale for change		To include Cohort 7 to the Exclusion criteria #13 exception.
Section to be changed		Section 7.1.2 Statistical design-Phase Ib (dose expansion)
Description of change		The Phase Ib (dose-expansion) portion of the trial will recruit approximately ~~90~~**130** patients with selected locally advanced or metastatic cancers at the dose and schedule recommended by the SRC.
Rationale for change		To include the patients that will be enrolled on Cohort 7
Section to be changed		Section 7.4 Interim Analyses
Description of change		**Interim efficacy analyses were not deemed necessary for the TMB high cohort 5 as recent literature already demonstrates an association between high TMB and better response rates for patients taking immune checkpoint inhibitors (R18-1492).**

		The interim analyses **for Cohort 6** will be conducted when: • 10 patients with squamous cervical and/or anal cancer have been treated, and the 10th patient has been on treatment for ~3 months. • 10 patients with squamous skin tumours have been treated, and the 10th patient has been on treatment for ~3 months. **The interim analysis for Cohort 7 will be conducted when 20 patients with vaginal or VSCC have been treated, and the 20th patient has been on treatment for ~3 months.**
Rationale for change		To add details about the Cohort 7 interim analysis
Section to be changed		Section 7.4 Interim Analyses
Description of change		• **Literature on preliminary data from older chemotherapy/targeted agent trials (R18-2645; R18-2646; R18-2647) and early phase immunotherapy trials (R18-2650; R18-2651) showed ORR ranges from 13% to 29% in patients with recurrent, inoperable VSCC. Therefore, an underlying ORR of 25% is assumed. The probability of observing 0 or 1 responder out of 20 and stopping at interim is 2%, and the probability of observing ≥20% ORR at final analysis is 82%. If the underlying ORR is 5%, the probability of stopping early is 74%, and the false positive probability of observing ≥20% ORR at final analysis is almost 0.**
Rationale for change		To provide the background information used to inform the Cohort 7 interim analysis parameters
Section to be changed		Table 7:4.1 Early stopping criterion and probabilities for the two-stage approach-selected patient groups

Description of change

Assumed underlying ORR	Total sample size	Stage 1 sample size	Early stopping criterion (obser ORR)	Early stop prob.	Observed ORR at final	Prob of observed ORR at final
Vaginal or VSCC patients						
5%	40	20	<10% (< 2 out of 20)	74%	>=20% (>= 8 out of 40)	0%
10%	40	20	<10% (< 2 out of 20)	39%	>=20% (>= 8 out of 40)	4%
15%	40	20	<10% (< 2 out of 20)	18%	>=20% (>= 8 out of 40)	25%
20%	40	20	<10% (< 2 out of 20)	7%	>=20% (>= 8 out of 40)	56%
25%	40	20	<10% (< 2 out of 20)	2%	>=20% (>= 8 out of 40)	82%
30%	40	20	<10% (< 2 out of 20)	1%	>=20% (>= 8 out of 40)	94%

Rationale for change		To provide early stopping criteria for Cohort 7
Section to be changed		Section 7.7.2 Determination of sample sizes for Phase Ib
Description of change		**For the vaginal or VSCC cohort (Cohort 7), probability calculations are provided in Table 7.4: 1 using the two-stage approach. If the stage 1 result is positive (i.e., at least 2 responders out of 20 patients), sample size for this cohort will be increased to 40 patients; otherwise, recruitment will be stopped in case of negative interim analysis.**
Rationale for change		To provide early stopping criteria for Cohort 7
Section to be changed		Section 9.1 Published References
Description of change		**R18-2645** **Horowitz NS, Olawaiye AB, Borger DR, Growdon WB, Krasner CN, Matulonis UA, Liu JF, Lee J, Brard L, Dizon DS. Phase II trial of erlotinib in women with squamous cell carcinoma of the vulva. Gynecol Oncol. 2012 Oct;127(1):141-6.** **R18-2646** **Witteveen PO, van der Velden J, Vergote I, Guerra C, Scarabeli C, Coens C, Demonty G, Reed N. Phase II study on paclitaxel in patients with recurrent, metastatic or locally advanced vulvar cancer not amenable to surgery or radiotherapy: a study of the EORTC-GCG (European Organisation for Research and Treatment of Cancer--Gynaecological Cancer Group). Ann Oncol. 2009 Sep;20(9):1511-6.** **R18-2647** **Monk BJ, Sill MW, Burger RA, Gray HJ, Buekers TE, Roman LD. Phase II trial of bevacizumab in the treatment of persistent or recurrent squamous cell carcinoma of the cervix: a gynecologic oncology group study. J Clin Oncol. 2009 Mar 1;27(7):1069-74.** **R18-2650** **Schellens JHM, Marabelle A, Zeigenfuss S, Ding J, Pruitt SK, Chung HC. Pembrolizumab for previously treated advanced cervical squamous cell cancer: Preliminary results from the phase 2 KEYNOTE-158 study. J Clin Oncol 35, 2017 (suppl; abstr 5514)** **R18-2651** **Hollebecque A, Meyer T, Moore KN, Machiels J-PH, De Greve J, López-Picazo JM. An open-label, multicohort, phase I/II study of nivolumab in patients with virus-associated tumors (CheckMate 358): Efficacy and safety in recurrent or metastatic (R/M) cervical, vaginal, and vulvar cancers. J Clin Oncol 35, 2017 (suppl; abstr 5504)**
Rationale for change		To provide references added for the Cohort 7 background
Section to be changed		Section 9.1 Published References

