Clinical Trial Protocol

Document Number:		**c16043709-08**
EudraCT No.:	2017-005042-29	
BI Trial No.:	1381.2	
BI Investigational Product:	BI 754111 and BI 754091	
Title:	An open label, Phase I dose-finding study of BI 754111 in combination with BI 754091 in patients with advanced solid cancers followed by expansion cohorts at the selected dose of the combination in patients with non-small cell lung cancer and other solid tumors	
Lay Title:	This study tests the new medicine BI 754111 alone or in combination with another new substance BI 754091 in patients with advanced cancer. The study tests different doses to find the best dose for continuous treatment.	
Clinical Phase:	Phase I	
Coordinating Investigator	[redacted]	
Trial Clinical Monitor:	[redacted] Phone: [redacted] Fax: [redacted]	
Status:	Final protocol (revised protocol [based on global Amendment 8])	
Version and Date:	**Version: 9.0**	**Date: 20 May 2020**

CLINICAL TRIAL PROTOCOL SYNOPSIS

Name of company:		**Boehringer Ingelheim**	
Name of finished product:		N.A.	
Name of active ingredient:		BI 754111 and BI 754091	
Protocol date: 09 Mar 2017	**Trial number:** 1381.2		**Revision date:** 20 May 2020

Title of trial:	An open label, Phase I dose-finding study of BI 754111 in combination with BI 754091 in patients with advanced solid cancers followed by expansion cohorts at the selected dose of the combination in patients with non-small cell lung cancer and other solid tumors
Clinical phase:	I
Objectives:	**Part I (Dose-Escalation Cohorts):** The objectives of the dose-escalation portions of the trial are to: • Investigate the safety, tolerability, and pharmacokinetics (PK) of escalating doses of BI 754111 in combination with BI 754091 (administered via intravenous [i.v.] infusion once every 3 weeks [q3w]) in patients with advanced and/or metastatic solid tumours. • Determine the maximum-tolerated dose (MTD) through monitoring dose-limiting toxicities (DLTs) and/or to determine the dose of the combination of BI 754111 plus BI 754091 to be used in the expansion phase (Part II). **Part II (Dose-Expansion Cohorts):** The objectives of the dose-expansion portion of the trial are to: • Further investigate the safety, tolerability, and PK of the selected expansion dose of the combination of BI 754111 plus BI 754091 in patients with non-small-cell lung cancer (NSCLC), microsatellite stable (MSS) metastatic colorectal cancer (mCRC), or any anti-PD-1 or anti-PD-L1 pretreated solid tumour with high tumour mutational burden (TMB) and/or microsatellite instability high (MSI-H) and/or DNA mismatch repair deficient (MMRd),as defined in the entry criteria • Explore the efficacy of the combination in patients with NSCLC, mCRC, or any solid tumour with high TMB and/or DNA MSI-H and/or MMRd (as defined in the entry criteria).
Methodology:	**Part I (Dose-Escalation Cohorts):** **For patients with solid tumours**: open-label, non-randomised, dose-escalation into consecutive cohorts of BI 754111 in combination with BI 754091. Dose escalation will be guided by Bayesian Logistic Regression Models (BLRMs) with overdose control for BI 754111 + BI 754091 combination therapy. **Part II (Dose-Expansion Cohorts):** Open-label, non-randomised, dose-expansion cohorts with the selected dose of the combination in patients with NSCLC, MSS mCRC, or any anti-PD-1 or anti-PD-L1 pretreated solid tumour with high TMB and/or MSI-H and/or DNA MMRd.
No. of patients:	**Part I (Dose-Escalation Cohorts):** Approximately 15 to 50 patients

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	Part II (Dose-Expansion Cohorts): 160 patients total
Total entered:	Approximately 175 to 210 patients are planned to be enrolled in this trial.
Each treatment:	**Part I:** a minimum of 3 patients with solid tumours per dose-escalation cohort **Part II:** 160 patients
Diagnosis:	**Part I (Dose-Escalation Cohorts):** Patients with a confirmed diagnosis of advanced, unresectable, and/or metastatic solid tumours **Part II (Dose Expansion Cohorts):** Patients with a confirmed diagnosis of advanced, unresectable, and/or metastatic solid tumours of one of the following types: • Second and 3rd line NSCLC patients who progressed on anti-PD-1 or anti-PD-L1 treatment after having achieved radiologically confirmed benefit (minimum of stable disease). • Anti-PD-1 and anti-PD-L1 naïve second line or greater microsatellite stable mCRC. • Anti-PD-1 or anti-PD-L1 pretreated (can include BI 754091) patients with any solid tumour with TMB high (≧10 mutations/Mb) and/or MSI-H and/or DNA MMRd • First line NSCLC patients with wildtype (wt) epidermal growth factor receptor [EGFR] and anaplastic lymphoma kinase [ALK] tumors of squamous or non-squamous origin.
Main criteria for inclusion:	**All Cohorts:** • Adult patients at least 18 years-of-age with no active use of systemic steroids, no active auto-immune disease, and a life expectancy of at least 12 weeks • Eastern Cooperative Oncology Group (ECOG) performance status 0-1 **Part I (Dose-Escalation Cohorts):** • Patients with a confirmed diagnosis of advanced, unresectable, and/or metastatic solid tumours (any type) • For patients in Part I with solid tumours: - For whom no therapy of proven efficacy exists, or who are not amenable to standard therapies. - Must have measurable lesions according to Revised Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 and iRECIST - Previous treatment with an anti-PD-1 mAb is allowed as long as the last administration of the anti-PD-1 mAb on the previous treatment is a minimum of 60 days prior to starting treatment in this trial. **Part II (Dose-Expansion Cohorts):**

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	All patients must have measurable disease according to RECIST Version 1.1, must have at least 1 tumour lesion amenable to biopsy, and must be medically fit and willing to undergo a biopsy before first treatment (if adequate archival tissue is not available) and, unless clinically contraindicated, after 6 weeks on therapy. • 2nd or 3rd-line NSCLC patients: - Must have progressed on anti-PD-1 or anti-PD-L1 treatment after having achieved radiologically confirmed benefit (minimum of stable disease) - Must have had a minimum duration of benefit of 4 months, and minimum treatment duration of 2 months on the previous anti-PD-1 or anti-PD-L1 treatment without experiencing disease progression during that period. - The anti-PD-1- or anti-PD-L1-containing treatment must have been the latest treatment regimen prior to enrolling in this trial - Latest treatment must be within >4 and <12 weeks before their first dose in this trial. Patients who have had anti-PD-1 or anti-PD-L1 monotherapy as their first-line NSCLC treatment regimen must have a PD-L1 expression level of ≥1% at baseline (local validated testing). • Anti-PD-1 or anti-PD-L1 treatment naïve patients with microsatellite stable mCRC - Patients must have had ≥1 lines of systemic treatment • Anti-PD-1 or anti-PD-L1 pretreated patients with high TMB (≥10 mutations/Mb) and/or MSI-H and/or DNA MMRd solid tumours • 1st-line squamous or non-squamous NSCLC patients: - Patients must be treatment naïve - Must be EGFR WT and ALK WT (only applicable to patients with non-squamous NSCLC) - Regardless of PD-L1 expression level. However, the number of patients with high level of PD-L1 expression (≥50% PD-L1) will be limited to a maximum of 10 (local validated testing)
Main criterion for exclusion:	• No previous treatment with anti-lymphocyte-activation gene 3 (LAG-3; CD223) agents. • Untreated brain metastasis(es) that may be considered active.
Test products:	BI 754111 and BI 754091
Doses:	**Part I (Dose-Escalation Cohorts):** **For patients with solid tumours**: Increasing doses of BI 754111 starting with 4 mg in combination with BI 754091 at the RPIID (240 mg q3w) or a lower dose selected by the 1381.2 Safety Review Committee upon review of evolving data from Study 1381.1 (an ongoing study of BI 754091 using a BLRM with overdose control in patients with advanced solid tumours). Dose escalation of BI 754111 in combination with BI 754091 will be guided by a BLRM with overdose control.

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	Part II (Dose-Expansion Cohorts): The selected expansion dose of the combination determined in Part I for patients with solid tumours. For all cohorts, administration will be on Day 1 of each 21-day cycle.
Mode of administration:	Intravenous infusion
Duration of treatment:	Administration will continue until progression of disease (PD), unacceptable toxicity, or a maximum treatment duration of 1 year. If the patient is benefiting clinically at 1 year, he/she may continue on treatment after a case-by-case review with the Medical Monitor and the sponsor. Patients may be treated beyond initial radiological progression on a case-by-case basis (and after discussion with the medical monitor), if the investigator feels that it is in the patient's best interest and patient consents to this.
Endpoints	**Part I (Dose-Escalation):** Primary Endpoint: • MTD of the BI 754111 plus BI 754091 combination • Number of patients experiencing DLTs during the combination MTD evaluation period (Cycle 1, the first cycle of BI 754111 plus BI 754091 combination therapy) in patients with solid tumours Main Secondary Endpoints: • PK parameters will be calculated for BI 754111 and for BI 754091: C_{max} and area under the curve $(AUC)_{0-504}$. • Number of patients experiencing DLTs from start of treatment until end of treatment (in all cycles) • Objective response (OR) for patients with solid tumours: - Confirmed complete response (CR) and partial response (PR) according to RECIST Version 1.1 for patients with solid tumours as assessed by the Investigator throughout the entire treatment period. **Part II (Dose-Expansion Cohorts):** Primary Endpoint: • Objective response: confirmed CR and PR according to RECIST Version 1.1 as assessed by the Investigator during the entire treatment. Secondary Endpoints: • Duration of response is the duration from the date of first documented PR or CR according to RECIST Version 1.1 as assessed by the Investigator to the date of PD or death. • Disease control (DC) (CR, PR, or stable disease [SD] according to RECIST Version 1.1, as assessed by the Investigator). • Progression-free survival (PFS) is the duration from the date of first treatment to the date of PD or death.

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	• Number of patients experiencing DLTs from start of treatment until end of treatment.
Safety criteria:	Adverse events (AEs) according to CTCAE Version 5, incidence of DLTs for determination of the MTD (Part A dose-escalation cohorts only), results of physical examinations, laboratory evaluations, vital signs, and electrocardiograms (ECGs).
Statistical methods:	Part I: Dose escalation will be guided by BLRMs with overdose control that will be fitted to binary toxicity outcomes. The estimate of parameters will be updated as data are accumulated using BLRMs. At the end of dose escalation, the toxicity probability at each dose (combination) level will be calculated to determine an estimate of the selected expansion dose of the combination of BI 754111 plus BI 754091. If there are too few or no DLTs for BLRM guided dose selection, PK and/or biomarker data will be taken into consideration for dose determination. Part II: Efficacy response endpoints will be summarised descriptively. For OR and DC, the frequency and proportion of patients and 95% two-sided confidence interval will be presented. For PFS and duration of response, the median and 95% two-sided confidence interval will be presented using the Kaplan-Meier method. No hypothesis testing is planned in this trial.

FLOW CHART 1: BI 1381.2 (REFMAL 485) TRIAL ASSESSMENTS: PART I: SOLID TUMOUR DOSE-ESCALATION COHORTS

Flow Chart 1		Trial Treatment Days[a,b] Cycle = 21 Days						Post-Treatment Days[b]		
	Screening	Escalation Cycles 1, 2, and 4					Cycle 3 and 5+	End-of-Treatment[n] (EOT) Visit	30-Day[b] Safety Follow-up	PFS Follow-up[h]
Assessments (Days)	**-28 to -1**	**1**	**2**	**4**	**8 (±1)**	**15 (±1)**	**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]	X	X	X	
ECOG Performance Status[d, e]	X	X					X[e]	X	X	
Vital Signs[d]	X	X	X	X	X	X	X	X	X	
12-Lead Digital Electrocardiogram[d, f]	X	X				X	X(C3,5,6,8,10,12, etc and C3D15)	X	(X)	
Haematology and Clinical Chemistry Labs[d]	X	X			X	X	X		X	
Troponin[q]	X	X (C4)			X (C1,2)	X (C1)	X (C3,5)			
Urinalysis[d]	X	X					X	X		
Pregnancy Test for Women of Child-Bearing Potential[d, g]	X	X[g]					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

FLOW CHART 1: BI 1381.2 (REFMAL 485) TRIAL ASSESSMENTS: PART I: SOLID TUMOUR DOSE ESCALATION COHORTS (Continued)

Flow Chart 1	Trial Treatment Days[a,b] Cycle = 21 Days							Post-Treatment Days[b]		
	Screening	**Escalation Cycles 1, 2,and 4**					**Cycle 3 and 5+**	**End-of-Treatment[n] (EOT) Visit**	**30-Day[b] Safety Follow-up**	**PFS Follow-up[h]**
Assessments (Days)	**-28 to -1**	**1**	**2**	**4**	**8 (±1)**	**15 (±1)**	**1 (±2)**	**(within 7 days of EOT)**	**(+2)**	
Survival[h]										X
Blood Samples for [redacted][o]		X					X[o]	X[o]	X[o]	
Blood Samples for BI 754111 PK[j,o]		X	X	X	X	X	X[o]	X[o]	X[o]	
Blood Samples for BI 754091 PK[j,o]		X	X	X	X	X	X[o]	X[o]	X[o]	
Tumour Assessments[d, k]	X	Every 6 weeks ±3 days for the first 6 months (then every 9 weeks ±3 days thereafter)								
Administration of Pre-Treatment Medication[p]		X					X			
Study Drug Infusion[l]		X					X			
DLT Assessment[m]		X	X	X	X	X	X	X		

Flow Chart 1 Footnotes (Solid Tumour Escalation)

a All cycles are 3 weeks (21 days) in duration. Patients will continue treatment with the study drugs until disease progression (PD) by RECIST and/or iRECIST, withdrawal of patient consent, an unacceptable toxicity occurs, or 1 year of treatment is completed, whichever occurs first. Patients will be allowed to stay on treatment in the case of initial radiological PD, if the Investigator feels that it is in the patient's best interest and the patient signs an informed consent describing this circumstance. In addition, patients benefiting clinically and 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 the combination of BI 754111 and BI 754091 is 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 hematology, 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, aspartate aminotransferase [AST], alanine aminotransferase [ALT], alkaline phosphatase, bilirubin, lactate dehydrogenase, serum glucose, creatine phosphokinase [CPK: if CPK is elevated, then CPK-MB, troponin I, and myoglobin should be reactively tested], serum urea nitrogen (or urea), serum uric acid, and thyroid panel [TSH, free T4, and free T3]), urinalysis, and screening pregnancy test should be done ≤14 days prior to initiation of treatment. Additionally, amylase and lipase should be analysed in case of symptoms of pancreatitis. If these assessments are performed within 72 hours of initiation of treatment, they do not need to be repeated on Cycle 1 Day 1 with the exception of the ECOG performance status, an abbreviated physical examination, vital signs (pre- and post-infusion), and a single ECG required prior to first trial dose. Tumour assessments (scans) should be performed ≤28 days prior to initiation of treatment and copies may be collected by the sponsor or designee. Refer to Section 5.3 for additional details. Vital signs are checked at every visit.

e Physical examinations will be done at screening, on Day 1 of each treatment cycle, at the 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, on Day 1 of every cycle through Cycle 6 and then on Day 1 of every other cycle thereafter (Cycles 8, 10, 12, etc.), on Day 15 of Cycles 1 through 4, at the EOT visit, and whenever the Investigator deems it necessary. An ECG is optional at the 30-day safety follow-up visit if the EOT visit ECG was normal and no drug-related abnormalities were detected in on-trial ECGs (see Section 5.3.3).

g Women of child-bearing potential must have a serum beta human chorionic gonadotropin (β-HCG) pregnancy test at screening. Thereafter, this test can be done in either serum or urine on Day 1 of each cycle, and at the EOT visit (see Section 5.3.4.4).

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

i Blood samples [redacted] will be collected from all patients as presented in the tables in Appendix 10.4. Each sample will be split into 3 aliquots to allow [redacted] for both BI 754111 and BI 754091 with one back-up sample (see Section 5.6.1).

j Pharmacokinetic (PK) blood sampling: there is extensive PK sampling for solid tumour cohorts during Cycles 1, 2, and 4. It is strongly recommended that the visit days and sampling time points outlined in the Appendix 10.4 tables be followed closely. The permitted visit windows noted in the table footnotes should only be used if medically indicated. Please note that there are separate assays for determination of BI 754111 and BI 754091. Therefore, when PK samples are drawn during combination dosing, 2 tubes must be drawn at each time point. In order to assess the stability of BI 754091 and BI 754111 in whole blood, one additional blood sample will be taken at 1 hour post infusion from all subjects of the first dose group that exceeds 200 mg BI 754111 (see Section 5.4.3).

k Tumour assessments should be done according to RECIST v1.1 and/or iRECIST, and should include computed tomography/positron emission tomography (CT/PET) scans of the chest and abdomen and, if clinically indicated, imaging of any other known or suspected sites of disease (e.g., pelvis, brain) using an appropriate method (CT/PET scan or magnetic resonance imaging [MRI]). The same radiographic procedure must be used throughout the trial. Assessments will be performed by the Investigator at screening and every 2 cycles (6 weeks ±5 days) for the first 6 months of treatment, once every 3 cycles (9 weeks ±5 days) thereafter, at the EOT visit (if not performed within the previous 4 weeks), and at the discretion of the Investigator and copies may be collected by the sponsor or designee.

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

m Dose-limiting toxicities (DLTs) will be collected throughout the trial and will be assessed for dose-escalation decisions following the first cycle of BI 754111 in combination with BI 754091 (see Section 4.1.5).

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

o PK [redacted] 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 (see the tables in Appendix 10.4 for specifics).

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

q A measurement of troponin-I is to be performed if possible. If troponin-I cannot be measured, troponin-T can be measured instead as long as this is marked in the database.

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

FLOW CHART 2: BI 1381.2 (REFMAL 485) TRIAL ASSESSMENTS: PART II: DOSE-EXPANSION COHORTS

Flow Chart 2		Trial Treatment Days[a,b] Cycle = 21 Days						Post-Treatment Days[b]		
	Screening	Expansion Cycles 1, 2, and 4					Cycles 3, 5+	End-of-Treatment[n] (EOT) Visit	30-Day[b] Safety Follow-up	PFS, OS Follow-up[h]
Assessments (Days)	**-28 to -1**	**1**	**2[p]**	**4[p]**	**8 (±1)**	**15 (±1)**	**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]	X	X	X	
ECOG Performance Status[d, e]	X	X					X[e]	X	X	
Vital Signs[d]	X	X	X (C1)	X (C1, 4)	X	X	X	X	X	
12-Lead Digital Electrocardiogram[d, f]	X	X				X	X[f] (C3,5,6,8,10, 12, etc and C3D15)	X	(X)	
Haematology and Clinical Chemistry Labs[d]	X	X			X	X	X		X	
Troponin[r]	X	X (C4)			X (C1,2)	X (C1)	X (C3,5)			
Urinalysis[d]	X	X					X	X		
Pregnancy Test for Women of Child-Bearing Potential[d, g]	X	X[g]					X[g]	X[g]		
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[h]										X

FLOW CHART 2: BI 1381.2 (REFMAL 485) TRIAL ASSESSMENTS: PART II: DOSE-EXPANSION COHORTS (Continued)

Flow Chart 2		Trial Treatment Days[a,b] Cycle = 21 Days						Post-Treatment Days[b]		
	Screening	Expansion Cycles 1, 2, and 4					Cycles 3, 5+	End-of-Treatment[n] (EOT) Visit	30-Day[b] Safety Follow-up	PFS, OS Follow-up[h]
Assessments (Days)	**-28 to -1**	**1**	**2 [p]**	**4 [p]**	**8 (±1)**	**15 (±1)**	**1 (±2)**	**(within 7 days of EOT)**	**(+2)**	
Blood Samples for [redacted]		X					X[o]	X[o]	X[o]	
Blood Samples for BI 754111 PK[j] (Cycles with extensive PKs are noted in parentheses)		X (C1,4)		X (C1,4)	X (C1,4)		X[j] (C8)	Xj	X[j]	
Blood Samples for BI 754091 PK[j] (Cycles with extensive PKs are noted in parentheses)		X (C1,4)		X (C1,4)	X (C1,4)		X[j] (C8)	X[j]	X[j]	
Blood Samples for Biomarkers [redacted]		X (C1&2)			X (C1)	X (C1)		X		
Plasma Samples for Biomarkers [redacted]		X (C1&2)	X (C1)		X (C1)	X (C1)		X		
Biopsy[l]	X						X (C3D1 only)	(X)		
Tumour Assessments[d, m]	X	Every 6 weeks ±3 days for 6 months (then every 9 weeks ±3 days thereafter)								
Administration of Pre-Treatment Medication[q]		X					X			
BI 754111 & BI 754091 Infusions		X					X			

Flow Chart 2 Footnotes (Expansion Cohorts)

a All cycles are 3 weeks (21 days) in duration. Patients will continue treatment with the study drugs until disease progression (PD) by RECIST and/or iRECIST, withdrawal of patient consent, an unacceptable toxicity occurs, or 1 year of treatment is completed, whichever occurs first. Patients will be allowed to stay on treatment in the case of initial radiological PD, if the Investigator feels that it is in the patient's best interest and the patient signs an informed consent describing this circumstance. In addition, patients benefiting clinically and 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 the combination of BI 754111 and BI 754091 is 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, aspartate aminotransferase [AST], alanine aminotransferase [ALT], alkaline phosphatase, bilirubin, lactate dehydrogenase, serum glucose, creatine phosphokinase [CPK: if CPK is elevated, then CPK-MB, troponin I, and myoglobin should be reactively tested], serum urea nitrogen [or urea], serum uric acid, and thyroid panel [TSH, free T4, and free T3]), urinalysis, and screening pregnancy test should be done ≤14 days prior to initiation of treatment. Additionally, amylase and lipase should be analysed in case of symptoms of pancreatitis. If these assessments are performed within 72 hours of initiation of treatment, they do not need to be repeated on Cycle 1 Day 1 with the exception of the ECOG performance status, an abbreviated physical examination, vital signs (pre- and post-infusion), and a single ECG required prior to first trial dose. Tumour assessments (scans) should be performed ≤28 days prior to initiation of treatment and copies may be collected by the sponsor or designee. Refer to Section 5.3 for additional details. Vital signs are checked at every visit.

e Physical examinations will be done at screening, on Day 1 of each treatment cycle, at the 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 (or analog ECG if digital not available) must be done before blood work or other procedures after 5 minutes of rest at screening, on Day 1 of every through Cycle 6 and then every other cycle thereafter (Cycles 8, 10, 12, etc.), on Day 15 of Cycles 1 through 4, at the EOT visit, and whenever the Investigator deems it necessary. An ECG is optional at the 30-day safety follow-up visit if the EOT visit ECG was normal and no drug-related abnormalities were detected in on-trial ECGs (see Section 5.3.3).

g Women of child-bearing potential must have a serum beta human chorionic gonadotropin (βHCG) pregnancy test at screening. Thereafter, this test can be done in either serum or urine on Day 1 of each cycle, and at the EOT visit (see Section 5.3.4.4).

h **Patients enrolled in Protocol Version 4.0 or later**: 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:** 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.

[redacted]

j Pharmacokinetic (PK) blood sampling: there is more intensive PK sampling during Cycles 1, 4, and 8 of dose-expansion. PK samples are also taken pre-treatment on Day 1 of all other cycles through Cycle 9 and then on Day 1 of every 3rd cycle. It is strongly recommended that the visit days and sampling time points outlined in the Appendix 10.4.2 table be followed closely. The permitted visit windows noted in the table footnotes should only be used if medically indicated. Please note that there are separate assays for determination of BI 754111 and BI 754091. Therefore, when PK samples are drawn during combination dosing, 2 tubes must be drawn at each time point.

[redacted]

l All patients in Part II (dose-expansion cohorts) must have tissue samples (fresh or archived [see requirements]) available for retrospective central PD-L1 testing. The following will be required (see Section 5.5.2.3 for details):
- A minimum of 2 core needle biopsies or 1 punch biopsy must be taken between screening and the day before first treatment with BI 754091. Otherwise, two 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) are acceptable.
- Two core-needle biopsies or 1 punch biopsy on treatment at the end of Cycle 2 (after 6 weeks of treatment), preferably from the same lesion.
- Another biopsy (optional) should be taken upon PD (according to RECIST v1.1 and iRECIST), if possible. An optional biopsy should also be taken if a patient has stable disease (SD) over 3 subsequent disease assessment periods.

m Tumour assessments should be done according to RECIST v1.1 and iRECIST and should include computed tomography/positron emission tomography (CT/PET) scans of the chest and abdomen and, if clinically indicated, imaging of any other known or suspected sites of disease (e.g., pelvis, brain) using an appropriate method (CT/PET scan or magnetic resonance imaging [MRI]). The same radiographic procedure must be used throughout the trial. In case of suspected (but not confirmed) bone metastasis at screening, tumour assessment at screening should include a bone scan. If bone lesions are already known or confirmed at screening, correlative imaging (X-ray or CT scan) should be performed. Correlative imaging should then be repeated at each tumour assessment (see Section 5.2.1 for more detail). Assessments will be performed by the Investigator at screening and every 2 cycles (6 weeks ±5 days) for the first 6 months of treatment, once every 3 cycles (9 weeks ±5 days) thereafter, at the EOT visit (if not performed within the previous 4 weeks), and at the discretion of the Investigator and copies may be collected by the sponsor or designee.

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

[redacted]

p The clinic will telephone the patients on Days 2 and 4 of Cycle 2 and Day 2 of Cycle 4 in order to check on any adverse events. The patients will not be required to go to the clinic on these days.

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

r A measurement or troponin-I is to be performed if possible. If troponin-I cannot be measured, troponin-T can be measured instead as long as this is marked in the database.

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

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ABBREVIATIONS

ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
ALK	Anaplastic lymphoma kinase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the curve
BI	Boehringer Ingelheim
BLRM	Bayesian Logistic Regression Model
C_{EOI}	Plasma concentration at the end of infusion
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CL	Drug clearance
CLIA	Clinical Laboratory Improvement Amendments
CNS	Central nervous system
C_{pre}	Plasma concentration pre-dose
CR	Complete response/remission
CRu	Complete remission unconfirmed
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
eGFR	Estimated glomerular filtration rate
EGFR	Epidermal growth factor receptor
EMA	European Medicines Agency
EOT	End-of-treatment visit
EWOC	Escalation with overdose control
FDG	Fluoro-deoxyglucose
FFPE	Formalin fixed and paraffin embedded
GCP	Good Clinical Practice
GEP	Gene-expression profile
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council Harmonisation
irAE	Immune-related adverse events
IRB	Institutional review board
iRECIST	Guidelines for response criteria for use in trials testing immunotherapeutics
IRT	Interactive Response Technology
ISF	Investigator Site File
i.v.	Intravenous

LAG-3	Lymphocyte-activation gene 3
mAb	Monoclonal antibody
MAP	Meta-analytic predictive (approach)
mCRC	Metastatic colorectal cancer
MDSC	Myeloid-deprived suppressor cell
MedDRA	Medical Dictionary for Drug Regulatory Activities
MHC-II	Major histocompatibility complex Class II
MRI	Magnetic resonance imaging
MSI-H	Microsatellite instability high
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
PR	Partial response/remission
q3w	Once every 3 weeks
RECIST	Response Evaluation Criteria in Solid Tumours
REP	Residual-effect period
RO	Receptor occupancy (assay)
RPIID	Recommended Phase II dose
SAE	Serious adverse event
SOP	Standard operating procedure
SRC	Safety Review Committee
TMB	Tumour mutational burden
T-regs	Regulatory T-cells
TSAP	Trial statistical analysis plan
ULN	Upper limit of normal

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Despite the recent advancements in cancer treatment, cancer remains a leading cause of death globally. Approximately 1,685,210 new cancer cases were expected to be diagnosed in 2016 (excluding carcinoma *in situ* [noninvasive cancer] of any site except urinary bladder and basal cell or squamous cell skin cancers). Approximately 595,690 people in the United States were expected to die of cancer in 2016 (R16-4925). In the majority of cases, the disease is diagnosed in late stages and the vast majority of patients progress on available treatment and succumb to their disease. These statistics clearly highlight the urgent need for novel therapeutic agents and treatment strategies to improve the treatment outcome for cancer patients.

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

T-cell activation is a highly regulated process that promotes T-cell proliferation, differentiation, survival, and cytokine production. Up-regulation of multiple co-regulatory receptors on activated T-cells provides a mechanism of fine tuning the immune response. Programmed cell death protein-1 (PD-1) and programmed death ligand-1 (PD-L1) pathway was the first negative immune co-regulatory (immune-checkpoint inhibitor) pathway described (R16-2361; R16-2363). Indeed, genetic inactivation of the PD-1/PD-L1 pathway in mice resulted in various autoimmune phenotypes (R16-2362; R16-2364). PD-1 expression in humans is largely restricted to immune cells (T-cells, B-cells, natural killer T-cells, activated monocytes and dendritic cells) and is upregulated upon T-cell activation (R15-6038, R16-2360), whereas PD-L1 protein is expressed on the surface of a wide range of human cancer cells (R16-2371). The physiologic function of the PD-1 pathway is to down-regulate the immune response once the antigen that stimulated the response is eliminated, thereby limiting collateral tissue damage.

Lymphocyte-activation gene 3 (LAG-3) is a cell-surface negative regulator of immune response involved in maintaining immunological tolerance via regulation of T-cell activation, proliferation, and response (R16-5356; R16-5359). LAG-3 is expressed on activated cytotoxic, helper as well as regulatory T-cells (T-regs). LAG-3 binds to major histocompatibility complex Class II (MHC-II) glycoproteins and negatively regulates T-cell activity (R16-5357; R16-5358). LAG-3 also regulates T-cell response via T-regs as loss of LAG-3 expression on T-regs results in loss of T-reg function (R16-5355).

Tumours use the immune-checkpoint pathways (such as the PD-1 and LAG-3 pathways) to evade anti-tumour immune responses. Tumour-infiltrating lymphocytes frequently express high levels of PD-1 in combination with other immune-checkpoint inhibitors including

LAG-3 (R16-0868, R16-5335), while the ligands for these checkpoint inhibitors (i.e., PD-L1/L2 and MHC-II, respectively) are expressed within the tumour microenvironment. Engagement of the co-inhibitory receptors PD-1 and LAG-3 by their respective ligands inhibits T-cell function preventing an anti-tumour immune response. It is now well established that blockade of the PD-1 axis of the immune-checkpoint program results in reactivation of T-cell function and the antitumour immune response leading to tumour growth inhibition in some patients. Treatment of patients with advanced melanoma, non-small-cell lung cancer (NSCLC), renal cell carcinoma, and many other tumour types with anti-PD-1 (nivolumab or pembrolizumab) or anti-PD-L1 (atezolizumab, durvalumab, and avelumab) monoclonal antibodies (mAbs) has resulted in highly durable responses in approximately 15% to 30% of patients (R15-3715; R15-3776; R15-3778; R15-6023; R16-0663; R16-0864; R16-0876; R16-1225; R16-1588; R16-3547).

1.2 DRUG PROFILES

1.2.1 BI 754111

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

1.2.2 BI 754091

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

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

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 in a subset of patients. The limited success achieved with checkpoint-inhibitor monotherapy (up to 80% of treated patients do not respond; R15-3588; R15-3778) in some studies may, in part, be attributed to redundancy in immune-checkpoint inhibitor pathways. Therefore, it is postulated that blockade of multiple checkpoint-inhibitor pathways may result in better anti-tumour activity and improved clinical outcome in a higher percentage of patients compared to checkpoint-inhibitor monotherapy. Clinical proof-of-concept for combination checkpoint-inhibitor treatment has come from clinical trials evaluating the safety and efficacy of combination PD-1 and CTLA4 mAb in patients with advanced NSCLC, small-cell lung cancer, and melanoma. For example, the combination of nivolumab (anti-PD-1 mAb) with ipilimumab (anti-CTLA-4 mAb) in patients with small-cell lung cancer increased objective-response rate (ORR) to 19% to 20% compared to 10% with nivolumab monotherapy (R16-2707). In previously untreated patients with advanced melanoma, the combination of nivolumab and ipilimumab increased median progression-free survival (PFS) to 11.5 months from a PFS of 2.9 and 6.9 months achieved by ipilimumab or nivolumab monotherapies, respectively, in patients with low PD-L1 levels (R15-3696). The combination of nivolumab and ipilimumab has also resulted in significant improvement in ORR in patients with previously untreated NSCLC (39% to 47% for ipilimumab dosed every 6 week or every 12 weeks, respectively) compared to the 23% ORR achieved by nivolumab monotherapy (R16-5545). Unfortunately, the improved efficacy of combined PD-1/CTLA4 came at the expense of safety. Grade 3 and 4 adverse event (AE) rates of 53% to 55% were reported with the full-dose combination of nivolumab and ipilimumab in patients with melanoma (R15-3696; R16-5544) and 33% to 37% with reduced dose and dosing frequency of the ipilimumab component in NSCLC (R15-3696; R16-5544). These findings clearly underscore the need for the development of more efficacious and better-tolerated alternative immunotherapy combinations.

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

combined blockade of the co-inhibitory receptors PD-1 and LAG-3 has the potential to better restore T-cell functionality and improve objective responses (ORs) and prolongation of overall survival in cancer patients. The combination of nivolumab and BMS-986016 (anti-LAG-3 mAb) has recently been shown to have antitumour activity and an acceptable safety profile in multiple solid tumours and hematological malignancies (R16-5204; R16-5218).

Collectively, the currently available data clearly demonstrate the clinical benefits that patients with many tumour types gain from checkpoint-inhibitor monotherapy. It is also clear that combination checkpoint-inhibitor treatment has resulted in improved efficacy compared to checkpoint-inhibitor monotherapy. There is now sufficient evidence that blockage of the PD-1 pathway leads to over-expression of other checkpoint inhibitors, including LAG3. This over expression of other checkpoint inhibitors may represent an escape pathway from the PD-1 pathway blockade. Therefore, it is possible that blocking multiple checkpoint inhibitors at the same time would lead to better response and potentially rescue some of the patients that have failed the PD-1 single-agent blockade, including patients with NSCLC (R15-3696; R16-0852; R16-0868, R16-0881; R16-2707; R16-5335; R16-5545).

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

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

BI 754111 has the potential to be less toxic than chemotherapy containing regimens and would reserve chemotherapy as a subsequent line of treatment for patients whose disease progresses.

Checkpoint inhibitor therapy has also proven effective (approximately 30-40% of patients achieved objective response) in a subset of patients with MSI-H or DNA mismatch repair deficient metastatic colorectal cancer (mCRC) which tend to be highly immunogenic cancers (R16-1497; R18-1746). However, these characteristics occur only in a small fraction of mCRC (~5%). The majority of mCRC patients are microsatellite stable for whom single agent immunotherapy has not been successful. As such, this trial will evaluate the utility of the combination BI754091 (anti-PD-1 mAb) with BI754111 (anti-LAG-3 mAb) in this microsatellite stable mCRC population who have progressed on the standard of care, a population with very high unmet medical need.

The trial will also include a cohort of patients with solid tumours whose disease progressed while taking an anti-PD-1 or anti-PD-L1 regimen and whose tumours have high tumour mutational burden (TMB; defined as ≥ 10 mutations/megabase of DNA) or high microsatellite instability (MSI-H). Both TMB-high and MSI-H are good predictive biomarkers of immunogenic tumours and response to immune checkpoint inhibitor therapy (R18-1492). As outlined above, the objective of this cohort is to explore the ability of the checkpoint inhibitor combination to restore immunotherapy responsiveness in this subset of anti-PD-1 or anti-PD-L1 resistant (both primary and acquired) with good predictive markers for response. If successful, such a regimen may provide a second immunotherapy treatment option with the potential for durable clinical benefit and possibly delay the need to initiate chemotherapy in some patients.

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

This 2-part trial is the first study with BI 754111 in humans and the second with BI 754091. The first part will include dose-escalation cohorts to determine the maximum-tolerated dose (MTD) and/or the selected expansion dose. The second part includes expansion cohorts at the selected expansion dose that will further evaluate the safety, tolerability, PK, biomarkers and the preliminary efficacy of the BI 754111 plus BI 754091 combination. 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 NSCLC, previously treated microsatellite stable metastatic colorectal cancer (mCRC), or any anti-PD-1 or anti-PD-L1 pretreated solid tumour with high tumour mutational burden (TMB ≥10 mut/MB) and/or microsatellite instability high (MSI-H) and/or DNA mismatch repair deficient (MMRd).

2.2 TRIAL OBJECTIVES

2.2.1 Part I (dose-escalation cohorts) objectives

The objectives of the dose-escalation portions of the trial are to:

- Investigate the safety, tolerability, and pharmacokinetics (PK) of escalating doses of BI 754111 in combination with BI 754091 (administered via intravenous [i.v.] infusion once every 3 weeks [q3w]) in patients with advanced and/or metastatic solid tumours.
- Determine the MTD through monitoring dose-limiting toxicities (DLTs) and/or to determine the dose of the combination of BI 754111 plus BI 754091 to be used in the expansion phase (Part II).

2.2.2 Part II (dose-expansion cohorts) objectives

The objectives of the dose-expansion portion of the trial are to:

- Further investigate the safety, tolerability, and PK of the selected expansion dose of the combination of BI 754111 plus BI 754091 in patients with NSCLC, microsatellite stable (MSS) metastatic colorectal cancer (mCRC), or any anti-PD-1 or anti-PD-L1 pretreated solid tumour with high tumour mutational burden (TMB) and/or microsatellite instability high (MSI-H), and/or DNA mismatch repair deficient (MMRd) as defined in the entry criteria [see Section 3.3].
- Explore the efficacy of the combination in patients with NSCLC, mCRC, or any solid tumour with high TMB and/or MSI-H and/or DNA MMRd (as defined in the entry criteria).

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 minimizing collateral-immune-mediated damage to healthy tissue. Immune-checkpoint inhibitors also play a major role in promoting and maintaining self-tolerance by inactivating auto-reactive T-cells. Therefore, manipulation of immune-checkpoint-inhibitor pathways unleashes the immune system and comes with a higher risk of inducing immune dysfunction leading to immune-related adverse events (irAEs). Indeed, mice deficient in PD-1 or its ligands (PD-Ll and PD-L2) were found to be highly prone to development of autoimmune diseases (R16-2362; R16-2364; R16-2968; R16-2969; R16-2970).

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

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

Treatment with BI 754111 and 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 treatments. These reactions occur infrequently and are typically managed based on symptoms using treatments ranging from histamine antagonists in mild cases to administration of epinephrine when symptoms of anaphylaxis are detected. Detailed irAE management guidelines are presented in Appendix 10.2.

BI 754111 or BI 754091/BI 754111 combination treatment should be permanently discontinued for Common Terminology Criteria for Adverse Events (CTCAE) Version 5 Grade 3 or 4 pneumonitis, Grade 3 or 4 adrenal insufficiency, Grade 3 or 4 or recurrent colitis of any grade, Grade 4 diabetes mellitus, Grade 4 hypophysitis, Grade 4 rash, any grade encephalitis, any recurrent Grade 3 or 4 AE, transaminase values >5 times the upper limit of normal (ULN) or total bilirubin >3 times ULN, inability to taper steroids to 10 mg or less prednisone or equivalent within 12 weeks, or persistent Grade 2 or 3 AEs that do not recover to Grade 1 or less within 12 weeks. Additional information of management of irAEs is provided in Appendix 10.2.

Please refer to the current version of the BI 754111 Investigator Brochure for the latest information on patients treated with BI 754111/BI 754091.

Based on pre-clinical data as well as clinical data obtained so far with BI 754091 as well as the combination of BI 754091 and BI 754111, the inhibitory effects of the combination of BI 754111 and BI 754091 may translate into a clinical benefit in cancer patients.

The benefit/risk ratio continues to be considered positive for patients with advanced cancers.

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, the potential for drug-induced liver injury (DILI) is under constant surveillance by sponsors and regulators. Therefore, this trial requires timely detection,

evaluation, and follow-up of laboratory alterations in selected liver laboratory parameters to ensure patients safety (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, non-randomised, multicentre trial of BI 754111 administered in combination with BI 754091 that will be conducted in 2 parts. The Part I portion of the trial will consist of consecutive dose-escalation cohorts of BI 754111 in combination with BI 754091 administered to patients with advanced solid tumours. Possible cohort scenarios for Part I are presented in Figure 3.1: 1.

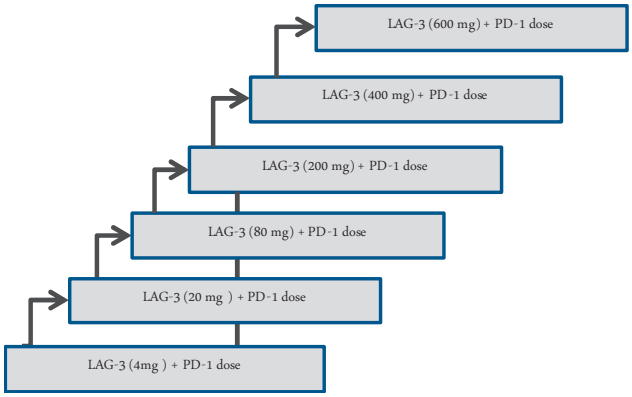


Figure 3.1: 1 Proposed Part I dose-escalation scheme

The dose-escalation phase will include intensive safety monitoring to ensure the safety of the patients and will be guided by Bayesian Logistic Regression Models (BLRM) with overdose control (EWOC). Following determination of the MTD and (or) the selected expansion dose of the combination of BI 754111 and BI 754091, Part II will commence to further characterise the combination at the doses determined in Part I in patients with NSCLC, mCRC, or any solid tumour with high TMB and/or MSI-H and/or DNA MMRd.

It is planned that approximately 15 to 50 patients will be enrolled in Part I. The total number of patients will depend on the number of dose escalations necessary. The BLRM estimates the MTD by updating estimates of the probability of observing a DLT during the MTD evaluation period for each dose (or dose combination) level in the trial as patient information becomes available.

In general, it will be permitted to escalate to a dose that fulfils the EWOC principle (refer to Section 7). Details on handling borderline cases will be described in the dose-escalation plan. Successive cohorts of patients will receive doses of BI 754111 and BI 754091 until one dose level above the human therapeutic dose for LAG-3 (currently estimated at 400 mg) 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. Only one component of the combination (BI 754111 or BI 754091) will be changed at one time. They will not be escalated simultaneously.

A 10% screen-failure rate is anticipated, which assumes the sites have 'pre-screened' to find generally eligible patients. Therefore, the 10% screen-failure rate should only be for failure due to laboratory values, scans, etc.

After patients in a cohort have either experienced a DLT or have been observed for at least the MTD evaluation period (see Section 7.3.1.1) without experiencing a DLT, the Bayesian model will be updated with the newly accumulated data. The overdose risk will then be calculated for the dose combination, and escalation will be permitted to all doses of the dose combination that fulfil the EWOC criterion. Hypothetical data scenarios (examples 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 models and on additional information (patient profiles), the members of the SRC will reach a joint recommendation on the next dose level of BI 754111 in the dose combination to be investigated and the size for the next dose-escalation cohort.

If DLTs are observed in the first 2 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. The SRC can declare any dose that fulfils the EWOC criterion as the dose to be tested in the expansion phase, independent of the MTD estimate.

Table 3.1: 1 Possible Cohort Scenarios for Solid Tumour Cohorts

Part I	**Dose-Escalation Cohorts in Solid Tumour (Doses determined by the SRC)**
Cohort A	LAG-3 Dose 1 (4 mg) & PD-1 Dose 1 (RPIID or a lower dose selected from the BI 1381.1 trial by the BI 1381.2 SRC)
Cohort B	LAG-3 Dose 2 (20 mg) & PD-1
Cohort C	LAG-3 Dose 3 (80 mg) & PD-1
Cohort D	LAG-3 Dose 4 (200 mg) & PD-1
Cohort E	LAG-3 Dose 5 (400 mg) & PD-1
Cohort F	LAG-3 Dose 6 (600 mg) & PD-1
Part II	**Dose-Expansion Cohorts**
Cohort G	Selected expansion dose in patients with 2nd and 3rd line NSCLC who progressed on anti-PD-1 or anti-PD-L1 treatment (as defined in the entry criteria)
Cohort H	Selected expansion dose in ≥ 2nd line microsatellite stable anti-PD-1 and anti-PD-L1 treatment-naïve mCRC.
Cohort I	Selected expansion dose in patients with any solid tumour with high TMB and/or MSI-H and/or DNA MMRd solid tumours who have received 1 prior anti-PD-1 or anti-PD-L1 treatment regimen.
Cohort J	Selected expansion dose in patients with 1st line epidermal growth factor receptor [EGFR] wildtype [WT] and anaplastic lymphoma kinase [ALK] WT NSCLC. Patients may have any level of PD-L1 expression, but only a maximum of 10 patients with PD-L1 high expression (≥50% PD-L1) will be enrolled.

Following determination of the dose from the Part I portion, 4 dose-expansion cohorts (2nd and 3rd line NSCLC, anti-PD1 and anti-PD-L1 treatment–naïve mCRC, any solid tumour with high TMB and/or MSI-H, and 1st-line NSCLC), will be enrolled into Part II. The Part II portion of the trial will further evaluate the safety, tolerability, PK profile, biomarkers, and efficacy of the combination of BI 754111 and BI 754091.

Patients will continue study treatment 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. Patients will be allowed to stay on treatment in the case of initial radiological PD, if the Investigator feels that it is in the patient's best interest. In addition, patients without PD may stay on treatment after 1 year on a case-by-case basis after discussion with the Medical Monitor and the sponsor.

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, management of the Trial Master File, some aspects of safety management and reporting, medical writing, and medical monitoring.

A Safety Review Committee (SRC), including representatives from clinical sites, the sponsor, and [redacted], will be established and is described in Section 3.1.2.

Relevant documentation on the participating investigators and other important participants, including their curricula vitae, will be filed in an 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 for development of shipment orders.

3.1.2 Safety Review Committee

Members of the SRC will include:

- [redacted] for the trial
- Principal Investigators, or delegates, from each investigational site
- BI Safety Physician, or delegate
- BI Team Member Medicine responsible for the project
- BI Project or Trial Statistician.

The BI Safety Physician, BI Team Member Medicine, 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 subject matter 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.

The SRC will be responsible for assessing the progress of the clinical trial, including making safety and efficacy assessments at specified intervals, making dose-escalation decisions for

BI 754111, making dose selection decisions for BI 754091, making decisions on the next cohort size, and recommending to the sponsor whether to continue, modify, or stop the trial. To support their decision making, the SRC will have unblinded access to data from this trial and the ongoing study, BI 1381.1, which evaluates escalating doses of BI 754091 monotherapy.

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

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

During Part I (dose-escalation) 3 patients with solid tumours per cohort is required, but the SRC may decide to increase the number by a maximum of 6 additional patients per cohort as needed. Decisions of the SRC will be guided by BLRMs 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. Relevant data for all patients enrolled in the trial will be entered in the eCRF.

3.3.1 Main diagnosis for trial entry

Patients included in the dose-escalation cohorts (Part I) are not eligible to enter the dose-expansion cohorts (Part II).

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
2. Patients ≥18 years of age at the time of signature of the ICF
3. Part I (dose escalation):

- Patients with a confirmed diagnosis of advanced, unresectable, and/or metastatic solid tumours (any type)
  - For whom no therapy of proven efficacy exists, or who are not amenable to standard therapies.
  - Must have measurable lesions according to RECIST v1.1
  - Previous treatment with an anti-PD-1 mAb is allowed as long as the last administration of the anti-PD-1 mAb on the previous treatment is a minimum of 60 days prior to starting treatment in this trial.

4. Part II (dose expansion):
   - Patients must have measurable disease per 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 (if adequate archival tissue is not available) and, unless clinically contraindicated, after 6 weeks on therapy.
   - Dose Expansion Cohorts: Patients with a confirmed diagnosis of advanced, unresectable, and/or metastatic solid tumours of one of the following types:
     - Second and 3rd line NSCLC patients:
       - Must have progressed on anti-PD-1 or anti-PD-L1 treatment after having achieved radiologically confirmed benefit (minimum of stable disease)
       - Must have had a minimum duration of benefit of 4 months and minimum treatment duration of 2 months on the previous anti-PD-1 or anti-PD-L1 treatment without experiencing disease progression during that period.
       - The anti-PD-1- or anti-PD-L1-containing treatment must have been the latest treatment regimen prior to enrolling in this trial
       - Must be within >4 and <12 weeks since the latest treatment and their first dose in this trial. Patients who have had anti-PD-1 or anti-PD-L1 monotherapy as their first-line NSCLC treatment regimen must have a PD-L1 expression level of ≥1% at baseline (local validated testing).
     - Anti-PD-1 or anti-PD-L1 treatment-naïve patients with microsatellite stable mCRC:
       - Patients must have had ≥ 1 line of treatment
       - Must have microsatellite stable disease (identified using any validated test)
       - Must be anti-PD-1 and anti-PD-L1 treatment naïve
     - Anti-PD-1 or anti-PD-L1 pretreated patients with any high TMB (≥10 mutations/Mb) and/or MSI-H and/or DNA MMRd solid tumours
       - Patients must have high TMB (≥ 10 mutations/Mb) and/or MSI-H and/or DNA mismatch repair deficient (MMRd) (measured using any validated test).
       - Patients must have received 1 prior anti-PD-1 or anti-PD-L1 treatment regimen.
     - 1st-line squamous or non-squamous NSCLC patients:
       - Patients must be treatment naïve

- Must be EGFR and ALK wild type (only applicable to patients with non-squamous NSCLC)
- Regardless of PD-L1 expression level. However, the number of patients with high level of PD-L1 expression (≥50% PD-L1) will be limited to a maximum of 10 patients

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. Male or female patients. Women of childbearing potential (WOCBP)[1] and men able to father a child must be ready and able to use highly effective methods of birth control (that result in a low failure rate of less than 1% per year when used consistently and correctly) during trial participation and for at least 6 months after the last administration of trial medication. A list of contraception methods meeting these criteria is provided in the patient information.

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 anti-tumour treatment, except BI 754091, within 4 weeks or within 5 half-life periods (whichever is shorter) prior to the initiation of trial treatment.
5. Any unresolved toxicities from prior therapy greater than CTCAE Grade 1 at the time of starting study treatment with the exception of alopecia and Grade 2 neuropathy due to prior platinum-based therapy
6. Prior treatment with anti-LAG-3 agents
7. Patients with NSCLC that has epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) rearrangements. (only applicable to patients with non-squamous NSCLC)
8. Presence of other active invasive cancers other than the one treated in this trial within 5 years prior to screening, with the exception of appropriately treated basal-cell carcinoma of the skin, *in situ* carcinoma of the uterine cervix, or other local tumours considered cured by local treatment
9. Untreated brain metastasis(es) that may be considered active. Patients with previously treated brain metastases may participate provided they are stable (i.e., without evidence

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

of PD by imaging for at least 4 weeks prior to the first dose of trial treatment, and any neurologic symptoms have returned to baseline), and there is no evidence of new or enlarging brain metastases.

10. Inadequate organ function or bone marrow reserve as demonstrated by the laboratory values presented in Table 3.3.3: 1.
11. Any of the following cardiac criteria:
    - Mean resting corrected QT interval (QTc) >470 msec
    - Any clinically important abnormalities (as assessed by the Investigator) in rhythm, conduction, or morphology of resting ECGs, e.g., complete left bundle branch block, third degree heart block
    - Any factors that increase the risk of QTc prolongation or risk of arrhythmic events such as heart failure, hypokalaemia, congenital long QT syndrome, family history of long QT syndrome or unexplained sudden death under 40 years-of-age, or any concomitant medication known to prolong the QT interval
    - Patients with an ejection fraction (EF) <55% or the lower limit of normal of the institutional standard will be excluded. Only in cases where the Investigator (or the treating physician or both) suspects cardiac disease with negative effect on the EF, will the EF be measured during screening using an appropriate method according to local standards to confirm eligibility (e.g., echocardiogram, multi-gated acquisition scan). A historic measurement of EF no older than 6 months prior to first administration of study drug can be accepted provided that there is clinical evidence that the EF value has not worsened since this measurement in the opinion of the Investigator or of the treating physician or both.
12. History of pneumonitis within the last 5 years
13. History of severe hypersensitivity reactions to other mAbs
14. Immunosuppressive corticosteroid doses (>10 mg prednisone daily or equivalent) within 4 weeks prior to the first dose of study treatment
15. Active autoimmune disease or a documented history of autoimmune disease, except vitiligo or resolved childhood asthma/atopy
16. Active infection requiring systemic treatment (antibacterial, antiviral, or antifungal therapy) at start of treatment in this trial
17. Known history of human immunodeficiency virus infection or an active hepatitis B or C virus infection
18. Interstitial lung disease
19. 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.

Table 3.3.3: 1 Laboratory values demonstrating inadequate organ function

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

3.3.4 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 appropriate flow chart (Flow Chart 1 or 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 the MTD evaluation period, 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 754111 and BI 754091 (where applicable) 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.

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

4. TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

4.1.1 Identity of the investigational medicinal products

4.1.1.1 BI 754111

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

Table 4.1.1.1: 1 BI 754111

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

4.1.1.2 BI 754091

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

Table 4.1.1.2: 1 BI 754091

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

4.1.2 Selection of doses in the trial

4.1.2.1 Starting dose of BI 754111

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.

The starting dose of BI 754111 in patients with solid tumours will be 4 mg (based on 0.05 mg/kg for an 80 kg patient) administered via i.v. infusion once every 3 weeks. The starting dose was based on the EC_{50} in the *in vitro* tetanus toxoid T-cell activation assay. In that assay, increasing concentrations of BI 754111 were combined with a fixed dose of BI 754091 and IFNγ secretion was measured as an indication of T-cell activation (n00250935; n00253546).

This starting dose is supported by the 13-week repeat-dose toxicity study in the cynomolgus monkey. Compared to the NOAEL in the Non-Human Primate study (C_{max} 6,440 µg/mL and AUC 734,000 µg/mL*h), the 4 mg starting dose to an 80 kg patient is expected to result in an exposure margin of approximately 5,300-fold and 4,900-fold based on the predicted human steady state exposure of C_{max} 1.2 µg/mL and AUC 150 µg/mL*h, respectively.

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).

4.1.2.2 Starting dose of BI 754091

The recommended Phase II dose of BI 754091 to be used in combination with BI 754111 is 240mg every 3 weeks. This dose of BI 754091 was determined by the SRC using the most recent safety information from another ongoing study, BI 1381.1. Based on emerging safety information in the 1381.1 and 1381.2 studies, the SRC may amend the dose of BI 754091 used in this study.

The dosing schedule of BI 754091 will be q3w, and is not anticipated to change.

4.1.3 Dose-escalation scheme

The dose of BI 754111 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 600 mg (as long as they fulfil the EWOC criterion) may be investigated if agreed upon by the Investigator and sponsor.

In the Part I dose-escalation cohorts, dosing of BI 754111 will be administered with BI 754091. The planned starting dose of BI 754091 will be the RPIID from study 1381.1 and the SRC will confirm this prior to starting dosing. The dose of BI 754091 may be increased or decreased based on DLTs and the overall safety profile of the combination. Possible cohort scenarios are presented in Table 3.1: 1. These scenarios may change based on ongoing safety evaluations.

Table 4.1.3: 1 Example of BI 754111 dose escalation*

Dose Escalation Rules		Example Dose Levels
Dose level	Increment from previous dose	Proposed dose
First	Starting dose	4 mg
Second	400%	20 mg*
Third	300%	80 mg*
Fourth	150%	200 mg*
Fifth	100%	400 mg*
Sixth	50%	600 mg*

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

At the end of each treatment cohort, the SRC will evaluate the available data. The SRC will review all safety data including, but not limited to, DLTs and all CTCAE Version 5 Grade ≥2 toxicity data during the first cycle of combination therapy for the solid tumour cohorts Updated safety data on other ongoing patients, including data in later cycles, will be discussed as well. Based on the findings of the SRC, 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 754111 or BI 754091 in any one patient. The dose may be delayed for a patient for one cycle, plus an additional 3 weeks, because of AEs following discussion with the Medical Monitor.

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

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

drug-related AEs are reported. Please see Appendix 10.2 for guidelines for management of immune-related adverse events.

In the event of an infusion-related reaction ≤ Grade 2, the infusion rate of study drug(s) may be decreased by 50% or interrupted until resolution of the event and re-initiated at 50% of the initial rate until completion of the infusion. In patients experiencing infusion-related reactions ≤ Grade 2, subsequent infusions may be administered at 50% of the initial rate. If an infusion-related reaction is Grade 3 or higher in severity at any point during the study, study drug(s) will be permanently discontinued (see Section 5.3.6.5.3).

4.1.5 Definition of dose-limiting toxicity

Dose-limiting toxicities (DLTs) will be recorded throughout the trial. Any DLT must be reported to the Medical Monitor by the Investigator or designee within 24 hours of first knowledge, and to the [redacted] as an SAE when appropriate. All DLTs will be agreed upon between the Sponsor, the Study Chair, the Medical Monitor, and the investigators after review of the data from each cohort. Only DLTs occurring in Part I during the first cycle of BI 754111 administered in combination with BI 754091 in the solid tumour cohorts will be used for dose-escalation decisions made by the SRC.

All relevant safety information (including DLTs) will be considered when selecting the selected expansion dose.

Previous anti-PD-l mAbs have been associated in the clinical setting with inflammatory adverse reactions resulting from increased or excessive immune-related adverse events (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 5. Any of the following AEs will be classified as DLTs following review by the Investigators and the Medical Monitor, unless unequivocally due to underlying malignancy or an extraneous cause.

Haematologic toxicities:
- Any Grade 5 toxicity
- Neutropenia ≥ Grade 4 lasting for >5 days
- Febrile neutropenia of any duration (ANC <1.0 X 10^9 cells/L and fever ≥38.5°C)
- Grade 4 thrombocytopenia, or Grade 3 thrombocytopenia with bleeding or a requirement for platelet transfusions
- Grade 4 anaemia unexplained by underlying disease.

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 sufficiently managed with or without systemic corticosteroid therapy and/or hormone replacement therapy, and the patient is asymptomatic.
  - Grade 3 tumour flare.
- Any Grade 4 or 5 AE
- Any Grade 2 pneumonitis of any duration
- Any Grade 2 uveitis, eye pain, or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within 2 weeks or requires systemic treatment
- Any ≥ Grade 2 toxicity that persists and results in an inability to administer 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 first cycle of BI 754111 in combination with BI 754091. 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 an SRC meeting (either scheduled or *ad hoc*) to recommend the next dose level and cohort size.

4.1.6 Definition of maximum-tolerated dose

The MTD may be considered reached if one of the following criteria is fulfilled:
1. The posterior probability of the true DLT rate in the target interval [0.16, 0.33) of the MTD is above 0.5, OR
2. At least 15 patients have been treated in the trial, of which at least 6 were 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 754111 and either:

- has completed the first cycle of BI 754111 in combination with BI 754091

OR

- has experienced a DLT during the first cycle of BI 754111 in combination with BI 754091 .

4.1.8 Method of assigning patients to treatment groups

After assessment of all inclusion and exclusion criteria, each eligible patient in the Part I dose-escalation portion of the trial will be assigned a dose of BI 754111 and a dose of BI 754091, as determined by the SRC.

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

The SRC must reach a consensus on whether to declare the MTD, escalate the dose any further, or de-escalate and/or expand recruitment into particular cohorts. Minutes from these meetings will be prepared and circulated to the trial team and each Investigator for comment prior to finalisation. Dose escalation will continue until at least one dose level higher than the estimated human therapeutic dose or until the trial is terminated for other reasons.

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

In the second part (Part II dose expansion cohorts), all patients will be treated with the schedule and dose determined by the assessment of DLTs, available PK, and available biomarker results from the Part I portion of the trial. Patient numbers will be assigned as enrolment (screening) occurs.

4.1.9 Administration of doses for each patient

BI 754111 and BI 754091 will be diluted and administered via i.v. infusion according to the details in the Pharmacy Manual.

For Part I solid-tumour cohorts, dosing will be sequential for doses <80 mg LAG3 with BI 754091 infused first followed by infusion of BI 754111. The infusion duration for each will be specified in the pharmacy manual. It is anticipated that the entire infusion time will take ~1 hour. For doses ≥80 mg LAG3, the infusion will be simultaneously (infusion duration ~1 hour).

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 products will be provided by BI. They will be packaged and labelled in accordance with the principles of Good Manufacturing Practice. Each site will be provided with an initial shipment of trial drug supply. 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. 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.

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 products' delivery to the trial site, the inventory at the site, the use by each patient, and the return to the sponsor or alternative disposal of unused products.

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

(after relevant reconciliations have been completed and records reviewed by the clinical monitor).

4.2 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 or special emergency procedures to be followed in this trial.

4.2.2 Concomitant medications

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

Concomitant therapy, with reasons for taking each treatment, must be recorded in the eCRF during the screening and treatment periods, starting at the date of signature of the ICF and ending at the 30-day follow-up visit. After the 30-day follow up, only concomitant therapy indicated for treatment of a related AE has to be reported. If a new anti-cancer treatment is started, it will be documented in the eCRF.

4.2.2.1 Permitted concomitant medications

- If medically feasible, patients taking regular medication should be maintained on it throughout the trial.
- To reduce the risk of infusion related reactions, patients are to be pre-treated with an antihistamine and acetaminophen or paracetamol. Pre-treatment should be administered at sufficient time prior to initiation of infusion to allow the agents to exert their effect.
- Supportive care and other medications that are considered necessary for the patient's well-being may be given at the discretion of the Investigator.
- Blood transfusions are allowed at any time during the trial, except to meet inclusion criteria. There must be at least 4 weeks between a patient's last transfusion and their screening laboratory assessment. Exceptions to this will be considered by the sponsor on a case-by-case basis.
- Patients already receiving erythropoietin at the time of screening for the trial may continue it, provided they have been receiving it for more than one month at the time trial treatment is started. Prophylactic erythropoietin should not be started during the first 3 weeks of any cohort, but may be started thereafter.
- 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 (in solid tumours) as it could interfere with the DLT evaluation for MTD/selected expansion dose determination. Following the first cycle of the dose-expansion phase (Part II), 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 of any Part II cohort. Lesions that have been exposed to radiotherapy are no longer evaluable, and may not be included in the assessment of the non-target lesions and the overall assessment. These lesions may also not be used for a trial biopsy. Unless in emergency situations, the 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, computed tomography (CT) scan contrast hypersensitivity) are acceptable upon discussion with the Medical Monitor.
- Live attenuated vaccines are prohibited during the trial through 30 days after the last dose of investigational product.
- Herbal preparations/medications are not allowed throughout the trial unless agreed to by the Principal Investigator. These herbal medications include, but are not limited to: St. John's wort, kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, and ginseng. If instructed by the Principal Investigator, patients should stop using these herbal medications 7 days prior to first dose of study treatment.

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 in this trial provided that they agree to use a highly-effective contraception method. These are methods of birth control per the International Committee on Harmonisation (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:
- Oral, injected, or implanted hormonal methods of contraception, or
- Intrauterine device or intrauterine 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 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 754111 and BI 754091 will be administered by i.v. infusion at the sites by the Investigator and/or trained site personnel, and dosing will be recorded in the eCRF. Therefore, actual dosing is expected to precisely follow the prescribed drug regimen. Missed or interrupted doses will be recorded in the eCRF with the associated reasons. The method of collecting dosing information assures that total exposure can be calculated programmatically taking into account any missing doses.

5. VARIABLES AND THEIR ASSESSMENT

5.1 TRIAL ENDPOINTS

5.1.1 Primary endpoints

The primary endpoint of Part I (dose escalation) of the trial is the:
- MTD of the BI 754111 plus BI 754091 combination
- Number of patients experiencing DLTs during the combination MTD evaluation period (first cycle of BI 754111 plus BI 754091 combination therapy) in patients with solid tumours.

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.

During the dose-escalation phase, BLRMs employing the EWOC principle will be used for selection of doses of BI 754111 and dose combinations to investigate, and for estimation of the combination MTD. Cohorts of patients will receive escalating doses of BI 754111 and in combination with BI 754091, doses of which may vary, until the MTD of the combination is reached or the selected expansion dose of the combination is determined. 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 the first cycle of BI 754111 plus BI 754091 combination therapy in the set of evaluable patients for the MTD. The corresponding methodology is described in Section 7.3.1.1 and Appendix 10.5. The MTD estimate or the selected expansion dose established during the dose-escalation portion will be re-investigated after the expansion portion by re-running the BLRM including all data from the escalation and expansion portions, in particular also considering the DLT information from all combination treatment cycles.

The primary endpoint of Part II (dose expansion cohorts) of the trial is:
- Objective response (OR) - confirmed complete response (CR) and partial response (PR) according to RECIST Version 1.1 as assessed by the Investigator during the entire treatment.

5.1.2 Secondary endpoints

5.1.2.1 Secondary endpoints of Part I (dose escalation) of the trial

The secondary endpoints of Part I (dose escalation) of the trial are the following:
- PK parameters to be calculated for BI 754111 after single and multiple doses of BI 754111 in combination with BI 754091, and also for BI 754091 after single and multiple doses of combination therapy include:
  - C_{max}: maximum measured concentration of BI 754111/ BI 754091 in plasma
  - AUC_{0-504}: area under the concentration-time curve of BI 754111 / BI 754091 in plasma over the time interval from 0 to 504 hours

- Number of patients experiencing DLTs from start of treatment until end of treatment (in all cycles)
- Objective response (OR) for patients with solid tumours: confirmed CR and PR according to RECIST Version 1.1 as assessed by the Investigator throughout the entire treatment period.

5.1.2.2 Secondary endpoints of Part II (dose expansion) of the trial

The secondary endpoints of Part II (dose expansion cohorts) of the trial are the following:

- Duration of response is the duration from the date of first documented PR or CR according to RECIST Version 1.1 as assessed by the Investigator to the date of PD or death.
- Disease control (CR, PR, or SD according to RECIST Version 1.1 as assessed by the Investigator.
- Progression-free survival (PFS) is the duration from the date of first treatment to the date of PD or death.
- Number of patients experiencing DLTs from start of treatment until end of treatment.

5.2 ASSESSMENT OF EFFICACY

5.2.1 Tumour assessments

The tumour response in patients with solid tumours will be evaluated according to RECIST Version 1.1 (R09-0262) and irRECIST (R15-2005).

The assessment by the Investigator and/or the local radiologist will be the basis for continuation or discontinuation of the trial in an individual patient (in addition to safety). The baseline imaging must have been performed within 4 weeks prior to treatment with the trial medication and the Investigator will record the target and non-target lesions in the eCRF. The same method of assessment and the same technique must be used to characterise each reported lesion at baseline and during treatment. Lesions in previously irradiated areas may not be used as target lesions. Tumour assessments will be performed at screening (as close as possible to the treatment start and no more than 28 days before the start of study treatment), every 2 cycles (6 weeks ±3 days) for the first 6 months, then every 3 cycles (9 weeks ±3 days) thereafter, and at the EOT visit (if not performed within the previous 4 weeks).

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

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

Digital copies of disease evaluation scans are to be collected and stored centrally for later radiomics assessment. It is planned to explore the potential for enhanced and improved baseline and on-treatment markers/ patterns of early efficacy based on comprehensive

quantitative CT metrics, i.e. radiomics features, assessed in standard-of-care medical imaging data.

5.3 ASSESSMENT OF SAFETY

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

DLTs observed during the MTD evaluation period (the first cycle of BI 754111 plus BI 754091 combination treatment) will be considered for MTD determination. However, all DLTs observed in all treatment cycles will be collected and will be considered for determining an expansion dose. The BLRM will be re-run to include the DLT information from all combination treatment 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 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 expansion dose 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 of Part I cohorts only.

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 of supine rest) will be recorded at the screening visit, before and after infusion during the first treatment, at every visit of treatment cycles (pre-infusion) including PK sampling days, at the EOT visit, and at the 30-day safety follow-up visit.

5.3.3 Electrocardiograms

Local ECGs will be done throughout the trial. The ECG should be assessed by a physician (cardiologist if available). There will not be a centralised analysis. Single digitalised ECGs (or analog ECG if digital not available) must be done after 5 minutes of rest at screening, on Day 1 of every cycle through Cycle 6 then every other cycle thereafter (Cycles 8, 10, 12, etc.), on Day 15 of Cycles 1 through 4, at the EOT visit, and whenever the Investigator deems it necessary. An ECG is optional at the 30-day safety follow-up visit if the EOT visit ECG was normal and no drug-related abnormalities were detected in on-trial ECGs.