Description of change		~~R16-0342 Bohnsack O, Hoos A, Ludajic K. Adaptation of the immune related response criteria: irRECIST. ESMO 2014. Ann Oncol. 2014; 25(suppl_4): iv361-iv372. 10.1093/annonc/mdu342.~~ ~~R17-3651 Castellucci E, He T, Goldstein DY, Halmos B, Chuy J. DNA Polymerase e Deficiency Leading to an Ultramutator Phenotype: A Novel Clinically Relevant Entity. Oncologist. 2017;22(5):497-502. doi: 10.1634/theoncologist.2017-0034. Epub 2017 May 2.~~ ~~R17-3767 Nebot-Bral L, Brandao D, Verlingue L, Rouleau E, Caron O, Despras E, et al. Hypermutated tumours in the era of immunotherapy: the paradigm of personalized medicine. Eur J Cancer. 2017;84:290-303. doi: 10. 1016/j.ejca.2017.07.026. Epub 2017 Aug 29.~~ ~~R17-3823 Luksza M, Riaz N, Makarov V, Balachandran VP, Hellmann MD, Solovyov A,et al. A neoantigen fitness model predicts tumour response to checkpoint blockade immunotherapy. Nature. 2017 Nov 8. doi:10.1038/nature24473. [Epub ahead of print]~~
Rationale for change		To remove references no longer used in the CSP.

Number of global amendment		6
Date of CTP revision		08 March 2021
EudraCT number		2017-005043-33
BI Trial number		1381.1
BI Investigational Product		BI 754091
Title of protocol		An open-label, Phase I trial to determine the maximum-tolerated dose and investigate safety, pharmacokinetics, and efficacy of BI 754091 in 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~~. Please note that formatting changes and minor changes to punctuation or spelling that do not affect meaning are not noted in this summary.		
Section to be changed		Title page

Description of change		BI Investigational Product name Ezabenlimab added
Rationale for change		An official name, **ezabenlimab**, has been assigned to BI 754091 during the time after the last CTP version update.
Section to be changed		Title page
Description of change		BI Trial Clinical [redacted] name changed to [redacted]
Rationale for change		Change in TCM responsibility.
Section to be changed		Synopsis (Endpoints for the Phase Ia Dose Escalation, Safety Criteria); Sections: 4.1.5 Definition of dose-limiting toxicity, 5.1.1 Primary endpoints, 5.3 Assesment of Safety, 5.3.6.6 Severity of adverse events,
Description of change		CTCAE Version **4.03** added along with Version 5.
Rationale for change		Patients entered before amendment 4 used V4.03 and patients entered afterwards used V5.0.
Section to be changed		Synopsis (Endpoints for the Phase Ia Dose Escalation: Secondary, Endpoints for the Phase Ia Dose Expansion: Primary); 5.1.1 Primary endpoints; 5.1.2.1 Secondary endpoints of the Phase Ia (dose escalation) portion of the trial; 5.1.3. Further endpoints.
Description of change		Definition of Response (Objective Response) has been corrected to **Confirmed** Response (**Confirmed** Objective response) throughout the CTP.
Rationale for change		Clarification of the endpoint definition.
Section to be changed		Synopsis (Endpoints for the Phase Ia Dose Expansion: Secondary); 5.1.2.1 Secondary endpoints of the Phase Ia (dose escalation) portion of the trial.
Description of change		The following definitions for the safety endpoints were added: -**Percentage of subjects with AEs** **-Percentage of subject with SAEs** **-Percentage of subjects with clinical relevant abnormalities in vital signs, laboratory evaluations or ECG parameters (note that clinically relevant abnormalities are those which have to be reported by the investigator as AEs).**
Rationale for change		To clarify the precise definition of the safety endpoints.
Section to be changed		Section 3.3.4.2 Discontinuation of the trial by the sponsor.
Description of change		The flowing paragraph was added: "**In case the trial is ended by the sponsor, the available clinical trial data will be analysed and reported approximately one year after the last patient has been enrolled. Patients who are still being treated with BI 754091 when the primary report of the trial is being prepared, will be kept on treatment in this trial and finalize the clinical observation period. Data of those patients will then be reported in a revised report and it will be noted in the primary report that such a revised report will be written.**"