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

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

5.3.4 Safety laboratory parameters

Blood (venous) samples will be collected at the times indicated in the appropriate flow chart (Flow Chart 1 or 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, creatine phosphokinase (CPK), AST, ALT, alkaline phosphatase, lactate dehydrogenase (LDH), bilirubin, total protein, albumin, urea nitrogen (or urea), and uric acid. Troponin will be tested according to the times listed in the flow charts (Flow Chart 1 or Flow Chart 2). In case of pathological CPK, then CPK-MB, additional troponin I, and myoglobin should be reactively tested and the findings documented. A measurement of troponin-I is to be performed if possible. If troponin-I cannot be measured, troponin-T can be measured instead as long as this is marked in the database.

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.

In case the criteria for hepatic injury are fulfilled, a number of additional measures will be performed (please see Section 5.3.6.5.4 and the Potential DILI Checklist provided in the ISF). The amount of blood taken from the patient concerned will be increased due to this additional sampling.

5.3.4.3 Urinalysis

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

5.3.4.4 Pregnancy test

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

5.3.5 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

A serious adverse event (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 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 assembled 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 'adverse event of special interest' (AESI) relates to any specific AE that has been identified at the project level as being of particular concern for prospective safety monitoring and safety assessment within this trial, e.g., the potential for AEs based on knowledge from other compounds in the same class. AESI need to be reported within the same time frame that applies to SAEs and according to the information in Section 5.3.6.8.

For this trial, DLTs, infusion-related AEs, potential DILI events, hepatic injury, and qualifying irAEs, as defined in Appendix 10.2, are AESIs (see Section 5.3.6.5.2, Section 5.3.6.5.3, and Section 5.3.6.5.4).

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 (irAEs)

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

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

In the event of an infusion-related reaction ≤ Grade 2, treat the symptoms accordingly with antihistamine or corticosteroids if needed. The infusion rate of BI 754111 and/or the combination of BI 754111 plus BI 754091 may be decreased by 50% or interrupted until resolution of the event and re-initiated at 50% of the initial rate until completion of the infusion. In patients experiencing infusion-related reactions ≤ Grade 2, subsequent infusions may be administered at 50% of the initial rate. If an infusion-related reaction is Grade 3 or higher in severity at any point during the study, permanently discontinue study drug(s).

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 754111 and 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 recognise and treat anaphylaxis. The trial site must have immediate access to emergency resuscitation teams and equipment in addition to the ability to admit patients to an intensive care unit if necessary.

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

- Allergic reaction
- Anaphylaxis
- 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 potential drug-induced liver injury (DILI)

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

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

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

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

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

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

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

Lab values meeting this definition of hepatic injury will need to be reported as an AESI. Please follow the flow chart in Figure 5.3.6.5:4: 1 for reporting hepatic injury / potential DILI cases.

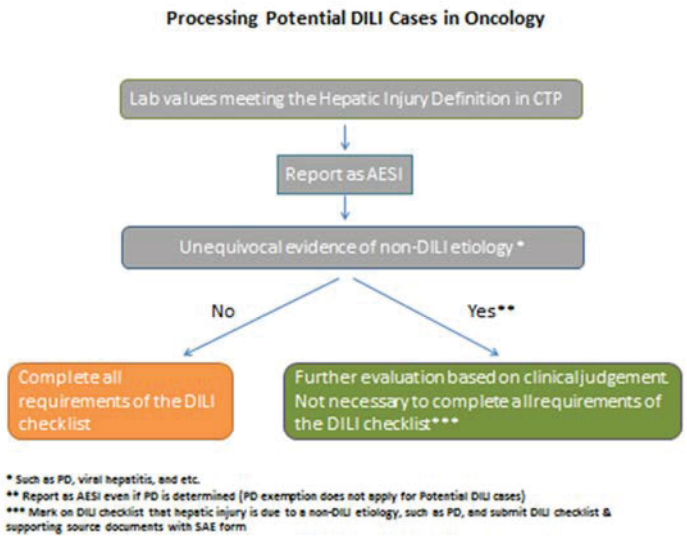


Figure 5.3.6.5:4: 1 Processing potential DILI cases in oncology

Hy's Law cases have the following 3 components:

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

5.3.6.6 Severity of adverse events

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

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 may occur weeks after discontinuation of the drug concerned).
- The event continued despite the withdrawal of the medication, taking into account the pharmacological properties of the compound (e.g., after 5 half-lives). Of note, this criterion may not be applicable to events whose time course is prolonged despite removing the original trigger.
- The event disappeared even though the trial drug treatment continued or remained unchanged.
- There may be additional arguments amongst those stated before, like alternative explanation (e.g., situations where other drugs or underlying diseases appear to provide a more likely explanation for the observed event than the drug concerned).

5.3.6.8 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 the 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.

The rules for Adverse Event Reporting exemptions still apply.

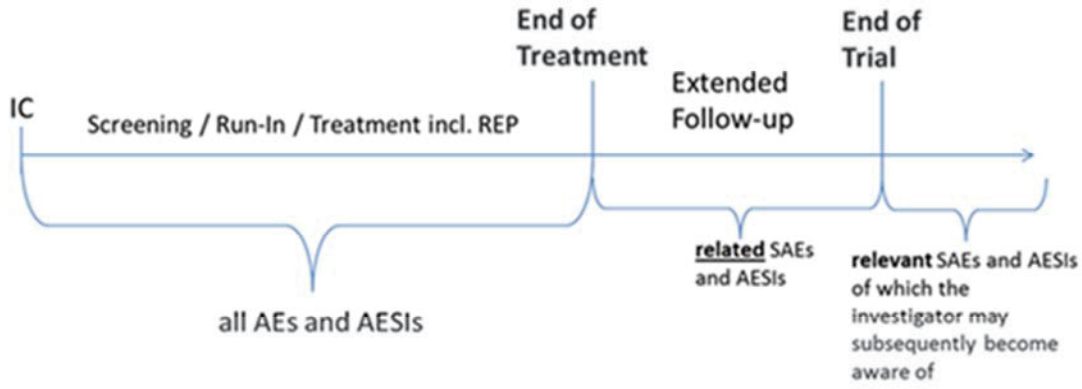


Figure 5.3.6.8.1: 1 Safety follow-up schema

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

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/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 exist prior trial inclusion they will be considered as baseline conditions.

All (S)AEs/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 Studies (Part A) should be used.

Similarly, potential drug exposure during pregnancy must be reported if a partner of a male trial participant becomes pregnant. This requires a written consent of the pregnant partner; in the event that consent cannot be obtained, information will be collected and reported in accordance with regulatory requirements.

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 Studies (Part B).

The ISF will contain the Pregnancy Monitoring Forms for Studies (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 Studies and not the SAE form is to be completed. If there is an SAE and/or AESI associated with the pregnancy an SAE form must be completed in addition.

5.3.6.10 Exemptions to AE/SAE Reporting

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

progression of the underlying malignancy, the event must be reported as an SAE on the SAE Form and on the eCRF.

Examples of exempted events of PD may be:

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

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

5.4 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

5.4.1 Assessment of pharmacokinetics

If data allow, the PK parameters of BI 754111 after single and multiple doses of BI 754111 in combination with BI 754091, and also for BI 754091 after single and multiple doses of combination therapy mentioned as secondary and further endpoints for Parts I and II (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] and [redacted] SOP 'SOP-1.PKA.03 Non-compartmental PK/PD Analysis').

If deemed necessary, further PK parameters (other than those defined see Section 5.1.2 and Section 5.1.3) might be calculated.

5.4.2 Methods of sample collection for pharmacokinetic analyses

For quantification of analyte plasma concentrations, blood will be drawn for both BI 754111 and BI 754091 (where appropriate) at the time points listed in the appropriate flow chart (Flow Chart 1 or Flow Chart 2) under PK sampling and specified in PK time schedules in Appendix 10.4 (Part I dose -escalation cohorts: Table 10.4.1: 1and Table 10.4.1: 2, and the Part II dose-expansion cohorts: Table 10.4.2: 1.

The 1 hour PK sample is to be drawn shortly after the end of the total infusion (of BI 754091 and BI 754111).

Pharmacokinetic sampling times and periods may be adapted by the Sponsor during the trial based on information obtained during trial conduct (e.g., preliminary PK data). Such changes would be implemented via non-substantial Clinical Trial Protocol Amendments.

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

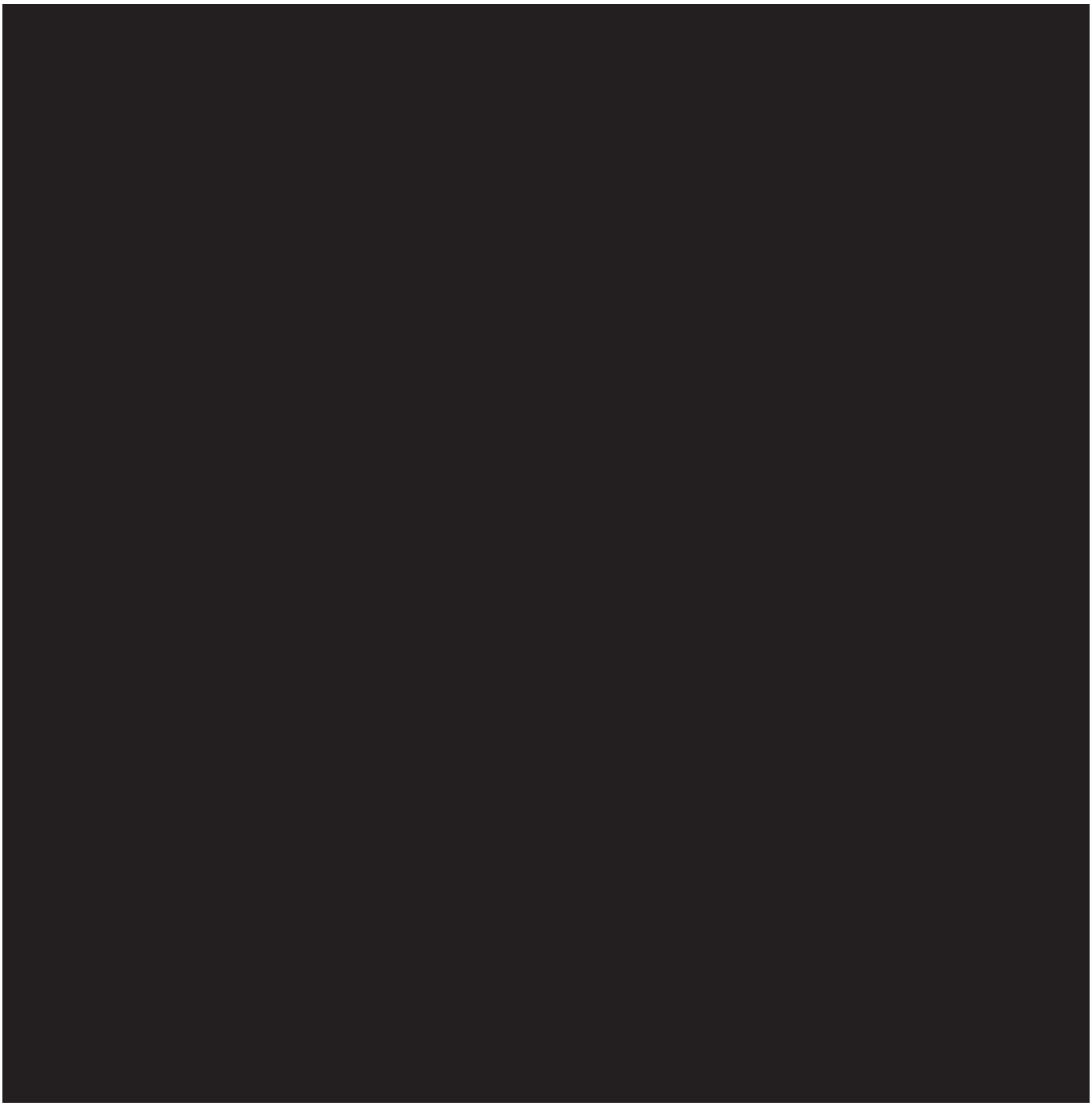
Plasma samples may be used for further methodological investigations (e.g., stability testing), however only data related to the analyte or bioanalytical assay will be generated by these additional investigations. The trial samples will be discarded after completion of the additional investigations but not later than 5 years after the final trial report has been signed.

[redacted]

[redacted]

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 Part II dose-expansion portion of the trial. In addition, biopsies should be taken according to the flow chart (Flow Chart 1 or Flow Chart 2) and Section 5.5.2.3. 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]

5.7 APPROPRIATENESS OF MEASUREMENTS

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

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

Patients meeting the inclusion and exclusion criteria for the part they are participating in and who have signed a written ICF, are eligible for participation in the trial. Patients will visit the clinical site at the time points specified in the appropriate flow chart (Flow Chart 1 or Flow Chart 2). 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 the combination of BI 754111 plus BI 754091, an EOT visit must occur as soon as possible (preferably within 7 days). After the EOT visit, the patient must undergo a follow-up evaluation 30 (+2) days after the last administration of study therapy.

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

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

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

The procedures required at each trial visit in both portions of the trial are presented in the relevant flow charts (Flow Chart 1 or Flow Chart 2) 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/positron emission tomography [PET] and/or magnetic resonance imaging [MRI] scan) according to RECIST Version 1.1 and iRECIST must be performed once every 2 cycles (meaning every 6 weeks if there are no delays in cycles but as close as possible to the end of the second of the 2 cycles of treatment if there was a delay) after the start of BI 754111 for the first 6 months, and then every 3 cycles (9 weeks) thereafter.

6.2.1 Screening period

The screening period may occur over a period of 28 days (period within the trial and before the first intake of BI 754111). For the detailed description of the tests to be performed during this period and their timing, please refer to the appropriate flow chart (Flow Chart 1 or Flow Chart 2).

6.2.1.1 Baseline conditions

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

6.2.1.2 Medical history

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

Previously administered chemotherapy, tyrosine kinase inhibitor treatment, vaccine therapy, antibodies therapy, immune therapy, and hormone therapy will be reported, including start and end dates (month and year may be sufficient), as well as whether therapy was given as neoadjuvant, adjuvant, or palliative therapy. The date of tumour progression after previous lines of treatment will be recorded, if known.

For first line NSCLC cohort, in medical history, last tumor size measurements taken prior to screening in the trial will be collected where available.

6.2.1.3 Concomitant therapies

Relevant concomitant diagnoses and/or therapies present at trial entry and/or during screening and relevant to the patient's safety during the trial as judged by the Investigator will be recorded in the eCRF (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 the relevant flow chart (Flow Chart 1 or Flow Chart 2) 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.

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.

6.2.3.4 Overall survival visits

Additional follow-up visits after the 30-day safety follow-up visit will be performed for patients in the dose-expansion cohorts who enrol 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 Phase I, open-label, dose-escalating trial to determine the MTD(s) for BI 754111 in combination with BI 754091 in patients with solid tumours to recommend a combination dose for Part II dose-expansion cohorts. In addition, the safety and PK profiles, biomarkers, and efficacy of BI 754111 in combination with BI 754091 will also be assessed.

7.1.1 Statistical design – Part I (dose escalation)

The objective of Part I of the trial is to determine the MTD(s) of BI 754111 in combination with BI 754091 and to recommend a combination dose for Part II (dose expansion cohorts). To determine the MTD(s), patients are entered sequentially into escalating dose cohorts and a combination BLRM will be applied.

7.1.1.1 Combination BLRM

The Part I dose escalation will be guided by a Bayesian 5-parameter logistic regression model with overdose control (see R15-4233).

The logistic regression model is defined as follows. Let $\pi_{1,d1}$ be the probability of having a DLT when giving dose d_1 of BI 754091 as monotherapy, and $\pi_{2,d2}$ the probability of having a DLT when giving dose d_2 of the combination partner BI 754111 as monotherapy, respectively. A logistic regression model is used to model the dose-toxicity relationship for each component individually:

BI 754091 part:
$\text{logit}(\pi_{1,d1}) = \log(\alpha_1) + \beta_1 \log(d_1/d_1^*)$

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

where $\text{logit}(\pi) = \log(\pi/(1-\pi))$, the reference doses $d_1^* = d_2^* = 200$ mg are set for BI 754091 and BI 754111, respectively.

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

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

In order to account for a potential positive (higher toxicity than expected under independence) or negative (lower toxicity than expected under independence) interaction

between BI 754091 and BI 754111, a dose-dependent interaction term $-\infty<\eta<\infty$ is introduced to the model by the following definition:

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

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

Since a Bayesian approach is applied, prior distributions f for each of the parameter vectors $\theta_1=(\log(\alpha_1),\log(\beta_1))$, $\theta_2=(\log(\alpha_2),\log(\beta_2))$ and for the interaction term η need to be specified. The prior distributions for θ_1 and θ_2 will be specified as mixtures of two multivariate normal distributions, i.e.
$f(\theta_k) = a_{1,k}\, f_1(\theta_k) + a_{2,k}\, f_2(\theta_k)$
with
$a_{1,k}$, $a_{2,k}$ the prior mixture weights, k=1,2 and
$f_i(\theta_k) = MVN(\mu_{ik}, \Sigma_{ik})$ (k=1,2),
the multivariate normal distribution of the i-th component with mean vector μ_{ik} and covariance matrix Σ_{ik}, where

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

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

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

The BLRM-recommended dose combination 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 dose combinations fulfilling the EWOC principle. Per EWOC it should be unlikely (i.e., <25% posterior probability) that the DLT rate at the dose combination will exceed 0.33. However, the maximum allowable dose increment for the subsequent cohort will be no more than 400% for each compound.

The MTD may be considered reached if 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 0.5, OR
At least 15 patients have been treated in the study, of which at least 6 at the MTD.

Prior derivation:

By the time BLRM is analyzed, safety data for BI 754091 are expected to be available from BI Study 1381.1. The information can be incorporated into the prior derivation meta-analytic predictive (MAP) approach. Exact details on the evaluations of the model using hypothetical data scenarios and operating characteristics are provided in the statistical appendix.

For illustrative purposes only, we assume the following hypothetical data on BI 754091 are available and describe how prior distribution is derived using the MAP approach (Table 7.1.1.1: 1). However, at the time when BLRM is performed for 1381.2, actual data available will be used instead.

Table 7.1.1.1: 1 Hypothetical data for BI 754091

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

* Hypothetical for BI 754091 tabulated for illustrative purposes only. Actual data source will be BI 1381.1 study.

The following steps were used to derive the prior distributions for all parameters:

For θ_1 (BI 754091):
The meta-analytic-predictive prior was derived using the information of BI 754091 from BI Study 1381.1. This mixture component was assigned 90% weight.
A high-toxicity weakly-informative component was added with 10% weight based on the a priori assumption that the median DLT rate at the starting dose of 80 mg would equal 3% and the median DLT rate at 600 mg would equal 50%. This yields $\mu_{12} = (-1.895, 0.545)$. The standard deviations were set such that large uncertainty about the parameter means is reflected, and the correlation was set to 0, thus yielding $\sigma_{12,11} = 2$, $\sigma_{12,22} = 1$ and $\rho_{12} = 0$, respectively.
For θ_2 (BI 754111):

A weakly-informative prior component was derived based on the a priori assumption that the median DLT rate at the starting dose of 4 mg would equal 5% and the median DLT rate at 200 mg would equal 20%. This yields $\mu_{12} = (-1.386, -0.921)$. The standard deviations were set such that large uncertainty about the parameter means is reflected, and the correlation was set to 0, thus yielding $\sigma_{21,11} = 2$, $\sigma_{21,22} = 1$ and $\rho_{21} = 0$, respectively. This mixture component was assigned 90% weight.
A high-toxicity weakly-informative component was added with 10% weight based on the a priori assumption that the median DLT rate at the starting dose of 80 mg would equal 3% and the median DLT rate at 600 mg would equal 50%. This yields $\mu_{22} = (-1.895, 0.545)$. The standard deviations were set such that large uncertainty about the parameter means is

reflected, and the correlation was set to 0, thus yielding $\sigma_{22,11} = 2$, $\sigma_{22,22} = 1$ and $\rho_{22} = 0$, respectively.

The prior distribution for η will be based on the a priori assumption of positive interaction between the two compounds, a normal distribution with mean 0.1 and standard deviation 0.707 was chosen. At the starting dose combination, the corresponding 95% prior interval covers an approximately 4-fold increase (or decrease) in the odds of a DLT over no interaction.

The parameters for prior distributions are given in Table 7.1.1.1: 2. The corresponding prior probabilities of a DLT at different dose combinations and the corresponding probabilities of under-dosing, targeted dosing and overdosing are shown in Table 7.1.1.1: 3. As can be seen from Table 7.1.1.1: 3, the highest dose combinations BI 754091 80 mg plus BI 754111 20 mg and the combination of BI 754091 240 mg and BI 754111 4 mg have prior probability of overdosing below 25%. Any dose combination at or below these levels fulfills the overdose criterion and is therefore a suitable starting dose combination.

Table 7.1.1.1: 2 Parameters for prior distributions

Parameter	Means, standard deviations, correlation	Mixture weight
$\log(\alpha_1)$, $\log(\beta_1)$: component 1	-2.987, -0.092, 0.876, 0.806, -0.121	0.90
$\log(\alpha_1)$, $\log(\beta_1)$: component 2	-1.895, 0.545, 2, 1, 0	0.10
$\log(\alpha_2)$, $\log(\beta_2)$: component 1	-1.386, -0.921, 2, 1, 0	0.90
$\log(\alpha_2)$, $\log(\beta_2)$: component 2	-1.895, 0.545, 2, 1, 0	0.10
η	0.1, 0.707, n/a	n/a

Table 7.1.1.1: 3 Prior probabilities of DLTs

Dose (mg)	Dose (mg)	Probability of true DLT rate in			Descriptive Statistics		Quantiles		
BI 754091	BI 754111	**[0,0.16)**	**[0.16,0.33)**	**[0.33,1]**	**Mean**	**StD**	**2.5%**	**50%**	**97.5%**
80	4	0.717	0.137	0.147	0.152	0.201	0.003	0.066	0.780
80	20	0.634	0.164	0.202	0.193	0.225	0.004	0.096	0.838
80	80	0.515	0.196	0.289	0.253	0.252	0.009	0.151	0.892
80	200	0.386	0.219	0.395	0.327	0.276	0.016	0.238	0.933
80	400	0.296	0.191	0.513	0.412	0.309	0.019	0.345	0.978
80	600	0.264	0.168	0.569	0.459	0.326	0.017	0.416	0.993
240	4	0.584	0.218	0.199	0.210	0.214	0.018	0.127	0.842
240	20	0.504	0.236	0.260	0.249	0.233	0.022	0.158	0.880
240	80	0.385	0.252	0.363	0.311	0.257	0.027	0.221	0.921
240	200	0.286	0.218	0.496	0.394	0.290	0.025	0.326	0.964
240	400	0.256	0.149	0.594	0.486	0.340	0.010	0.464	0.994
240	600	0.267	0.116	0.617	0.530	0.372	0.003	0.568	0.999
400	4	0.431	0.268	0.301	0.280	0.246	0.028	0.192	0.936
400	20	0.362	0.273	0.364	0.317	0.257	0.032	0.232	0.949
400	80	0.277	0.250	0.474	0.381	0.278	0.034	0.309	0.968
400	200	0.245	0.172	0.583	0.467	0.321	0.017	0.431	0.989
400	400	0.268	0.105	0.627	0.541	0.378	0.003	0.595	0.999
400	600	0.294	0.075	0.631	0.568	0.408	0.000	0.700	1.000

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

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 reasonable behaviour as assessed by these metrics. More details can be found in Appendix 10.5. The simulations were conducted using R Version 3.2.2 in conjunction with WinBUGS Version 1.4.

7.1.2 Statistical design – Part II (dose expansion cohorts)

Part II (dose expansion cohorts) of the trial will be designed as multiple open-label cohorts. Cohorts of approximately 40 patients with 2nd or 3rd line NSCLC, 40 patients with mCRC, 40 patients with any solid tumour with high TMB and/or MSI-H (as defined in the entry criteria, see Section 3.3), and 40 patients with 1st line NSCLC (this cohort will include up to 10 patients with PD-L1 expression ≥50%) 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.

7.2 NULL AND ALTERNATIVE HYPOTHESES

No formal hypothesis testing is planned in this trial.

7.3 PLANNED ANALYSES

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

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

7.3.1 Primary endpoint analyses

7.3.1.1 Primary endpoint analyses for Part I

In order to identify the MTD(s) and the recommended dose(s) for Part II of the trial, the number of patients with DLTs at each dose combination during the Part I MTD evaluation period (the first cycle of the BI 754111 plus BI 754091 combination) must be presented by descriptive statistics. Patients who discontinue during the first treatment cycle 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 Part I and Part II, will be summarised at each dose level. The BLRM will be rerun to re-evaluate the MTD and selected expansion dose together with all relevant data collected during Part II.

7.3.1.2 Primary endpoint analyses for Part II

The primary endpoint for Part II of the trial is OR defined by confirmed CR or PR according to RECIST 1.1 as assessed by the Investigator. Overall response will be analysed in terms of

OR rate (ORR), defined as the proportion of patients with best overall response of CR or PR determined and confirmed by RECIST 1.1. The ORR will be calculated and presented with 95% two-sided confidence intervals using the exact Clopper-Pearson method.

7.3.2 Secondary endpoint analyses

7.3.2.1 Secondary endpoint analyses for Part I

The number of patients experiencing DLTs from start of treatment until end of treatment will be summarized by descriptive statistics.

Analyses of OR are described in Section 5.1.2.1. Overall response will be analysed in terms of OR rate (ORR), defined as the proportion of patients with best overall response of CR or PR. The ORR will be calculated and presented with 95% two-sided confidence intervals using the exact Clopper-Pearson method.

Details on statistical inference for PK parameters, e.g., dose proportionality using C_{max} and AUC_{0-504}, etc., and all other secondary endpoints analysis will be specified in the TSAP.

7.3.2.2 Secondary endpoint analyses for Part II

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

Duration of objective response (DoR) - for all patients with an OR, the duration of OR will be calculated as follows:
For patients with disease progression or death:
- Duration of OR [days] = date of outcome – date of first assessment indicating OR + 1

For patients without disease progression or death:
- Duration of OR (censored) [days] = date of outcome – date of first assessment indicating OR + 1

The censoring rules for OR (i.e., outcome and date of outcome) are described in the TSAP. The outcome will be assessed according to RECIST 1.1.

Kaplan-Meier estimates will be used to calculate median duration of OR.

Progression-free survival (PFS) is defined as time from first drug intake until disease progression or death from any cause, whichever occurs earlier. The date of progression will be based on the Investigator assessment according to RECIST 1.1.

For patients with ‘event’ as an outcome for PFS:
- PFS [days] = date of outcome – date of start of treatment + 1

For patients with ‘censored’ as an outcome for PFS:
- PFS (censored) [days] = date of outcome – date of start of treatment + 1

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

Kaplan-Meier estimates will be used to display the distribution of PFS with 95% confidence intervals, using Greenwood's variance estimate.

Analyses of PK parameters, i.e., C_{max} and AUC_{0-504} will be described in Section 7.3.5. More details will be provided in 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 (001-MCS-36-472_RD-01 [2.0] and [redacted] SOP 'SOP-1.PKA.03 Non-compartmental PK/PD Analysis').

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, exploratory analysis of PK will be done during the dose escalation part and may also be done during the expansion part, 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.

An interim futility analysis will be performed for Cohort G, I, and J in Part II. Until a decision from the futility analysis is made, the enrolment for that cohort will not be stopped. The two-stage design is planned to stop further enrolment if the defined efficacy boundary (see Table 7.7.2: 1 and Table 7.7.2: 3) is not met at the first stage.

The interim analysis for Part II will be conducted when:

- The last patient contributing to the interim analysis has completed the third on-treatment imaging assessment (i.e. end of cycle 6).

If the last patient contributing to the interim analysis discontinues earlier than the third on-treatment imaging, the interim futility analysis will be done at approximately 4 months after the first administration of that patient.

Data from 1381-0002 and 1381-0004 may be pooled for the interim futility decision making, if applicable. If considered necessary, an evaluation of the efficacy and safety aspects will be performed. Results of this evaluation will be documented and archived. If applicable, such an analysis will be defined in more detail in the TSAP.

7.5 HANDLING OF MISSING DATA

In general, no imputation will be performed on missing efficacy data. For PFS data, every effort will be made to obtain date of progression for patients known to have progressed. Detailed censoring rules will be specified in the TSAP. Missing baseline laboratory values will be imputed by the respective values from the screening visit. No other imputations will be performed on missing data although every effort will be made to obtain complete information on all AEs, with particular emphasis on potential DLTs. For partial or missing AE onset and/or end dates, BI internal rules will be followed (see Reference Document 001-MCG-156_RD01 “Handling of missing and incomplete AE dates”).

7.6 RANDOMISATION

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

7.7 DETERMINATION OF SAMPLE SIZE

7.7.1 Determination of sample size for Part I

For Part I, no formal statistical power calculations of sample size were performed. Approximately 50 patients for Part I (dose-escalation) are expected. Fewer or more patients might be needed based on the recommendation of the SRC and the actual number of cohorts tested.

7.7.2 Determination of sample size for Part II

For Cohorts G and I, it is considered clinically meaningful based on the current literature for the combination of BI 754111 and BI 754091 to achieve an underlying ORR of 25%. A futility boundary of an ORR of 10% will be used for the interim analysis. Assuming an underlying ORR of 25%, the probability of observing <2 responders out of 20 patients and stopping at the interim is 2%, and the probability of observing an ORR ≥20% at the final analysis is 81%. Alternatively, assuming an underlying ORR of 5%, the probability of stopping at the interim is 74% and the probability of observing an ORR ≥20% at the final analysis is 0%. Table 7.7.2: 1 summarizes the early stopping criteria and probabilities of observing certain ORRs based on different assumptions of the underlying ORR.

Table 7.7.2: 1 Early stopping criteria and probabilities of the two-stage approach in Cohorts G and I

Assumed underlying ORR	Early stopping criterion (observed ORR)	Early stopping probability	Observed ORR at final analysis	Probability of observed ORR at final analysis
5%	<10% (<2 out of 20)	74%	≥20% (≥8 out of 40)	0%
10%	<10% (<2 out of 20)	40%	≥20% (≥8 out of 40)	4%
15%	<10% (<2 out of 20)	18%	≥20% (≥8 out of 40)	24%

Table 7.7.2: 1 Early stopping criteria and probabilities of the two-stage approach in Cohorts G and I (continued)

20%	<10% (<2 out of 20)	7%	≥20% (≥8 out of 40)	55%
25%	<10% (<2 out of 20)	2%	≥20% (≥8 out of 40)	81%
30%	<10% (<2 out of 20)	1%	≥20% (≥8 out of 40)	95%

For Cohort H, it is planned that 40 patients will be enrolled and no interim futility analysis will be performed. Based on the current literature, it is considered clinically meaningful if the combination of BI 754111 and BI 754091 will achieve an underlying ORR of 20%. With 40 evaluable patients, an ORR of 15% or more would be observed with a probability of approximately 84% assuming a true response rate of 20%. The probability of observing a false positive signal, e.g., to observe an ORR of at least 15% if the underlying true ORR is 5%, is around 1%. Table 7.7.2: 1 summarizes the probability of observing certain ORRs based on different assumptions of the underlying ORR.

Table 7.7.2: 2 Probabilities of observing certain objective response rates in Cohort H

True underlying OR rate	Patients in each cohort	Probability to observe at least		
		ORR ≥ 10% (≥ 4 patients with OR)	ORR ≥ 15% (≥ 6 patients with OR)	ORR ≥ 20% (≥ 8 patients with OR)
20%	40	97.2%	83.9%	56.3%
15%	40	87.0%	56.7%	24.4%
10%	40	57.7%	20.6%	4.2%
5%	40	13.8%	1.4%	0.1%

For Cohort J, it is planned that a total of 40 patients will be enrolled, with a maximum of 10 patients with PD-L1 high expression (≥ 50% PD-L1). In CheckMate 026, the ORR was 21% with nivolumab (N=101) compared with 26% in the chemotherapy group (N=81) for 1st line NSCLC patients with 1%≤ PD-L1 <50% (R19-0527). In KEYNOTE-189, the ORR was 48.4% (95% CI, 39.5-57.4) with pembrolizumab plus chemotherapy (N=128) compared with 20.7% (95% CI, 11.2-33.4) with chemotherapy alone (N=58) for patients with 1%≤ PD-L1 <50%; the ORR was 32.3% (95% CI, 24.3-41.2) with pembrolizumab plus chemotherapy (N=127) compared with 14.3% (95% CI, 6.7-25.4) with chemotherapy alone (N=63) for patients with PD-L1 <1% (P18-03589). Based on the above literature, it is deemed clinically meaningful if the underlying ORR for the combination of BI 754111 and BI 754091 will be 40% for patients with PD-L1 < 50%, and a futility boundary of 20% will be used for the interim analysis of this population in Cohort J. With 30-40 evaluable patients and assuming an underlying ORR of 40%, the probability of observing <4 responders out of 17 patients and stopping at the interim is 5%, and the probability of observing an ORR ≥35% at the final analysis is between 70% to 77%. Alternatively, assuming an underlying ORR of 15%, the

probability of stopping at the interim is 76% and the probability of observing an ORR ≥35% at the final analysis is 0%. Table 7.7.2: 3 summarizes the early stopping criteria and probabilities of observing certain ORRs based on different assumptions of the underlying ORR.

Table 7.7.2: 3 Early stopping criteria and probabilities of the two-stage approach in Cohort J

Assumed underlying ORR	Early stopping criterion (observed ORR)	Early stopping probability	Observed ORR at final analysis	Probability of observed ORR at final analysis
Assuming 30 patients with PD-L1 <50%				
15%	<20% (<4 out of 17)	76%	≥35% (≥11 out of 30)	0%
20%	<20% (<4 out of 17)	56%	≥35% (≥11 out of 30)	2%
25%	<20% (<4 out of 17)	36%	≥35% (≥11 out of 30)	10%
30%	<20% (<4 out of 17)	20%	≥35% (≥11 out of 30)	26%
35%	<20% (<4 out of 17)	11%	≥35% (≥11 out of 30)	48%
40%	<20% (<4 out of 17)	5%	≥35% (≥11 out of 30)	70%
Assuming 40 patients with PD-L1 <50%				
15%	<20% (<4 out of 17)	76%	≥35% (≥14 out of 40)	0%
20%	<20% (<4 out of 17)	56%	≥35% (≥14 out of 40)	2%
25%	<20% (<4 out of 17)	36%	≥35% (≥14 out of 40)	10%
30%	<20% (<4 out of 17)	20%	≥35% (≥14 out of 40)	29%
35%	<20% (<4 out of 17)	11%	≥35% (≥14 out of 40)	54%
40%	<20% (<4 out of 17)	5%	≥35% (≥14 out of 40)	77%

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, the ICH Harmonised Tripartite Guideline for GCP, relevant BI SOPs, and other relevant regulations.

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

The Investigator will inform the sponsor immediately of any urgent safety measures taken to protect the trial 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 finalisation 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 or delegate 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 or delegate obtains written consent of the patient's own free will with the ICF after confirming that the patient understands the contents. The Investigator or delegate 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., retraining) 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 the 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 treatment in 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 specifically 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, and 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)

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

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

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

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

10.2 MANAGEMENT OF IMMUNE-RELATED ADVERSE EVENTS

Management of immune-related adverse event toxicities associated with anti-PD-1 mAbs are presented below. **BI 754091 and BI 754111 should be permanently discontinued for Grade 3-4 pneumonitis, Grade 3-4 adrenal insufficiency, Grade 4 diabetes mellitus, any grade encephalitis, Grade 4 hypophysitis, Grade 4 rash, Grade 3-4 or recurrent colitis of any grade, any recurrent Grade 3-4 AE, transaminase >5 times ULN or total bilirubin >3 times ULN (unless unequivocally attributably to another cause), inability to taper steroids to 10 mg or less prednisone or equivalent within 12 weeks, or persistent Grade 2-3 AEs that do not recover to Grade 1 or less within 12 weeks.**

- Pneumonitis:

- For Grade 2 events, treat with systemic corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 28 days.
- Add prophylactic antibiotics for opportunistic infections in the case of prolonged steroid administration.
- For Grade 3-4 events immediately treat with i.v. steroids. Administer additional anti-inflammatory measures, as needed.
- BI 754091 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 (unless unequivocally attributably to another cause), inability to taper steroids to 10 mg or less prednisone or equivalent within 12 weeks, or persistent Grade 2-3 AEs that do not recover to Grade 1 or less within 12 weeks.

- Renal failure or nephritis:
  - For Grade 2 events, treat with corticosteroids.
  - For Grade 3-4 events, treat with systemic corticosteroids.
  - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 28 days.
  - BI 754091 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. In the event of an infusion-related reaction ≤ Grade 2, treat the symptoms accordingly with antihistamine or corticosteroids if needed, the infusion rate of study drug(s) may be decreased by 50% or interrupted until resolution of the event and re-initiated at 50% of the initial rate until completion of the infusion. In patients experiencing infusion-related reactions ≤ Grade 2, subsequent infusions may be administered at 50% of the initial rate. If an infusion related reaction is Grade 3 or higher in severity at any point during the study, permanently discontinue study drug(s).

10.3 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 [redacted] BLOOD SAMPLING

10.4.1 Schedules for PK, [redacted] blood sampling – Part I dose-escalation cohorts

Table 10.4.1: 1 Time schedule for PK and [redacted] sampling - Part I dose-escalation cohorts (Cycles 1, 2, and 4 for solid tumour cohorts)

Treatment Cycles	Day	Time Point [b] [hh:min]	CRF Time /PTM	Event	PK BI 754111 & BI 754091[c]	[redacted]
1, 2, and 4	1	Just before BI 754091 (or combination) SOI	-1:00 to -0:05	Blood sampling	X	[redacted]
		0:00	0:00	Start of BI 754091 Infusion (or combination of BI 754111 / BI 754091)	---	
		Shortly after end of BI 754111 infusion[a]	1:00	Blood sampling	X[d]	
		4 hours post BI 754091 SOI[a]	4:00	Blood sampling	X	
		7 hours post BI 754091 SOI[a]	7:00	Blood sampling	X	
	2	24 hours post BI 754091 SOI	24:00	Blood sampling	X	
	4	72 hours post BI 754091 SOI	72:00	Blood sampling	X	
	8 **(±1)**	168 hours post BI 754091 SOI	168:00	Blood sampling	X	
	15 **(±1)**	336 hours post BI 754091 SOI	336:00	Blood sampling	X	

[redacted] BI = Boehringer Ingelheim; CRF = Case Report Form; PK = pharmacokinetics; PTM = Planned Time; SOI = Start of infusion

a The planned total infusion duration is 1 hour. For cohorts receiving doses of BI 754111 <80 mg, the overall infusion duration (BI 754091+BI 754111) should also be as close to 1 hour as possible. **In the event that total 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 (e.g., 1.25 hours post SOI)**. For cohorts receiving combination treatment using doses of BI 754111 <80 mg, the 1 hour PK sample is to be drawn shortly after the end of the BI 754111 infusion. Actual date and clock time of SOI, end of infusion and blood draws have to be recorded.

b **The following windows of time are allowed for PK sampling:**

- **Predose (PTM -0:05): within 1 hour before next drug infusion**
- **Shortly after the end of infusion (PTM 1:00): within ±5 min of the end of infusion**
- **4 and 7 hours post SOI (PTM 4:00 and 7:00): ±15 minutes**
- **24 and 72 hours post SOI (PTM 24:00 to 72:00): ±1 hour**
- **168 and 336 hours post SOI (PTM 168:00 to 336:00): ±24 hour.**

Note: Time windows have been specified for procedural reasons; deviations do not automatically lead to exclusion of samples from data evaluation.

c The specified blood volume for both BI 754111 and BI 754091 will be drawn into separate blood-drawing tubes. However, they should be collected in parallel at the specified time points after the start of the BI 754091 (or combination) infusion.
d. An additional blood sample will be taken one time from all subjects of the first dose group that exceeds 200 mg BI 754111.

Table 10.4.1: 2 Time schedule for PK, [redacted] sampling - Part I dose-escalation cohorts (Solid tumour cohorts: Cycles 3, 5 to 12, 14, and 17 only)

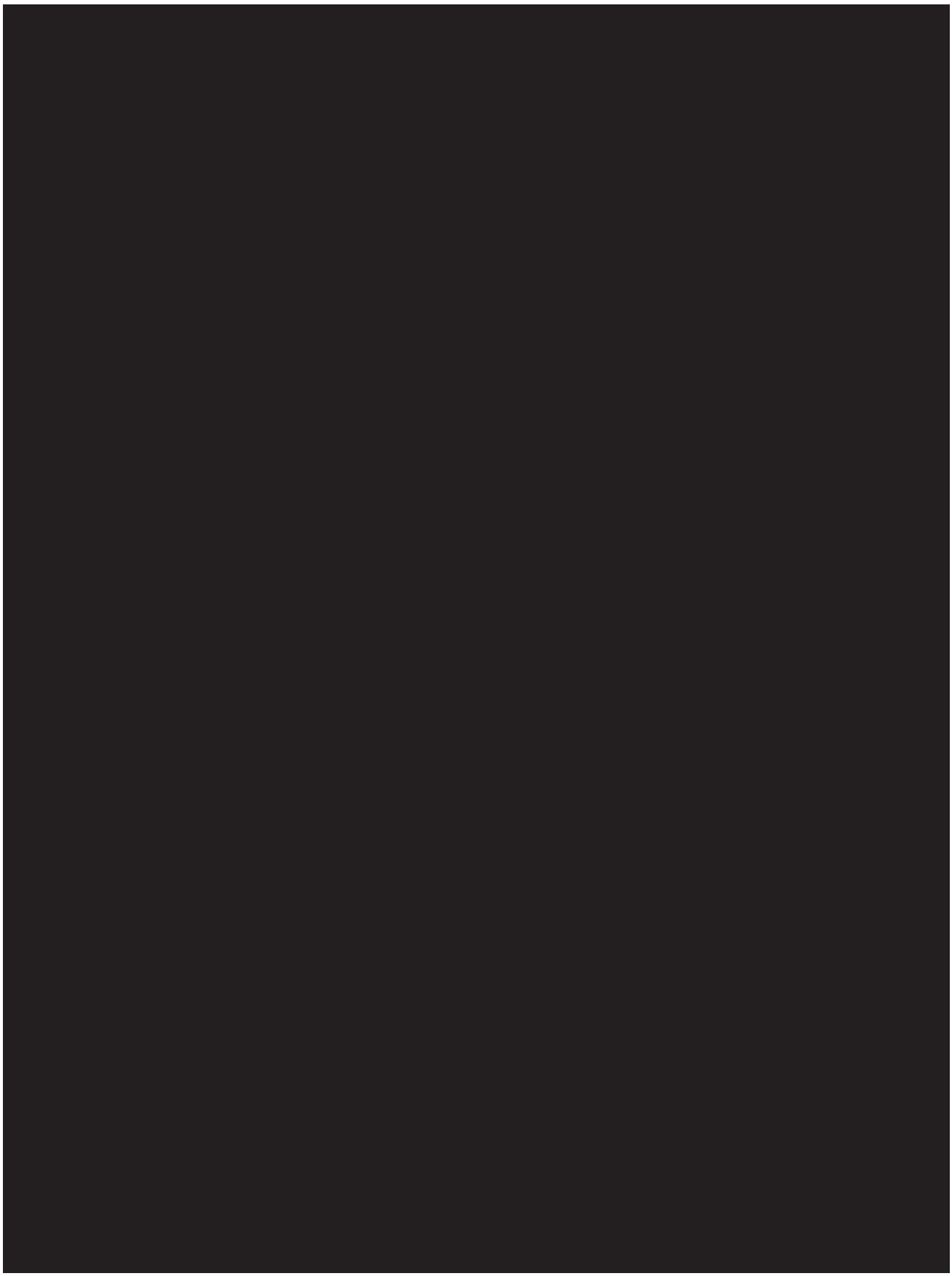
Treatment Cycle	Day	Time Point [a] [hh:min]	CRF Time /PTM	Event	PK BI 754111 and BI 754091 [b]	[redacted]
3, 5 to 12, 14, and 17	1	Just before BI 754091 (or combination) SOI	-0:05	Blood sampling	X	[redacted]
		0:00	0:00	Start of BI 754091 infusion (or combination of BI 754111/ BI 754091)	---	
EOT				Blood sampling	X	[redacted]
FU				Blood sampling	X	[redacted]

[redacted]; BI = Boehringer Ingelheim; CRF = Case Report Form; EOT = end of treatment; FU = follow up; MDSC = myeloid-deprived suppressor cell; PBMC = peripheral blood mononuclear cells; PK = pharmacokinetics; PTM = Planned Time;; SOI = start of infusion

a The following windows of time are allowed for PK sampling: Predose (PTM -0:05): within 1 hour before next drug infusion

Note: Time windows have been specified for procedural reasons; deviations do not automatically lead to exclusion of samples from data evaluation.

b The specified blood volumes for both BI 754111 and BI 754091 will be drawn into separate blood-drawing tubes. However, they should be collected in parallel at the specified time points after the start of the BI 754091 (or combination) infusion.



10.5 STATISTICAL APPENDIX INCLUDING MODEL PERFORMANCE AND DATA SCENARIOS

One combination BLRM with overdose control is introduced in Section 7.1 with the prior distributions for the model parameters fully specified. Once patients in each cohort have completed the combination MTD evaluation period, the prior distribution will be updated through Gibbs sampling procedures with the accumulated DLT data from the MTD evaluation period. Posterior probabilities for the rate of DLTs will be summarised from BLRM. Selection of the next dose will be based on these probabilities as well as on other safety and laboratory data.

The purpose of this statistical appendix is to evaluate the model behaviour and model performance. To evaluate the model behaviour, Section 10.5.1 illustrates a series of different scenarios that mimic the ones which might arise during the actual study conduct. On-study recommendations for the next dose combinations 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 10.5.1: 1).

In order to understand the long-term performance of the model, Section 10.5.2 presents 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 summarised in Table 10.5.2: 2. For simplicity reasons, a cohort size of 3 patients who are all evaluable is assumed. In case a DLT is observed, an additional 3 patients will be added to the current dose cohort. The simulations for scenarios and operating characteristics were conducted using R Studio Version 3.2.2 in conjunction with WinBUGS 1.4.3.

10.5.1 Hypothetical data scenarios

Hypothetical data scenarios during dose escalation 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 3 patients who are all evaluable. At the 1st occurrence of a DLT, additional 3 patients will be added to the current cohort. 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 1A represents the case that no DLT is observed in the first 3 patients at the starting dose combination of BI 754091 240 mg plus BI 754111 4 mg (denoted by 240 mg/4 mg for easier reference). In this case, 240 mg/80 mg is recommended as the next highest dose.

In Scenario 1B, 1 DLT is observed in the first cohort, i.e., 240 mg/4 mg. The next allowed dose combination by the model remains 240 mg/4 mg.

Based on Scenario 1B, Scenario 1D illustrates a case where 1 DLT is observed in the first 3 patients and additional 3 patients have been enrolled. No additional DLTs have occurred. The next allowed dose combination from the model is 240 mg /20 mg.

On the other hand, Scenario 1E represent a case that 1 DLT is observed in the first 3 patients and additional 1 DLT is observed in the subsequent 3 patients treated, i.e., 2 DLTs out of 6 patients are observed at 240 mg / 4 mg. Model shows current dose exceeded threshold, i.e., 25.8 >25% and hence dose escalation stops.

Scenario 1C represents a more extreme case that 2 DLTs are observed in the first cohort of three patients, i.e., 240 mg/4 mg. In this case, the model suggests current dose has already exceeded the overdose threshold, i.e., 63.0% >25%, and hence no further dose can be recommended.

Scenarios 2A – 2E represent the cases that the first two cohorts have completed evaluation at 240 mg/4 mg and 240 mg/20 mg, respectively. In Scenario 2A, no DLTs are observed in the 240 mg/4 mg cohort or 240 mg/20 mg cohort, model suggests 240 mg/80 mg as next recommended dose combination. In Scenario 2C, no DLTs are observed in the first 240 mg/4 mg cohort but 1 DLT out of 6 patients is observed in the 240 mg/20 mg cohort, the model recommends 240 mg/80 mg as next dose combinations for considerations of further escalation.

Scenarios 2B, 2D and 2E represents the 3 cases with higher toxicity, i.e., 1 out of 3, 2 out of 6, and 3 out of 6 patients experienced DLTs. The recommended dose combinations are to remain current dose, remain current dose, and decrease to 240 mg/4 mg for Scenarios 2B, 2D and 2E, respectively.

Table 10.5.1: 1 Hypothetical data scenarios

Scenario	Dose comb. BI754091/ BI754111 (mg/mg)	# DLT	# Pat	Current Dose: P(OD)	Next allowed dose comb. (mg)*	Summary of toxicity by Combination model		
						P(under dose)	P(target dose)	P(over dose)
1A	240/4	0	3	0.036	240/80	0.546	0.275	0.180
1B	240/4	1	3	0.223	240/4	0.431	0.346	0.223
1C	240/4	2	3	0.631	None	n/a	n/a	n/a
1D	240/4	1 0	3 3	0.065	240/20	0.516	0.348	0.136
1E	240/4	1 1	3 3	0.258	None	n/a	n/a	n/a
2A	240/4 240/20	0 0	3 3	0.020	240/80	0.664	0.241	0.095
2B	240/4 240/20	0 1	3 3	0.123	240/20	0.527	0.350	0.123
2C	240/4 240/20	0 0 1	3 3 3	0.043	240/80	0.489	0.346	0.165
2D	240/4 240/20	0 1 1	3 3 3	0.151	240/20	0.400	0.449	0.151
2E	240/4 240/20	0 1 **2**	3 3 3	0.391	240/4	0.312	0.493	0.195

*The next dose combinations allowed by model are all listed. In actual trial dose escalation, only 1 compound will be escalated at each cohort.

10.5.2 Operating Characteristics

Operating characteristics are a way to assess the long-run behaviour of a model by illustrating the precision of design in estimating the MTD. Under an assumed true dose-toxicity curve, metrics such as the probability of recommending a dose with true DLT rate in the target interval can be approximated via simulation.
Table 10.5.2: 1 describes 3 assumed true dose-toxicity scenarios which were used to assess the operating characteristics of the combination model. These scenarios reflect a wide range of possible cases as follows:

- Scenario C1: aligned with prior means
- Scenario C2: low-toxicity scenario
- Scenario C3: high-toxicity scenario

Table 10.5.2: 1 Assumed True Dose-Toxicity Scenarios

Scenario C1, P(DLT)	Dose BI 754111 (mg)					
Dose BI 754091 (mg)	4	20	80	200	400	600
80	**0.170**	**0.200**	**0.240**	**0.320**	0.400	0.450
240	**0.220**	**0.280**	**0.320**	0.400	0.460	0.550
400	**0.260**	**0.300**	0.360	0.480	0.500	0.600
Scenario C2, P(DLT)	Dose BI 754111 (mg)					
Dose BI 754091 (mg)	4	20	80	200	400	600
80	0.040	0.080	**0.180**	**0.200**	**0.25**	**0.300**
240	0.080	**0.180**	**0.200**	**0.250**	**0.30**	0.350
400	**0.180**	**0.200**	**0.250**	**0.300**	0.35	0.400
Scenario C3, P(DLT)	Dose BI 754111 (mg)					
Dose BI 754091 (mg)	4	20	80	200	400	600
80	**0.250**	**0.280**	**0.320**	0.400	0.500	0.650
240	**0.280**	**0.320**	0.400	0.500	0.650	0.750
400	**0.320**	0.400	0.500	0.650	0.750	0.850

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

For each of these scenarios, 1000 trials were simulated. Each cohort consisted of 3 patients and dose escalation complied with the following rules:

- Escalate to the dose combination which maximizes the probability of the targeted toxicity region and satisfies the overdose criterion if it is ≤400% increase from the current dose.
- If the recommended dose combination satisfying the overdose criterion is > 400% increase in dose for each compound, then escalate to the highest dose combination which is ≤ 400% increase from the current dose for each compound.
- If any DLT occurs, extra 3 patients will be tested at the current dose combination.

The MTD was considered reached if the following conditions are satisfied:

- The next recommended dose is the same as the current dose;
- At least 1 DLT is observed;
- At least 6 patients have been treated at the MTD dose combination declared by the model;
- At least 15 patients have been evaluated OR the posterior probability of targeted toxicity reaches 50%.

It was then assessed how often a dose was declared as MTD with true DLT rate in the underdose, 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	Mean (Min-Max)	Mean (Min-Max)
C1: Aligned with prior	0	69.0	2.8	28.2	17.82 (6-30)	4.111 (1-13)
C2: Low Tox	23.5	73.8	0.1	0.8	22.38 (6-36)	3.402 (1-11)
C3: High Tox	0	45.6	4.1	50.3	14.98 (6-33)	4.346 (1-13)

In Scenario C1, which reflects the case that the true dose-toxicity is approximately aligned with prior means, almost all of the simulated trials identified the MTD. Approximately 69.0% of trials were in the target interval and none of them were in the underdose interval. There were 2.8% in the overdose interval (see for three dose combinations with underlying true DLT rates between 36% and 60%) and 28.2% of the trials were prematurely stopped either because the MTD was not identified or because the probability of overdose associated with the simulated starting dose had already exceeded the 25% threshold.

Scenario C2 (Low-toxicity scenario) shows similar results with previous Scenario 1 overall. Only 0.1% of the simulated trials declared a MTD with a true DLT rate in the overdose interval. Most of the simulated trials, i.e., approximately 99%, identified the MTD with 73.8% in the target dose interval and 23.5% are in the underdose interval.

Scenario C3 (High-toxicity scenario) illustrates a case with higher-than-expected toxicity. In this case, approximately 46% of the simulated trials identified the MTD within the target interval. Approximately 4% of the simulated trials declared the MTD in the overdose interval. Due to higher toxicity in this scenario, approximately 50% of the simulated trials were prematurely stopped for similar reasons as in Scenario 1.

By reviewing the metrics presented in Table 10.5.2: 2, it can be seen that the model is not sensitive to different scenarios of true DLT rates. Across three scenarios, the average number of patients participated in dose-escalation ranges from 14.98 to 17.82 and the average number of DLTs observed ranged from 3.402 to 4.346. In general, this model is conservative due to

the overdose control criteria. In all scenarios, the probabilities of recommending a dose combination with true P(DLT) ≥33% as MTD are much smaller than probabilities of recommending a dose combination with true P(DLT) between 16% and 33% as MTD.

In summary, the considered data scenarios demonstrate reasonable operating characteristics of the model. On-study recommendations based on the model are consistent with the clinical decision making process, and should be considered in conjunction with other available clinical information by the SRC in deciding the dose combinations to be tested in order to determine the MTD estimates.

11. DESCRIPTION OF GLOBAL AMENDMENTS

Number of global amendment		1
Date of CTP revision		08 May 2017
EudraCT number		Not applicable
BI Trial number		BI 1381.2
BI Investigational Product(s)		BI 794111 and BI 754091
Title of protocol (previous - see below for title update)		An open label, Phase I dose-finding study of BI 754111 as monotherapy and in combination with BI 754091 in patients with advanced cancer followed by expansion cohorts at the RPIID of the combination in patients with NSCLC and other tumour types
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		Protocol title
Description of change		An open label, Phase I dose-finding study of BI 754111 ~~as monotherapy and~~ in combination with BI 754091 in patients with advanced ~~cancer~~**solid cancers and of BI 754111 monotherapy with subsequent combination with BI 754091 in patients with follicular lymphoma,** followed by **an** expansion cohort~~s~~ at the RPIID of the combination in patients with ~~NSCLC and other tumour types~~**non-small cell lung cancer**
Rationale for change		In response to the FDA review and the subsequent design change, the title was changed to more accurately describe the study.

Section to be changed		Synopsis and Section 2.2.1 Part I (dose-escalation cohorts) objectives
Description of change		The objectives of the dose-escalation portions of the trial are to: • Investigate the safety, tolerability, and pharmacokinetics (PK) of escalating doses of BI 754111 ~~as monotherapy for 2 cycles (2 doses~~ **in combination with BI 754091** (administered via intravenous [i.v.] infusion once every 3 weeks [q3w]) in patients with advanced and/or metastatic solid tumours ~~and.~~ • **Investigate the safety, tolerability, and PK of escalating doses of BI 754111 as monotherapy for 2 cycles (2 doses administered via i.v. infusion q3w) in** patients with relapsed/refractory follicular lymphoma (FL) • Investigate the safety, tolerability, and PK of escalating doses of BI 754111 in combination with BI 754091 (administered via i.v. infusion q3w) added on to BI 754111 starting at Cycle 3 in patients with ~~advanced and/or metastatic solid tumours and patients with relapsed/refractory FL, and investigate the PK of BI 754091 in combination with escalating doses of BI 754111~~**relapsed/refractory FL** ~~• Investigate the safety, tolerability, and PK of escalating doses of BI 754111 in combination with BI 754091 with both of these monoclonal antibodies (mAbs) administered together from start of trial treatment in patients with advanced and/or metastatic solid tumours and investigate the PK of BI 754091 in combination with escalating doses of BI 754111~~ • Determine the maximum-tolerated dose (MTD) through monitoring dose-limiting toxicities (DLTs) and/or to determine the recommended Phase II dose (RPIID) of the combination of BI 754111 plus BI 754091 • Assess LAG-3 receptor occupancy (RO) in peripheral blood in patients with FL.
Rationale for change		In response to the FDA review, the study design changed to begin with combination dosing in patients with solid tumours. BI 754111 monotherapy will still be tested in patients with follicular lymphoma.
Section to be changed		Synopsis and Section 2.2.2 Part II (dose-expansion cohorts) objectives
Description of change		The objectives of the dose-expansion portion of the trial are to: • Further investigate the safety, tolerability, and PK of the RPIID of the combination of BI 754111 plus BI 754091 in patients with NSCLC (as defined in the entry criteria) ~~and other tumour types (to be specified at a later date via protocol amendment)~~ • Explore the efficacy of the combination in patients with NSCLC (as defined in the entry criteria) ~~and other tumour types (to be specified at a later date via protocol amendment)~~.

Rationale for change		In response to the FDA review, statements regarding potential additional expansion cohorts are removed from the protocol.
Section to be changed		Synopsis - Methodology
Description of change		**Part I (Dose-Escalation Cohorts):** ~~Open~~**For patients with solid tumours: open**-label, non-randomised, dose-escalation ~~cohorts~~ **(into consecutive cohorts of BI 754111 in combination with BI 754091** **For patients with FL: open-label, non-randomised, dose-escalation into** consecutive cohorts of BI 754111 monotherapy for 2 cycles, with BI 754091 added to BI 754111 starting at Cycle 3~~, and cohorts of BI 754111 in combination with BI 754091 administered simultaneously). Cohorts for FL will start after a dose/dose combination has been cleared in cohorts of solid tumours~~. Dose escalation **in both patient populations** will be guided by Bayesian Logistic Regression Models (BLRMs) with overdose control for BI 754111 ~~monotherapy as well as for the BI 754111~~ + BI 754091 combination therapy **as well as for BI 754111 monotherapy in patients with FL**. **Part II (Dose-Expansion Cohort):** Open-label, non-randomised, dose-expansion cohorts with the RPIID of the combination in ~~different tumour types treated in parallel cohorts~~**patients with NSCLC**.
Rationale for change		In response to the FDA review, dose expansion is more accurately described as being limited to a single cohort at this time.
Section to be changed		Synopsis - No. of patients
Description of change		**Part I (Dose-Escalation Cohorts):** Approximately ~~20~~**25** to 40 patients **Part II (Dose-Expansion Cohorts):** ~~Approximately 90~~**30** patients total **Part I:** ~~a minimum of~~ 3 patients with solid tumours per dose-escalation cohort **Part II:** ~~approximately~~ 30 patients ~~per dose expansion cohort~~
Rationale for change		To more accurately reflect the plausible number of subjects in dose escalation, and to address the FDA comment to limit dose expansion to a single cohort at this time.

Section to be changed		Synopsis - Diagnosis
Description of change		**Part II (Dose Expansion Cohorts):** **Second and 3rd line** NSCLC patients who progressed on anti-PD-1 or anti-PD-L1 treatment after having achieved radiologically confirmed benefit (minimum of stable disease) with a minimum treatment duration of 6 months on the previous anti-PD-1 or anti-PD-L1 treatment. The anti-PD-1 or anti-PD-L1-containing treatment (excluding anti-PD-1 or anti-PD-L1 in combination with chemotherapy) must have been the latest treatment regimen prior to enrolling into this trial with >4 and <12 weeks between latest treatment and their first dose in this trial. Patients that have had anti-PD-1 or anti-PD-L1 as their first-line NSCLC treatment regimen must have a PD-L1 expression level of ≥50% at baseline. ~~Other indications may be evaluated in additional expansion cohorts.~~
Rationale for change		To clarify requirements for patients with NSCLC and to clearly limit dose-expansion to one cohort at this time.
Section to be changed		Synopsis - Main criteria for inclusion and Section 3.3.2
Description of change		• For patients in Part I with solid tumours: - For whom no therapy of proven efficacy exists, or who are not amenable to standard therapies. - Must have measurable lesions according to Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 and irRECIST - Previous treatment with an anti-PD-1 mAb is allowed as long as the last administration of the anti-PD-1 mAb on the previous treatment is a minimum of 60 days prior to **starting**~~the first BI 754091~~ treatment **in this trial**. • For patients in Part I with FL: - ~~Whose disease has progressed during or within 6 months of treatment with at least 1 prior chemotherapeutic regimen, or who are not amenable to standard therapies.~~ - **Patients with histologically confirmed, relapsed or refractory FL for which there are no further treatment options available known to provide clinical benefit**
		• Part II (dose expansion): - **Second and 3rd line** NSCLC patients who progressed on anti-PD-1 or anti-PD-L1 treatment after having achieved radiologically confirmed benefit (minimum of stable disease) with a minimum treatment duration of 6 months on the previous anti-PD-1 or anti-PD-L1 treatment. The anti-PD-1- or anti-PD-L1-containing treatment (excluding anti-PD-1 or anti-PD-L1 in combination with chemotherapy) must have been the latest treatment regimen prior to enrolling in this trial with >4 and <12 weeks between the latest treatment and their first

		dose in this trial. Patients who have had anti-PD-1 or anti-PD-L1 as their first-line NSCLC treatment regimen must have a PD-L1 expression level of ≥50% at baseline (local confirmed testing).
Rationale for change		Clarifications in the inclusion criteria to harmonize with the revised study design and provide clear definitions of follicular lymphoma and NSCLC patients
Section to be changed		Synopsis - Doses
Description of change		**Part I (Dose-Escalation Cohorts):** **For patients with solid tumours**: Increasing doses of BI 754111 starting with ~~80~~ **4** mg **in combination with** BI 754091 at the RPIID ~~(RPIID if determined in trial 1381.1 before the start of trial 1381.2, otherwise a~~ **or a lower** dose ~~that has been evaluated as safe from 1381.1)~~ ~~will be added to the BI 754111 at the beginning of Cycle 3 or will be given simultaneously at the start of Cycle 1 (simultaneous cohorts starting at or near the RPIID of the combination). The dose of BI 754091 will be chosen~~**selected** by the 1381.2 Safety Review Committee upon review of evolving data from ~~the~~**Trial 1381.1 (an** ongoing study ~~1381.1 (a study~~ of escalating doses of BI 754091 using **a** BLRM with overdose control in patients with **advanced** solid tumours). Dose escalation of BI 754111 ~~monotherapy and~~ in combination with BI **754091 will be guided by a BLRM with overdose control.**

		For patients with FL: **Recruitment in this cohort will start after a dose combination (of ≥200 mg BI 754111) is cleared in cohorts of patients with solid tumours. Cohorts in patients with FL will be started with BI 754111 monotherapy at 2 dose levels lower than the last (highest) dose level in patients with solid tumours. In case the 200 mg dose of BI 754111 is not reached, the starting dose for FL cohorts will be two dose levels lower than the highest dose cleared in the solid cancer patients, or 4 mg if no two lower dose levels are available. After 2 cycles of monotherapy, BI** 754091 will be **added. The dose of BI 754091 will be selected by the SRC (same as described above for solid tumours). Dose escalation of BI 754111 monotherapy as well as of the combination therapy after BI 754091 being added will be** guided by BLRMs with overdose control. **Part II (Dose Expansion Cohorts):** The RPIID of the combination determined in Part I~~.~~ **for patients with solid tumours.** **For all cohorts, administration will be on Day 1 of 21-day cycles.**
Rationale for change		Based on the recommendation of the FDA, the starting dose of BI 754111 has been set at 4 mg and the solid tumour cohorts will start with combination therapy.
Section to be changed		Synopsis - Duration of treatment
Description of change		~~One or both mAbs~~**Administration** will ~~be administered on Day 1 of 21-day cycles~~ **continue** until progression of disease (PD~~) or~~), unacceptable toxicity, **or a maximum treatment duration of 1 year**. If the patient is benefiting clinically at 1 year, he/she may continue after a case-by-case review with the Medical Monitor and the sponsor.
Rationale for change		To clarify treatment stopping criteria
Section to be changed		Synopsis - Endpoints
Description of change		Primary Endpoint: • MTD of the BI 754111 plus BI 754091 combination • **Number of patients experiencing DLTs during the combination MTD evaluation period (Cycle 1, the first cycle of BI 754111 plus BI 754091 combination therapy) in patients with solid tumours** • Number of patients experiencing DLTs during the monotherapy MTD evaluation period (first two cycles of BI 754111) **in patients with FL** • Number of patients experiencing DLTs during the combination MTD evaluation period (**Cycle 3, the** first cycle of BI 754111 plus BI 754091 combination therapy**) in patients with FL**.
Rationale for change		Clarifications required due to change in study design

Section to be changed		Flow Charts
Description of change		• New Flow Chart for dose-escalation follicular lymphoma patients added to clarify that extensive PK testing in this patient population would be during Cycles 1, 2, and 3. Footnotes aligned with the FL patient population. • The Flow Chart for dose escalation in patients with solid tumours was updated to show extensive PK testing during Cycles 1, 2, and 4 and receptor occupancy testing was moved (FL patients only). Footnotes were aligned with the solid tumour patient population. • The titles of all Flow charts were continued to subsequent pages
Rationale for change		For clarity and to distinguish the extensive PK testing schedules between the patient populations.
Description of change		A row for troponin testing was added to all charts, CPK testing will occur at every cycle (not just at baseline), and Section 5.3.4.2 was updated.
Rationale for change		To enhance cardiac safety testing
Description of change		Flow Chart 1 (Solid tumour cohorts) Footnote a - All cycles are 3 weeks (21 days) in duration. Patients will continue treatment with the ~~study drug or~~ study drugs until disease progression (PD) by RECIST and/or irRECIST, withdrawal of patient consent, an unacceptable toxicity occurs, or 1 year of treatment is completed, whichever occurs first. Patients will be allowed to stay on treatment in the case of initial radiological PD, if the Investigator feels that it is in the patient's best interest. In addition, patients without PD may stay on trial 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 754111 is first administered for the Part I monotherapy cohorts or when~~ the combination of BI 754111 and BI 754091 is administered.
Rationale for change		In response to the FDA review, the study design changed to begin with combination dosing in patients with solid tumours.
Description of change		All Flow Charts Footnote f (and Section 5.3.3)- 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,~~ **on** Day 1 of every **cycle through Cycle 6 and then on Day 1 of every other** ~~third~~ cycle thereafter (Cycles ~~8~~**6**, ~~10~~**9**, 12, etc.), **on Day 15 of Cycles 1 through 4,** at the EOT visit, and whenever the Investigator deems it necessary. An ECG is optional at the 30-day safety follow-up visit if the EOT visit ECG was normal and no drug-related abnormalities were detected in on-trial ECGs (see Section 5.3.3).
Rationale for change		To enhance cardiac safety testing

Description of change		All Flow Charts Footnote g (and Section 5.3.4.4) - Women of child-bearing potential must have a serum beta human chorionic gonadotropin (βHCG) pregnancy test at screening. **Thereafter, this test can be done in either serum or urine** on Day 1 of each cycle, and at the EOT visit **(see Section 5.3.4.4**. ~~Beginning with Cycle 3, urine dipstick tests can be done on Day 1 of odd-numbered cycles (Cycles 3, 5, 7, etc.).~~
Rationale for change		To clarify that serum or urine can be tested following the screening test, and for consistency across the program.
Description of change		All Flow Charts PK Footnotes - changed to specify that extensive PK sampling is done during Cycles 1, 2, and 4 for dose-escalation solid tumour cohorts and the dose-expansion cohort and are done during Cycles 1, 2, and 3 for the FL cohorts.
Rationale for change		For clarity and to distinguish the extensive PK testing schedules between the patient populations since the FL cohorts now have a separate Flow Chart.
Description of change		All Flow Charts End-of-treatment footnote - If the decision is made to permanently discontinue study treatments during a scheduled visit, **both BI 754091 and BI 754111 should be discontinued together and** the EOT visit should be performed instead of the scheduled visit assessments.
Rationale for change		In response to the FDA review, to clarify that both study drugs will be discontinued together, if necessary.
Section to be changed		2.3 Benefit Risk
Description of change		Based on these pre-clinical data, as well as clinical data obtained with BI 754091 and other anti-PD-1 mAbs, the inhibitory effects of the combination of BI 754111 and BI 754091 may translate into a clinical benefit in cancer patients. ~~All doses planned to be tested are expected to have some clinical activity.~~ The dose-escalation scheme for BI 754111 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.
Rationale for change		Based on the recommendation of the FDA, the starting dose of BI 754111 was set at 4 mg, which is not in the range currently predicted to have clinical activity. This change, however, increases patient safety during first dosing in this first-time-in-man study.