Rationale for change		Clarification of the data handling rules after trial discontinuation by the sponsor.
Section to be changed		Flow Chart 2 and Footnote "r"; Section 5.5.2.1 Biomarker assessments in blood samples; Table 10.4.2.1 and foot note 1.
Description of change		Footnote "**r**" was added: **Only patients completed the activity up to until the cut of date for the primary report. All remaining patients will undergo EOT and 30 days visits safety procedures only.** The following test was added: **Only patients completed this activity up to until the cut of date for the primary report.**
Rationale for change		After the trial discontinuation by the sponsor, PK/PD and biomarker sampling will not be collected for patients continuing in the study after the cut-off date for primary report DBL. These additional data are not anticipated to provide significant benefit to the patients or the sponsor.
Section to be changed		[redacted]
Description of change		
Rationale for change		
Section to be changed		
Description of change		
Rationale for change		
Section to be changed		Section 5.4.1 Assessment of pharmacokinetics; Section 7.3.5 Pharmacokinetic and pharmacodynamic analyses
Description of change		Descriptions of the following BI internal SOPs deleted:

		~~(001-MCS-36-472_RD-01 [2.0] and Venn Life Sciences SOP 'SOP-1.PKA.03 Non-compartmental PK/PD Analysis').~~ ~~(001-MCS-36-472_RD-01 [actual version] and Venn Life Sciences SOP 'SOP-1.PKA.03 Non-compartmental PK/PD Analysis').~~
Rationale for change		During the trial conduct the SOPs were updated therefore the references listed in the CTP are not needed.
Section to be changed		Section 7.1.1 Statistical design – Phase 1a (dose escalation)
Description of change		The first cycle dose has been corrected in the paragraph below: "The objective of the Phase Ia portion of the trial is to determine the MTD and the RP2D. first cycle at dose d, d* = **800** ~~3200~~ mg"
Rationale for change		Mistake in writing has been corrected.

Number of global amendment		8
Date of CTP revision		07 March 2023
EudraCT number		2017-005043-33
BI Trial number		1381.1
BI Investigational Product		BI 754091
Title of protocol		An open-label, Phase I trial to determine the maximum-tolerated dose and investigate safety, pharmacokinetics, and efficacy of BI 754091 in 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~~. Please note that formatting changes and minor changes to punctuation or spelling that do not affect meaning are not noted in this summary.		
Section to be changed		Synopsis – Duration of treatment; Flow chart 1 and 2, foot note 1.
Description of change		From: BI 754091 will be given on Day 1 of 21-day cycles for up to 1 year, or until progressive disease (PD) or unacceptable toxicity in the absence of other withdrawal criteria. If the patient is benefiting clinically at 1 year, he/she may continue after a case by case review with the sponsor. To: BI 754091 will be given on Day 1 of 21-day cycles for up to 1 year, or until progressive disease (PD) or unacceptable toxicity in the absence of other withdrawal criteria. If the patient is benefiting clinically at 1 year, he/she may continue after a case by case review with the sponsor, but no longer than 31 August 2023.
Rationale for change		Treatment duration limitation added due to BI 754091 monotherapy program discontinuation.
Section to be changed		Section 3.1 Overall trial design and plan
Description of change		Last sentence modified as follows: In addition, patients without PD may stay on trial after 1 year on a case-by-case basis after discussion with the Medical Monitor and the sponsor, but no longer than 31 August 2023. After this date treatment with the ezabenlimab will no longer be available.
Rationale for change		Treatment duration limitation added due to BI 754091 monotherapy program discontinuation.
Section to be changed		Section 3.3.4.2 Discontinuation of the trial by the sponsor
Description of change		Addition: 5. Termination of the development program by the sponsor.
Rationale for change		Trial discontinuation criterium added. Although a preliminary assessment of the available data from the ongoing clinical program for the ezabenlimab exhibit signs of antitumour activity and a manageable safety profile for an overall positive benefit risk ratio, careful review of the full data set performed in the context of the current standards of care for the indications under study has led to the decision taken by the sponsor to discontinue the BI 754091 mono-therapy program, and terminate further expansion of the study.
Section to be changed		Section 4.1.11 Packaging, labelling, and re-supply
Description of change		Addition: No re-supply will be possible after 31 August 2023.

Rationale for change		To emphasize that the study medication will not be available after 31 August 2023.
Section to be changed		Section 6.2.3.1 End-of-treatment visit.
Description of change		Addition: For patients still on treatment with ezabenlimab at the time point of this protocol amendment, the investigators are asked to prepare for discontinuation of patients from the current investigational treatment with ezabenlimab and to switch them to alternative available treatment options outside of the current protocol no later than by the final availability of ezabenlimab in August 2023 the latest. After this date treatment with the ezabenlimab will no longer be available. For these patients only EOT visit will be performed. 30-day post-treatment safety visit as well as Progression-free survival visits are not applicable.
Rationale for change		To provide an updated guidance for the EOT visit.

APPROVAL / SIGNATURE PAGE

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Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
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Approval-Clinical Program		07 Mar 2023 15:39 CET
Verification-Paper Signature Completion		08 Mar 2023 16:49 CET

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