Section to be changed		Section 3.1 Overall trial design and plan
Description of change		This is a Phase I, open-label, non-randomised, multicentre trial of BI 754111 administered ~~as a single agent and~~ in combination with BI 754091 that will be conducted in 2 parts. The Part I portion of the trial will ~~include~~**consist of** consecutive **dose-escalation** cohorts of BI ~~754111 monotherapy for 2 cycles with BI 754091 added from Cycle 3 onward, and cohort(s) of BI~~ 754111 in combination with BI 754091 administered ~~simultaneously. The planned study population for Part I includes cohorts of~~**to** patients with advanced solid tumours. **Once combination dose escalation in solid tumors has reached the 200 mg BI 754111 dose level, dose-escalation cohorts in patients with FL will be initiated at two BI 754111 dose levels lower than the BI 754111 dose completed in the solid-tumor cohorts. In case the 200 mg dose of BI 754111 is not reached, the starting dose for FL cohorts will be two dose levels lower than the highest dose cleared in the solid-tumour cohorts, or 4 mg if no two lower dose levels are available. The FL cohorts will start with 2 cycles of BI 754111 monotherapy to assess the PK and receptor occupancy of BI 754111 before adding BI 754091 at the start of Cycle 3 and continuing treatment until disease progression or unacceptable toxicity. At least three FL dose levels will be assessed (unless infeasible) for PK purposes,** and ~~cohorts of patients with follicular lymphoma (FL). Cohorts for patients with FL will start after a dose has been cleared in cohorts of patients with solid tumours.~~**dose escalation in FL cohorts will continue at least until a mean receptor occupancy >90% is achieved.** Possible cohort scenarios for Part I are presented in ~~and~~ Figure 3.1: 1. ~~Simultaneous administration cohort will start at the RPIID of the combination, once the RPIID of the combination has been determined in the cohorts where BI 754091 is added to BI 754111 starting at Cycle 3. Dose escalation of BI 754111 will continue until one dose level higher than the RPIID of the combination if allowed by the BLRMs.~~ Figure 3.1: 1 has been updated based on the new study design. The dose-escalation phase will include intensive safety monitoring to ensure the safety of the patients and will be guided by Bayesian Logistic Regression Models (BLRM) with overdose control (EWOC) ~~for BI 754111 monotherapy and for combination treatment~~. Following determination of the MTD and (or) the RPIID of the combination of BI 754111 and BI 754091, Part II will commence to further characterise the combination at the doses determined in Part I in ~~parallel~~**patients with NSCLC. Additional** cohorts of patients with ~~NSCLC and other~~ tumour types ~~that~~ may ~~include relapsed/refractory follicular lymphoma (to~~ be ~~specified at a later date~~**added** via protocol amendment.

		It is planned that approximately ~~20~~**25** to 40 patients will be enrolled in Part I. The total number of patients will depend on the number of dose escalations necessary. The BLRM estimates the MTD ~~of the combination~~ by updating estimates of the probability of observing a DLT during the ~~first cycle of BI 754111/BI 754091 combination therapy~~ **MTD evaluation period** for each dose **(or dose combination)** level in the trial as patient information becomes available. **Three separate BLRMs are specified for BI 754111 monotherapy in FL patients, the combination of BI 754111 and BI 754091 in solid tumour patients, and the combination of BI 754111 and BI 754091 in FL patients, respectively.** The DLT information from the LAG-3 monotherapy periods **in patients with FL, the DLT information from the combination therapy period in patients with solid tumours and FL**, as well as the DLT information of BI 754091 collected in the 1381.1 study will ~~be used to construct the priors for the BLRM, and therefore included~~**all be used** in the dose-escalation decision-making process. In general, it will be permitted to escalate to a dose that fulfils the EWOC principle (refer to Section 7). Details on handling borderline cases will be described in the dose-escalation plan. **Successive cohorts of patients will receive doses of BI 754111 and BI 754091 until one dose level above the human therapeutic dose for LAG-3 (currently estimated at 400 mg) is reached. A cohort size of 3 patients will be treated at each dose level.changed at one time. They will not be escalated simultaneously. Additional patients (up to 6 more) could be added to some previously evaluated cohorts to expand the safety and PK evaluation. Only one component of the combination (BI 754111 or BI 754091) will be changed at one time. They will not be escalated simultaneously.** If a DLT is observed during the BI 754111 monotherapy period **in an FL cohort**, three additional patients will be added to that cohort. The patient that experienced the DLT will not be able to receive treatment with BI 754091. If there are other patients at that dose level in the LAG-3 monotherapy phase and they did not experience a DLT, they can have BI 754091 added and continue. The DLT will be immediately reviewed by **the** SRC and the **remaining** patients will be monitored carefully as they continue to the combination treatment. A 10% screen-failure rate is anticipated, which assumes the sites have ‘pre-screened’ to find generally eligible patients. Therefore, the 10% screen-failure rate should only be for failure due to laboratory values, scans, etc.

		~~Successive cohorts of patients will receive doses of BI 754111 and BI 754091 until one dose level above the estimated human therapeutic dose for LAG-3 is reached. A cohort size of a minimum of 3 patients and up to 6 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. Only one component of the combination (BI 754111 or BI 754091) will be escalated at one time. They will not be escalated together.~~ After all patients in a cohort have either experienced a DLT or have been observed for at least the MTD evaluation period (**see Section** 7.3.1.1~~2 cycles of BI 754111 monotherapy plus the first cycle after BI 754091 is added to BI 754111, and in the first cycle of BI 754111 in combination with BI 754091 administered simultaneously [simultaneous cohorts]~~) without experiencing a DLT, the Bayesian models will be updated with the newly accumulated data. Table 3.1: 1 is updated to separate the solid tumour cohorts from the FL cohorts for clarity and to take into consideration the new study design. Following determination of the MTD and/or the RPIID from the Part I portion, a cohort of ~~approximately~~ 30 patients with NSCLC (as defined in the entry criteria) will be enrolled into Part II. The Part II portion of the trial will further evaluate the safety, tolerability, PK profile, biomarkers, and efficacy of the combination of BI 754111 and BI 754091. ~~Other expansion cohorts in other tumour types (to be specified at a later date via protocol amendment) may be added to Part II of the trial.~~
Rationale for change		In response to the FDA review, the study design has been changed and it is clarified that the only expansion cohort currently planned is in patients with NSCLC, and that potential additional expansion cohorts may be added to the protocol by amendment.
Section to be changed		3.1.2 Safety Review Committee
Description of change		**BI Project or Trial Statistician**
Rationale for change		A member of the BI Biostatistics group is added as a member of the SRC.
Section to be changed		3.2 Discussion of Trial Design
Description of change		During Part I (dose-escalation) ~~a minimum of~~ 3 patients with solid tumours per cohort is required, but the SRC may decide to increase the number by **a maximum of** 6 additional patients per cohort as needed. Decisions of the SRC will be guided by BLRMs ~~(one for BI 754111 monotherapy and one for BI 754111 + BI 754091 combination therapy)~~ 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

Rationale for change		To add precision to the description of cohort size and for clarity.
Section to be changed		3.3.2 Inclusion Criteria (in addition to the main criteria noted for the synopsis previously)
Description of change		Part I (dose escalation): • Patients with a confirmed diagnosis of advanced, unresectable, and/or metastatic solid tumours (any type) and patients with **histologically confirmed** relapsed/refractory FL.
Rationale for change		To clarify this inclusion criterion.
Description of change		Inclusion #7 and #8 ~~Females of~~ **Male or female patients. Women of childbearing potential (WOCBP)* (*A woman is considered of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile.** **Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. Tubal ligation is NOT a method of permanent sterilisation. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.) and men able to father a** child~~-bearing potential who have had a negative serum pregnancy test at start of treatment, who are willing~~ **must be ready and able** to use highly effective ~~contraceptive measures from the time~~**methods of birth control (that result in a low failure rate** of ~~screening until~~ **less than 1% per year when used consistently and correctly) during trial participation and for at least** 6 months after ~~trial discontinuation, who are not or will not be breast feeding, and who agree to have pregnancy tests at regular visits during~~**the last administration of** trial. **A list of contraception methods meeting these criteria is provided in the patient information.** ~~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.~~ ~~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.~~
Rationale for change		To align text with BI template contraception language

Section to be changed		Section 3.3.3 Exclusion criterion added:
Description of change		**Patients that have epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) rearrangements**
Rationale for change		In response to an FDA recommendation, this exclusion criterion is added.
Section to be changed		Table 3.3.3: 1 Laboratory values
Description of change		(Re: Serum Creatinine) >1.5 X ULN or ~~creatinine clearance~~ **estimated glomerular filtration rate (eGFR)** <30 mL/min/**1.73 m^2** (Chronic Kidney Disease Epidemiology ~~[~~CKD-EPI]~~)~~ Collaboration equation); confirmation of ~~creatinine clearance~~ **eGFR** is only required when creatinine is >1.5 X ULN.
Rationale for change		For accuracy and to align with IDMS standards.
Section to be changed		Section 4.1.2.1 Starting dose of BI 754111
Description of change		~~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 has the potential to offer the patients some 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, BI 754111 will be tested at a flat starting dose of 80 mg (based on 1 mg/kg for an 80 kg patient) to be administered via i.v. infusion q3w.~~ The starting dose of **BI 754111 in patients with solid tumors will be 4 mg (based on 0.05 mg/kg for an 80 kg patient) administered via i.v. infusion once every 3 weeks. The starting dose was based on the EC_{50} in the *in vitro* tetanus toxoid T-cell activation assay. In that assay, increasing concentrations of BI 754111 were combined with a fixed dose of BI 754091 and IFNγ secretion was measured as an indication of T-cell activation (**n00250935; n00253546). **This starting dose** ~~80 mg~~ is supported by the 13-week repeat-dose toxicity study in **the** cynomolgus ~~monkeys, which was conducted with BI 754111 and included a BI 754111/BI 754091 combination arm. The~~ **monkey. Compared to the NOAEL in the Non-Human Primate study (C_{max} 6,440 µg/mL and AUC 734,000 µg/mL*h), the 4 mg starting dose to an** 80 ~~mg (based on 1 mg/kg for an average 80 kg patient) starting dose administered q3w~~**kg patient** is **expected to result in an exposure margin of approximately 5,300-fold and 4,900-fold based on the** predicted ~~to have~~ human steady state exposure **of** C_{max} ~~of 24~~ **1.2** µg/mL and ~~area under the curve (~~AUC~~) of 3,000~~**150** µg/mL*h~~. The NOAEL was considered to be 100~~**, respectively.**

		Once combination dose escalation in solid tumors has reached the 200 ~~mg/kg from the 13-week toxicity study in cynomolgus monkeys. Therefore, the safety margins are 268 times greater and 245 times greater (based on C_{max} and AUC, respectively) with a dose of 1 mg/kg q3w than they are~~ **BI 754111 dose levels, dose-escalation cohorts in patients** with ~~the NOAEL in cynomolgus monkeys~~**FL will be initiated at two BI 754111 dose levels lower than the BI 754111 dose completed in the solid-tumor cohorts. In case the 200 mg dose of BI 754111 is not reached, the starting dose for FL cohorts will be two dose levels lower than the highest dose cleared in the solid-tumour cohorts, or 4 mg if no two lower dose levels are available. The FL cohorts will start with 2 cycles of monotherapy then BI 754091 will be added**.
Rationale for change		Based on the recommendation of the FDA, the starting dose of BI 754111 has been set at 4 mg and the solid tumour cohorts will start with combination therapy.
Section to be changed		Section 4.1.3 Dose escalation scheme
Description of change		In the Part I dose-escalation cohorts, dosing of BI 754111 will be administered ~~as monotherapy for 2 cycles, and~~**with** BI 754091 ~~will be added at the start of Cycle 3~~. The planned starting dose of BI 754091 will be the RPIID from study 1381.1 and the SRC will confirm this prior to starting ~~combination~~ dosing. The dose of BI 754091 may be increased or decreased based on DLTs and the overall safety profile of the combination. ~~It is planned that one or more cohorts in which both mAbs will be administered together at or near the RPIID of the combination beginning with Cycle 1 Day 1 (simultaneous cohorts) will be conducted later in the dose-escalation part of the trial.~~ Possible cohort scenarios are presented in Table 3.1: 1. These scenarios may change based on ongoing safety evaluations. Table 4.1.3: 1 was updated with the new planned dosing scheme. At the end of each treatment cohort, the SRC will evaluate the available data. The SRC will review all safety data including, but not limited to, DLTs and all CTCAE Version 4.03 Grade ≥2 toxicity data during the first **cycle of combination therapy for the solid tumour cohorts and during the** 2 cycles of BI 754111 monotherapy plus the first cycle of ~~the combination. For the simultaneous-start cohorts, the safety data generated during the first cycle of the BI 754111 plus BI 754091~~ combination ~~will be evaluated by the SRC prior to dose escalation~~**therapy for the FL cohorts**. Updated safety data on other ongoing patients, including data in later cycles, will be discussed as well. Based on the findings of the SRC, a decision on the next dose level to be tested will be made.
Rationale for change		Updated based on the new study design.

Section to be changed		Section 4.1.4 Dose modifications
Description of change		There will be no dose reductions or escalations of BI 754111 or BI 754091 in any one patient. The dose may be delayed for a patient for one cycle, plus an additional 3 weeks, because of AEs following discussion with the Medical Monitor. **During combination therapy, if treatment is held or discontinued due to an AE(s), both BI 754091 and BI 754111 will be held or discontinued together. If treatment is to be restarted after resolution (≤ Grade 1) of the AE(s), both BI 754091 and BI 754111 must be started together.** **The study drug(s) should be permanently discontinued for Grade 3 to 4 pneumonitis, Grade 3 to 4 adrenal insufficiency, Grade 4 diabetes mellitus, any grade encephalitis, Grade 4 hypophysitis, Grade 4 rash, Grade 3 to 4 colitis or recurrent colitis of any grade, any recurrent Grade 3 to 4 AE, transaminase increases >5 times ULN or total bilirubin >3 times ULN (unless unequivocally attributed to another cause), inability to taper steroids to 10 mg or less prednisone or equivalent within 12 weeks, or persistent Grade 2 to 3 AEs that do not recover to Grade 1 or less within 12 weeks. Study drug(s) should also be permanently discontinued for Grade 3 to 4 AEs that are classified as immune-related by the Investigator that are not listed in Appendix 10.1. Study drug(s) should be permanently discontinued if ≥ Grade 4 drug-related AEs are reported. Please see Appendix 10.2 for guidelines for management of immune-related adverse events.** **In the event of an infusion-related reaction ≤ Grade 2, the infusion rate of study drug(s) may be decreased by 50% or interrupted until resolution of the event and re-initiated at 50% of the initial rate until completion of the infusion. In patients experiencing infusion-related reactions ≤ Grade 2, subsequent infusions may be administered at 50% of the initial rate. If an infusion-related reaction is Grade 3 or higher in severity at any point during the study, study drug(s) will be permanently discontinued (see Section 5.3.6.5.3).**
Rationale for change		In response to an FDA recommendation, clarifications were added concerning holding or discontinuing both study drugs when required. Links were added to the detailed descriptions of management of irAEs and infusion reactions.

Section to be changed		Section 4.1.5 Dose-limiting toxicities
Description of change		Dose-limiting toxicities (DLTs) will be recorded throughout the trial. Any DLT must be reported to the Medical Monitor by the Investigator or designee within 24 hours of first knowledge, and to the [redacted] as an SAE when appropriate. All DLTs will be agreed upon between the Sponsor, the Study Chair, the Medical Monitor, and the investigators after review of the data from each cohort. Only DLTs occurring in Part I during **the first cycle of BI 754111 administered in combination with BI 754091 in the solid tumour cohorts and during** the first 2 cycles of BI 754111 monotherapy plus the first cycle after BI 754091 is added to BI 754111~~, or~~ in ~~the first cycle of BI 754111 in combination with BI 754091 administered simultaneously~~ **the FL cohorts** will be used for dose-escalation decisions made by the SRC. All relevant safety information (including DLTs) will be considered when selecting the RPIID. Previous anti-PD-l mAbs have been associated in the clinical setting with inflammatory adverse reactions resulting from increased or excessive immune**-related adverse events** ~~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. Any of the following ~~drug related~~ AEs will be classified as DLTs following review by the Investigators and the Medical Monitor**, unless equivocally due to underlying malignancy or an extraneous cause**. • ~~For patients with solid tumours:~~ • **Any Grade 5 toxicity** • Neutropenia ≥ Grade 4 lasting for >~~7~~**5** days • ~~Any grade febrile~~**Febrile** neutropenia **of any duration (ANC <1.0 X 10^9 cells/L and fever ≥38.5°C)** • ~~Neutropenia Grade 3 with documented infection~~ • Any **Grade 4 thrombocytopenia, or** Grade 3 thrombocytopenia with bleeding or a requirement for platelet transfusions • ~~**For patients with** follicular lymphoma:~~ - ~~Neutropenia ≥ Grade 4 lasting for >7 days despite growth factor support~~ - ~~Any grade febrile neutropenia that does not resolve within 48 hours with appropriate treatment (antibiotics, antifungal, antiviral agents and growth factors)~~ - ~~Grade 4 thrombocytopenia lasting >7 days, or Grade 3-4 thrombocytopenia with clinically significant bleeding.~~ - ~~Failure to recover platelets to ≥75 x 10^9/L by 6 weeks after dose administration~~

		• ~~Failure to recover neutrophils (absolute neutrophil count [ANC]) ≥1.0 x 10^9/L by 6 weeks after dose administration.~~ Non-haematological toxicities (only those that changed): - Grade 3 endocrine disorders (thyroid, pituitary, and/or adrenal insufficiency) that are **sufficiently** managed with or without systemic corticosteroid therapy and/or hormone replacement therapy, and the patient is asymptomatic. - Grade 3 tumour flare. • Any Grade 2 ~~drug related~~**pneumonitis of any duration** • **Any Grade 2** uveitis, eye pain, or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within 2 weeks or requires systemic treatment • Any ~~treatment related~~ ≥ Grade 2 toxicity that persists and results in an inability to administer BI 754091 on Cycle 2 Day 1. Late immune-related DLTs are irAEs that meet the same grading criteria as DLT criteria but occur after ~~the first 2 cycles of BI 754111 monotherapy plus the first cycle after BI 754091 is added to BI 754111, or after~~ the first cycle of BI 754111 in combination with BI 754091 administered simultaneously **in the solid tumour cohorts or after the first 2 cycles of BI 754111 monotherapy plus the first cycle after BI 754091 is added to BI 754111 during the FL cohorts**~~, but 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 an SRC meeting (either scheduled or *ad hoc*) to recommend the next dose level and cohort size.
Rationale for change		In response to an FDA recommendation, clarifications were added to the dose-limiting toxicity criteria.
Section to be changed		4.1.7 Definition of evaluable patient
Description of change		For decisions on dose escalation, an evaluable patient is defined as a patient who has received BI 754111 and either: • **has completed the first cycle of BI 754111 in combination with BI 754091 in the solid tumour cohorts or** has completed the first 2 cycles of BI 754111 monotherapy plus the first cycle after BI 754091 is added to BI 754111~~, or in the first cycle of BI 754111 in combination with BI 754091 administered simultaneously~~ **in the FL cohorts** OR

		• has experienced a DLT **during the first cycle of BI 754111 in combination with BI 754091 in the solid tumour cohorts or** during the first 2 cycles of BI 754111 monotherapy plus the first cycle after BI 754091 is added to BI 754111, ~~or in the first cycle of BI 754111 in combination with BI 754091 administered simultaneously~~ **in the FL cohorts.**
Rationale for change		To align with the new study design
Section to be changed		4.1.8 Method of assigning patients to treatment groups
Description of change		After assessment of all inclusion and exclusion criteria, each eligible patient in the Part I dose-escalation portion of the trial will be assigned a dose of BI 754111 and a dose of BI 754091, ~~if enrolled into a cohort dosing both mAbs at the same time,~~ as determined by the SRC.
Rationale for change		To clarify that this is true for all patients.
Section to be changed		4.1.9 Administration of doses for each patient
Description of change		BI 754111 and BI 754091 will be diluted and administered via i.v. infusion according to the details in the Pharmacy Manual. **For Part I solid tumour cohorts, dosing will be sequential for doses <200 mg LAG3 with BI 754091 infused first followed by infusion of BI 754111. The infusion duration for each will be specified in the Pharmacy Manual. It is anticipated that the entire infusion time will take ~1 hour. For doses ≥200 mg LAG3, the infusion will be simultaneously (infusion duration ~1 hour).** **For Part I FL cohorts, patients will receive BI 754111 monotherapy for 2 cycles before dosing with BI 754091 is added.**
Rationale for change		Due to the new study design, the study will beginning with combination dosing. Therefore, clarifications on the dosing sequence are added.
Section to be changed		5.1.1 Primary endpoints
Description of change		The primary endpoint of Part I (dose escalation) of the trial is the: • MTD of the BI 754111 plus BI 754091 combination • Number of patients experiencing DLTs during the combination MTD evaluation period (first cycle of BI 754111 plus BI 754091 combination therapy) **in patients with solid tumours.** • Number of patients experiencing DLTs during the monotherapy MTD evaluation period (first two cycles of BI 754111 monotherapy**) in patients with FL** • **Number of patients experiencing DLTs during the combination MTD evaluation period (Cycle 3, the first cycle of BI 754111 plus BI 754091 combination therapy) for patients with FL**
Rationale for change		Clarifications based on the new study design

Section to be changed		5.1.2.1 Secondary endpoints
Description of change		The secondary endpoints of Part I (dose escalation) of the trial are the following: • PK parameters to be calculated for BI 754111 after single **and multiple** doses of BI 754111 monotherapy **(FL cohort)** and in combination with BI 754091, and also for BI 754091 after ~~the first dose~~**single and multiple doses** of combination therapy include: - C_{max}: maximum measured concentration of BI 754111/ BI 754091 in plasma - AUC_{0-504}: area under the concentration-time curve of BI 754111 / BI 754091 in plasma over the time interval from 0 to 504 hours
Rationale for change		To add clarification based on the new study design
Section to be changed		5.2.1 Tumour assessments
Description of change		The tumour response **in patients with solid tumors** will be evaluated according to RECIST Version 1.1 (R09-0262) and irRECIST (~~R16-0342,~~ **R15-2005**). **For FL patients, contrast enhanced CT should be used. PET/CT scan should be done at baseline for all FL patients. For patients with fluoro-deoxyglucose (FDG)-avid FL, PET/CT scan should be used and repeated at week 12, week 24, and if CT results are compatible with a complete response. Additional PET/CT scans can be done at the discretion of the Investigator. Response will be evaluated**~~For patients with follicular lymphoma, response will be evaluated using local PET/CT scans~~ using Cheson response criteria for malignant lymphoma as outlined in 2007 (R10-1462) and revised in 2014 (R14-3387). **For the FL cohorts, bone marrow biopsies and aspirates will be taken at screening. Patients with bone marrow disease evident by the screening bone marrow biopsy or aspirates, should have repeat bone marrow and aspirate to assess bone marrow response if a complete response is suggested by imaging or if novel or recurrent bone marrow involvement is suspected. The bone marrow biopsy and aspirate should be collected within 2 weeks of detection of response in other lesions.** The assessment by the Investigator and/or the local radiologist will be the basis for continuation or discontinuation of the trial in an individual patient (in addition to safety). The baseline imaging must have been performed within 4 weeks prior to treatment with the trial medication and the Investigator will record the target and non-target lesions in the eCRF. The same method of assessment and the same technique must be used to characterise each reported lesion at baseline and during treatment. Lesions in previously irradiated areas may not be used as target lesions. Tumour assessments **(including bone marrow assessment for patients with FL)** will be performed at screening (as close as possible to the treatment start and no more than 28 days before the start of study treatment), every 2 cycles (6 weeks

		±3 days) for the first 6 months, then every 3 cycles (9 weeks ±3 days) thereafter, and at the EOT visit (if not performed within the previous 4 weeks).
Rationale for change		Clarifications for tumour assessments in patients with FL were added.
Section to be changed		Section 5.3.4.3 Urinalysis
Description of change		Urine will be analysed for pH, glucose, erythrocytes, leukocytes, protein, and nitrite by dipstick (semi-quantitative measurements) during the screening visit**, on Day 1 of each cycle**, at the EOT visit, and as clinically indicated. In case of pathological findings, further evaluation must be performed and the findings documented.
Rationale for change		To align with information in the flow charts.
Section to be changed		5.3.4.2 Biochemistry
Description of change		The standard biochemistry panel will consist of glucose, sodium, potassium, chloride, calcium, phosphate, venous bicarbonate HCO_3, urea, creatinine, **creatine phosphokinase (CPK),** AST, ALT, alkaline phosphatase, lactate dehydrogenase (LDH), bilirubin, total protein, albumin, urea nitrogen, and uric acid. In addition, cholesterol, triglycerides, **and** c-peptide~~, and creatine phosphokinase (CPK)~~ will be done at baseline and when clinically indicated. **Troponin will be tested according to the times listed in the flow charts.** In case of pathological CPK, then CPK-MB, **additional** troponin I, and myoglobin should be reactively tested and the findings documented.
Rationale for change		To enhance cardiac safety testing
Section to be changed		5.4.1 Assessment of pharmacokinetics
Description of change		If data allow, the PK parameters of BI 754111 after single and multiple doses of BI 754111 monotherapy **(FL cohort)** and in combination with BI 754091, and also for BI 754091 after ~~the first dose~~**single and multiple doses** of combination therapy mentioned as secondary and further endpoints for Parts I and II (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 [actual version] and Kinesis SOP 'SOP-1.PKA.03 Non-compartmental PK/PD Analysis').
Rationale for change		To clarify following study design change
Section to be changed		5.4.2 Methods of collection for pharmacokinetic analysis
Description of change		**For cohorts receiving combination treatment using doses of BI 754111 <80 mg, the 1 hour PK sample is to be drawn before and as close as possible to the end of the infusion.**
Rationale for change		To stress the importance of the timing of the of the 1 hour PK samples in the early cohorts.

Section to be changed		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 Part II dose-expansion portion of the trial. In addition, an optional biopsy should be taken after treatment discontinuation, if possible. ~~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.
Rationale for change		To clarify that paired biopsies will not be taken during dose escalation.
Section to be changed		Section 7.1 and Appendix 10.5
Description of change		The statistical methods were updated to reflect the new study design and starting dose. The sections were fully replaced and are not presented as such here.
Rationale for change		To update the statistical methods based on the study design changes.
Section to be changed		Section 9 References (new references added)
Description of change		**R15-2005 Bohnsack O, Ludajic K, Hoos A. Adaptation of the immune-related response criteria: irRECIST. 39th Ann Cong of the European Society for Medical Oncology (ESMO), Madrid, 26-30 Sep 2014 (Poster).** **n00250935 [redacted] Tetanus toxoid assay for BI 754091 in combination with BI 754111. 20 Jul 2016.** **n00253546 [redacted] Anti-LAG-3 mAb BI 754111 – Prediction of Human Pharmacokinetics and Therapeutic Dose. Report in preparation.** ~~R16-0342~~ Removed
Rationale for change		For completeness in the text and to add new study information
Section to be changed		10.2 Management of immune-related adverse events
Description of change		Management of immune-related **adverse** event toxicities associated with anti-PD-1 mAbs are presented below. BI 754091 and BI 754111 should be permanently discontinued for Grade 3-4 pneumonitis, Grade 3-4 adrenal insufficiency, Grade 4 diabetes mellitus, any grade encephalitis, Grade 4 hypophysitis, Grade 4 rash, Grade 3-4 or recurrent colitis of any grade, any recurrent Grade 3-4 AE, transaminase >5 times ULN or total bilirubin >3 times ULN **(unless unequivocally attributed to another cause)**, inability to taper steroids to 10 mg or less prednisone or equivalent within 12 weeks, or persistent Grade 2-3 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 **(unless unequivocally attributed to another cause),** inability to taper steroids to 10 mg or less prednisone or equivalent within 12 weeks, or persistent Grade 2-3 AEs that do not recover to Grade 1 or less within 12 weeks.
Rationale for change		To clarify for the Investigators
Section to be changed		Section 10.4 Sampling tables
Description of change		Table 10.4.1: 1 Time schedule for PK, [redacted] - Part I dose-escalation cohorts (Cycles 1 & 2 only **for FL cohorts and Cycles 1, 2, and 4 for solid tumour cohorts**) Added to Footnote a - **For cohorts receiving combination treatment using doses of BI 754111 <80 mg, the 1 hour PK sample is to be drawn before and as close as possible to the end of the infusion.** Added Footnote c - **BI 754111 monotherapy will only be administered during the first 2 cycles for patients in the FL cohorts. All solid-tumour cohorts will begin immediately with simultaneously or sequential (only cohorts with doses <200mg LAG3) administration of the 2 study drugs.** Added Footnote e - **An additional blood sample will be taken one time from all subjects of the first dose group that exceeds 200 mg BI 754111.** Deleted previous Footnote e - [redacted] ~~testing results to be reported for both BI 754111 and BI 754091 (for simultaneous cohorts in patients with solid tumours).~~
Rationale for change		To clarify due to study design changes and to emphasize the importance of drawing the 1 hour PK samples as close to infusion end as possible.

Description of change		Table 10.4.1: 2 Time schedule for PK, [redacted], and receptor occupancy (RO) sampling - Part I dose-escalation cohorts (Cycle 3 **FL cohorts** only) Added to Footnote a - The planned **total** infusion duration is ~1 hour **(refer to pharmacy manual for specific infusion times depending on dose)**. **For cohorts receiving combination treatment using doses of BI 754111 <80 mg, the 1 hour PK sample is to be drawn before and as close as possible to the end of the infusion.** Deleted previous Footnote d - [redacted] ~~testing results to be reported for both BI 754111 and BI 754091 (for simultaneous cohorts in patients with solid tumours).~~
Rationale for change		To clarify due to study design changes and to emphasize the importance of drawing the 1 hour PK samples as close to infusion end as possible.
Description of change		Table 10.4.1: 3 Time schedule for PK, [redacted] and receptor occupancy (RO) sampling - Part I dose-escalation cohorts (**FL cohorts:** Cycles 4 to 12, 14, and 17 only**; Solid tumour cohorts: Cycles 3, 5 to 12, 14, and 17 only**) Footnote a - The following windows of time are allowed for PK sampling: Predose (PTM -0:05): within 1 hour before next drug infusion ~~Immediately before end of infusion (PTM 1:00): within ±5 min of the end of infusion~~ ~~4 and 7 hours post SOI (PTM 4:00 and 7:00): ±15 minutes~~ ~~24 through 336 hours post SOI (PTM 24:00 to 336:00): ±1 hour.~~ Deleted previous Footnote c - [redacted] ~~testing results to be reported for both BI 754111 and BI 754091 (for simultaneous cohorts in patients with solid tumours).~~
Rationale for change		To clarify due to study design changes
Section to be changed		10.4.2 Schedules for PK, [redacted] – Part II dose-expansion cohort~~s~~
Description of change		Table 10.4.2: 1 Time schedule for PK, [redacted] blood samplings - Part II dose-expansion cohort~~s~~ (Cycles 1, 2, and 4 only) Deleted Footnote e ~~e PBMC/MDSC testing will be in cohorts of patients with NSCLC only.~~
Rationale for change		To clarify that there is currently one dose expansion cohort planned. The footnote is obsolete because only the cohort in NSCLC is planned at this time.

Number of global amendment		2
Date of CTP revision		23 August 2017
EudraCT number		Not applicable
BI Trial number		BI 1381.2
BI Investigational Product(s)		BI 794111 and BI 754091
Title of protocol		An open label, Phase I dose-finding study of BI 754111 in combination with BI 754091 in patients with advanced solid cancers and of BI 754111 monotherapy with subsequent combination with BI 754091 in patients with follicular lymphoma, followed by an expansion cohort at the RPIID of the combination in patients with non-small cell lung cancer
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		

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		Flow chart footnotes and Section 5.3.4.2 Biochemistry
Description of change		**Additionally, amylase and lipase should be analysed in case of symptoms of pancreatitis.**
Rationale for change		Additional safety testing added in case of pancreatitis
Section to be changed		Flow chart footnotes 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.

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.
Section to be changed		Study Flow Chart 1 Footnote j
Description of change		[…] In order to assess the stability of **BI 754091 and** BI 754111 in whole blood, one additional blood sample will be taken at 1 hour post infusion from all subjects of the first dose group that exceeds 200 mg BI 754111 (see Section 5.4.3).
Rationale for change		To enable whole blood stability testing to be performed correctly in BI 754091.
Section to be changed		Study Flow Chart 2 Footnote k
Description of change		Pharmacokinetic (PK) blood sampling: there is extensive PK sampling for FL cohorts during Cycles 1, 2, and 3. It is strongly recommended that the visit days and sampling time points outlined in the Appendix 10.4 tables be followed closely. The permitted visit windows noted in the table footnotes should only be used if medically indicated. Please note that there are separate assays for determination of BI 754111 and BI 754091. Therefore, when PK samples are drawn during combination dosing, 2 tubes must be drawn at each time point. ~~In order to assess the stability of BI 754111 in whole blood, one additional blood sample will be taken at 1 hour post infusion from all subjects of the first dose group that exceeds 200 mg BI 754111 (see Section 5.4.3).~~
Rationale for change		Whole blood stability testing will not be done in the follicular lymphoma cohorts.
Section to be changed		Table 3.1: 1
Description of change		Changes made to Cohort H and I rows
Rationale for change		Corrections
Section to be changed		Section 3.3.3 Exclusion Criterion #4
Description of change		4. Any investigational or anti-tumour treatment within **4 weeks or within 5 half-life periods (whichever is shorter)**~~30 days~~ prior to the initiation of trial treatment. FL patients on chemotherapy immediately prior to current study may initiate treatment in this trial within 15 days of last chemotherapy dose following sponsor agreement.
Rationale for change		To clarify that the wash-out period may be shorter for drugs with a short half-life
Section to be changed		Table 3.3.3: 1
Description of change		International Normalized Ratio (INR) **(only tested if clinically indicated)**
Rationale for change		To clarify that coagulation parameters need only be tested if clinically indicated
Section to be changed		Section 4.1.9 Administration of doses for each patient
Description of change		For Part I solid tumour cohorts, dosing will be sequential for doses <**80**~~200~~ mg LAG3 with BI 754091 infused first followed by infusion of BI 754111. The infusion duration for each will be specified in the pharmacy manual. It is anticipated that the entire infusion time will take ~1 hour. For doses ≥**80**~~200~~ mg LAG3, the infusion will be simultaneously (infusion duration ~1 hour).
Rationale for change		To align the protocol with the Pharmacy Manual

Section to be changed		Section 4.2.2.1 Permitted concomitant medications
Description of change		[…] For symptom control, palliative radiotherapy is permitted for any lesion in the dose-escalation part of the trial, except during the first **cycle (in solid tumours) and the first** 3 cycles **(in FL)** as it could interfere with the DLT evaluation for MTD/RPIID determination. […]
Rationale for change		To improve clarity concerning palliative radiation allowed for the different disease states
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		[redacted]
Description of change		
Rationale for change		Additional further endpoints are planned.
Section to be changed		[redacted]
Description of change		
Rationale for change		

Section to be changed		Section 7.1.1.2 Combination BLRM for follicular lymphoma cohorts
Description of change		The parameters for prior distributions are given in **Table 7.1.1.2: 3**~~Table 7.1.1.1:2~~. The corresponding prior probabilities of a DLT at different dose combinations and the corresponding probabilities of under-dosing, targeted dosing and overdosing are shown in **Table 7.1.1.2: 4**~~Table 7.1.1.2: 3~~. Alignment of some data points within the tables of this section were corrected.
Rationale for change		To link to correct tables and display correct alignment
Section to be changed		Section 7.4 Interim analyses
Description of change		[…] No formal interim analysis of PK data is planned. However, exploratory analysis of PK will be done during the dose escalation part **and may also be done during the expansion part, if considered reasonable**. ~~Furthermore, an exploratory analysis of immunogenicity may be performed at least once during the escalation part.~~ ~~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. […]
Rationale for change		To clarify interim analyses of PK data
Section to be changed		Table 10.4.1: 1 and New Table 10.4.1:2
Description of change		Information for follicular lymphoma (FL) patients is removed from Table 10.4.1:1 (including Footnote c) and a new Table 10.4.1: 2 was created for FL patients during Cycles 1 and 2. Information for FL patients during Cycle 3 is still in a separate table, now numbered Table 10.4.1: 3. Additions made to the table and footnote specifying the timings of BI 75411 and BI 754091 infusions. Last footnote (now Footnote c): The specified blood volume for both BI 754111 and BI 754091 will be drawn into separate blood-drawing tubes. **However, they should be collected in parallel** at the specified time points **after the start of the BI 754091 infusion**~~(solid tumour cohorts)~~.
Rationale for change		Removing the FL cohort information to a separate table will clarify this information for the sites. To further stress that even though in some cases, BI 754111 and BI 754091 are infused sequentially, the PK sampling for BI 754111 and BI 754091 can still be collected at the same time. The time point reference remains after the start of the first infusion.

Number of global amendment		3
Date of CTP revision		31 January 2018
EudraCT number		Not applicable
BI Trial number		BI 1381.2
BI Investigational Product(s)		BI 794111 and BI 754091
Title of protocol		An open label, Phase I dose-finding study of BI 754111 in combination with BI 754091 in patients with advanced solid cancers and of BI 754111 monotherapy with subsequent combination with BI 754091 in patients with follicular lymphoma, followed by an expansion cohort at the RPIID of the combination in patients with non-small cell lung cancer
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		

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		Title page
Description of change		1. EudraCT No.: 2017-005042-29 Added 2. Coordinating Investigator role added and [redacted] Physician [redacted] removed: [redacted]
Rationale for changes		1. The row for EudraCT number had previously been removed from the template in error.

		2. Sites will be initiated in Europe, thus requiring a Coordinating Investigator rather than a Physician [redacted].
Section to be changed		Synopsis page 1 Trial sites
Description of change		~~Approximately 10 sites in Canada and the USA~~
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		Synopsis - other changes to the synopsis are described as changes in the relevant sections in the body of the protocol.
Section to be changed		All Flow Charts Footnote c
Description of change		[…]clinical chemistry (sodium, potassium, phosphate, chloride, creatinine, calcium, venous bicarbonate HCO_3, albumin, total protein, aspartate aminotransferase [AST], alanine aminotransferase [ALT], alkaline phosphatase, bilirubin, lactate dehydrogenase, serum glucose, ~~c-peptide [baseline only], serum cholesterol [baseline only], serum triglycerides [baseline only],~~ creatine kinase [CK: if CK is elevated, then CK-MB, Troponin I, and myoglobin should be reactively tested, with further follow-up as clinically warranted], serum urea nitrogen, serum uric acid, and thyroid panel [TSH, free T4, and free T3]), […]
Rationale for change		It has been determined that these tests are not needed.
Section to be changed		Flow Chart 3 Footnote h
Description of change		~~Additional progression-free survival (PFS) follow-up visits after the 30-day safety follow-up visit will only be performed for patients who did not progress on treatment. These will be performed once every 12 weeks at least (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.~~**Patients enrolled in Protocol Version 4.0: 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: 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.**
Rationale for change		To add overall survival (OS) visits to the protocol going forward and to clarify PFS visits in previous versions.

Section to be changed		Flow Chart 2 - follicular lymphoma dose-escalation
Description of change		New row added for Biomarker [redacted] blood collections New Footnote r added: Blood samples for biomarker [redacted] the dose-escalation cohorts in patients with FL only during Cycle 1 on Day 1 (pre-treatment), Day 8, Day 15, during Cycle 2 on Day 1 (pre-treatment), and again during Cycle 3 on Day 1 (pre-treatment), Day 8, Day 15, during Cycle 4 on Day 1 (pre-treatment), and at the 30-day follow-up visit.
Rationale for change		This information will be an integral part of the dose-selection process moving forward in patients with FL.
Section to be changed		Flow Chart 3
Description of change		Footnote k: Blood samples for [redacted] only during Cycle 1 on Day 1 (pre-treatment), Day 8, Day 15, during Cycle 2 on Day 1 (pre-treatment), and at the **end-of-treatment**~~30 day follow up~~ visit. Footnote l: All patients in Part II (dose-expansion cohorts) must have tissue samples (fresh or archived [see requirements]) available for retrospective central PD-L1 testing. The following will be required (see Section 5.5.2.3 for details): - ~~If available and taken within 6 months of study start, 22 to 25 (4-5 µm) sections from an archival FFPE block should be collected. If adequate archival tissue is not available, 3 fine-needle biopsies must be taken between screening and the day before the first study drug treatment. For patients who do not have historic PD-L1 data derived from an FDA-approved test, part of this material may be used for local testing to obtain this information.~~ **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 screening and the day before first treatment with BI 754091.** - Two **core**~~fine~~-needle biopsies **or 1 punch biopsy** on treatment at the end of Cycle 2 (after 6 weeks of treatment), **preferably from the same lesion**. - Another biopsy (optional) should be taken upon PD (according to RECIST v1.1 and irRECIST), if possible. **An optional biopsy should also be taken if a patient has** ~~S~~**s**table disease (SD) over ~~4 months would also be qualified as a response (see Section 5.1.2.2), and a biopsy (optional)~~

		~~would be taken at that time point~~**3 subsequent disease assessment periods**. Footnote o: PK **samples are to be collected during Cycles 1, 4, and 8, at the EOT visit, and the 30-day safety follow-up,** and [redacted] blood samplings are to be collected during Cycles 1 through **9, Cycle** 12, Cycle 1**5**4, Cycle 1**8**~~7~~, **and every 3rd cycle thereafter,** at the EOT visit, and the 30-day safety follow-up (see the tables in Appendix 10.4 for specifics).
Rationale for change		Footnote k: to align with the updates to Tables 10.4.2: 1. Footnote l: to clarify the requirements for biopsies to assure that enough tissue is available for the required testing, and to clarify when an optional biopsy should be taken in the event of prolonged stable disease. Footnote o: to align with the updates to Tables 10.4.2: 1.
Section to be changed		Section 2.1 Rationale for conducting the trial
Description of change		[…] **This 2-part trial is the first study with BI 754111 in humans and the second with BI 754091. The first part will include dose-escalation cohorts to determine the maximum-tolerated dose (MTD) and/or the recommended Phase II dose (RPIID). The second part includes expansion cohorts at the RPIID that will further evaluate the safety, tolerability, PK, biomarkers and the preliminary efficacy of the BI 754111 plus BI 754091 combination. The dose-escalation portion of the trial will enrol patients with advanced and/or metastatic solid tumours and FL, while the dose-expansion portion will enrol patients with advanced and/or metastatic NSCLC.**
Rationale for change		To further expand on the rationale for conducting the trial, particularly for the dose-expansion cohort that will begin recruitment soon.
Section to be changed		Section 2.2.1 Part I (dose-escalation cohorts) objectives
Description of change		Investigate the safety, tolerability, and PK of escalating doses of BI 754111 in combination with BI 754091 (administered via i.v. infusion q3w), **with BI 754091** added on to BI 754111 starting at Cycle 3 in patients with relapsed/refractory FL
Rationale for change		To clarify that BI 754091 is added to BI 754111 starting at Cycle 3.

Section to be changed		Table 3.1: 1
Description of change		Several rows in this table were edited to be more explicit about the dosing combinations. In addition, the dose-expansion NSCLC population was clarified: Recommended Phase II combination dose **(RPIID)** in patients with **2nd and 3rd line** NSCLC **who progressed on anti-PD-1 or anti-PD-L1 treatment** (as defined in the entry criteria)
Rationale for change		To clarify dosing for the sites and to add more specific information about the expansion cohort.
Section to be changed		Section 3.3.3 Exclusion criteria
Description of change		[…] 7. Patients **with NSCLC** that has~~ve~~ epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) rearrangements 8. Presence of other active invasive cancers other than the one treated in this trial **within 5 years prior to screening**, with the exception of **appropriately treated**~~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. […] 12. Any of the following cardiac criteria: - Mean resting corrected QT interval (QTc) >470 msec - **Any clinically important abnormalities (as assessed by the Investigator) in rhythm, conduction, or morphology of resting ECGs, e.g., complete left bundle branch block, third degree heart block** **- Any factors that increase the risk of QTc prolongation or risk of arrhythmic events such as heart failure, hypokalaemia, congenital long QT syndrome, family history of long QT syndrome or unexplained sudden death under 40 years-of-age, or any concomitant medication known to prolong the QT interval** **- Patients with an ejection fraction (EF) <55% or the lower limit of normal of the institutional standard will be excluded. Only in cases where the Investigator (or the treating physician or both) suspects cardiac disease with negative effect on the EF, will the EF be measured during screening using an appropriate method according to local standards to confirm eligibility (e.g., echocardiogram, multi-gated acquisition scan). 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.** - ~~Any clinically important abnormalities 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 <55% or the lower limit of normal of the institutional standard.~~
Rationale for change		Criterion #7: To clarify the patient population Criterion #8: To clarify exclusion of other active cancers and to align language across current studies with BI 754091. Criterion #12: To clarify exclusion due to cardiac criteria and to align language across current studies with BI 754091.
Section to be changed		Section 3.3.4.2 Discontinuation of the trial by the sponsor
Description of change		[…] **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 their 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		[redacted]
Description of change		

		[redacted]
Rationale for change		To clarify the further endpoints for Part I.
Section to be changed		[redacted]
Description of change		
Rationale for change		To clarify the further endpoints for Part II.
Section to be changed		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, creatinine, creatine phosphokinase (CPK), AST, ALT, alkaline phosphatase, lactate dehydrogenase (LDH), bilirubin, total protein, albumin, urea nitrogen (or urea), and uric acid. ~~In addition, cholesterol, triglycerides, and c-peptide will be done at baseline and when clinically indicated.~~ Troponin will be tested according to the times listed in the flow charts. In case of pathological CPK, then CPK-MB, additional troponin I, and myoglobin should be reactively tested and the findings documented. […]
Rationale for change		It has been determined that these tests are not needed.
Section to be changed		Section 5.3.6.5.2 Immune-related adverse events (irAE)
Description of change		[…] The sponsor has defined a list of ~~potential~~ irAEs in Table 10.1: 1~~ in Appendix 10.1~~ **that must be reported as AESIs**. ~~These irAEs must be reported as AESIs.~~ If an Investigator determines another irAE~~event~~ (not on the list) should be a**n** ~~potential ir~~AESI, the Investigator may also report that event as an AESI.

		Immune-related AEs are AEs associated with immunotherapy treatments that appear to be associated with the immune therapy's mechanism of action. These adverse reactions, which can be severe, may involve the gastrointestinal, skin, liver, endocrine, respiratory, renal, or other organ systems. **All immune-related events are to be reported as AEs. Some irAEs also need to be reported as AESIs as defined by t~~T~~**he sponsor ~~has defined a list of potential irAEs~~ in Table 10.1: 1. ~~These irAEs must be reported as AESIs.~~ If an Investigator determines ~~another~~ **a Grade 3 event** (not on the list) **to be immune-related,** ~~should be a potential irAE,~~ the Investigator ~~may~~ **should** also report that event as an AESI.
Rationale for change		To clarify the reporting of irAEs as AESI.
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 **(**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.
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
Description of change		If data allow, the PK parameters of BI 754111 after single and multiple doses of BI 754111 monotherapy (FL cohort) and in combination with BI 754091, and also for BI 754091 after single and multiple doses of combination therapy mentioned as secondary and further endpoints for Parts I and II (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] and [redacted] ~~Kinesis~~ SOP 'SOP-1.PKA.03 Non-compartmental PK/PD Analysis').
Rationale for change		[redacted] BV has changed their name to [redacted] ED BV.

Section to be changed		Section 5.4.2 Methods of sample collection for pharmacokinetic analyses
Description of change		[…] The 1 hour PK sample is to be drawn **shortly after**~~before and as close as possible to~~ the end of the total infusion (of BI 754091 and BI 754111). **Pharmacokinetic sampling times and periods may be adapted by the Sponsor during the trial based on information obtained during trial conduct (e.g., preliminary PK data). Such changes would be implemented via non-substantial Clinical Trial Protocol Amendments.** […]
Rationale for change		To clarify when the 1-hour PK sample should be taken and to explain that sampling times may be changed in the future as more knowledge is gained.
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	
Description of change	
Rationale for change	

Section to be changed	
Description of change	
Rationale for change	

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 in the dose-expansion cohort who enrol 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 has been added to further endpoints for the dose-expansion part of the study, so this visit has been added to the study plan table (Flow Chart 3) for patients going forward and this section has been 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		[redacted]
Description of change		
Rationale for change		
Section to be changed		Section 7.4 Interim analysis
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.~~ […]
Rationale for change		Clarification
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		Tables 10.4.1: 1, 10.4.1: 2, and 10.4.1: 3: A few changes were made in the body of each of the tables for clarity and the footnotes changed (where applicable):
Description of change		a The planned total infusion duration is 1 hour. For cohorts receiving doses of BI 754111 <80 mg, the overall infusion duration (BI 754091+BI 754111) should also be as close to 1 hour as possible. In the event that total 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 (e.g., 1.25 hours post SOI). For cohorts receiving combination treatment using doses of BI 754111 <80 mg, the 1 hour PK sample is to be drawn ~~before and as close as possible to~~**shortly after** the end of the BI 754111 infusion. Actual date and clock time of SOI, end of infusion and blood draws have to be recorded. b The following windows of time are allowed for PK sampling: • Predose (PTM -0:05): within 1 hour before next drug infusion • **Shortly after** ~~Immediately before~~ the end of infusion (PTM 1:00): within ±5 min of the end of infusion […] c The specified blood volume for both BI 754111 and BI 754091 will be drawn into separate blood-drawing tubes. However, they should be collected in parallel at the specified time points after the start of the BI 754091 **(or combination)** infusion.
Rationale for change		To improve clarity and to make it clear when certain PK samples should be drawn.
Section to be changed		Tables 10.4.1: 2, 10.4.1: 3, and 10.4.1: 4:
Description of change		A column for PBMC testing was added to each table.
Rationale for change		To clarify that this testing is to be done for patients with FL.
Section to be changed		Table 10.4.1: 4 Footnote b was updated:
Description of change		b The specified blood volumes for both BI 754111 and BI 754091 will be drawn into separate blood-drawing tubes. ~~at the specified time points~~**However, they should be collected in parallel at the specified time points after the start of the BI 754091 (or combination) infusion.**
Rationale for change		To clarify the method for PK sampling when tubes for BI 754091 and BI 754111 are drawn at the same time point.
Section to be changed		Table 10.4.2: 1: Sampling in the expansion cohort
Description of change		One new table with updated and corrected sampling times replaced the 2 previous tables. The footnotes were updated as described for the dose-escalation tables, where applicable.
Rationale for change		New information from the dose-escalation cohorts has triggered a shift in sampling times.

Number of global amendment		4
Date of CTP revision		29 May 2018
EudraCT number		Not applicable
BI Trial number		BI 1381.2
BI Investigational Product(s)		BI 794111 and BI 754091
Title of protocol (previous - see below for title update)		An open label, Phase I dose-finding study of BI 754111 in combination with BI 754091 in patients with advanced solid cancers and of BI 754111 monotherapy with subsequent combination with BI 754091 in patients with follicular lymphoma, followed by an expansion cohort at the RPIID of the combination in patients with non-small cell lung cancer, metastatic colorectal cancer, solid tumors with high tumour mutational burden and/or microsatellite instability
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		

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		Protocol Title
Description of change		An open label, Phase I dose-finding study of BI 754111 in combination with BI 754091 in patients with advanced solid cancers~~ and of BI 754111 monotherapy with subsequent combination with BI 754091 in patients with follicular lymphoma,~~ followed by expansion cohort**s** at the ~~RPIID~~ **selected dose** of the combination in patients with~~-~~non-small cell lung cancer~~, metastatic colorectal cancer, solid tumors with high tumour mutational burden and/or microsatellite instability~~**and other solid tumors**

Rationale for changes		The title was updated to more accurately describe the study with the changes made in this amendment
Rationale for change		The FL cohort is removed from the protocol
Section to be changed		Sections 7.1.1.2, 7.1.1.3, 10.5.1.2 and the Flowchart for the FL cohort
Description of change		These sections were removed entirely
Rationale for change		The FL cohort has been difficult to recruit and the participating investigators indicate that the likelihood of finding patients for these cohorts was very small. Additionally, newly available data indicated that LAG3 expression is not detectable in PBMCs from patients with FL making the objective of measuring receptor occupancy in these patients not attainable.
Rationale for change		The FL cohort is removed from the protocol
Section to be changed		Protocol Title, Synopsis, Amendment Text
Description of change		Any text mentioning the FL cohort was removed from these sections.
Rationale for change		The FL cohort has been difficult to recruit and the participating investigators indicate that the likelihood of finding patients for these cohorts was very small. Additionally, newly available data indicated that LAG3 expression is not detectable in PBMCs from patients with FL making the objective of measuring receptor occupancy in these patients not attainable.
Section to be changed		Protocol Title, Amendment Text, Synopsis
Description of change		~~RPHD~~ **selected expansion dose**
Rationale for changes		The text has been updated to allow more flexibility in selection of the expansion dose(s) in this study.
Section to be changed		Synopsis - other changes to the synopsis are described as changes in the relevant sections in the body of the protocol.
Section to be changed		Flow Chart ~~3~~**2**
Description of change		What was Flow Chart 3 became Flow Chart 2
Rationale for change		The original Flow Chart 2 for FL patients was removed.

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 the study drugs until disease progression (PD) by RECIST and/or iRECIST, withdrawal of patient consent, an unacceptable toxicity occurs, or 1 year of treatment is completed, whichever occurs first. Patients will be allowed to stay on treatment in the case of initial radiological PD, if the Investigator feels that it is in the patient's best interest **and the patient 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 the combination of BI 754111 and BI 754091 is administered.
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 Medication, and Adverse Events removed from Cycle 2 Day 2 and 4, and Cycle 4 Day 4. Footnote j was updated with the additional text: **PK samples are also taken pre-treatment on Day 1 of all other cycles through Cycle 9 and then on Day 1 of every 3rd cycle.** Footnote h was updated with the addtioanl text: patients enrolled in protocol version 4.0 **or later** Footnote k: was updated with remove of ~~with NSCLC~~ Footnote l was updated: **A minimum of 2 core needle biopsies or 1 punch biopsy must be taken between screening and the day before first treatment with BI 754091. Otherwise,** ~~T~~two 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) **are acceptable**.; ~~otherwise, a minimum of 2 core needle biopsies or 1 punch biopsy must be taken between screening and the day before first treatment with BI 754091~~ Footnote o was updated: ~~PK samples are to be collected during Cycles 1, 4, and 8, at the EOT visit, and the 30-day safety follow-up, and~~ [redacted] blood samplings are to be collected… Footnote p was added: **The clinic will telephone the patients on Days 2 and 4 of Cycle 2 in order to check on any adverse events. The patients will not be required to go to the clinic on these days.**
Rationale for change		The flow chart was updated to clarify when PK samples are to be collected, what tissue should be taken for biomarker testing, and to clarify when patients need to come to the clinic on Cycles 1, 2, and 4.

Section to be changed		Abbreviations
Description of change		Abbreviations for ALK-Anaplastic lymphoma kinase, mCRC-Metastatic colorectal cancer, MSI-H-microsatellite instability high, and TMB-Tumour mutational burden were added. The abbreviation for FL-Follicular lymphoma was removed and irRECIST-Immune-Related Response Evaluation Criteria in Solid Tumours was changed to iRECIST-Guidelines for response criteria for use in trials testing immunotherapeutics
Rationale for change		To align the list of abbreviations to what is used in the amendment text.
Section to be changed		2.1 Rationale for performing the trial
Description of change		**Multiple immune checkpoint inhibitors have been approved for the treatment of patients metastatic NSCLC including pembrolizumab, nivolumab and atazolizumab. In second line NSCLC, blockade of the PD-1 pathway with an anti-PD-1 or anti-PD-L1 mAbs results in significant improvement in response rate (approximately 20 % Vs. 9%) and a significant improvement in overall survival (approximately 3 moths) compared to standard of care chem**otherapy (**R16-0878**; **R15-3715**; **R16-1875**;R16-5828**).** **It is postulated that treating patients with immune check point inhibitor early in their treatment continuum, while there immune system is still relatively intact, may maximize the chance of response and prolonged survival. To this end, immune checkpoint inhibitor have made remarkable changes to the standard of care for previously untreated patients with advanced NSCLC. Pembrolizumab monotherapy resulted in significant improvement in response rates, progression free survival and overall survival in previously untreated patients with NSCLC whose tumors express high level expression of PD-L1 of (to ≥50%) when compared to standard of care chemotherapy (R16-4803). As a result, pembrolizumab monotherapy is now a well-established treatment of choice as the replacement for cytotoxic chemotherapy in the first-line (R16-4803). However, approximately half the patients treated with pembrolizumab in this setting do not respond (response rate of 44.8%) and will require other immune therapy combination to achieve clinical benefit. Indeed, recent data have demonstrated that response rates in previously untreated NSCLC by combining pembrolizumab with chemotherapy can be improved (approximately 61% and 48%-55%) in patients with ≥50% and ≥1% PD-L1 expression, respectively, by combination pembrolizumab with chemotherapy (R16-4804; P18-03589). However, the combination of pembrolizumab with chemotherapy is associated with a significant increase in toxicity, owing to the chemotherapy component, than checkpoint inhibitor monotherapy (R16-4804; P18-03589). Therefore, finding more tolerable, less toxic checkpoint inhibitor combination to treat previously untreated NSCLC patients is of immense interest.**

		Checkpoint inhibitor therapy has also proven effective (approximately 30-40% of patients achieved objective response) in a subset of patients with MSI-H or DNA mismatch repair deficient metastatic colorectal cancer (mCRC) which tend to be highly immunogenic cancers (R16-1497; R18-1746). However, these characteristics occur only in a small fraction of mCRC (~5%). The majority of mCRC patients are microsatellite stable for whom single agent immunotherapy has not been successful. As such, this trial will evaluate the utility of the combination BI754091 (anti-PD-1 mAb) with BI754111 (anti-LAG-3 mAb) in this microsatellite stable mCRC population who have progressed on the standard of care, a population with very high unmet medical need. **The trial will also include a cohort of patients with solid tumours whose disease progressed while taking an anti-PD-1 or anti-PD-L1 regimen and who's tumours have high tumour mutational burden (TMB; defined as ≥ 10 mutations/megabase of DNA) or high microsatellite instability MSI-H. Both TMB-high and MSI-H are good predictive biomarkers of immunogenic tumours and response to immune checkpoint inhibitor therapy (R18-1492). As outlined above, the objective of this cohort is to explore the ability of the checkpoint inhibitor combination to restore immunotherapy responsiveness in this subset of anti-PD-1 or anti-PD-L1 resistant (both primary and acquired) with good predictive markers for response. If successful, such a regimen may provide a second immunotherapy treatment option with the potential for durable clinical benefit and possibly delay the need to initiate chemotherapy in some patients.** ~~While LAG-3 is not expressed on peripheral T-cells in healthy volunteers or most patients with solid tumours, it appears to be expressed on T-cells of patients with B-cell malignancies (R16-5218). Hence we will include patients with follicular lymphoma (FL) in order to measure LAG-3 receptor occupancy in that patient population.~~
Rationale for change		Background information was added for the new patient populations to be studied in this amendment.
Section to be changed		Section 2.1 Rationale for Performing the Trial
Description of change		This 2-part trial is the first study with BI 754111 in humans and the second with BI 754091. The first part will include dose-escalation cohorts to determine the maximum-tolerated dose (MTD) and/or the **selected expansion dose**~~recommended Phase II dose (RPIID)~~. The second part includes expansion cohorts at the **selected expansion dose**~~RPIID~~ that will further evaluate the safety, tolerability, PK, biomarkers and the preliminary efficacy of the BI 754111 plus BI 754091 combination. The dose-escalation portion of the trial will enrol patients with advanced and/or metastatic solid tumours~~ and FL~~, while the dose-expansion portion will enrol patients with advanced and/or metastatic NSCLC**, previously treated microsatellite stable**

		metastatic colorectal cancer (mCRC), or any anti-PD-1 or anti-PD-L1 pretreated solid tumour with high tumour mutational burden (TMB ≥10 mut/MB) and/or microsatellite instability high (MSI-H) and/or DNA mismatch repair deficient (MMRd).
Rationale for change		The rationale was updated to more accurately describe the study with the changes made in this amendment and to provide a rationale for these changes.
Section to be changed		Section 2.2 Trial Objectives
Description of change		The following changes were made to the Part I (dose-escalation) trial objectives: • ~~Investigate the safety, tolerability, and PK of escalating doses of BI 754111 as monotherapy for 2 cycles (2 doses administered via i.v. infusion q3w) in patients with relapsed/refractory FL~~ • ~~Investigate the safety, tolerability, and PK of escalating doses of BI 754111 in combination with BI 754091 (administered via i.v. infusion q3w), with BI 754091 added on to BI 754111 starting at Cycle 3 in patients with relapsed/refractory FL~~ • Determine the MTD through monitoring dose-limiting toxicities (DLTs) and/or to determine the **dose**~~RPHD~~ of the combination of BI 754111 plus BI 754091 **to be used in the expansion phase (Part II).** • ~~Assess LAG-3 receptor occupancy (RO) in peripheral blood in patients with FL.~~ The objectives of the Part II (dose-expansion) portion of the trial are to: • Further investigate the safety, tolerability, and PK of the ~~RPHD~~ **selected expansion dose** of the combination of BI 754111 plus BI 754091 in patients with NSCLC), **microsatellite stable (MSS) metastatic colorectal cancer (mCRC), or any PD-1 or PD-L1 pretreated solid tumour with high tumour mutational burden (TMB) and/or microsatellite instability high (MSI-H) and/or DNA/MMRd,** ~~(~~as defined in the entry criteria [see Section 3.3].~~)~~ • Explore the efficacy of the combination in patients with NSCLC**, mCRC, or any solid tumour with high TMB and/or MSI-H and/or DNA/MMRd and/or MMRd** (as defined in the entry criteria).
Rationale for change		The trial objectives were updated to more accurately describe the study focus with the changes made in this amendment.

Section to be changed		Section 2.3 Benefit-Risk Assessment
Description of change		**BI 754091 monotherapy is currently being tested in patients in the BI 1381.1 clinical trial. As of 27-Mar-2018, 36 patients with advanced/metastatic solid tumors have been treated with BI 754091 monotherapy. Nine patients were treated in the dose escalation phase of trial 1381.1 with 3 patients treated at each of 80mg, 240mg and 400mg dose levels, all administered Q3W. The remaining 27 patients were treated in the dose expansion phase of the same trial with 240 mg BI 754091 (the RPIID) Q3W. BI 745091 was well tolerated with no reported dose limiting toxicities (DLTs), treatment related SAE or treatment related deaths. The most frequently reported AEs (reported in >10% of the patients) were fatigue (47.2%), nausea (30.6%), decreased appetite (22.2%), constipation (19.4%), abdominal pain (16.7%) cough (16.7%), diarrhea (13.9 %), arthralgia (13.9%), vomiting (11.1%), and hypokalaemia (11.1%), headache (11.1%) and dyspnea (11.1%). The majority of these AEs were CTCAE grade 1 and 2. Grade 3 and 4 AEs were reported in 47.2% and 5.6% of patients, respectively. Of the grade 3 events, only the AST elevation is reported as related to trial drug. The reported grade 4 AEs were disease progression and sepsis, neither of which was deemed treatment related. Immune-related AEs included 1 Grade 2 hypothyroidism, 1 Grade 2 ALT increased, 1 Grade 3 AST increased, 2 Grade 1 rash, 2 Grade 1 rash maculo-papular and 1 Grade 1 pruritus.** **Preliminary efficacy analyses indicate that there are 5 patients with partial response (PR) and approximately 10 patients with disease stabilization on BI 754091 monotherapy in the 1381.1. The PRs were reported in two patients with triple negative breast cancer, one patient with ovarian cancer, one patient with renal cancer, and one patient with stomach cancer. All of these PRs occurred in patients receiving the 240 mg q3w dose of BI 754091. Pharmacokinetic data of BI 754091 are available from 9 patients in the dose escalation part of the ongoing clinical phase I study 1381.1 in which three dose levels (80, 240 and 400 mg) of BI 754091 as monotherapy have been tested (each in 3 patients). The details of the preliminary analysis are provided in section 6.2 of the BI 754091 IB.** ~~BI 754111 has not been tested in humans thus far.~~
Rationale for change		To better describe the current status of BI 754091 in patients.

Section to be changed		Section 2.3 Benefit-Risk Assessment
Description of change		**BI 754111 has only been administered to human subject in the dose escalation part of this trial. Six dose levels of BI 754111 (4mg, 20mg, 80mg, 200mg, 400mg and 600mg) have been tested during this trial in combination with 240 mg BI 754091 q3w. Thus far (27-Mar-2018 data lock point), the combination treatment is well tolerated with no DLTs, or treatment related deaths reported. One case of CTCAE Grade 3 ALT and Grade 2 AST elevation has been reported as treatment-related SAE. The most frequently reported AEs in patients treated with combination BI 754091 and BI 754111 are Nausea (23.7%), Fatigue (23.7%), decreased appetite (10.5%), hypokalaemia (10.5%) Pyrexia (10.5%) and cough (10.5%). The majority of these events were CTCAE Grades 1 and 2. Grade 3 AEs occurred at a frequency of 18.4% and no grade 4 events were reported. Of the grade 3 AEs, infusion related reaction, maculopapular rash and ALT elevation were reported as possibly related to study drugs. The only Grade 5 event was respiratory failure, occurring in the context of pneumonia and sepsis and progressive disease. These events were unrelated to trial drugs. The pattern of immune-related AEs for the combination treatment was similar to that observed for BI 754091 monotherapy. Thus far, 2 Grade 2 hypothyroidism, 1 Grade 3 rash maculopapular, 1 Grade 3 ALT increase and 1 Grade 3 infusion related reaction have been reported as immune related AEs.** ~~BI 754091 is currently being tested in patients in the BI 1381.1 clinical trial.~~ Preliminary clinical safety information is not yet available, but will be closely monitored during the conduct of this trial. ~~Repeat-dose administrations of BI 754091 at 0, 3, 30, or 100 mg/kg (via i.v. injection) once per week for 13 weeks in the cynomolgus monkey were well tolerated. No test article related adverse changes in body weight, food consumption, respiratory rate, 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, immune-phenotyping, 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 **preliminary** clinical data obtained with BI 754091 ~~and other anti-PD-1 mAbs,~~ **as well as the combination of BI 754091 and BI 754111,** the inhibitory effects of the combination of BI 754111 and BI 754091 may translate into a clinical benefit in cancer patients. ~~The dose-escalation scheme for BI 754111 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.~~

Rationale for change		To better describe the current status of BI 75411 and the combination of BI 75411 plus BI 754091 in patients.
Section to be changed		Sections 2.3 Benefit-Risk Assessment; Section 4.1.3 Dose-escalation scheme; Section 5.3 Assessment of Safety; Section 5.3.6.6 Severity of adverse events; and Synopsis
Description of change		Adverse event will be coded and graded per the Common Terminology Criteria for Adverse Events (CTCAE) Version **5.0** ~~4.03~~.
Rationale for change		A new CTCAE has been release and will now be used for this study.
Section to be changed		Section 3.1 Overall Trial Design and Plan and Figure 3.1.1. and Table 3.1.1.
Description of change		All descriptions of the FL cohort was removed from this section.
Rationale for change		The FL cohort was removed from the study.
Section to be changed		Section 3.1 Overall Trial Design and Plan
Description of change		Following determination of the MTD and (or) the ~~RPIID~~ **selected expansion dose** of the combination of BI 754111 and BI 754091, Part II will commence to further characterise the combination at the doses determined in Part I in patients with NSCLC, **mCRC, or any solid tumour with high TMB and/or MSI-H and/or MMRd.**
Rationale for change		The overall trial design and plan was updated to more accurately describe the study with the changes made in this amendment. Specifically, the patient populations to be enrolled on the study have been updated.
Section to be changed		Table 3.1.1 Possible Cohort Scenarios for Solid Tumour Cohorts
Description of change		3 additional possible cohorts were added to the study **Cohort H: Selected expansion dose in ≥ 2nd line microsatellite stable anti-PD-1 and anti-PD-L1 treatment-naïve mCRC.** **Cohort I Selected expansion dose in patients with any solid tumour with high TMB or MSI-H and/or MMRd solid tumours who have received 1 prior PD-1 or PD-L1 treatment regimen.**
Rationale for change		The table of possible cohorts has been updated to include the cohorts to be added with this amendment.

Section to be changed		Section 3.1 Overall Trial Design and Plan
Description of change		Following determination of the ~~MTD and/or the RPHD~~ **dose** from the Part I portion, **3 dose-expansion cohorts (2nd and 3rd line NSCLC, anti-PD-1 and anti-PD-L treatment –naïve mCRC, and any solid tumour with high TMB and/or MSI-H)**, ~~a cohort of 30 patients with NSCLC (as defined in the entry criteria)~~ will be enrolled into Part II.
Rationale for change		The overall trial design and plan was updated to more accurately describe the study with the changes made in this amendment. Specifically, the new cohorts to be added with this amendment have been described.
Section to be changed		Section 3.1 Overall Trial Design and Plan
Description of change		Patients will continue study treatment 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)** ~~and/or Immune-Related Response Evaluation Criteria in Solid Tumours (irRECIST) or response criteria for malignant lymphoma (R14-3387) for patients with FL,~~ withdrawal of patient consent, an unacceptable…
Rationale for change		iRECIST will replace irRECIST
Section to be changed		Section 3.3.2 Inclusion Criteria and Synopsis
		• Part I (dose escalation): • ~~•~~ Patients with a confirmed diagnosis of advanced, unresectable, and/or metastatic solid tumours (any type) ~~and patients with histologically confirmed relapsed/refractory FL.~~ ~~• Patients with solid tumours:~~ o For whom no therapy of proven efficacy exists, or who are not amenable to standard therapies. o Must have measurable lesions according to RECIST v1.1 o Previous treatment with an anti-PD-1 mAb is allowed as long as the last administration of the anti-PD-1 mAb on the previous treatment is a minimum of 60 days prior to starting treatment in this trial. ~~• Patients with FL:~~ o ~~Patients with histologically confirmed, relapsed or refractory FL for whom there are no treatment options available known to provide clinical benefit.~~
Description of change		~~o Must have at least one measurable lesion of at least 1.5 cm in long diameter as defined in the Revised Response Criteria for Malignant Lymphoma (R10-1462; R14-3387).~~ ~~o Must be anti-PD-1 and anti-PD-L1 naïve.~~

		~~o Autologous stem cell transplantation (SCT) is allowed as long as the transplant was completed ≥100 days prior to starting treatment in this trial.~~ ~~o Allogeneic SCT is not allowed.~~ • Part II (dose expansion): • ~~Second and 3rd line NSCLC patients who progressed on anti-PD-1 or anti-PD-L1 treatment after having achieved radiologically confirmed benefit (minimum of stable disease) with a minimum treatment duration of 6 months on the previous anti-PD-1 or anti-PD-L1 treatment. The anti-PD-1- or anti-PD-L1-containing treatment (excluding anti-PD-1 or anti-PD-L1 in combination with chemotherapy) must have been the latest treatment regimen prior to enrolling in this trial with >4 and <12 weeks between the latest treatment and their first dose in this trial. Patients who have had anti-PD-1 or anti-PD-L1 as their first-line NSCLC treatment regimen must have a PD-L1 expression level of ≥50% at baseline (local confirmed testing).~~Patients must have measurable disease per 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 (if adequate archival tissue is not available) and, unless clinically contraindicated, after 6 weeks on therapy. • **Dose Expansion Cohorts:** o **Second and 3rd line NSCLC patients:** ▪ **Must have progressed on anti-PD-1 or anti-PD-L1 treatment after having achieved radiologically confirmed benefit (minimum of stable disease)** ▪ **Must have had a minimum duration of benefit of 6 months and minimum treatment duration of 2 months on the previous anti-PD-1 or anti-PD-L1 treatment without experiencing disease progression during that period.** ▪ **The anti-PD-1- or anti-PD-L1-containing treatment must have been**

		the latest treatment regimen prior to enrolling in this trial ▪ **Must be within >4 and <12 weeks since the latest treatment and their first dose in this trial. Patients who have had anti-PD-1 or anti-PD-L1 monotherapy as their first-line NSCLC treatment regimen must have a PD-L1 expression level of ≥1% at baseline (local validated testing).** ○ **Anti-PD-1 or anti-PD-L1 treatment-naïve patients with microsatellite stable mCRC patients:** ▪ **Patients must have had ≥ 1 line treatment** ▪ **Must have microsatellite stable disease (identified using any validated test)** ▪ **Must be anti-PD-1 and anti-PD-L1 treatment naïve** ○ **Anti-PD-1 or anti-PD-L1 pretreated patients with any high TMB (≥10 mutations/Mb) and/or MSI-H and/or DNA MMRd solid tumours** ▪ **Patients must have high TMB (≥ 10 mutations/Mb) and/or MSI-H and/or DNA mismatch repair deficient (MMRd) (measured using any validated test).**
Rationale for change		The inclusion criteria have been updated to more accurately describe the study with the changes made in this amendment.

Section to be changed		Section 3.3.2 Exclusion Criteria and Synopsis
Description of change		~~1.~~ Any investigational or anti-tumour treatment within 4 weeks or within 5 half-life periods (whichever is shorter) prior to the initiation of trial treatment. ~~FL patients on chemotherapy immediately prior to current study may initiate treatment in this trial within 15 days of last chemotherapy dose following sponsor agreement.~~ ~~1.~~ 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. ~~Known central nervous system (CNS) involvement in patients with FL (i.e., current clinical CNS symptoms deemed by the Investigator to be related to lymphoma CNS involvement [clinical assessment per Investigator's judgement is sufficient]) is excluded.~~ ~~2. Lymphoma in transformation or transformed~~ ~~1.~~ Immunosuppressive corticosteroid doses (>10 mg prednisone daily or equivalent) within 4 weeks prior to the first dose of study treatment. ~~Corticosteroids used for symptom control in patients with FL is allowed (upon discussion with sponsor). In such cases the patient must be on >10 mg prednisone daily or equivalent 2 weeks prior to starting treatment in this trial.~~ ~~2.~~
Rationale for change		The exclusion criteria have been updated to remove FL-related criteria
Section to be changed		Table 3.3.3.1
Description of change		Laboratory values demonstrating inadequate organ function for FL patients has been removed.
Rationale for change		The FL cohort has been removed from this study.
Section to be changed		Section 4.1.2.1
Description of change		**The recommended Phase II dose of BI 754091 to be used in combination with BI 754111 is 240mg every 3 weeks.** The**is starting** dose of BI 754091 **was** ~~in this study will be~~ determined by the SRC using the most recent safety information from another ongoing study, BI 1381.1. ~~In the BI 1381.1 study, 80 mg was the starting dose of BI 754091 and escalating doses are selected by the SRC (informed by a BLRM with overdose control design).~~ Based on emerging safety information in the 1381.1 and 1381.2 studies, the SRC may amend the dose of BI 754091 used in this study. ~~The SRC will determine the selected dose of BI 754091 for each cohort of this study and communicate it to the investigators.~~

Rationale for change		The recommended Phase II dose of BI 754091 has been identified.
Section to be changed		Section 5.3
Description of change		~~For combination therapy,~~ DLTs observed during the MTD evaluation period (the first cycle of BI 754111 plus BI 754091 combination treatment) will be considered for MTD determination. However, all DLTs observed in all treatment cycles will be collected and will be considered for determining an ~~RPIID~~expansion . The BLRM will be re-run to include the DLT information from all combination treatment cycles. Based on both estimates, the recommended dose for further development will be selected. ~~For BI 754111 monotherapy, DLTs observed during the 2 cycles of the BI 754111 treatment will be analyzed by the monotherapy BLRM described in Section 7.1.1.2 with recommendations provided to support the decision of next dose escalation.~~
Rationale for change		Text revised since FL population, and therefore monotherapy treatment, was removed.
Section to be changed		Section 5.4.2 Methods of sample collection for pharmacokinetic analyses
Description of change		~~After completion of the trial,~~ **P~~p~~**lasma samples may be used for further methodological investigations (e.g., stability testing), **h~~H~~**owever only data related to the analyte or bioanalytical assay will be generated by these additional investigations.
Rationale for change		The PK sample collection has been updated to allow for collection of plasma samples that may be needed for validation exercises needed prior to completion of the trial.
Section to be changed		[redacted]
Description of change		
Rationale for change		
Section to be changed		
Description of change		

		[redacted]
Rationale for change		
Section to be changed		Section 7.1.2 Statistical design- Part II (dose expansion **cohorts**)
Description of change		Part II (dose expansion **cohorts**) of the trial will be designed as **multiple**~~single arm~~ open-label cohorts. C~~A c~~ohorts of approximately 40 patients with 2nd or 3rd line NSCLC, **40 patients with mCRC, and 40 patients with any solid tumour with high TMB and/or MSI-H** (as defined in the entry criteria, see Section 3.3) at the dose and schedule recommended by the SRC.
Rationale for change		The statistical design section has been updated to include the new cohorts added in this amendment.
Section to be changed		Section 7.7.2 Determination of sample size for Part II
Description of change		For ~~Part II~~ **Cohorts G and I**, it is assumed that the combination of BI 754111 and BI 754091 will have an ORR of at least 25%. ~~For a cohort w~~**W**ith ~~30~~ **40** evaluable patients **per cohort**, an ORR of 20% or more would be observed with a probability of approximately ~~80~~**82**% assuming a true response rate of 25%. The probability of observing a false positive signal, e.g., to observe at least an ORR of 20% if the underlying true ORR is 10%, is around ~~7~~**4**%.
Rationale for change		The sample size description has been updated to include the new cohorts added in this amendment.

Section to be changed		Section 7.7.2 Determination of sample size for Part II
Description of change		**For Cohort H, it is planned that 40 patients will be enrolled. Based on the current literature, it is considered clinically meaningful if the combination of BI 754111 and BI 754091 will achieve an underlying ORR of 20%. With 40 evaluable patients, an ORR of 15% or more would be observed with a probability of approximately 84% assuming a true response rate of 20%. The probability of observing a false positive signal, e.g., to observe an ORR of at least 15% if the underlying true ORR is 5%, is around 1%. Table 7.7.2.2 summarises the probability of observing certain ORRs based on different assumptions of the underlying ORR.**
Rationale for change		The text has been added to provide the statistical information for the newly added Cohort I (≥ 2nd line microsatellite stable PD-1 and PD-L1 treatment- naïve mCRC patients).
Section to be changed		**Table 7.7.2.3 Probabilities of observing certain objective response rates in Cohort H**
Description of change		The table was added to show the probabilities to observe defined changes in ORR when 40 patients are enrolled into this cohort.
Rationale for change		The table has been added to provide the statistical probabilities in the newly added Cohort H (≥ 2nd line microsatellite stable PD-1 and PD-L1 treatment- naïve mCRC patients).
Section to be changed		Section 9.1 Published references
Description of change		**R16-1875** **Borghaei H, et al. Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. N Engl J Med 2015;373:1627-1639.** **R16-4803** **Reck M, Rodriguez-Abreu D, Robinson AG, Hui R, Csoszi T, Fulop A, et al, KEYNOTE-024 Investigators Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. N Engl J Med 2016;375:1823-1833.** **R16-4804** **Langer CJ, Gadgeel SM, Borghaei H, Papadimitrakopoulou VA, Patnaik A, Powell SF, et al, KEYNOTE-021 Investigators Carboplatin and pemetrexed with or without pembrolizumab for advanced, non-squamous non-small-cell lung cancer: a randomised, phase 2 cohort of the open-label KEYNOTE-021 study. Lancet Oncol, 2016; 17: 1497-1508.** **R16-4925** **American Cancer Society. Cancer facts & figures 2016. http://www.cancer.org/acs/groups/content/@research/documents/document/acspc-0470 79.pdf (access date: 20 October); Atlanta: American Cancer Society 2016.** **R16-5828** **Rittmeyer A, Barlesi F, Waterkamp D, Park K, Ciardiello F, Pawel J von, et al Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung**

		cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. Lancet 2017;389:255-265. **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.** **P18-03589** **Gandhi L, Rodriguez-Abreu D, Gadgeel S, Esteban E, Felip E, Angelis F de, et al, KEYNOTE-189 Investigators Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. N Engl J Med. 2018 doi:10.1056/NEJMoa1801005 [Epub ahead of print].** **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]** **R18-1746** **Overman MJ, McDermott R, Leach JL, Lonardi S, Lenz HJ, Morse MA, Desai J, et al., Nivolumab in patients with metastatic DNA mismatch repair-deficient or microsatellite instability-high colorectal cancer (CheckMate 142): an open-label, multicentre, phase 2 study. Lancet Oncol. 2017 Sep;18(9):1182-1191. doi: 10.1016/S1470-2045(17)30422-9.**
Rationale for change		To provide the relevant references for iRECIST assessments and the updated tumour mutational burden cut-off are added.
Section to be changed		Table 10.4.1: 1 Time schedule for PK and [redacted] sampling - Part I dose-escalation cohorts (Cycles 1, 2, and 4 for solid tumour cohorts) Table 10.4.1: 2 Time schedule for PK, [redacted] sampling - Part I dose-escalation cohorts (Cycles 1 & 2 for FL cohorts) Table 10.4.1: 3 Time schedule for PK, [redacted] sampling - Part I dose-escalation cohorts (Cycle 3 FL cohorts only) Table 10.4.2: 1 Time schedule for PK, [redacted] blood samplings - Part II dose-expansion cohorts
Description of change		A window of ±1 day has been added to PK collection on days 8 and 15, and the following footnotes have been added to the tables:
		• **24 and 72 hours post SOI (PTM 24:00 to 72:00): ±1 hour** • **168 and 336 hours post SOI (PTM 168:00 to 336:00): ±24 hour.**

		The following tables were removed Table 10.4.1: 2 Time schedule for PK, [redacted] sampling - Part I dose-escalation cohorts (Cycles 1 & 2 for FL cohorts) Table 10.4.1: 3 Time schedule for PK, [redacted] sampling - Part I dose-escalation cohorts (Cycle 3 FL cohorts only)
Rationale for change		The PK tables have been updated to provide more flexibility and better defined windows for the collection of PK samples.

Number of global amendment		5
Date of CTP revision		3 July 2018
EudraCT number		2017-005042-29
BI Trial number		BI 1381.2
BI Investigational Product(s)		BI 794111 and BI 754091
Title of protocol (previous - see below for title update)		An open label, Phase I dose-finding study of BI 754111 in combination with BI 754091 in patients with advanced solid cancers followed by expansion cohorts at the selected dose of the combination in patients with non-small cell lung cancer and other solid tumors
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		

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		**No. of patients:**
Description of change		**Part I (Dose-Escalation Cohorts):** Approximately 15 to 50 patients **Part II (Dose-Expansion Cohorts):** ~~120~~**160** patients total
Rationale for changes		The number of patients was updated to include Cohort J in the dose expansion part of the amendment.

Section to be changed		**Total entered:**
Description of change		Approximately ~~135~~**175** to ~~170~~**210** patients are planned to be enrolled in this trial.
Rationale for changes		The number of patients was updated to include Cohort J in the dose expansion part of the amendment.

Section to be changed		**Each treatment:**
Description of change		Part I: a minimum of 3 patients with solid tumours per dose-escalation cohort Part II:~~120~~**160** patients
Rationale for changes		The number of patients was updated to include Cohort J in the dose expansion part of the amendment.

Section to be changed		Synopsis-Diagnosis
Description of change		Part I (Dose-Escalation Cohorts): Patients with a confirmed diagnosis of advanced, unresectable, and/or metastatic solid tumours Part II (Dose Expansion Cohorts): • Second and 3rd line NSCLC patients who progressed on anti-PD-1 or anti-PD-L1 treatment after having achieved radiologically confirmed benefit (minimum of stable disease). • Anti-PD-1 and anti-PD-L1 naïve second line or greater microsatellite stable mCRC.
		• Anti-PD-1 or anti-PD-L1 pretreated (can include BI 754091) patients with any solid tumour with TMB high (≥10 mutations/Mb) and/or MSI-H and/or DNA MMRd **First line NSCLC patients with wildtype (wt) epidermal growth factor receptor [EGFR] and anaplastic lymphoma kinase [ALK] tumors of squamous or non-squamous origin.**

Rationale for changes		A 1st-line NSCLC expansion cohort was added and the description of diagnoses was updated.
Section to be changed		Synopsis-Main Criteria for Inclusion
Description of change		All Cohorts: • Adult patients at least 18 years-of-age with no active use of systemic steroids, no active auto-immune disease, and a life expectancy of at least 12 weeks • Eastern Cooperative Oncology Group (ECOG) performance status 0-1 Part I (Dose-Escalation Cohorts): • Patients with a confirmed diagnosis of advanced, unresectable, and/or metastatic solid tumours (any type) • For patients in Part I with solid tumours: - For whom no therapy of proven efficacy exists, or who are not amenable to standard therapies. - Must have measurable lesions according to Revised Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 and iRECIST - Previous treatment with an anti-PD-1 mAb is allowed as long as the last administration of the anti-PD-1 mAb on the previous treatment is a minimum of 60 days prior to starting treatment in this trial. Part II (Dose-Expansion Cohorts): All patients must have measurable disease according to RECIST Version 1.1, must have at least 1 tumour lesion amenable to biopsy, and must be medically fit and willing to undergo a biopsy before first treatment (if adequate archival tissue is not available) and, unless clinically contraindicated, after 6 weeks on therapy. All patients must not have had previous LAG-3 targeted treatment • 2nd or 3rd-line NSCLC patients: - Must have progressed on anti-PD-1 or anti-PD-L1 treatment after having achieved radiologically confirmed benefit (minimum of stable disease) - Must have had a minimum duration of benefit of ~~6~~**8** months **for non-squamous NSCLC patients who received immunotherapy plus chemotherapy in a first line setting, or 6 months for all other patients**, and minimum treatment duration of 2 months on the previous anti-PD-1 or anti-PD-L1 treatment without experiencing disease progression during that period. - The anti-PD-1- or anti-PD-L1-containing treatment must have been the latest treatment regimen prior to enrolling in this trial - Latest treatment must be within >4 and <12 weeks before their first dose in this trial. Patients who have had anti-PD-1 or anti-PD-L1 monotherapy as their first-line NSCLC treatment regimen must have a PD-L1 expression level of ≥1% at baseline (local validated testing). • Anti-PD-1 or anti-PD-L1 treatment naïve patients with microsatellite stable mCRC - Patients must have had ≥1 lines of systemic treatment • Anti-PD-1 or anti-PD-L1 pretreated patients with high TMB (≥10 mutations/Mb) and/or MSI-H and/or DNA MMRd solid tumours

		• **1st-line squamous or non-squamous NSCLC patients:** - **Patients must be treatment naïve** - **Must be EGFR WT and ALK WT** - **Any PD-L1 expression level. However, the number of patients with high level of PD-L1 expression (≥50% PD-L1) will be limited to a maximum of 10 (local validated testing)**
Rationale for changes		A 1st-line NSCLC expansion cohort was added. Therefore, the inclusion criteria was updated. Additionally, the definition of stable disease now requires 8 months for non-squamous NSCLC patients who received immunotherapy plus chemotherapy in a first line setting, or 6 months for all other patients, instead of 6 months duration of benefit
Section to be changed		Synopsis-Doses
Description of change		Increasing doses of BI 754111 starting with 4 mg in combination with BI 754091 at the RPIID (240 mg q3w) or a lower dose selected by the 1381.2 Safety Review Committee upon review of evolving data from Study 1381.1 (an ongoing study of ~~of~~ BI 754091 using a BLRM with overdose control in patients with advanced solid tumours).
Rationale for changes		Typographical error corrected
Section to be changed		Section 2.1-Rationale for Performing Trial
Description of change		To this end, immune checkpoint ~~inhibitor~~**inhibitors** have made remarkable changes to the standard of care for previously untreated patients with advanced NSCLC
Rationale for changes		A typographical error was corrected.
Section to be changed		Section 2.1-Rationale for Performing Trial
Description of change		Therefore, finding more tolerable, less toxic checkpoint inhibitor combination to treat previously untreated NSCLC patients is of immense interest**. As such, this trial aims to test the safety and efficacy of chemotherapy-sparing combination of BI 754091 with BI 754111 in patients with previously untreated NSCLC. The combination of BI 754091 with BI 754111 has the potential to be less toxic than chemotherapy containing regimens and would reserve chemotherapy as a subsequent line of treatment for patients whose disease progresses.**
Rationale for changes		A 1st-line NSCLC expansion cohort was added. Therefore, additional text was added to provide the rationale.

Section to be changed		Table 3.1: 1 Possible Cohort Scenarios for Solid Tumour Cohorts
Description of change		*The following cohort was added to this table:* **Cohort J** | **Selected expansion dose in patients with 1st line epidermal growth factor receptor [EGFR] wildtype [WT] and anaplastic lymphoma kinase [ALK] WT NSCLC. Patients may have any level of PD-L1 expression, but only a maximum of 10 patients with PD-L1 high expression (≥50% PD-L1) will be enrolled.**
Rationale for changes		A 1st-line NSCLC expansion cohort was added to the list of cohorts in this table.
Section to be changed		Section 3.1-Overall Trial Design
Description of change		Following determination of the dose from the Part I portion, 4 dose-expansion cohorts (2nd and 3rd line NSCLC,~~,~~ anti-PD1 and anti-PD-L1 treatment–naïve mCRC,~~ and~~ any solid tumour with high TMB and/or MSI-H**, and 1st-line NSCLC**), will be enrolled into Part II.
Rationale for changes		A 1st-line NSCLC expansion cohort was added to the study design description.
Section to be changed		Section 3.3.2 -Selection of Trial Population
Description of change		Part II (dose expansion): • Patients must have measurable disease per 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 (if adequate archival tissue is not available) and, unless clinically contraindicated, after 6 weeks on therapy. • Dose Expansion Cohorts: - Second and 3rd line NSCLC patients: • Must have progressed on anti-PD-1 or anti-PD-L1 treatment after having achieved radiologically confirmed benefit (minimum of stable disease) • Must have had a minimum duration of benefit of ~~8~~6 months **for non-squamous NSCLC patients who received immunotherapy plus chemotherapy in a first line setting,** or 6 months for all other patients, and minimum treatment duration of 2 months on the previous anti-PD-1 or anti-PD-L1 treatment without experiencing disease progression during that period. • The anti-PD-1- or anti-PD-L1-containing treatment must have been the latest treatment regimen prior to enrolling in this trial

		• Must be within >4 and <12 weeks since the latest treatment and their first dose in this trial. Patients who have had anti-PD-1 or anti-PD-L1 monotherapy as their first-line NSCLC treatment regimen must have a PD-L1 expression level of ≥1% at baseline (local validated testing). - Anti-PD-1 or anti-PD-L1 treatment-naïve patients with microsatellite stable mCRC: • Patients must have had ≥ 1 line treatment • Must have microsatellite stable disease (identified using any validated test) • Must be anti-PD-1 and anti-PD-L1 treatment naïve - Anti-PD-1 or anti-PD-L1 pretreated patients with any high TMB (≥10 mutations/Mb) and/or MSI-H and/or DNA MMRd solid tumours • Patients must have high TMB (≥ 10 mutations/Mb) and/or MSI-H and/or DNA mismatch repair deficient (MMRd) (measured using any validated test). • Patients must have received 1 prior anti-PD-1 or anti-PD-L1 treatment regimen. - **1st-line squamous or non-squamous NSCLC patients:** • **Patients must be treatment naïve** • **Must be EGFR wild type** • **Must be ALK wild type** • **Any PD-L1 expression level. However, the number of patients with high level of PD-L1 expression (≥50% PD-L1) will be limited to a maximum of 10 patients**
Rationale for changes		A 1st-line NSCLC expansion cohort was added. Therefore, inclusion criteria for this cohort was added to this section. Additionally, the definition of stable disease now requires 8 months for non-squamous NSCLC patients who received immunotherapy plus chemotherapy in a first line setting, or 6 months for all other patients, instead of 6 months duration of benefit.
Section to be changed		Section 5.2.1
Description of change		Digital copies of disease evaluation scans are to be collected and stored centrally for ~~future analysis~~ **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 changes		To provide information regarding the planned use of scans.

Section to be changed		Section 7.1.2-Statistical design-Part II (dose expansion cohorts)
Description of change		Part II (dose expansion cohorts) of the trial will be designed as multiple open-label cohorts. Cohorts of approximately 40 patients with 2nd or 3rd line NSCLC, 40 patients with mCRC, ~~and~~ 40 patients with any solid tumour with high TMB and/or MSI-H (as defined in the entry criteria, see Section 3.3)**, and 40 patients with 1st line NSCLC (this cohort will include up to 10 patients with PD-L1 expression ≥50%)** at the dose and schedule recommended by the SRC.
Rationale for changes		A 1st-line NSCLC expansion cohort was added and the summary of the number of patients on each cohort has been updated.
Section to be changed		Section 7.7.2-Determiniation of sample size for Part II
Description of change		*The following text was added:* **For Cohort J, it is planned that a total of 40 patients will be enrolled, with a maximum of 10 patients with PD-L1 high expression (≥ 50% PD-L1). Based on the current literature, it is deemed clinically meaningful if the underlying ORR for the combination of BI 754111 and BI 754091 will be 40% for patients with PD-L1 < 50%. With approximately 30 patients with PD-L1 <50%, an ORR of 35% or more would be observed with a probability of approximately 71% assuming a true response rate of 40%. The probability of observing a false positive signal, e.g., to observe at least an ORR of 35% if the underlying true ORR is 20%, is around 3%. Table 7.7.2: 3 summarizes the probability of observing certain ORRs based on different assumptions of the underlying ORR.** **Table 7.7.2: 3 Probabilities of observing certain objective response rates in Cohort J**
Rationale for changes		A 1st-line NSCLC expansion cohort was added and the statistical summary of for the cohort was added.

True underlying OR rate	**Patients with PD-L1 <50%**	**Probability to observe at least**	
		ORR ≥ 35% (≥ 11 patients with OR)	**ORR ≥ 40% (≥ 12 patients with OR)**
50%	**30**	**95.1%**	**90.0%**
45%	**30**	**86.5%**	**76.7%**
40%	**30**	**70.9%**	**56.9%**
35%	**30**	**49.2%**	**34.5%**
30%	**30**	**27.0%**	**15.9%**
25%	**30**	**10.6%**	**5.1%**
20%	**30**	**2.6%**	**0.9%**

Number of global amendment		6
Date of CTP revision		26 Feb 2019
EudraCT number		2017-005042-29
BI Trial number		BI 1381.2
BI Investigational Product(s)		BI 754111 and BI 754091
Title of protocol (previous - see below for title update)		An open label, Phase I dose-finding study of BI 754111 in combination with BI 754091 in patients with advanced solid cancers followed by expansion cohorts at the selected dose of the combination in patients with non-small cell lung cancer and other solid tumors
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		
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		**Flow Chart 1**
Description of change		A new row **"Administration of Pre-Treatment Medication[p]** "and footnote "**p- Pre-treatment medications (antihistamine and acetaminophen or paracetamol) should be administered at sufficient time prior to initiation of infusion to allow the agents to exert their influence.**" was added.
Rationale for changes		Pre-treatment medication has been added to the study prior to administration of the study treatment in order to reduce the risk of infusion related reactions.
Section to be changed		**Flow Chart 1 footnote a**
Description of change		In addition, patients **benefiting clinically and** 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 the combination of BI 754111 and BI 754091 is administered.
Rationale for changes		Language explaining how long patients can receive study treatment have been aligned throughout the protocol in order to clarify that as long as the investigator determines a patient is clinically benefiting from study drug (regardless of RECIST status), they can continue on study drug if sponsor and Medical Monitor agree.
Section to be changed		**Flow Chart 2**
Description of change		A new row **"Administration of Pre-Treatment Medication[q]"**and footnote "**q- Pre-treatment medications (antihistamine and acetaminophen or paracetamol) should be administered at sufficient time prior to initiation of infusion to allow the agents to exert their influence.**" was added.
Rationale for changes		Pre-treatment medication has been added to the study prior to administration of the study treatment in order to reduce the risk of infusion related reactions.
Section to be changed		**Flow Chart 2**
Description of change		Footnote "p" has been marked on Expansion Cycles 1, 2, and 4 Days 2 and 4.
Rationale for changes		The footnote has been added to correct portion of the flow chart.
Section to be changed		**Flow Chart 2 footnote a**
Description of change		a In addition, patients benefiting clinically and 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 the combination of BI 754111 and BI 754091 is administered.

Rationale for changes		Language explaining how long patients can receive study treatment have been aligned throughout the protocol in order toclarify that as long as the investigator determines a patient is clinically benefiting from study drug (regardless of RECIST status), they can continue on study drug if sponsor and Medical Monitor agree.
Section to be changed		**Flow Chart 2 footnote p**
Description of change		p The clinic will telephone the patients on Days 2 and 4 of Cycle 2 **and Day 2 of Cycle 4** in order to check on any adverse events. The patients will not be required to go to the clinic on these days.
Rationale for changes		Additional text has been added to clarify that patients do not need to go to the clinic on Day 2 of Cycle 4. This was previously communicated to sites in a protocol clarification letter dated 20 November 2018.
Section to be changed		2.3 BENEFIT-RISK ASSESSMENT
Description of change		**As of 18 April 2019, a total of 106 patients were treated with the combination of BI 754091 and BI 754111 in this study. The currently available clinical data indicate that BI 754111 in combination with BI 754091 is well tolerated. The most common AEs were reported in the GI disorders and general disorders and administration site conditions system organ classes. The majority of reported events were mild to moderate in severity (Grade1 and 2). The benefit/risk ratio continues to be considered positive for patients with advanced cancers. Please refer to the current version of the BI 754111 Investigator Brochure for further details.** ~~As of 30 November 2018, 50 patients with advanced/metastatic solid tumors have been treated with BI 754091 as monotherapy in the 1381.1 trial.~~ ~~The most frequently reported AEs (reported in >10% of the patients) were fatigue (40%), nausea (28.0%), decreased appetite (18.0%), arthralgia (16.0%), cough (16.0%), abdominal pain (14.0%), constipation (14.0%), diarrhea (14.0 %), vomiting (14.0), back pain (12.0%) and dyspnea (12.0%). Headache, hypokalaemia, muscular chest pain, myalgia, pruritis and rash, each occurred at a frequency of 10.0%. The majority of these AEs were CTCAE grade 1 and 2.~~ ~~Grade 3 and 4 AEs were reported in 38.0% and 4.0% of patients, respectively. Of the grade 3 events, only the AST elevation event was reported as related to trial drug. The reported grade 4 AEs were 1 (2.0%) case of disease progression and 1 (2.0%) case of sepsis, neither of which was deemed treatment related.~~ ~~Consistent with the similar drug class labels, most immune related (irAEs) were reported in the GI, Skin and Endocrine SOCs. The majority of the irAEs were Grades 1 and 2, the only Grade 3 irAE was AST increase.~~

		~~Preliminary efficacy analyses for study 1381.1 indicate that there have been 6 patients with partial response (PR) and 20 patients with stable disease as best response on BI 754091 monotherapy in the 1381.1 trial. The PRs were reported in two patients with triple negative breast cancer, one patient with fallopian tube cancer, one patient with renal cancer, one patient with stomach cancer and one patient with endometrial cancer. All of these PRs occurred in patients receiving the 240 mg q3w dose of BI 754091.~~ ~~A similar safety profile of BI 754091 monotherapy was observed in 6 Japanese patients with solid tumors evaluated in the Asian trial 1381.4.~~ ~~The details of the preliminary analysis are provided in section 6.2 of the BI 754091 IB.~~ ~~BI 754091 has also been administered in combination with BI 754111 (monoclonal IgG4pro antibody targeting the human LAG-3) to 86 patients with advanced/metastatic solid tumors in trial 1381.2. Fifty five of these patients have been treated with 240 mg BI 754091 in combination with increasing doses of BI 754111 (Q3W). In the dose expansion portion of the study, 31 patients have been treated with 240 mg BI 754091 in combination with 600 mg BI 754111 Q3W.~~ ~~As of 30 November 2018, the combination treatment has been well tolerated with no DLTs occurring during the MTD evaluation period of the dose escalation part of the trial and no treatment related deaths have been reported. The most frequently reported AEs in patients treated with combination BI 754091 and BI 754111 were nausea (23.3%), fatigue (22.2%), diarrhoea (15.1%) and vomiting (15.1%). The majority of AEs were CTCAE Grades 1 and 2. Grade 3 and 4 AEs occurred at a frequency of 24.4% and 1.2 %, respectively. Of the grade 3 AEs, colitis, diarrhea (2 cases), infusion related reaction (2 cases), aseptic meningitis and maculopapular rash were reported as possibly related to study drugs. The only Grade 5 event was respiratory failure, occurring in the context of AEs pneumonia, sepsis and progressive disease. These events (including the fatal event) were unrelated to trial drugs.~~ ~~Infusion related reactions have been reported in approximately 7% of patients treated with the combination of BI 754091 and BI 754111, none reported with BI 754091 monotherapy. The majority of the events were reported in patients receiving 240 mg of BI 754091 in combination with 600 mg of BI 754111, with 2 events reported in patients receiving 240 mg of BI 754091 in combination with 20 mg of BI 754111. The majority were of CTCAE Grade 2. Two events were Grade 3 events and led to treatment discontinuation. The reported infusion related reactions occurred during the infusion mostly at cycle 2 or cycle 3.~~ ~~Preliminary efficacy data show 25 patients have achieved best response of stable disease (SD) to date and 3 patients have achieved best response of partial response (PR). PR was reported for 1 patient with anal cancer treated with 240mg BI 754091 in combination with 200 mg BI 754111, 1 patient with microsatellite stable rectal cancer treated with 240mg BI 754091 in combination with 600 mg BI 754111 and 1 patient with TNBC treated with 240mg BI 754091 in combination with 600 mg BI 754111.~~

		Based on ~~these~~ pre-clinical data~~,~~ as well as preliminary clinical data obtained with BI 754091 as well as the combination of BI 754091 and BI 754111, the inhibitory effects of the combination of BI 754111 and BI 754091 may translate into a clinical benefit in cancer patients.
Rationale for changes		More recent safety and efficacy information has been added to update the benefit risk section of the protocol. In addition, the risk of infusion related reactions has been described.
Section to be changed		3.3.3 Exclusion criteria
Description of change		4. Any investigational or anti-tumour treatment, **except BI 754091,** within 4 weeks or within 5 half-life periods (whichever is shorter) prior to the initiation of trial treatment.
Rationale for changes		Additional text has been added to clarify that prior use of BI 754091 is not exclusionary. This was previously communicated to sites in a protocol clarification letter dated 09 January 2019.
Section to be changed		4.2.2.1 Permitted concomitant medications
Description of change		• ~~Pre-medication will not be required, but may be utilised following the first dose of BI 754111 or the first dose of combination therapy, as appropriate. This includes medications for the management of nausea, diarrhoea, and vomiting for which the patient must be treated according to institutional standards.~~ • **To reduce the risk of infusion related reactions, patients are to be pre-treated with an antihistamine and acetaminophen or paracetamol. Pre-treatment should be administered at sufficient time prior to initiation of infusion to allow the agents to exert their effect.**
Rationale for changes		Pre-treatment medication has been added to the study prior to administration of the study treatment in order to reduce the risk of infusion related reactions.

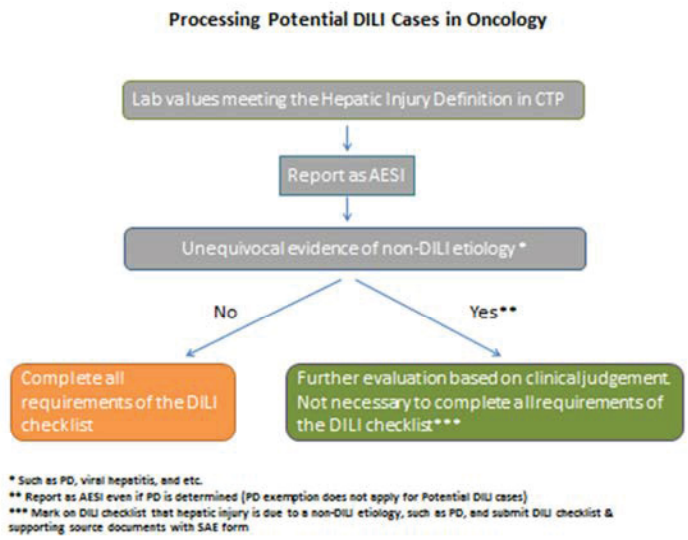
Section to be changed		[redacted]
Description of change		
Rationale for changes		

Section to be changed		5.3.4.2 Biochemistry
Description of change		**In case the criteria for hepatic injury are fulfilled, a number of additional measures will be performed (please see section 5.3.6.5.4 and the Potential DILI Checklist provided in the ISF) The amount of blood taken from the patient concerned will be increased due to this additional sampling.**
Rationale for changes		Language about drug-induced liver injury has been updated to clarify that the Potential DILI Checklist should always be completed when specified liver elevations occur.

Section to be changed		5.3.6.5 Adverse events of special interest (AESIs)
Description of change		For this trial, DLTs, infusion-related AEs, **potential** DILI events, hepatic injury, and qualifying irAEs, as defined in Appendix 10.2, are AESIs (see Section 5.3.6.5.2, Section 5.3.6.5.3, and Section 5.3.6.5.4).
Rationale for changes		Language about drug-induced liver injury has been updated per BI revised template text to clarify that all liver elevations meeting potential Hy's Law criteria require expedited reporting as an AESI on the SAE form

Section to be changed		5.3.6.5.3 Infusion-related reactions
Description of change		**To reduce the risk of infusion-related reactions, patients are to be pre-treated with an antihistamine and acetaminophen or paracetamol. Pre-treatment should be administered at sufficient time prior to initiation of infusion to allow the agents to exert their effect.**

		In the event of an infusion-related reaction ≤ Grade 2, **treat the symptoms accordingly with antihistamine or corticosteroids if needed. T**~~t~~he infusion rate of BI 754111 and/or the combination of BI 754111 plus BI 754091 may be decreased by 50% or interrupted until resolution of the event and re-initiated at 50% of the initial rate until completion of the infusion. In patients experiencing infusion-related reactions ≤ Grade 2, subsequent infusions may be administered at 50% of the initial rate. **If an infusion-related reaction is Grade 3 or higher in severity at any point during the study, permanently discontinue study drug(s).**
Rationale for changes		Pre-treatment medication has been added to the study prior to administration of the study treatment in order to reduce the risk of infusion related reactions. In addition, more detail has been provided on what to do in the event of a Grade 3 or higher infusion related reaction.
Section to be changed		5.3.6.5.4 Hepatic injury and drug-induced liver injury (DILI)
Description of change		5.3.6.5.4 Hepatic injury and **potential** drug-induced liver injury (DILI)
Rationale for changes		The section has been expanded to include potential DILIs.
Section to be changed		5.3.6.5.4 Hepatic injury and potential drug-induced liver injury (DILI)
Description of change		Hepatic injury definition: **A hepatic injury is defined by the following alterations of hepatic laboratory parameters:** • **an elevation of AST (Aspartate Aminotransferase) and/or ALT (Alanine Aminotransferase) ≥3 fold ULN combined with an elevation of total bilirubin ≥2 fold ULN measured in the same blood draw sample, or** • **aminotransferase (ALT, and/or AST) elevations ≥10 fold ULN.** ~~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.~~ **These lab findings constitute a hepatic injury alert and the patients showing these lab abnormalities need to be followed up according to the "Potential DILI Checklist" provided in the ISF.** **In case of clinical symptoms of hepatic injury (icterus, unexplained encephalopathy, unexplained coagulopathy, right upper quadrant abdominal pain, etc.) without lab results (ALT, AST, total bilirubin) available, the investigator should make sure these parameters are analysed, if necessary in an unscheduled blood test. Should the results meet the criteria of hepatic injury alert, the procedures described in the "Potential DILI Checklist" should be followed.**

Rationale for changes		Language about drug-induced liver injury has been updated to clarify the criteria for liver abnormalities which prompt reporting as AESI and completion of the Potential DILI Checklist.
Section to be changed		5.3.6.5.4 Hepatic injury and potential drug-induced liver injury (DILI)
Description of change		**Lab values meeting the hepatic injury definition will need to be reported as AESI. Please follow the flowchart below for reporting hepatic injury / potential DILI cases.** 
Rationale for changes		A decision tree is provided to illustrate when the Potential DILI Checklist is initiated and wen it can be considered complete.
Section to be changed		5.3.6.9 Pregnancy
Description of change		**Similarly, potential drug exposure during pregnancy must be reported if a partner of a male trial participant becomes pregnant. This requires a written consent of the pregnant partner; in the event that consent cannot be obtained, information will be collected and reported in accordance with regulatory requirements.**
Rationale for changes		Pregnancy risk language has been updated to provide guidance for partners of male trial participants.
Section to be changed		5.3.6.10 Exemptions to SAE Reporting
Description of change		5.3.6.10 Exemptions to **AE**/SAE Reporting
Rationale for changes		The header has been corrected to reflect the section content.

Section to be changed		7.1 INTERIM ANALYSES
Description of change		An interim futility analysis will be performed for Cohort G, I, and J in Part II. Until a decision from the futility analysis is made, the enrolment for that cohort will not be stopped. The two-stage design is planned to stop further enrolment if the defined efficacy boundary (see Table 7.7.2: 1 and Table 7.7.2: 3) is not met at the first stage. The interim analysis for Part II will be conducted when: • The last patient contributing to the interim analysis has completed the third on-treatment imaging assessment (i.e. end of cycle 6). If the last patient contributing to the interim analysis discontinues earlier than the third on-treatment imaging, the interim futility analysis will be done at approximately 4 months after the first administration of that patient.
Rationale for changes		The text provides detail about interim futility analyses added to the study for Cohorts G, I , and J.
Section to be changed		7.7.2 Determination of sample size for Part II
Description of change		For Cohorts G and I, **it is considered clinically meaningful based on the current literature for the combination of BI 754111 and BI 754091 to achieve an underlying ORR of 25%. A futility boundary of an ORR of 10% will be used for the interim analysis. Assuming an underlying ORR of 25%, the probability of observing <2 responders out of 20 patients and stopping at the interim is 2%, and the probability of observing an ORR ≥20% at the final analysis is 81%. Alternatively, assuming an underlying ORR of 5%, the probability of stopping at the interim is 74% and the probability of observing an ORR ≥20% at the final analysis is 0%. Table 7.7.2: 1 summarizes the early stopping criteria and probabilities of observing certain ORRs based on different assumptions of the underlying ORR.** ~~it is assumed that the combination of BI 754111 and BI 754091 will have an ORR of at least 25%. With 40 evaluable patients per cohort, an ORR of 20% or more would be observed with a probability of approximately 82% assuming a true response rate of 25%. The probability of observing a false positive signal, e.g., to observe at least an ORR of 20% if the underlying true ORR is 10%, is around 4%. Table 7.7.2: 1 summarizes the probability of observing certain ORRs based on different assumptions of the underlying ORR.~~ Table 7.7.2: 1 **Early stopping criteria and probabilities of the two-stage approach** ~~Probabilities of observing certain objective response rates~~ in Cohorts G and I

Assumed underlying ORR	Early stopping criterion (observed ORR)	Early stopping probability	Observed ORR at final analysis	Probability of observed ORR at final analysis
5%	**<10% (<2 out of 20)**	**74%**	**≥20% (≥8 out of 40)**	**0%**
10%	**<10% (<2 out of 20)**	**40%**	**≥20% (≥8 out of 40)**	**4%**

15%	**<10% (<2 out of 20)**	**18%**	**≥20% (≥8 out of 40)**	**24%**
20%	**<10% (<2 out of 20)**	**7%**	**≥20% (≥8 out of 40)**	**55%**
25%	**<10% (<2 out of 20)**	**2%**	**≥20% (≥8 out of 40)**	**81%**
30%	**<10% (<2 out of 20)**	**1%**	**≥20% (≥8 out of 40)**	**95%**

~~True underlying OR rate~~	~~Patients in each cohort~~	~~Probability to observe at least~~		
		~~ORR ≥ 20% (≥ 8 patients with OR)~~	~~ORR ≥ 25% (≥ 10 patients with OR)~~	~~ORR ≥ 30% (≥ 12 patients with OR)~~
~~40%~~	~~40~~	~~99.8%~~	~~98.4%~~	~~92.9%~~
~~35%~~	~~40~~	~~98.8%~~	~~93.6%~~	~~79.5%~~
~~30%~~	~~40~~	~~94.5%~~	~~80.4%~~	~~55.9%~~
~~25%~~	~~40~~	~~81.8%~~	~~56.0%~~	~~28.5%~~
~~20%~~	~~40~~	~~56.3%~~	~~26.8%~~	~~8.8%~~
~~15%~~	~~40~~	~~24.4%~~	~~6.7%~~	~~1.2%~~
~~10%~~	~~40~~	~~4.2%~~	~~0.5%~~	~~0.0%~~

For Cohort H, it is planned that 40 patients will be enrolled **and no interim futility analysis will be performed**.

Rationale for changes		The text provides detail about interim futility analyses added to the study for Cohorts G and I and clarifies that there will not be an interim futility analysis added for Cohort H.
Section to be changed		7.7.2 Determination of sample size for Part II
Description of change		For Cohort J, it is planned that a total of 40 patients will be enrolled, with a maximum of 10 patients with PD-L1 high expression (≥ 50% PD-L1). **In CheckMate 026, the ORR was 21% with nivolumab (N=101) compared with 26% in the chemotherapy group (N=81) for 1st line NSCLC patients with 1%≤ PD-L1 <50% (R19-0527). In KEYNOTE-189, the ORR was 48.4% (95% CI, 39.5-57.4) with pembrolizumab plus chemotherapy (N=128) compared with 20.7% (95% CI, 11.2-33.4) with chemotherapy alone (N=58) for patients with 1%≤ PD-L1 <50%; the ORR was 32.3% (95% CI, 24.3-41.2) with pembrolizumab plus chemotherapy (N=127) compared with 14.3% (95% CI, 6.7-25.4) with chemotherapy alone (N=63) for patients with PD-L1 <1% (P18-03589).** Based on the **above** ~~current~~ literature, it is deemed clinically meaningful if the underlying ORR for the combination of BI 754111 and BI 754091 will be 40% for patients with PD-L1 < 50%~~.~~**, and a futility boundary of 20% will be used for the interim analysis of this population in Cohort J. With 30-40 evaluable patients and assuming an underlying ORR of 40%, the probability of observing <4 responders out of 17 patients and stopping at the interim is 5%, and**

the probability of observing an ORR ≥35% at the final analysis is between 70% to 77%. Alternatively, assuming an underlying ORR of 15%, the probability of stopping at the interim is 76% and the probability of observing an ORR ≥35% at the final analysis is 0%. Table 7.7.2: 3 summarizes the early stopping criteria and probabilities of observing certain ORRs based on different assumptions of the underlying ORR. ~~With approximately 30 patients with PD-L1 <50%, an ORR of 35% or more would be observed with a probability of approximately 71% assuming a true response rate of 40%. The probability of observing a false positive signal, e.g., to observe at least an ORR of 35% if the underlying true ORR is 20%, is around 3%. Table 7.7.2.: 3 summarizes the probability of observing certain ORRs based on different assumptions of the underlying ORR.~~

Table 7.7.2.: 3 **Early stopping criteria and probabilities of the two-stage approach** ~~Probabilities of observing certain objective response rates~~ in Cohort J

Assumed underlying ORR	Early stopping criterion (observed ORR)	Early stopping probability	Observed ORR at final analysis	Probability of observed ORR at final analysis
Assuming 30 patients with PD-L1 <50%				
15%	**<20% (<4 out of 17)**	**76%**	**≥35% (≥11 out of 30)**	**0%**
20%	**<20% (<4 out of 17)**	**56%**	**≥35% (≥11 out of 30)**	**2%**
25%	**<20% (<4 out of 17)**	**36%**	**≥35% (≥11 out of 30)**	**10%**
30%	**<20% (<4 out of 17)**	**20%**	**≥35% (≥11 out of 30)**	**26%**
35%	**<20% (<4 out of 17)**	**11%**	**≥35% (≥11 out of 30)**	**48%**
40%	**<20% (<4 out of 17)**	**5%**	**≥35% (≥11 out of 30)**	**70%**
Assuming 40 patients with PD-L1 <50%				
15%	**<20% (<4 out of 17)**	**76%**	**≥35% (≥14 out of 40)**	**0%**
20%	**<20% (<4 out of**	**56%**	**≥35% (≥14 out**	**2%**

	17)		**of 40)**	
25%	**<20% (<4 out of 17)**	**36%**	**≥35% (≥14 out of 40)**	**10%**
30%	**<20% (<4 out of 17)**	**20%**	**≥35% (≥14 out of 40)**	**29%**
35%	**<20% (<4 out of 17)**	**11%**	**≥35% (≥14 out of 40)**	**54%**
40%	**<20% (<4 out of 17)**	**5%**	**≥35% (≥14 out of 40)**	**77%**

~~True underlying OR rate~~	~~Patients with PD-L1 <50%~~	~~Probability to observe at least~~	
		~~ORR ≥ 35% (≥ 11 patients with OR)~~	~~ORR ≥ 40% (≥ 12 patients with OR)~~
~~50%~~	~~30~~	~~95.1%~~	~~90.0%~~
~~45%~~	~~30~~	~~86.5%~~	~~76.7%~~
~~40%~~	~~30~~	~~70.9%~~	~~56.9%~~
~~35%~~	~~30~~	~~49.2%~~	~~34.5%~~
~~30%~~	~~30~~	~~27.0%~~	~~15.9%~~
~~25%~~	~~30~~	~~10.6%~~	~~5.1%~~
~~20%~~	~~30~~	~~2.6%~~	~~0.9%~~

Rationale for changes		The section is updated to outline the futility boundary for Cohort J.
Section to be changed		8.1 TRIAL APPROVAL, PATIENT INFORMATION, INFORMED CONSENT
Description of change		The Investigator **or delegate** 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 **or delegate** obtains written consent of the patient's own free will with the ICF after confirming that the patient understands the contents. The Investigator **or delegate** must sign (or place a seal on) and date the ICF.
Rationale for changes		Language has been added to allow a delegate review the study with patients prior to consent, rather than only allowing the Investigator to do this. If local laws/regulations/practice require Investigators personally consent patients, local laws/regulations/practice will be followed. This was previously communicated to sites in a protocol clarification letter dated 10 October 2018.

Section to be changed		9.1 PUBLISHED REFERENCES
Description of change		~~R16-4925 American Cancer Society. Cancer fact & figures 2016. http://www.cancer.org/acs/groups/content/@research/documents/document/acspc-0470-79.pdf (access date: 20 October); Atlanta: American Cancer Society 2016.~~
Rationale for changes		A duplicate reference has been removed from the list of references.
Section to be changed		9.1 PUBLISHED REFERENCES
Description of change		R19-0527 Carbone DP, Reck M, Paz-Ares L, Creelan B, Horn L, Steins M, et al, CheckMate 026 Investigators First-line nivolumab in stage IV or recurrent non-small-cell lung cancer. N Engl J Med 376 (25), 2415 - 2426 (2017).
Rationale for changes		A reference has been added to the study.
Section to be changed		10.2 MANAGEMENT OF IMMUNE-RELATED ADVERSE EVENTS
Description of change		• Infusion reactions: Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. **In the event of an infusion-related reaction ≤ Grade 2, treat the symptoms accordingly with antihistamine or corticosteroids if needed, the infusion rate of study drug(s) may be decreased by 50% or interrupted until resolution of the event and re-initiated at 50% of the initial rate until completion of the infusion. In patients experiencing infusion-related reactions ≤ Grade 2, subsequent infusions may be administered at 50% of the initial rate. If an infusion related reaction is Grade 3 or higher in severity at any point during the study, permanently discontinue study drug(s).**
Rationale for changes		More detail has been provided on what to do in the event of an infusion related reaction.

Number of global amendment		7
Date of CTP revision		05 Sept 2019
EudraCT number		2017-005042-29
BI Trial number		BI 1381.2
BI Investigational Product(s)		BI 754111 and BI 754091
Title of protocol (previous - see below for title update)		An open label, Phase I dose-finding study of BI 754111 in combination with BI 754091 in patients with advanced solid cancers followed by expansion cohorts at the selected dose of the combination in patients with non-small cell lung cancer and other solid tumors
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		
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 Diagnosis**
Description of change		Part II (Dose Expansion Cohorts): **Patients with a confirmed diagnosis of advanced, unresectable, and/or metastatic solid tumours of one of the following types:**
Rationale for changes		Text has been added to clarify the patient population to be enrolled.
Section to be changed		**Synopsis Main criteria for inclusion**
Description of change		**Part II (Dose-Expansion Cohorts):** All patients must have measurable disease according to RECIST Version 1.1, must have at least 1 tumour lesion amenable to biopsy, and must be medically fit and willing to undergo a biopsy before first treatment (if adequate archival tissue is not available) and, unless clinically contraindicated, after 6 weeks on therapy. ~~All patients must not have had previous LAG-3 targeted treatment~~ • 2nd or 3rd-line NSCLC patients: - Must have progressed on anti-PD-1 or anti-PD-L1 treatment after having achieved radiologically confirmed benefit (minimum of stable disease) - Must have had a minimum duration of benefit of ~~4~~8 months ~~for non-squamous NSCLC patients who received immunotherapy plus chemotherapy in a first line setting, or 6 months for all other patients~~, and minimum treatment duration of 2 months on the previous anti-PD-1 or anti-PD-L1 treatment without experiencing disease progression during that period. - The anti-PD-1- or anti-PD-L1-containing treatment must have been the latest treatment regimen prior to enrolling in this trial - Latest treatment must be within >4 and <12 weeks before their first dose in this trial. Patients who have had anti-PD-1 or anti-PD-L1 monotherapy as their first-line NSCLC treatment regimen must have a PD-L1 expression level of ≥1% at baseline (local validated testing).
Rationale for changes		The definition of stable disease is being updated to requires 4 months of prior benefit (instead of 8/6 months). The original definition was too restrictive resulting in patients that had experienced prior benefit from anti-PD-1 being excluded from the trial.
Section to be changed		Synopsis Endpoints and Section 5.1.2.2 Secondary endpoints of Part II (dose expansion) of the trial
Description of change		<u>Secondary Endpoints:</u> • Duration of response is the duration from the date of first documented PR or CR according to RECIST Version 1.1 as assessed by the Investigator to the date of PD or death. • Disease control (DC) (CR, PR, or stable disease [SD] according to RECIST Version 1.1, as assessed by the Investigator). • Progression-free survival (PFS) is the duration from the date of first treatment to the date of PD or death. • ~~PK parameters (C_{max} and AUC_{0-504}) will be calculated for BI 754111~~

		~~and BI 754091.~~ • Number of patients experiencing DLTs from start of treatment until end of treatment.
Rationale for changes		The secondary endpoints have been revised to more accurately reflect what endpoints are needed to meet the secondary objectives, and to clarify the PK parameters of the study.
Section to be changed		**Flow Chart 1**
Description of change		Footnote q has been added to troponin collection "q A measurement of troponin-I is to be performed if possible. If troponin-I cannot be measured, troponin-T can be measured instead as long as this is marked in the database. "
Rationale for changes		To allow for the measurement of troponin-T if the site is unable to assay troponin-I.
Section to be changed		**Flow Chart 1 and 2**
Description of change		Assessments will be performed by the Investigator at screening and every 2 cycles (6 weeks ±**5**~~3~~ days) for the first 6 months of treatment, once every 3 cycles (9 weeks ±**5**~~3~~ days) thereafter, at the EOT visit (if not performed within the previous 4 weeks), and at the discretion of the Investigator and copies may be collected by the sponsor or designee
Rationale for changes		The window of response assessments has been broadened from 3 to 5 days to allow more flexibility.
Section to be changed		**Flow Chart 2**
Description of change		Footnote r has been added to troponin collection "r A measurement of troponin-I is to be performed if possible. If troponin-I cannot be measured, troponin-T can be measured instead as long as this is marked in the database. "
Rationale for changes		To allow for the measurement of troponin-T if the site is unable to assay troponin-I.
Section to be changed		**Flow Chart 2**
Description of change		The "X" Vital Signs for Expansion Cycles 1, 2, and 4 Day 2 has been changed to X (C1).
Rationale for changes		Per footnote "p", "The clinic will telephone the patients on Days 2 and 4 of Cycle 2 and Day 2 of Cycle 4…". Therefore, vital signs would not be taken on Day 2 of Cycle 2 and Cycle 4.
Section to be changed		**Flow Chart 2**
Description of change		The "X" Vital Signs for Expansion Cycles 1, 2, and 4 Day 2 has been changed to X (C1, 4).
Rationale for changes		Per footnote "p", "The clinic will telephone the patients on Days 2 and 4

		of Cycle C and Day 2 of Cycle 4…". Therefore, vital signs would not be taken on Day 4 of Cycle 2.
Section to be changed		**Section 3.3.2 Inclusion Criteria**
Description of change		4. Part II (dose expansion): • Patients must have measurable disease per 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 (if adequate archival tissue is not available) and, unless clinically contraindicated, after 6 weeks on therapy. • Dose Expansion Cohorts: - Second and 3rd line NSCLC patients: • Must have progressed on anti-PD-1 or anti-PD-L1 treatment after having achieved radiologically confirmed benefit (minimum of stable disease) • Must have had a minimum duration of benefit of ~~8~~**4** months ~~for non-squamous NSCLC patients who received immunotherapy plus chemotherapy in a first line setting~~, or 6 months for all other patients, and minimum treatment duration of 2 months on the previous anti-PD-1 or anti-PD-L1 treatment without experiencing disease progression during that period.
Rationale for changes		The definition of stable disease is being updated to requires 4 months of prior benefit (instead of 8/6 months). The original definition was too restrictive resulting in patients that had experienced prior benefit from anti-PD-1 being excluded from the trial.
Section to be changed		[redacted]
Description of change		

		[redacted]
Rationale for changes		

Section to be changed		**Section 5.3.4.2 Biochemistry**
Description of change		**A measurement of troponin-I is to be performed if possible. If troponin-I cannot be measured, troponin-T can be measured instead as long as this is marked in the database.**
Rationale for changes		To allow for the measurement of troponin-T if the site is unable to assay troponin-I.

Number of global amendment		8
Date of CTP revision		20 May 2020
EudraCT number		2017-005042-29
BI Trial number		BI 1381.2
BI Investigational Product(s)		BI 754111 and BI 754091
Title of protocol (previous - see below for title update)		An open label, Phase I dose-finding study of BI 754111 in combination with BI 754091 in patients with advanced solid cancers followed by expansion cohorts at the selected dose of the combination in patients with non-small cell lung cancer and other solid tumors
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		
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, Section 3.3.2 Inclusion Criteria 4**
Description of change		- Must be EGFR WT **and ALK WT (only applicable to patients with non-squamous NSCLC)**

		~~▪ ALK WT~~
Rationale for changes		The Sponsor acknowledges that patients with squamous NSCLC are not routinely tested for EGFR and ALK alterations since these are very rare in this histology and EGFR and ALK TKIs are not indicated as first line treatment option in this setting. The Sponsor will consider such patients to be included in the trial if the Investigator can document the squamous histology of the tumor and the standard of care at the institution does not include sequencing of such patients.
Section to be changed		**Synopsis, Section 3.3.2 Inclusion Criteria 4**
Description of change		**Regardless of** ~~Any~~ PD-L1 expression level.
Rationale for changes		This is to clarify that "any" PD-L1 expression includes 0%
Section to be changed		**Flowchart 2, Footnote f and Section 5.3.3 Electrocardiograms**
Description of change		Single digitalised ECGs **(or analog ECG if digital not available)** must be done….
Rationale for changes		With the addition of sites in EU, it is possible that some sites don't have digitized ECGs and in this case, analog ECG could be used
Section to be changed		**Section 2.3 Benefit-Risk Assessment**
Description of change		~~As of 30 November 2018, 50 patients with advanced/metastatic solid tumors have been treated with BI 754091 as monotherapy in the 1381.1 trial.~~ ~~The most frequently reported AEs (reported in >10% of the patients) were fatigue (40%), nausea (28.0%), decreased appetite (18.0%), arthralgia (16.0%), cough (16.0%), abdominal pain (14.0%), constipation (14.0%), diarrhea (14.0 %), vomiting (14.0), back pain (12.0%) and dyspnea (12.0%). Headache, hypokalaemia, muscular chest pain, myalgia, pruritis and rash, each occurred at a frequency of 10.0%. The majority of these AEs were CTCAE grade 1 and 2.~~ ~~Grade 3 and 4 AEs were reported in 38.0% and 4.0% of patients, respectively. Of the grade 3 events, only the AST elevation event was reported as related to trial drug. The reported grade 4 AEs were 1 (2.0%) case of disease progression and 1 (2.0%) case of sepsis, neither of which was deemed treatment related.~~ ~~Consistent with the similar drug class labels, most immune-related (irAEs) were reported in the GI, Skin and Endocrine SOCs. The majority of the irAEs were Grades 1 and 2, the only Grade 3 irAE was AST increase.~~ ~~Preliminary efficacy analyses for study 1381.1 indicate that there have been 6 patients with partial response (PR) and 20 patients with stable~~

		~~disease as best response on BI 754091 monotherapy in the 1381.1 trial. The PRs were reported in two patients with triple negative breast cancer, one patient with fallopian tube cancer, one patient with renal cancer, one patient with stomach cancer and one patient with endometrial cancer. All of these PRs occurred in patients receiving the 240 mg q3w dose of BI 754091.~~ ~~A similar safety profile of BI 754091 monotherapy was observed in 6 Japanese patients with solid tumors evaluated in the Asian trial 1381.4.~~ ~~The details of the preliminary analysis are provided in section 6.2 of the BI 754091 IB.~~ ~~BI 754091 has also been administered in combination with BI 754111 (monoclonal IgG4pro antibody targeting the human LAG-3) to 86 patients with advanced/metastatic solid tumors in trial 1381.2. Fifty five of these patients have been treated with 240 mg BI 754091 in combination with increasing doses of BI 754111 (Q3W). In the dose expansion portion of the study, 31 patients have been treated with 240 mg BI 754091 in combination with 600 mg BI 754111 Q3W.~~ ~~As of 30 November 2018, the combination treatment has been well tolerated with no DLTs occurring during the MTD evaluation period of the dose escalation part of the trial and no treatment related deaths have been reported. The most frequently reported AEs in patients treated with combination BI 754091 and BI 754111 were nausea (23.3%), fatigue (22.2%), diarrhoea (15.1%) and vomiting (15.1%). The majority of AEs were CTCAE Grades 1 and 2. Grade 3 and 4 AEs occurred at a frequency of 24.4% and 1.2 %, respectively. Of the grade 3 AEs, colitis, diarrhea (2 cases), infusion related reaction (2 cases), aseptic meningitis and maculopapular rash were reported as possibly related to study drugs. The only Grade 5 event was respiratory failure, occurring in the context of AEs pneumonia, sepsis and progressive disease. These events (including the fatal event) were unrelated to trial drugs.~~ ~~Infusion related reactions have been reported in approximately 7% of patients treated with the combination of BI 754091 and BI 754111, none reported with BI 754091 monotherapy. The majority of the events were reported in patients receiving 240 mg of BI 754091 in combination with 600 mg of BI 754111, with 2 events reported in patients receiving 240 mg of BI 754091 in combination with 20 mg of BI 754111. The majority were of CTCAE Grade 2. Two events were Grade 3 events and led to treatment discontinuation. The reported infusion related reactions occurred during the infusion mostly at cycle 2 or cycle 3.~~ ~~Preliminary efficacy data show 25 patients have achieved best response of stable disease (SD) to date and 3 patients have achieved best response of partial response (PR). PR was reported for 1 patient with anal cancer treated with 240mg BI 754091 in combination with 200 mg BI 754111, 1 patient with microsatellite stable rectal cancer treated with 240mg BI 754091 in combination with 600 mg BI 754111 and 1 patient with TNBC treated with 240mg BI 754091 in combination with 600 mg BI 754111.~~ Please refer to the current version of the BI 754111 Investigator Brochure

		for ~~further details~~ **the latest information on patients treated with BI 754111/BI 754091**. Based on ~~these~~ pre-clinical data~~,~~ as well as ~~preliminary~~ clinical data obtained with BI 754091 as well as the combination of BI 754091 and BI 754111, the inhibitory effects of the combination of BI 754111 and BI 754091 may translate into a clinical benefit in cancer patients. ~~Therefore, treatment with BI 754111 and BI 754091 is expected to provide patients with clinical benefit at an acceptable risk~~. The benefit/risk ratio continues to be considered positive for patients with advanced cancers.
Rationale for changes		The text was updated to include the most recent clinical data on the study drugs.
Section to be changed		**Section 3.3.3 Exclusion Criteria 7**
Description of change		**(only applicable to patients with non-squamous NSCLC)**
Rationale for changes		This additional text aligns exclusion criteria 5 with inclusion criteria 4
Section to be changed		**Section 6.2.1.2 Medical history**
Description of change		**For first line NSCLC cohort, in medical history, last tumor size measurements taken prior to screening in the trial will be collected where available.**
Rationale for changes		Collecting historical tumor size measurements to understand tumor growth kinetics in this patient population.
Section to be changed		**Section 7.4 Interim Analyses**
Description of change		**Data from 1381-0002 and 1381-0004 may be pooled for the interim futility decision making, if applicable. If considered necessary, an evaluation of the efficacy and safety aspects will be performed. Results of this evaluation will be documented and archived. If applicable, such an analysis will be defined in more detail in the TSAP** .
Rationale for changes		This provides an opportunity for pool analysis.

APPROVAL / SIGNATURE PAGE

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Document Name: clinical-trial-protocol-version-09

Title: An open label, Phase I dose-finding study of BI 754111 in combination with BI 754091 in patients with advanced solid cancers followed by expansion cohorts at the selected dose of the combination in patients with non-small cell lung cancer and other solid tumors

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval-Team Member Medicine	[redacted]	22 May 2020 17:24 CEST
Author-Trial Statistician		22 May 2020 19:15 CEST
Approval-Therapeutic Area [redacted]		25 May 2020 08:21 CEST
Author-Trial Clinical Pharmacokineticist		25 May 2020 09:54 CEST
Approval-Translational Medicine Expert		25 May 2020 16:50 CEST
Verification-Paper Signature Completion		09 Jun 2020 05:00 CEST
Verification-Paper Signature Completion		15 Jun 2020 16:54 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed