Clinical Trial Protocol

	Document Number:	**c21115267-03**
EudraCT No.:	2017-005046-30	
BI Trial No.:	1381-0003	
BI Investigational Product(s):	[^{89}Zr]Zr-BI 754111, BI 754091 and BI 754111	
Title:	An open label Phase I PET imaging study to investigate the bio-distribution and tumor uptake of [^{89}Zr]Zr-BI 754111 in patients with advanced non-small cell lung cancer and head and neck squamous cell carcinoma treated with BI 754111 in combination with BI 754091	
Lay Title:	This study tests how BI 754111 is distributed in patients with advanced non-small cell lung cancer or patients with head and neck cancer who are treated with BI 754091	
Clinical Phase:	Phase I	
Trial Clinical Monitor:	[redacted] Phone: [redacted] Fax: [redacted]	
Principal / Coordinating Investigators:	[redacted] PO box [redacted] Phone: [redacted] Fax: [redacted] [redacted] PO box [redacted] Phone: [redacted] Fax: [redacted]	
Status:	Final Protocol (Revised Protocol (based on global amendment 2))	
Version and Date:	**Version: 3.0**	**Date: 27 Jan 2020**

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name:	Boehringer Ingelheim
Finished product name:	N/A
Active ingredient name:	[^{89}Zr]Zr-BI 754111, BI 754111 and BI 754091
Protocol date:	01 August 2018
Revision date:	27 January 2020
Trial number:	1381-0003
Title of trial:	An open label Phase I PET imaging study to investigate the bio-distribution and tumor uptake of [^{89}Zr]Zr-BI 754111 in patients with advanced non-small cell lung cancer and head and neck squamous cell carcinoma treated with BI 754111 in combination with BI 754091
Principal Investigators:	[redacted] PO box [redacted] Tel: [redacted] Fax: [redacted] [redacted] PO box [redacted] Tel: [redacted] Fax: [redacted]
Trial site(s):	[redacted] PO box [redacted]
Clinical phase:	I
Trial rationale:	This trial will use a non-invasive method to determine tumor and tissue drug concentration and support Pharmacokinetics (PK) modelling. It will be evaluated whether [^{89}Zr]Zr-BI 754111 uptake may serve as a Positron Emission Tomography (PET) imaging based selection biomarker for Lymphocyte-Activation Gene 3 (LAG-3) overexpression within tumors as a potential resistance mechanism for preceding checkpoint inhibitor treatment
Trial objective(s):	The main objective of this study is to determine the biodistribution and intra-tumor accumulation of [^{89}Zr]Zr-BI 754111 at baseline and its change upon treatment
Trial endpoint(s):	Primary endpoint: Standardized uptake values (SUVs) of [^{89}Zr]Zr-BI 754111 for tumor uptake at baseline and post BI 754111 dose
Trial design:	This is an open-label, non-randomised study divided into two Parts • Part 1: dosimetry and feasibility assessment of [^{89}Zr]Zr-BI 754111 PET/ Computed Tomography (CT) • Part 2: assessment of tumor uptake of [^{89}Zr]Zr-BI 754111 at various doses of BI754111 treatment

	Both Parts include a baseline assessment and an on-treatment assessment of [^{89}Zr]Zr-BI 754111 tumor uptake. During the on-treatment assessment, it is planned to explore at least 2 doses of BI 754111. *The study will be performed in a staggered approach.* Part 2 will commence based on Study Monitoring Committee (SMC) decision after review of all available data from Part 1.
Total number of patients entered:	Up to 40 patients are planned to be entered in this trial
Number of patients on each treatment:	Part 1: up to 5 patients Part 2: up to 35 patients
Diagnosis:	• Patients with advanced or metastatic non small cell lung cancer (NSCLC) who have failed on or after preceding anti-programmed cell death protein-1 (PD-1) or anti-programmed death ligand-1 (PD-L1) based treatment with at least 3 months stable disease before progression • Patients with recurrent and metastatic head and neck squamous cell carcinoma (HNSCC) who have been treated with at least one previous systemic chemotherapy or are chemotherapy intolerant/unresponsive. Previous treatment with an anti PD-1/PD-L1 is allowed
Main criteria for inclusion:	• Adult patients of legal 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 • Must have at least one PET imageable and evaluable lesion of 20mm • Must have at least one tumor lesion amenable to biopsy. This lesion should be PET imageable and evaluable as defined above and the biopsy should be obtained before the first BI 754091 administration, unless medically contra-indicated. In the latter case, 25 4µm-sections from an archival biopsy taken at relapse after the previous treatment are acceptable • Must have evaluable lesion(s) according to Revised Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 and for cancer immunology trials (iRECIST) Patients with NSCLC: • must have histologically confirmed NSCLC • must have received anti-PD-1 or anti-PD-L1 as Part of last treatment with at least 3 months stable disease and are progressing on this anti-PD1/PD-L1 based treatment. Patients with HNSCC. • must have histologically confirmed, recurrent metastatic HNSCC • must have progressed after previous systemic chemotherapy, or not eligible for receiving standard (radio) chemotherapy. Previous treatment with an anti PD-1/PD-L1 is allowed.
Main criteria for exclusion:	No previous treatment with anti-lymphocyte-activation gene 3 (LAG-3; CD223) agents.
Test product(s):	[^{89}Zr]Zr-BI 754111, BI 754111 and BI 754091
dose:	• [^{89}Zr]Zr-BI 754111: Approximately 4mg - 37MBq other mass doses of BI 754111 may be explored to achieve optimal tumor uptake

	• BI 754111: Recommended dose for the expansion phase of trial 1381-0002. Other doses, in the range of the doses tested in the dose escalation Part of trial 1381-0002, may be applied at Cycle2. • BI 754091: 240mg Doses administration at Cycle1 (baseline assessment phase): • Cycle1 Day1: 1st administration of BI 754091 • No later than day8: 1st administration of [89Zr]Zr-BI 754111 Doses administration at cycle 2 (on-treatment phase) and further cycles: • Cycle 2 Day1: 1st administration of BI 754111 treatment in combination with BI 754091 followed by the 2nd administration of [89Zr]Zr-BI 754111 • In Part 2 during Cycle2, at least 2 different BI 754111 treatment doses in combination with BI 754091 will be assessed in patients tested positive for tumor LAG-3 expression • Cycle3 Day1 and further cycles: administration of the recommended expansion dose of BI 754111 treatment in combination with BI 754091
method and route of administration:	Intravenous infusion for BI 754111 and BI 754091 - once every 3 weeks Intravenous infusion for [^{89}Zr]Zr-BI 754111 - once at Cycle1 and, if applicable, once at Cycle2
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 sponsor
Statistical methods:	For both Parts of the study (Part 1 and Part 2) endpoints will be analysed by descriptive statistics. In Part 2, an exploratory analysis might be performed to model the association between BI 754111 treatment dose vs tumor uptake values (SUVs). These evaluations will be performed only if at least 3 different BI 754111 doses are investigated with a sufficient number of patients per dose (minimum of 3 patients per dose cohort). Association between tumor uptake and other imaging/efficacy or biomarker assessments will be investigated using generalized linear models. In addition, parameter-free correlation techniques, e.g. Kendall tau, will be provided where applicable. These analyses will be based on all data collected in the study.

FLOW CHART

Trial Periods	**Screening Period**	**Dosimetry and feasibility/specificity**					**Treatment Period**					**End of treatment**	**End of trial**
		Cycle 1(*): Baseline assessment phase					**Cycle 2(*): On-treatment assessment phase**				**Cycle 3 and further**	**Treatment stop**	**30-Day safety FU**
Visit	**Screening**	**C1V1**	**C1V2**	**C1V3**	**C1V4**	***C1V5[13]***	**C2V1**	**C2V2**	**C2V3**	***C2V4[13]***	**C3V1+**	**EOT**	**30dFU**
Days	**-15**	**Day 1**									**1**	**(***)**	**+30**
Time window for visits											**(±2)**	**(within 7days)**	**(+2)**
Informed consent(s)(**)	x												
Demographics	x												
Medical history (including documentation of disease	x												
Physical examination[1]	x	x	x				x				x	x	x
Vital signs[1]	x	x	x				x				x	x	x
ECOG performance status	x	x					x				x	x	x
Laboratory tests: hemato,	x	x[2]					x				x	x	x
Urinalysis	x	x[2]					x				x	x	
Pregnancy test for women of child-bearing potential (βHCG)	x	x[2]					x				x	x	
12 lead-ECG	x	x[2]					x				x[10]		
Review of in-/exclusion criteria	x												
FDG PET/CT	x[3-9]												
Administration of Pre-treatment medication[12]							*x*				*x*		
Infusion BI754091 treatment		x					x				x		
Infusion BI754111 treatment							x				x		
PK BI754111 blood sampling		x	x	x	*x*	*x*	x	x	x	*x*	x[6]	x	

Trial Periods	**Screening Period**	**Dosimetry and feasibility/specificity**					**Treatment Period**					**End of treatment**	**End of trial**
		Cycle 1(*): Baseline assessment phase					**Cycle 2(*): On-treatment assessment phase**				**Cycle 3 and further**	**Treatment stop**	**30-Day safety FU**
Visit	**Screening**	**C1V1**	**C1V2**	**C1V3**	**C1V4**	***C1V5[13]***	**C2V1**	**C2V2**	**C2V3**	***C2V4[13]***	**C3V1+**	**EOT**	**30dFU**
Days	**-15**	**Day 1**									**1**	**(***)**	**+30**
ADA BI754111 blood sampling		x					*x*				x[11]	x	
Tumor biopsy	x[4]					*x[4]*							
BM blood sample Immunophenotyping		x				x	x			x[5]	x[5]	x	
Infusion [^{89}Zr]Zr-BI 754111			x[7]				x[8]						
PK radioactivity blood sampling			x[7]	x[7]	x[7]	*x[7]*		x[8]	x[8]	*x[8]*			
[^{89}Zr]Zr-BI 754111 PET + low dose CT scans			(x[7])	x[7]	x[7]	*x[7]*		x[8]	x[8]	*x[8]*			
CT-scan for tumor assessment[9]	←within 28 days prior to 1st BI754111						Every 6 weeks for 6 months (then every 9 weeks)---→						
Adverse events/SAEs/AESIs	x												
Concomitant therapy	x												
Completion of patient Participation													x
Vital status collection (*****)													x

(*) All cycles will last for 21 days. Cycle1 starts with the first administration of anti-PD-1 treatment BI 754091. Specific PET scan procedures will take place only during Cycle1 (baseline assessment) and Cycle2 (on-treatment assessment).

(**) The informed consent for trial Participation should be signed prior to any trial procedure. Re-consenting may become necessary when new relevant information becomes available and should be conducted according to the sponsor's instructions. A separate informed consent should be signed for biobanking if agreed by the patient.

(***) When a decision is taken to discontinue all treatment drugs, the EOT visit should be done instead of the scheduled visit.

(****) After the individual patient's end of the trial the investigator should report only any occurrence of cancer of new histology, related SAEs and related AESIs of which the investigator may become aware of and only via the SAE form, please see Section 5.2.6.2.1.

(*****) Completion of patient Participation and vital status collection should also be completed if the patient withdraws prematurely following treatment start (see Section 3.3.3).

1. At days of any drug administration (incl. [^{89}Zr]Zr-BI 754111), a physical examination and vital signs (pre- and post infusions) are required.
2. Laboratory assessments (hemato, chemistry, urinalysis and pregnancy test) and 12-lead Electrocardiogram (ECG) do not need to be repeated at Day1 if performed at screening within 72 hours prior to first administration of anti-PD-1 treatment BI 754091.

3. Standard static diagnostic Fluorodeoxyglucose –Positron Emission Tomography (FDG-PET)/CT should be done at screening prior to first administration of anti-PD-1 treatment BI 754091. In case FDG-PET is coupled with the baseline tumor assessment, it should be done within 7 days prior to first BI 754091 administration.
4. Tumor biopsy: 2 core needle tumor biopsies (or equivalent) are to be taken from an imageable and evaluable lesion prior to first BI 754091 administration, unless medically contra-indicated. In the latter case, 25 4µm-sections from an archival biopsy taken at relapse after the previous treatment are acceptable. For PD-1/PD-L1 pre-treated patients, if available, 5 sections of an archived tumor biopsy taken prior to the anti-PD-1/PD-L1 treatment should be obtained. *Optional: one, if feasible, two biopsies (2 core needle biopsies each) are to be taken for autoradiography and Flow cytometry analysis within 48h after the last ^{89}Zr-BI 754111 PET scan of C1. The biopsies are to be taken from two different lesions based on the results of the PET scans: one lesion with tracer uptake (= positive) and one lesions without visible tracer uptake (= negative). See Section 5.4.1 for details.*
5. Biomarker (BM) blood sampling for immunophenotyping is to be done at Cycle1 Day1 *and Day7±1 day post [^{89}Zr]Zr-BI 754111* , at Cycle2 Day1 (prior to BI 754111 treatment infusion) *and Day 7± 1day post [^{89}Zr]Zr-BI 754111* (=Cycle 2 Day7± 1day for LAG-3 negative patients), Cycle3 Day1 and EOT. See Blood Sample Flow Chart for time schedule.
6. Blood sampling for BI 754111 PK concentration will be performed at Cycle1 "baseline assessment phase" (before [^{89}Zr]Zr-BI 754111 infusion, after [^{89}Zr]Zr-BI 754111 infusion and during the first *and each subsequent* PET scan procedure, at Cycle2 "on-treatment assessment phase" (*pre-treatment*, *after [^{89}Zr]Zr-BI 754111 infusion* and *at* each PET scans procedures, at Cycles *3*, 4, 7 (prior to BI 754111 treatment infusion) and at the EOT visit. See Blood Sample Flow Chart for a more detailed time schedule.
7. **Timing of baseline assessment procedures** for [^{89}Zr]Zr-BI 754111 PET scanning:
   - [^{89}Zr]Zr-BI 754111 is to be administered no later than day 8 (within day 1 to 8)
   - **Only for patient in Part 1:** PET/CT scan for dosimetry is to be done 1-2 hours after [^{89}Zr]Zr-BI 754111 administration
   - [^{89}Zr]Zr-BI 754111 PET for LAG-3 combined with low dose CT scan for tumor volume: 2 (before CTP 3.0)-*3(after CTP 3.0)* scans between 24 h and up to 7 days post [^{89}Zr]Zr-B I754111 injection
   - Blood sampling for radioactivity concentration: samples will be taken *post [^{89}Zr]Zr-BI 754111 injection and at* each [^{89}Zr]Zr-BI 754111 PET scanning. See Blood Sample Flow Chart for detailed time schedule.
8. **Timing of on-treatment assessement procedures** for [^{89}Zr]Zr-BI 754111 PET scanning:
   - [^{89}Zr]Zr-BI 754111 administration is to be done at day 1 following the administration of BI 754111/BI 754091 combined treatment
   - [^{89}Zr]Zr-BI 754111 PET for LAG-3 combined with low dose CT scan for tumor volume: 2 (before CTP 3.0)-*3(after CTP3.0)* scans between 24 h and up to 7 days post [^{89}Zr]Zr-BI 754111 administration
   - Blood sampling for radioactivity concentrations: samples will be taken *post [^{89}Zr]Zr-BI754111 injection and at* each [^{89}Zr]Zr-BI 754111 PET scanning. See Blood Sample Flow Chart for time schedule
9. Tumor assessment should be done according to RECIST 1.1 and iRECIST using CT-scan/MRI/PET. The baseline tumor assessment should be done within 28days prior to first administration of the anti-LAG-3 treatment BI754111.
   - If done at screening, the baseline RECIST/iRECIST tumor assessment should be performed within 7 days prior to first administration of anti-PD-1 treatment BI 754091 and can be combined with FDG-PET/CT
   - If done at C1, the baseline RECIST/iRECIST tumor assessment can be performed after the administration of [^{89}Zr]Zr-B I754111 in combination with a PET/CT scan assessment

     Thereafter, tumor assessment will be repeated every 6 weeks (+/-3 days) during the first 6 months and every 9 weeks (+/-3 days) thereafter. A tumor assessment should be done at EOT to confirm disease progression if not done earlier
10. 12-lead ECG is to be done at each Cycle until Cycle6 and every other Cycle thereafter (i.e at Cycle8, Cycle10…). It can be repeated when investigator deems it necessary.

11. Blood sampling for BI 754111 immunogenicity assessment (i.e. ADA determination) will be performed at Cycle1 "baseline assessment phase" within 1 week before [^{89}Zr]Zr-BI 754111 infusion*, at cycle 2,* at Cycle4 and Cycle7 (prior to BI 754111 treatment infusion) and at the EOT visit. See Blood Sample Flow Chart for time schedule.
12. *Pre-treatment (antihistamine and acetaminophen or paracetamol) should be administered at sufficient time prior to initiation of infusion to allow the agents to exert their influence*
13. *Visits only applicable after CTP v 3.0*

For further details on procedures, please refer to specific sections in the protocol.

BLOOD SAMPLE FLOW CHART

Table 1 Time schedule for PK, ADA and biomarker blood sampling in Cycle 1 *(before CTP amendment 2.0)*

Treatment Cycle	Visit	Time Point Description	PK BI 754111	ADA BI 754111	BM Immuno-pheno-typing	PK Radioactivity
1	1	Day 1, within 1 hour prior to BI 754091 infusion	x	x	x	
		BI 754091 infusion				
	2	within 8 days after BI 754091 infusion: **[^{89}Zr]Zr-BI 754111 infusion**				
		1 hour after [^{89}Zr]Zr-BI 754111 infusion	x			
		within 30 min **before Dosimetry PET scan***				x*
		1-2 hours after [^{89}Zr]Zr-BI 754111 infusion: **Dosimetry PET scan***				
	3	within 30 min **before PET scan 1**	x			
						x
		≥24hours post [^{89}Zr]Zr-BI 754111 **PET scan 1**				
	4	within 30 min **before PET scan 2**				x
					x	
		≤ 7 days post [^{89}Zr]Zr-BI 754111 **PET scan 2**				

* Only for patients in Part 1, not applicable in Part 2

ADA = anti-drug antibodies; PK = Pharmacokinetics; EOT = end of treatment

Table 2 Time schedule for PK, ADA and biomarker blood sampling in Cycle 2 and onwards *(before CTP amendment 2.0)*

Treatment Cycle	Visit	Time Point Description	PK BI 754111	ADA BI 754111	BM Immuno-pheno-typing	PK Radioactivity
2	1	Day 1, within 1 hour prior to BI 754091 + BI 754111 infusion			x	
		BI 754091 + BI 754111 infusion				
		after BI 754091 + BI 754111 infusion: **[^{89}Zr]Zr-BI 754111** infusion**				
		1 hour after [^{89}Zr]Zr-BI 754111 Infusion**	x**			
	2	within 30 min **before PET scan 1**	x**			
						x**
		≥24hours post [^{89}Zr]Zr-BI 754111 **PET scan 1**				
	3	within 30 min **before PET scan 2****	x**			
					x**	
						x**
		≤ 7 days post [^{89}Zr]Zr-BI 754111 **PET scan 2****				
3	1	Day 1, within 1 hour prior to BI 754091 + BI 754111 infusion			x	
4	1	Day 1, within 1 hour prior to BI 754091 + BI 754111 infusion	x	x		
7	1	Day 1, within 1 hour prior to BI 754091 + BI 754111 infusion	x	x		
EOT	EOT	at treatment discontinuation	x	x	x	

** These procedures are not applicable in Part 2 for patients with tumor tested negative for LAG-3 expression except the sample for immunophenotyping that should be taken at day7 (± 1day)

Table 3 Time schedule for PK, ADA and biomarker blood sampling in Cycle 1 *(after CTP amendment 2.0)*

Treatment Cycle	**Visit**	**Time Point Description**	**PK BI 754111**	**ADA BI 754111**	**BM Immuno-pheno-typing**	**PK Radioactivity**
1	1	within *3* hours prior to BI 754091 infusion	x	x	x	
		BI 754091 infusion				
	2	within 8 days after BI 754091 infusion: **[^{89}Zr]Zr-BI 754111 infusion**				
		+5 min post ***end of [^{89}Zr]Zr-BI 754111 infusion***	*x*			*x*
		+ 30 min post ***end of [^{89}Zr]Zr-BI 754111*** *infusion*	*x*			*x*
		+ 60 min post **end of [^{89}Zr]Zr-BI 754111** infusion	x			*x*
		+ 120 min post end of ***[^{89}Zr]Zr-BI 754111*** *infusion*	*x*			*x*
	3	*Planned time ~+24hs (within 1 to 2 days) post* [^{89}Zr]Zr-BI 754111 **PET scan 1**				
		within 30 min ***after*** **PET scan 1**	x			x
	4	*Planned time~+48hours (within 2 to 4 days)* post [^{89}Zr]Zr-BI 754111 **PET scan 2**				
		within 30 min **after PET scan 2**	*x*			x
	5	*Planned time~+96 hours (within 4 to 7 days) post [^{89}Zr]Zr-BI 754111* ***PET scan 3***				
		within 30 min ***after PET scan 3***	*x*			*x*
		At day 7± 1day			x	

ADA = anti-drug antibodies; PK = Pharmacokinetics; EOT = end of treatment

Table *4* Time schedule for PK, ADA and biomarker blood sampling in Cycle 2 and onwards *(after CTP amendment 2.0)*

Treatment Cycle	Visit	Time Point Description	PK BI 754111	ADA BI 754111	BM Immuno-pheno-typing	PK Radioactivity
2	1	within *3* hour prior to BI 754091 + BI 754111 infusion	*x*	*x*	x	
		BI 754091 + BI 754111 infusion				
		after BI 754091 + BI 754111 infusion: **[^{89}Zr]Zr-BI 754111** infusion**				
		*+5 min post **[^{89}Zr]Zr-BI 754111 infusion****	*x***			*x***
		*+30 min post **[^{89}Zr]Zr-BI 754111 infusion****	*x***			*x***
		+60 min post **[^{89}Zr]Zr-BI 754111 infusion****	x**			*x***
		*+120 min post **[^{89}Zr]Zr-BI 754111 infusion****	*x***			*x***
	2**	*Planned time ~+24hs (within 1 to 2 days)* post [^{89}Zr]Zr-BI 754111 **PET scan 1****				
		within 30 min ***after* PET scan 1****	x**			x**
	3**	*Planned time~+48hours (within 2 to 4 days)* post [^{89}Zr]Zr-BI 754111 **PET scan 2****				
		within 30 min ***after* PET scan 2****	x**			x**
	4**	*Planned time~+96 hours (within 4 to 7 days)* post [^{89}Zr]Zr-BI 754111 **PET scan 3****				
		within 30 min ***after* PET scan 3****	*x***			*x***
		At day 7± 1day			x	

Table *4* Time schedule for PK, ADA and biomarker blood sampling in Cycle 2 and onwards *(after CTP amendment 2.0)* (cont.)

Treatment Cycle	**Visit**	**Time Point Description**	**PK BI 754111**	**ADA BI 754111**	**BM Immuno-pheno-typing**	**PK Radioactivity**
3	1	within 1 hour prior to BI 754091 + BI 754111 infusion	*x*		x	
4	1	within 1 hour prior to BI 754091 + BI 754111 infusion	x	x		
7	1	within 1 hour prior to BI 754091 + BI 754111 infusion	x	x		
EOT	EOT	at treatment discontinuation	x	x	x	

** These *visits and* procedures are not applicable in Part 2 **for patients with tumor tested negative for LAG-3 expression** except the sample for immunophenotyping that should be taken at day7 (± 1day)

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ABBREVIATIONS

ADA	Anti-Drug Antibodies
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine aminotransferase
AST	AsPartate aminotransferase
AUC	Area under the Curve
β-hCG	Beta human chorionic gonadotropin
BI	Boehringer Ingelheim
BM	Biomarker
BOR	Best Overall Response
Bx	Tumor Biopsy
C	Cycle
CA	Competent Authority
CCMO	Centrale Commissie Mensgebonden Onderzoek
CI	Confidence Interval
CKD-EPI	Chronic Kidney Disease Epidemiology
CL	Total clearance of the analyte in plasma following intravascular administration
CML	Clinical Monitor Local
CPK	Creatinine Phosphokinase
CR	Complete Response
CRA	Clinical Research Associate
CRF	Case Report Form, paper or electrocic (sometimes referred to as “eCRF”)
CT scan	Computed Tomography scan
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	Cytotoxic T-lymphocyte-associated protein 4
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
D	Day
DHEA	Dehydroepiandrosterone
DILI	Drug Induced Liver Injury
DLT	Dose Limiting Toxicities
EANM	European Association of Nuclear Medicine
EC	Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eDC	Electronic Data Capture
e.g.	for example
eGFR	estimated Glomerular Filtration Rate
EOT	End Of Treatment
EU	European Union
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration
FC	Flow Chart

FDG-PET	Fluorodeoxyglucose –Positron Emission Tomography
FFPE	Formalin Fixed Paraffin Embedded
FU	Follow-up
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GI	Gastro-intestinal
HNSCC	Head and Neck Squamous Cell Carcinoma
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ICRP	International Commission on Radiological Protection'
iCPD	Confirmed Progression as per iRECIST
i.e.	that is
IEC	Independent Ethics Committee
IFN	Interferon
IHC	Immunohistochemistry
IMPD	Investigational Medicinal Product Documentation
INR	International Normalized Ratio
irAEs	immune-related Adverse Events
IRB	Institutional Review Board
IPV	Important Protocol Violation
ISF	Investigator Site File
IUD	Intrauterine Device
iUPD	Unconfirmed Progression as per iRECIST
IUS	Intrauterine hormone-releasing System
i.v.	intravenous
LAG-3	Lymphocyte-Activation Gene 3
LDH	Lactate dehydrogenase
LPDD	Last Patient Drug Discontinuation
mAb	Monoclonal Antibody
MBq	Megabecquerel
MedDRA	Medical Dictionary for Drug Regulatory Activities
MDSC	Myeloid-Derived Suppressor Cell
METc	Medisch-Ethische Toetsingscommissies
MHC-II	Major Histocompatibility Complex Class II
MRI	Magnetic Resonance Imaging
mSv	Millisievert
MTD	Maximum Tolerated Dose
NK	Natural Killer
NLNT	New Lesion-Non-Target
NLT	New Lesions-Target
NSCLC	Non-Small-Cell Lung Cancer
OPU	Operating Unit
OR	Overall Response/Objective Response
ORR	Overall Response Rate/Objective Response Rate
PBPK	Physiologically based pharmacokinetic
PD	Progressive Disease

PD-1	Programmed cell death protein-1
PD-L1/-L2	Programmed death ligand-1/-2
PET	Positron Emission Tomography
PK	Pharmacokinetics
RPIID	Recommended Phase II Dose
PR	Partial Response
QTc	Corrected QT interval
Q3W	Every 3 weeks
RECIST	Response Evaluation Criteria in Solid Tumours
iRECIST	Modified Response Evaluation Criteria in Solid Tumours (RECIST 1.1) for cancer immunology trials
ROI	Regions of Interest
RP2D	Recommended Phase 2 Dose
SAE	Serious Adverse Event
SD	Stable Disease
SMC	Study Monitoring Committee
SOC	Standard of Care
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reactions
SUVs	Standardized Uptake Values
TCM	Trial Clinical Monitor
TILs	Tumor-infiltrating lymphocytes
TNBC	Triple Negative Breast Cancer
TNM	TNM Classification of Malignant Tumours
TP	Time Point
T-reg	Regulatory T-cell
TS	Treated Set
TSAP	Trial Statistical Analysis Plan
TSH	Thyroid Panel
ULN	Upper Limit of Normal
V	Visit
[redacted]	
WHO	World Health Organization
WMA	World Medical Association
WOCBP	Woman of childbearing potential
Zr	Zirconium

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).

LAG-3 expression has been reported to be associated with advanced head and neck squamous cell carcinoma (HNSCC). Its expression has been found to be upregulated on tumor-infiltrating lymphocytes (TILs) and was significantly associated with a high pathological grade, larger tumor size and positive lymph node status. Increased LAG-3 expression was

also found in recurrent HNSCC and metastatic lymph nodes hinting to a function of LAG-3 in tumor recurrence and metastasis (R18-1377).
Tumors use the immune-checkpoint pathways (such as the PD-1 and LAG-3 pathways) to evade anti-tumor immune responses. Tumor-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 tumor microenvironment.

Engagement of the co-inhibitory receptors PD-1 and LAG-3 by their respective ligands inhibits T-cell function preventing an anti-tumor 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 antitumor immune response leading to tumor growth inhibition in some patients. Treatment of patients with advanced melanoma, non-small-cell lung cancer (NSCLC), renal cell carcinoma, and many other tumor 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)

The therapeutic efficacy of mAbs including those modulating the immune system and the cancer immune phenotype do not only depend on the specific target, the avidity and effector function of the antibodies but most importantly also on the degree of their uptake and distribution within tumor lesion(s). The latter is mainly influenced by the heterogenous nature of the tumor tissue, e.g. heterogeneity of tumor blood flow, interstitial flow and pressure, hypoxia, necrosis (R18-2174, R18-2173). Positron emission tomography (PET using zirconium-89 [^{89}Zr]-labeled mAbs is an attractive non-invasive method to improve the understanding of the in vivo behavior and distribution of the monoclonal antibody allowing to (1) confirm and quantify tumor uptake of mAbs; (2) learn about uptake in critical normal organs to anticipate toxicity; and (3) elucidate the interpatient variations in pharmacokinetics and tumor targeting. The PET Center at [redacted] has a longstanding experience in performing ^{89}Zr-immuno-PET trials (P18-06060, R18-2168, R18-2169, R18-2170, R18-2171).

This is the first study that aims to determine the tissue and tumor distribution of the anti-LAG-3 mAb BI 754111. BI 754111 has been radio-labelled with Zr-89. [^{89}Zr]Zr-BI 754111 will be administered during Cycle 1 before any administration of anti-LAG-3 mAb (BI 754111) treatment to determine its distribution and tumor uptake. A second administration of [^{89}Zr]Zr-BI 754111 will occur at the beginning of Cycle 2 (Cycle2 Day1) directly following the first administration of a certain dose of anti-LAG-3 mAb BI 754111. The tissue distribution of [^{89}Zr]Zr-BI 754111 will be monitored using a PET/CT scanner at multiple time points after [^{89}Zr]Zr-BI 754111 and after [^{89}Zr]Zr-BI 754111 + BI 754111 administration respectively. The data from the study will be used to determine the distribution of BI 754111 to the organs in the body and to tumorous tissue(s) in order to support dose finding and physiologically based pharmacokinetic (PBPK) modelling of the BI 754111 treatment.
The trial is divided into two Parts. After confirmation of the blockade of the [^{89}Zr]Zr-

BI 754111 uptake by a therapeutic dose of BI 754111, the second Part of the study will be performed.
This second Part will assess the tumor uptake of [^{89}Zr]Zr-BI 754111 in combination with various treatment doses of BI 754111. Various doses of BI 754111will be used to determine the best ratio of [^{89}Zr]Zr-BI 754111/BI 754111 to achieve an optimal tumor penetration. Furthermore, it should also explore the relation between tumor uptake of [^{89}Zr]Zr-BI 754111 at baseline and tumor response after adding a therapeutic dose of BI 754111 to the anti-PD1 therapy.

1.2 DRUG PROFILE

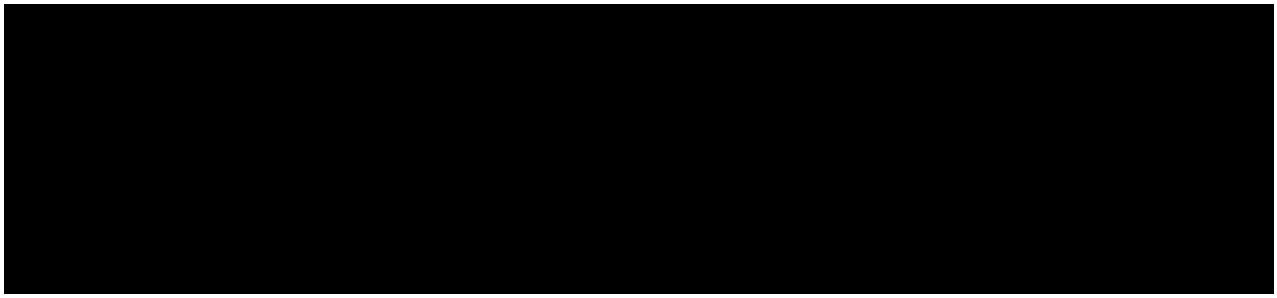
1.2.1 BI 754111

BI 754111 is a humanised IgG4Pro mAb against LAG-3 that is being developed as an intravenous (i.v.) infusion for the treatment of cancer. BI 754111 has highly human frameworks and a low predicted immunogenicity score. 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 [89Zr]Zr-BI 754111

BI 754111 has been radiolabeled with Zr-89 using p-isothiocyanatobenzyl-desferrioxamine (Df–Bz–NCS) as a chelate. [^{89}Zr]Zr-BI 754111 was prepared according to a standard procedure (R18-1541). For a more detailed descriptions of [^{89}Zr]Zr-BI 754111 please refer to to the current BI 754111 Investigator's Brochure (IB) and the related Investigational Medicinal Product Documentation (IMPD).

1.2.3 BI 754091



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

1.3 RATIONALE FOR PERFORMING THE TRIAL

Most patients with locally advanced or metastatic tumors 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-tumor activity and improved clinical outcome in a higher percentage of patients 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 LAG-3. This over expression of other checkpoint inhibitors may represent an escape pathway from the PD-1 pathway blockade. Therefore, it is possible that blocking multiple checkpoint inhibitors at the same time would lead to better response and potentially rescue some of the patients that have failed the PD-1 single-agent blockade, including patient with NSCLC (R15-3696, R16-0852, R16-0868, R16-0881, R16-2707, R16-5335, R16-5545). Multiple immune-checkpoint inhibitor combinations are currently in development including the combination of anti-PD-1 and anti-LAG-3 mAbs with encouraging preliminary results (R16-5204, R16-5218).

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

Still, some aspects of LAG-3 expression and BI 754111 biodistribution (inside and outside the tumor lesions) remain unclear. For example, it is unclear which patients may benefit from combining anti-LAG-3 and anti-PD1/anti-PDL1 therapies. Even though tumor LAG-3 expression assessed on biopsies may serve as a predictive biomarker, this has limitations such as difficult to reach sites, low yields of tumor cells in the obtained bioptic sample, tumor heterogeneity resulting in sampling bias and risks for complications of the bioptic procedure (pneumothorax, bleeding). A non-invasive and more comprehensive way to study the expression of LAG-3 and the kinetic behavior of BI 754111 is needed. PET using radiolabeled BI 754111, i.e. [^{89}Zr]Zr-BI 754111, as tracer may offer a unique way of studying the interaction between LAG-3 expression and BI 754111 distribution. This non-invasive and repeatable technique may allow for studying the spatial and temporal variations in uptake of BI 754111.

Therefore, the aim of this study is to evaluate [^{89}Zr]Zr-BI 754111 PET imaging as a non-invasive method to determine the biodistribution of the therapeutic antibody at the site of action (i.e. in the tumor) and as a non-invasive method to determine LAG-3 expression at the site of action (i.e. in the tumor). These readouts are considered supportive to inform BI 754111 dose finding and potentially also for future patient selection.

Another aim of this study is to explore whether an association can be established between the tumor [^{89}Zr]Zr-BI 754111 uptake at baseline and the anti-tumor efficacy of BI 754111 therapy when combined with the anti-PD-1 BI 754091. It is assumed that [^{89}Zr]Zr-BI 754111 uptake will be related to LAG-3 expression. In addition, additional markers for the status of the immune system before/during therapy will be assessed in biopsies and blood samples to allow for better interpretation of the impact of LAG-3 overexpression as determined by LAG-3 immune PET in the context of other potential mechanisms of resistance. The combination of the major resistance mechanisms may vary in each patient.

While LAG-3 is not expressed on peripheral T-cells in healthy volunteers or most patients with solid tumors, it appears to be expressed on T-cells of patients with HNSCC (R18-1377). In NSCLC tumors that responded to anti-PD-1/anti-PD-L1 therapy, increase in LAG-3 expression may be a mechanism of acquired resistance to anti-PD-1/PD-L1 therapy. Therefore, intratumoral expression of LAG-3 may be a good enrichment marker for patient selection for PD-1/LAG-3 combination therapy. Hence, in this study, we will include patients with HNSCC and NSCLC (upon progression after an initial response to anti-PD-1/anti-PD-L1 therapy) in order to measure LAG-3 receptor occupancy in this patient population.

The therapeutic benefit or specific adverse events in patients cannot always be anticipated during the trial setup. Later on there may be new scientific knowledge about biomarkers and other factors contributing to diseases or the action of a drug. In order to be able to address future scientific questions, patients will be asked to voluntarily donate biospecimens for banking (please see Section 5.4). If the patient agrees, banked samples may be used for future biomarker research and drug development projects, e.g. to identify patients that are more likely to benefit from a treatment or experience an adverse event (AE), or to gain a mechanistic or genetic understanding of drug effects and thereby better match patients with therapies.

1.4 BENEFIT - RISK ASSESSMENT

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

Data from immune-checkpoint clinical trials show that irAEs occur frequently in patients treated with anti Cytotoxic T-lymphocyte-associated protein 4 (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). The irAEs affect mainly the gastrointestinal tract (including diarrhea 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 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.

Preliminary efficacy analyses indicate that there are *6* patients with Partial response (PR) and *20* patients with disease stabilization on BI 754091 monotherapy in the 1381-0001. The PRs were reported in 2 patients with triple negative breast cancer, 1 patient with fallopian tube cancer, 1 patient with renal cancer, 1 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.

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 240 mg BI 754091 in combination with 200 mg BI 754111, 1 patient with microsatellite stable rectal cancer treated with 240 mg BI 754091 in combination with 600 mg BI 754111 and 1 patient with Triple Negative Breast Cancer (TNBC) treated with 240 mg BI 754091 in combination with 600 mg BI 754111.

Based on these pre-clinical and clinical data treatment with BI 754111 and BI 754091 is expected to provide patients with clinical benefit at an acceptable risk.

Risk linked to radiation burden: A single injection of 37 MBq 89Zr-mAb is expected to result in a radiation burden of ~ 20 mSv. In addition, every low dose CT scan adds 3 mSv to the radiation burden.
The first 3 patients in part 1 of the study will receive 2 injections of 89Zr-mAb followed by 5 PET scans (3 after the first and 2 after the second injection). This results in a radiation dose of 55 mSv.
The following patients in part 1 (maximum 2) will receive 2 injections of 89Zr-mAb followed by 4 PET scans. This results in a radiation dose of 52 mSv.
After administration, no shielding is required, and the subject can go home immediately. It is recommended that prolonged physical contact with small children (hugging, holding for more than a few hours per day) is avoided in the days following injection of 89Zr-mAb.
In part 2 five LAG-3 negative patients will receive 1 injection of 89Zr-mAb followed by 2 (before CTP 3.0*) or 3 (after CTP 3.0)* PET scans. This results in a radiation dose of 26 *or 29* mSv.

In part 2 up to 30 LAG-3 positive patients will receive 2 injections of 89Zr-mAb followed by 4 (before CTP 3.0*) or 6 (after CTP 3.0)* PET scans. This results in a radiation dose of 52 *or 58* mSv.

All patients in this trial will undergo a diagnostic [^{18}F]FDG-PET with a dose of 200 MBq, resulting in a radiation burden of 4 mSv, followed by a low dose CT of 3 mSv. Patients for whom FDG-PET is not part of standard of care, this will add 7 mSv to the total radiation dose related to the study.

Overall, the total radiation dose will represent 52 to 65 mSv.

Optimalisation of the radiation dose is achieved via splitting of the protocol in two parts.
Optimal mAb dose for imaging will be established in part 1, whereafter the patients in part 2 will be imaged at this optimal dose.
In order to ensure the accuracy of quantitation, 37 MBq is the minimum level of activity that can be used per injection.
There are no risk increasing / decreasing factors.
Justification of this study is provided through the intended benefit of mitigating serious diseases in the future (category 3b).
In conclusion, the radiation burden for this study has been optimized, is justified and falls within the dose limits as discussed in NCS-26/ICRP-62 (R18-2184)

Even so, patients should be advised of the potential risks of side effects from investigational trial treatments. While some may be anticipated, others may be rare and unknown with irreversible and/or life-threatening effects. Patients should also be advised that there are other unknown risks associated with Participation in a clinical trial.

Although rare, a potential for drug-induced liver injury (DILI) is under constant surveillance by sponsors and regulators. Therefore, this trial requires timely detection, evaluation, and follow-up of laboratory alterations in selected liver laboratory parameters to ensure patients´ safety, see also Section 5.2.6, adverse events of special interest (AESI).

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

2.1.1 Main objective(s)

The main objective of this study is to determine the biodistribution and intra-tumor accumulation of [^{89}Zr]Zr-BI 754111 at baseline and its change upon treatment.

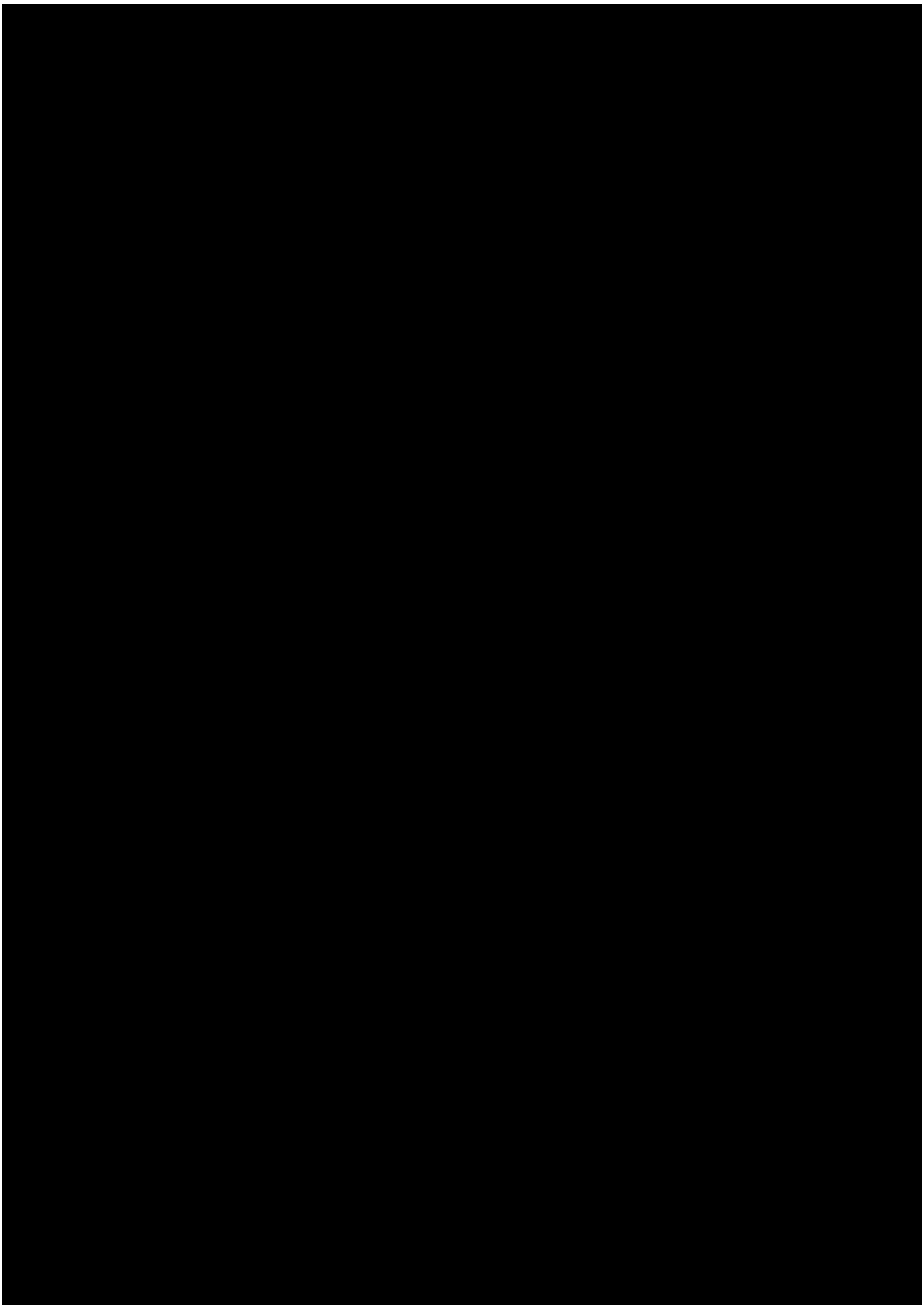
2.1.2 Primary endpoint(s)

The primary endpoint of this study is:
Standardized uptake values (SUVs) of [^{89}Zr]Zr-BI 754111 for tumor uptake at baseline (Cycle1) and post BI 754111 dose (up to Cycle2 Day8)

2.1.3 Secondary endpoint(s)

There is no secondary endpoint in this study.

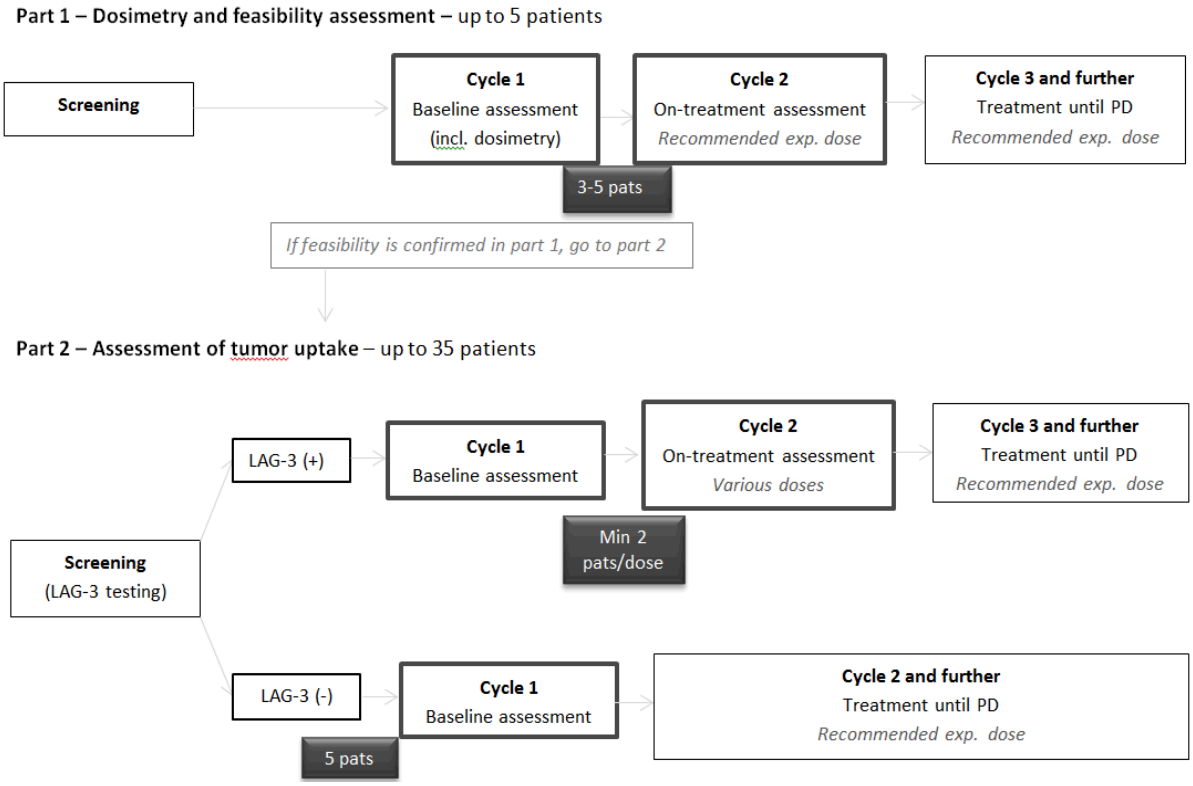
[redacted]



3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

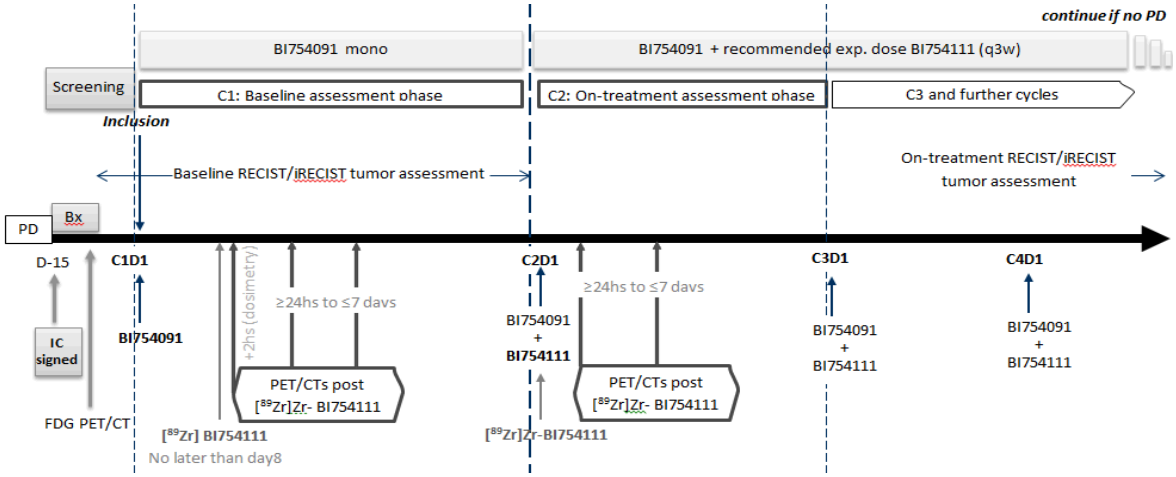
This is a Phase I open label, non-randomized bio-distribution trial to be conducted in one specialized center. The trial is divided in 2 Parts as described below in Figure 3.1:1 and will be conducted in a staggered approach.



Recommended exp. dose is the BI 754111 dose recommended for the expansion phase of trial 1381-0002.

Figure 3.1: 1 Overall design

- **Part 1** is intended to assess the dosimetry of [^{89}Zr]Zr-BI 754111, to optimize the imaging time window and the feasibility of [^{89}Zr]Zr-BI 754111 PET to assess tumor distribution and uptake of BI 754111. The BI 754111 dose administered in this Part will be the dose recommended for the expansion phase of trial 1381-0002. The whole body biodistribution of [^{89}Zr]Zr-BI 754111 will be assessed and optimal tumor uptake parameters will be developed. See Figure 3.1: 2.



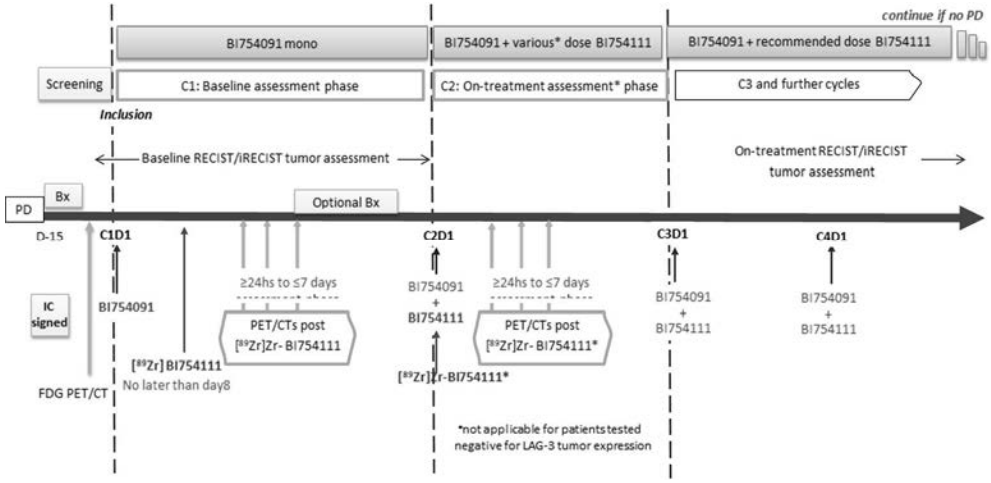
PD= Progression of Disease Bx=Tumor Biopsy

Figure 3.1: 2 Part 1: dosimetry and feasibility assessment

- **Part 2** will be initiated following a positive SMC decision after review of all available data from Part 1 in order to assess whether a blockade of [^{89}Zr]Zr-BI 754111 has been demonstrated. Patients will be tested for tumor LAG-3 expression at screening. During cycle 1, all patients will undergo baseline PET assessments. During cycle 2 (on-treatment PET assessment), at least 2 doses levels of BI 754111 treatment will be explored in patients tested positive for tumor LAG-3 expression. At least 2 patients should be included per dose cohort. See Figure 3.1: 3.

Up to five patients tested negative for LAG-3 expression will be included in Part 2. These patients will not be part of dose exploration but will be offered treatment with BI 754111 at the dose recommended for the expansion phase of trial 1381-0002. Hence, they will not undergo the on-treatment PET/CT assessment procedures.

After cycle 2, all patients will be treated at the recommended dose.



PD= Progression of Disease Bx=tumor biopsy *PET/CT post [^{89}Zr]Zr-BI 754111: 2 before CTP 3.0, 3 after CTP 3.0*

Figure 3.1: 3 Part 2: assessment of tumor uptake

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

Part 1 will assess the feasibility of the methods. The patients included in Part 1 will have a [^{89}Zr]Zr-BI 754111 infusion for a baseline PET assessment (prior to first BI 754111 treatment) at Cycle1 and another [^{89}Zr]Zr-BI 754111 infusion for on-treatment PET assessment (following first BI 754111 treatment) at Cycle2. The baseline PET assessment will include a dosimetry to investigate the tracer ([^{89}Zr]Zr-BI 754111) dose. During the on-treatment PET assessment, the patients will be administered the dose of BI 754111 recommended for the expansion phase of trial 1381-0002. This dose of BI 754111 treatment will be tested first to evaluate whether a blockade of the [^{89}Zr]Zr-BI 754111 is possible.

It is estimated that up to 5 patients will be included in Part 1.
The data obtained from these patients will be analysed and reviewed on a regular basis by the SMC. During the SMC reviews, the mass dose of [^{89}Zr]Zr-BI 754111 might be adapted as needed *based on all imaging data available*. Part 2 will commence based on SMC decision after review of all available data from Part 1.

Part 2 will assess the tumor uptake of [^{89}Zr]Zr-BI 754111. The patients will be prospectively tested for LAG-3 tumor expression.
The patient tested positive for LAG-3 tumor expression will be included in different dose-cohorts, each cohort exploring one dose of BI 754111 treatment during cycle 2. It is planned to explore at least 2 doses of BI 754111 treatment in this study. At least 2 patients with LAG-3 expressing tumor are needed in each dose cohort in order to assess the degree of blockade of [^{89}Zr]Zr-BI 754111 uptake upon a certain BI 754111 dose.
A cohort of maximum 5 patients tested negative for LAG-3 expression will be included in Part 2. These patients will undergo the baseline PET assessment for [^{89}Zr]Zr-BI 754111 tumor uptake but they will not be considered for dose exploration and will not proceed for the on-treatment PET assessment.

For each patient in Part 2, *the cold dose BI 754091 necessary to optimize [^{89}Zr]Zr-BI 754111*, the dose of BI 754111 treatment to be applied at cycle 2 and the imaging timepoints will be confirmed by the SMC with reference to the data available.

Up to 35 patients might need to be included in Part 2.

In both Parts:
At screening, all patients should provide two core needle tumor biopsies for LAG-3 IHC testing. These two core needle tumor biopsies (or equivalent) are to be taken from a PET-imageable and evaluable lesion prior to first BI 754091 administration

All patients will be administered the anti-PD-1 treatment BI 754091 alone at day 1 of cycle 1. Thereafter, the anti-LAG-3 treatment BI 754111 will be added to BI 754091 at day 1 of cycle 2 and this combination treatment will be administered on the first day of each cycle.

3.3 SELECTION OF TRIAL POPULATION

Up to 40 patients will be recruited into this trial.
A log of all patients enrolled into the trial (i.e. who have signed informed consent) will be maintained in the Investigator Site File (ISF) at the investigational site irrespective of whether they have been treated with investigational drug or not.
If a patient is enrolled in error (does not meet all inclusion criteria or meets one or more exclusion criteria on the day of enrolment), the sponsor should be contacted immediately.

3.3.1 Main diagnosis for trial entry

This trial will include patients with:

- NSCLC: Patients with advanced or metastatic disease who have failed on or after preceding anti-PD-1 or anti-PD-L1 based treatment with at least 3 months stable disease before progression
- HNSCC: Patients with recurrent and metastatic disease who have been treated with at least one previous systemic chemotherapy or are chemotherapy intolerant/unresponsive (previous treatment with anti- PD-1/ PD-L1 is allowed).

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

3.3.2 Inclusion criteria

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

1. Provision of signed and dated, written Informed Consent Form (ICF) prior to any trial-specific procedures, sampling, or analyses
2. Patients of legal age (according to local legislation) at the time of signature of the ICF
3. Patients with histologically confirmed diagnosis of recurrent NSCLC who received anti-PD-1 or anti-PD-L1 as Part of last treatement with at least 3 months of stable disease (i.e.patients with confirmed response (PR or CR) regardless of duration of response or stable disease (SD) for a minimum of 3 months) and have become refractory to anti-PD-1/ anti-PD-L1 based treatment
   OR
   Patients with histologically confirmed diagnosis of recurrent metastatic HNSCC who progressed after platinum based therapy or not indicated for receiving standard (radio) chemotherapy (previous treatment with anti- PD-1/ PD-L1 is allowed)
4. Eastern Cooperative Oncology Group (ECOG, R01-0787) score: 0 to 1
5. Patient must have at least one PET imageable and evaluable tumor lesion of 20mm
6. Patients must have at least one tumor lesion amenable to biopsy. This lesion should be PET imageable and evaluable as defined above and the biopsy should be obtained before first BI 754091 administration, unless medically contra-indicated. In the latter case, 25 4µm sections from an archival biopsy taken at relapse after the previous treatment are acceptable
7. Must have evaluable lesion(s) according to Revised Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 and iRECIST

8. Life expectancy of at least 12 weeks after the start of the treatment according to the Investigator's judgement

9. 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 per International Conference on Harmonisation (ICH) M3 (R2) (that result in a low failure rate of less than 1% per year when used consistently and correctly) 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.

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.

3.3.3 Exclusion criteria

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

1. Not having fully recovered from major surgery before they enter into the trial according to investigator judgment or planned for major surgery within 12 months after screening, e.g. hip replacement
2. Patients who must or wish to continue the intake of restricted medications (see Section 4.2.2.1) or any drug considered likely to interfere with the safe conduct of the trial
3. Patients not expected to comply with the protocol requirements or not expected to complete the trial as scheduled
4. Previous treatment in this trial
5. Any investigational or anti-tumor treatment within 4 weeks or within 5 half-life periods (whichever is shorter) prior to the initiation of trial treatment.
6. 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
7. Prior treatment with anti-LAG-3 agents
8. Presence of other active invasive cancers other than the one treated in this trial, with the exception of resected/ablated basal or squamous-cell carcinoma of the skin or carcinoma *in situ* of the cervix, or other local tumors considered cured by local treatment
9. Untreated brain metastasis(es) that may be considered active. Patients with previously treated brain metastases may Participate provided they are stable (i.e., without evidence of PD by imaging for at least 4 weeks prior to the first dose of trial treatment, and any neurologic symptoms have returned to baseline), and there is no evidence of new or enlarging brain metastases
10. Inadequate organ function or bone marrow reserve as demonstrated by the 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 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.

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 patient or unlikely to complete the trial or unable to comply with the protocol procedures
20. Women who are pregnant, nursing, or who plan to become pregnant in the trial

Table 3.3.3: 1 Laboratory values demonstrating inadequate organ function

Laboratory Parameter	**Values**
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

ULN = Upper Limit of Normal

3.3.4 Withdrawal of patients from therapy or assessments

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

3.3.4.1 Withdrawal from trial treatment

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

- The patient wants to withdraw from trial treatment, without the need to justify the decision.

- The patient needs to take concomitant medication that interferes with the investigational product or other trial medication (see Section 4.2.2.1)
- The patient can no longer be treated with trial medication for other medical reasons (such as surgery, adverse events, other diseases, or pregnancy) (see Section 4.1.2.4).
- 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.

Even if the trial treatment is discontinued, the patient remains in the trial and, given his/her agreement, the patient will undergo the procedures for the EOT visit and the safety follow up as outlined in the Flow Chart (FC) and Section 6.2.3.
For all patients the reason for withdrawal from trial treatment (e.g. AEs) must be recorded in the CRF. These data will be included in the trial database and reported.

If a patient should become pregnant during the trial, the treatment with BI 754111 or [^{89}Zr]Zr-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 5.2.6.2.4 for information on pregnancy forms). The data of the patient will be collected and reported in the eCRF until the last patient's last visit and any events occurring thereafter will be reported in the BI drug safety database.

3.3.4.2 Withdrawal of consent for trial Participation

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

3.3.4.3 Discontinuation of the trial by the sponsor

BI 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 trial protocol, or the contract impairing the appropriate conduct of the trial

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

4. TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

4.1.1 Identity of the Investigational Medicinal 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 Day1 of each 3-week Cycle
Method and route of administration:	I.V. infusion

4.1.1.2 [^{89}Zr]Zr-BI 754111

Details of the drug product, [^{89}Zr]Zr-BI 754111, are presented in Table 4.1.1.2: 1. Additional details are presented in the [^{89}Zr]Zr-BI 754111 IMPD

Table 4.1.1.2: 1 [^{89}Zr]Zr-BI 754111

Substance:	[^{89}Zr]Zr-BI 754111
Pharmaceutical formulation:	Solution for infusion
Source:	[redacted]
Unit strength:	0.2 mg/mL
Posology:	Up to 2 administrations
Method and route of administration:	I.V. infusion via a pump in 10 min

4.1.1.3 BI 754091

Details of the drug product, BI 754091, are presented in Table 4.1.1.3: 1. Additional details are presented in the BI 754091 IB and Pharmacy Manual.

Table 4.1.1.3: 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 Day1 of each 3-week Cycle
Method and route of administration:	I.V. infusion

4.1.2 Selection of doses in the trial and dose modifications

4.1.2.1 [^{89}Zr]Zr-BI 754111

The tracer dose will consist of 4mg BI 754111 and 37 MBq Zr-89 in a total volume of 20mL. This dose is based on the lowest dose of BI 754111 tested in the dose escalation Part of trial 1381-0002.

4.1.2.2 BI 754111

BI 754111 treatment will be administered at doses expected to be therapeutically active based on non-clinical and clinical data.
The first dose to be investigated is the dose recommended for the expansion phase of trial 1381-0002. This dose was selected based on the data obtained in 1381-0002 dose-escalation cohorts, where 3 to 9 patients each received BI 754111 at dose levels of 4, 20, 80, 200, 400 and 600mg in combination with a flat dose of 240mg BI 754091. No DLTs or AESIs were observed in the dose escalation Part and maximum tolerated dose (MTD) was considered not reached.

The first administration of BI 754111 treatment will take place at Cycle2 Day1.
In Part 2, various doses cohorts will be investigated sequentially. In each cohort, the dose applied at Cycle2 Day1 will depend on the magnitude of the blockade observed in the previous dose cohort. It is expected to explore at least two different dose levels of BI 754111 in this trial.
From Cycle3 Day1, the dose BI 754111 dose recommended for the expansion phase of trial 1381-0002 will be be applied to all patients.
The treatment will be administered via infusion q3w.

4.1.2.3 BI 754091

BI 754091 will be administered at a flat dose of 240mg to be administered via infusion q3w.

[redacted]

4.1.2.4 Dose modification for BI 754111 and BI 754091 treatments

There will be no dose reductions or escalations of BI 754091 or BI 754111 in any one patient. All patients (including patients allocated to a different dose of BI 754111 treatment during the on-treatment assessment phase (Cycle2) in Part 2), will take the recommended expansion phase dose of BI 754111 (determined in the 1381-0002 trial) starting from Cycle 3 onward.

The dose may be delayed for up to 6 weeks because of AEs, following discussion with the sponsor.

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

The study treatments BI 754091 and BI 754111 should be permanently discontinued for CTCAE Version 5.0 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 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.

4.1.3 Method of assigning patients to treatment groups

After assessment of all in- and exclusion criteria, each eligible patient will be entering the trial in their respective study Part.

In Part 1, the patients will be entered sequentially.

After review of Part 1 data, the SMC will make the decision whether or not to initiate Part 2. Patients tested positive for tumor LAG-3 expression will be treated in various dose cohorts of BI 754111 and these dose cohorts will be managed sequentially based on the SMC decision. During the conduct of Part 2, up to five patients tested without LAG-3 expressing tumor will be entered sequentially.

The appropriate medication number will be assigned. Note that the medication number is different from the patient number (the latter is assigned directly after informed consent was obtained). Site personnel will enter the medication number in the CRF.

4.1.4 Drug assignment and administration of doses for each patient

The tracer dose (approximately 4mg in 20mL) of [^{89}Zr]Zr-BI 754111 will be injected intravenously via a pump in 10 min with flushing (10 mL physiologic saline). The mass dose might be adapted as per SMC decision. The injection will take place at the department of [redacted] Each patient will be administered [^{89}Zr]Zr-BI 754111 up to 2 times during the trial, once at Cycle1 no later than Day8 and at Cycle2 after the administration of BI 754091/BI 754111 treatment, if applicable (all patients in Part 1 and only patients tested positive for tumor LAG-3 expression in Part 2).

BI 754091 will be administered via intravenous infusion at the dose of 240mg. The first administration of BI 754091 treatment will take place at Cycle1 Day1 for each patient.

BI 754111 will be administered via intravenous infusion at the recommended expansion dose per trial 1381-0002. The first administration of BI 754111 treatment will take place at Cycle2 Day1 for each patient.
In Part 2, patients tested positive for tumor LAG-3 expression will be administered a lower or a higher dose of BI 754111 treatment at Cycle2 only. The dose allocated at these patients in Cycle2 will be confirmed by the SMC.

At Cycle2 and onwards, BI 754091 and BI 754111 treatment will be administered concomitantly.

For the preparation and administration of BI 754091 and BI 754111, please refer to the instruction provided in the ISF.

For each compound, the different timepoints of administration and the different doses are summarized in the table below.

Table 4.1.4: 1 Administration of doses per study part

Treatment Cycle	Study Part	Day	Dose to be administered
Cycle1 Baseline assessment	Part 1 and Part 2	C1 Day1	BI 754091 treatment: 240mg
		No later than day8	[^{89}Zr]Zr-BI 754111: 4mg or adapted mass dose
Cycle2 On-treatment assessment	Part 1	C2 Day1	BI 754091 treatment: 240mg BI 754111 treatment: recommended exp. dose
			[^{89}Zr]Zr-BI 754111: 4mg or adapted mass dose
	Part 2	C2 Day1	BI 754091 treatment: 240mg BI 754111 treatment: allocated dose per SMC decision
			[^{89}Zr]Zr-BI 754111: 4mg or adapted mass dose
Cycle 3 and further cycles	Part 1 and Part 2	Cx Day1	BI 754091 treatment: 240mg BI 754111 treatment: recommended exp. dose

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

In this open-label trial, treatment allocation will not be concealed throughout the trial. The CRF will contain information on allocated treatment.

4.1.5.2 Unblinding and breaking the code

Not applicable.

4.1.6 Packaging, labelling, and re-supply

The investigational products BI 754091 and BI 754111 will be provided by BI. [^{89}Zr]Zr-BI 754111 will be produced at the [redacted] campus, with a production license being in place. Production is performed under the responsibility of the hospital pharmacist (Qualified Person).
All products will be packaged and labelled in accordance with the principles of Good Manufacturing Practice (GMP). Re-supply to the site will be managed by BI in collaboration with the investigational site, which will also monitor expiry dates of supplies available at the site.
For details of packaging and the description of the label, refer to the ISF.

4.1.7 Storage conditions

BI 754091 and BI 754111 will be kept in their original packaging and in a secure limited access storage area according to the recommended storage conditions on the medication label. A temperature log must be maintained for documentation.

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

[^{89}Zr]Zr-BI 754111 should be stored at 2-8°C until use. Prior to drawing up in a syringe it should be warmed up to room temperature. It can be kept in a syringe for approximately 1 hour.

4.1.8 Drug accountability

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

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

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

These records will include dates, quantities, batch/serial numbers, expiry ('use- by') dates, and the unique code numbers assigned to the investigational product and trial patients. The investigator/pharmacist/investigational drug storage manager will maintain records that document adequately that the patients were provided the doses specified by the CTP and reconcile all investigational products received from the sponsor. 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, 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.
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.

Permitted concomitant medications include:

- If medically feasible, patients taking regular medication should be maintained on it throughout the trial.
- *To reduce the risk of IRRs, 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 eligibility criteria.
- 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 during the trial, except during the biodistribution imaging phases as it could interfere with the imaging evaluation. Palliative radiotherapy is allowed provided that the reason for radiotherapy does not reflect PD and does not interfere with response assessment. Lesions that have been exposed to radiotherapy are no longer evaluable, and may not be included in the assessment of the non-target lesions and the overall assessment. Unless in emergency situations, the BI Medical Monitor should be contacted prior to the administration of palliative radiotherapy.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

- No other investigational therapy or anticancer agent should be given to patients. If such agents are required for a patient, then the patient must first be withdrawn from the trial.
- Immunosuppressive medications including, but not limited to systemic corticosteroids at doses exceeding 10 mg/day of prednisone or equivalent, methotrexate, azathioprine, and tumor 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.

4.2.2.2 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.

4.2.2.3 Contraception requirements

Due to the advanced stage of disease of Phase I trial patient populations and the high medical need, WOCBP (for the definition please refer to Section 3.3.2) can be included in this trial provided that they agree to use a highly-effective contraception method.

WOCBP and men able to father a child must use highly effective methods of birth control per the ICH M3 (R2) that result in a low failure rate of less than 1% per year when used consistently and correctly.
WOCBP and men able to father a child must use two medically approved methods of birth control throughout the trial, and for a period of at least 6 months after last trial drug intake. They must use one barrier method, i.e. condom or occlusive cap with spermicide, or vasectomized Partner, and one highly effective non-barrier method including oral, injected or implanted hormonal contraceptives, intrauterine device or system.

Male patients: men whose Partner is a WOCBP must 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.

Female patients: WOCBP must use highly-effective methods of birth control per ICH M3 (R2) that results in a low failure rate of less than 1% per year when used consistently and correctly during the study, and for a period of at least 3 months after the last dose of study drug.

Acceptable methods of birth control for this trial are:
- Combined (estrogen and progestogen containing) hormonal birth control that prevents ovulation (oral, intravaginal, transdermal).
- Progestogen-only hormonal birth control that prevents ovulation (oral, injectable, implantable).
- Intrauterine device (IUD) or intrauterine hormone-releasing system (IUS).
- Bilateral tubal occlusion
- Vasectomised sexual Partner with documented absence of sperm.

Or

- Patients must abstain from male-female sex. This is defined as being in line with the preferred and usual lifestyle of the patient. Periodic abstinence e.g. calendar, ovulation, symptothermal, post-ovulation methods; declaration of abstinence for the duration of exposure to study drug; and withdrawal are not acceptable.

Details of these contraception methods are described in the patient information in the ICF.

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. ASSESSMENTS

5.1 ASSESSMENT OF EFFICACY

The treatment efficacy will be assessed according to RECIST Version 1.1 (R09-0262) and iRECIST (R17-0923) for the evaluation of the tumor response in patients with solid tumors. An overview of iRECIST will be found in Appendix 10.3.
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 start with anti-LAG-3 treatment BI 754111 and the Investigator will record the target and non-target lesions in the eCRF. The same method of assessment and the same technique must be used to characterise each reported lesion at baseline and during treatment. Lesions in previously irradiated areas may not be considered measurable at baseline unless the lesions occurred after irradiation.
The baseline tumor assessment will be performed as close as possible (and no more than 28 days) to the start of the anti-LAG-3 treatment BI 754111 (i.e. within the week before Cycle1 Visit1 or during Cycle 1). Further assessments will be performed every 2 Cycles during the first 6 months and at the EOT visit (if not performed within the last 4 weeks). Following 6 months of treatment, tumor assessments can be done once every 3Cycles, and at the discretion of the Investigator.

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.

Copies of CT/ Magnetic Resonance Imaging (MRI)/PET scan data will be collected by the sponsor for later radiomics assessment. It is planned to explore the potential for enhanced and improved baseline and on-treatment markers/ patterns of early efficacy based on comprehensive quantitative CT metrics, i.e. radiomics features, assessed in standard-of-care medical imaging data.

5.2 ASSESSMENT OF SAFETY

5.2.1 Physical examination

A complete physical examination will be performed at the time points specified in the Flow Chart. It includes at a minimum general appearance, neck, lungs, cardiovascular system, abdomen, extremities, and skin.
Measurement of height and body weight will be performed at the time points specified in the Flow Chart.
The results must be included in the source documents available at the site.

5.2.2 Vital signs

Vital signs will be evaluated at the time points specified in the Flow Chart, prior to blood sampling.

This includes systolic and diastolic blood pressure and pulse rate (electronically or by palpation count for 1 minute) in a seated position after 5 minutes of rest. The results must be included in the source documents available at the site.

5.2.3 Safety laboratory parameters

Blood (venous) samples will be collected at the times indicated in the Flow Chart and will be analysed by the sites' local safety laboratories. 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.
The tests to be performed are described in Table 5.2.3: 1.

Table 5.2.3: 1 Safety laboratory tests

Hematology	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
Biochemistry	Standard safety panel: glucose, sodium, potassium, chloride, calcium, phosphate, venous bicarbonate HCO_3, creatinine, creatinine phosphokinase (CPK), AST, ALT, alkaline phosphatase, lactate dehydrogenase (LDH), bilirubin, total protein, albumin, urea nitrogen (or urea), uric acid and troponin
	Baseline additional panel then when clinically indicated: cholesterol, triglycerides, c-peptide, and creatine phosphokinase
	In case of pathological creatine phosphokinase: CPK-MB, additional troponin I and myoglobin should be reactively tested and the findings documented
	Thyroid panel (TSH, free T4, and free T3): at the time of each standard biochemistry panel
	To be analysed in case of symptoms of pancreatitis: amylase and lipase
Urinalysis	Urine (pH, glucose, erythrocytes, leukocytes, protein, and nitrite) will be analysed by dipstick (semi-quantitative measurements) during the screening visit, at the EOT visit, and as clinically indicated. In case of pathological findings, further evaluation must be performed and the findings documented
Pregnancy test	Beta human chorionic gonadotropin (β-HCG) pregnancy test in urine or serum will be performed for women of childbearing potential at screening, within 14 days prior to first trial treatment, on Day 1 of each cycle prior to administration of the treatment drug(s), before the start of each repeated cycle, and at the EOT visit.

In case the criteria for hepatic injury are fulfilled, a number of additional measures will be performed (please see Section 5.2.6.1.4 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.

5.2.4 Electrocardiogram

The 12-lead ECGs must be administered by a qualified technologist and results will be recorded as scheduled in the Flow Chart. The investigator or a designee will evaluate whether the ECG is normal or abnormal and whether it is clinically relevant, if abnormal. ECGs may be repeated for quality reasons and the repeated recording used for analysis.
Additional ECGs may be recorded for safety reasons. Dated and signed printouts of ECG with findings should be documented in patient's medical record.
Clinically relevant abnormal findings will be reported either as baseline condition (if identified at the screening visit) or otherwise as adverse events and will be followed up and/or treated as medically appropriate.

5.2.5 Other safety parameters

Not applicable

5.2.6 Assessment of adverse events

5.2.6.1 Definitions of AEs

5.2.6.1.1 Adverse event

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

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

5.2.6.1.2 Serious adverse event

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

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

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

5.2.6.1.3 AEs 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 5.2.6.2, subsections "AE Collection" and **AE reporting to sponsor and timelines**".

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

5.2.6.1.4 Adverse events of special interest (AESIs)

The term AESI relates to any specific AE that has been identified at the project level as being of Particular concern for prospective safety monitoring and safety assessment within this trial, e.g. the potential for AEs based on knowledge from other compounds in the same class. AESIs need to be reported to the sponsor's Pharmacovigilance DePartment within the same timeframe that applies to SAEs, please see above.

The following are considered as AESIs: irAEs, infusion-related AEs, potential DILI events, and hepatic injury are AESIs (see below).

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-relate 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.

Infusion-related reactions
To reduce the risk of IRRs, 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 for the patient.

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

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

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 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 SAE according to the outcome of the review and assessment in line with standard safety reporting processes.

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

- an elevation of AST and/or ALT ≥3 fold ULN combined with an elevation of total bilirubin ≥2 fold ULN measured in the same blood draw sample, and/or
- *Mark peak* ALT, and/or AST elevation ≥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 "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 DILI checklist should be followed.
Lab values meeting this definition of hepatic injury will need to be reported as an AESI.
Please follow the flowchart below for reporting hepatic injury / potential DILI cases.

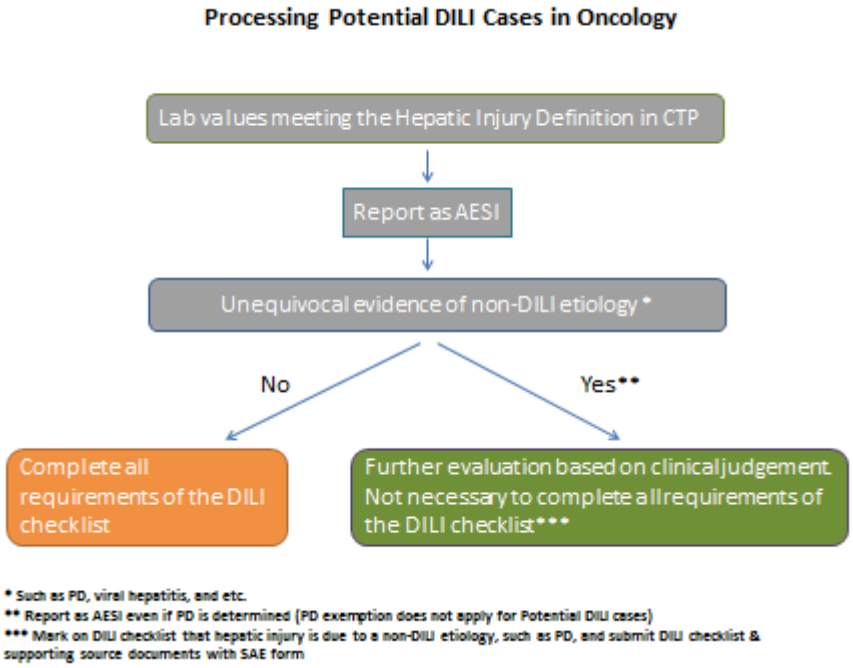


Figure 5.2.6.1.4: 1 Processing of potential DILI cases

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 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 hepatitis A, B, or C; prexisting or acute liver disease, or another drug capable of causing the observed injury.*

5.2.6.1.5 Intensity (severity) of AEs

The intensity (severity) of AEs should be classified and recorded in the eCRF according to the CTCAE Version 5.0.

5.2.6.1.6 Causal relationship of AEs

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

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

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

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

- No plausible time to onset of the event relative to the time of drug exposure is evident (e.g. pre-treatment cases, diagnosis of cancer or chronic disease within days/weeks of drug administration; an allergic reaction weeks after discontinuation of the drug concerned)
- Continuation of the event despite the withdrawal of the medication, taking into account the pharmacological properties of the compound (e.g. after 5 half-lives).
- Of note, this criterion may not be applicable to events whose time course is prolonged despite removing the original trigger.
- 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).
- Disappearance of the event even though the trial drug treatment continues or remains unchanged.

5.2.6.2 Adverse event collection and reporting

5.2.6.2.1 AE Collection

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

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

The rules for Adverse Event Reporting exemptions still apply.

5.2.6.2.2 AE reporting to sponsor and timelines

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

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

5.2.6.2.3 Information required

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

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

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

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

5.2.6.2.4 Pregnancy

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

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

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

5.2.6.2.5 Exemptions to SAE reporting

Protocol specified outcome events should be collected on the appropriate CRF page only.

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

However, when there is evidence suggesting a causal relationship between the study drug(s) and the progression of the underlying malignancy, the event must be reported as an SAE on the SAE Form and on the eCRF.

Examples of exempted events of PD may be:
- Progression of underlying malignancy (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.

Lab values meeting the hepatic injury definition as defined in Section 5.2.6.1.4 will need to be reported as AESI. PD reporting exemption does not apply to hepatic injury.

5.3 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

5.3.1 Assessment of pharmacokinetics

Plasma concentration of BI 754111 will be listed and evaluated descriptively. PK parameters will be calculated by non-comPartimental methods according to BI internal Standard Operating Procedure (SOP) (001-MCS-36-472).

5.3.2 Methods of sample collection

For quantification of analyte plasma concentrations, blood will be drawn for BI 754111 at the time points specified in PK time schedules in the Blood Sample Flow Chart. Pharmacokinetic sampling times and periods may be adapted by the Sponsor during the trial based on information obtained during trial conduct.

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

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

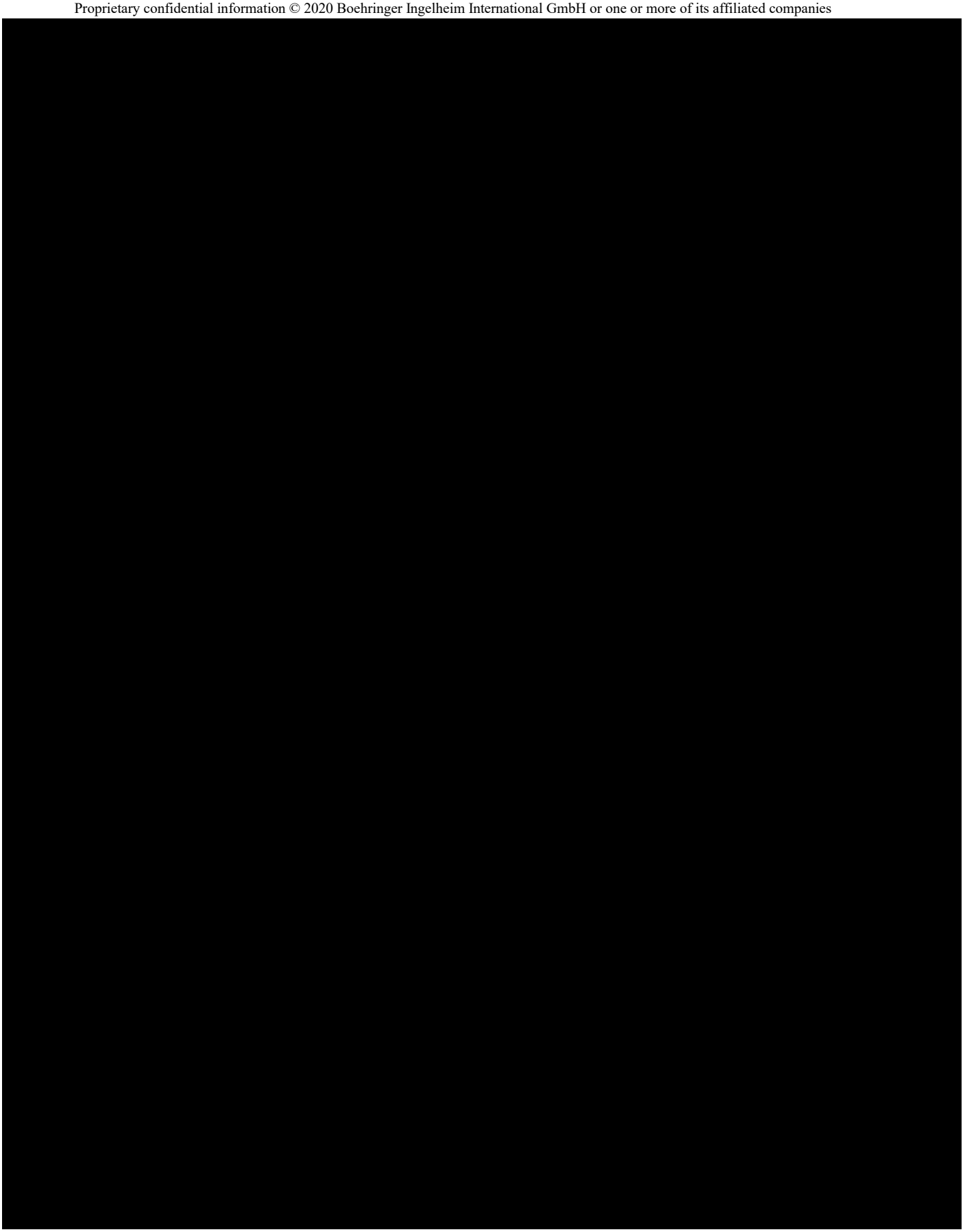
Plasma samples may be used for further methodological investigations (e.g., stability testing), however only data related to the analyte or bioanalytical assay will be generated by these investigations. The trial samples will be discarded not later than 5 years after the final trial report has been signed.

[redacted]

5.3.4 Pharmacokinetic – pharmacodynamic relationship

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

[redacted]



[redacted]

5.6 OTHER ASSESSMENTS

5.6.1 FDG-PET/CT procedure

A standard static diagnostic FDG-PET will be performed during screening for the assessment of tumor viability and necrosis. This procedure will be performed in accordance with European Association of Nuclear Medicine (EANM) FDG-PET/CT procedures guidelines for tumor imaging (R18-1536).

5.6.2 [^{89}Zr]Zr-BI 754111 PET scan procedure

All PET scans will be performed on a PET/CT scanner (e.g. [redacted] Ingenuity TF). All patients will undergo whole body PET scans at various time points, e.g. t = 72 and t = 144 hours post-injection. The PET scans will be preceded by a 30 mAs low-dose CT, used for attenuation correction and anatomical localization of the PET-signal. Following CT, a total body PET scan will be acquired. PET scans consist of 10-12 bed positions, depending on the length of the patient, of various time lengths, usually 5 minutes each. Total acquisition time per scan, including low dose CT will be around 60 minutes.
PET data will be normalized and corrected for randoms, tissue attenuation, decay, scatter and dead time. PET-CT data will be reconstructed with TF-OSEM, resulting in a transaxial spatial resolution of ~7 mm in the centre of the field of view. Regions of interest (ROIs) will be defined using the CT images which are co-registered to the PET-CT data. ROIs around the organs which accumulate 89Zr (e.g. liver, lung and other metastatic lesions) will be drawn manually directly on the PET images. All tissue concentrations will be related to the blood concentration (venous samples). The radioactivity concentrations in all regions for all imaging time points will be recorded digitally in a spreadsheet.
Quantitative accuracy of 89Zr-PET scans was previously confirmed in [redacted] center using phantom studies and comparisons between PET-derived and biopsy tumor radioactivity concentrations (R18-1538, R18-1539).

A blood sample *(~6* mL) will be drawn *at four early time points post injection of [^{89}Zr]Zr-BI 754111 (after CTP 3.0) and at* each [^{89}Zr]Zr-BI 754111 PET scan to determine ^{89}Zr-kinetics based on measurements of radioactivity. See Blood Sample Flow Chart for time schedule.
The detailed procedures of [^{89}Zr]Zr-BI 754111 PET/CT scanning will be described in the lab manual at the site.

Analysis of PET data:
Tumor volumes of interest will be delineated using semi-automated in-house developed software. SUV_{max}, SUV_{mean} and SUV_{peak} will be calculated for the tumor and visible lymph nodes (R18-1536, R18-1537).

5.6.3 Assessment of anti-drug antibodies (ADAs)

The presence of anti-drug antibodies (ADAs) against BI 754111 will be assessed using a validated immunoassay in a tiered approach (screening, confirmatory, and titration analysis as appropriate).

For ADA assessments (BI 754111), the specified blood volume will be drawn into blood-drawing tubes at the time points listed in the Blood Sample Flow Chart and the detailed blood sampling schedule. Details on sample characteristics, processing, handling, and shipment are provided in the Laboratory Manual.

After completion of the trial, plasma samples may be used for further methodological investigations, e.g., stability testing. However, only data related to the ADAs will be generated by these additional investigations. The trial samples will be discarded after completion of the additional investigations, but not later than 5 years after the final trial report has been signed.
Note that for some disease indications, it may be necessary to use plasma samples collected prior to administration of study treatments in order to assess the performance of the ADA assay.

5.7 APPROPRIATENESS OF MEASUREMENTS

All assessments have been planned in accordance with traditional oncology Phase I trial methodology except the iRECIST that is a new guideline for response assessment in trial testing immunotherapeutics and is still to be validated, so this guideline will be used as an exploratory efficacy assessment in this trial.
All PET scan acquisition procedures that will be performed in this trial are standard.

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

Patients that have met the inclusion criteria and not met the exclusion criteria for the Part they are participating in and who have signed a written ICF, are eligible for Participation in the trial. Patients will visit the clinical site at the time points specified in the Flow Chart.

Each cycle has duration of 21 days.
At Cycle1 and Cycle2, the visit will be conducted through multiple days, driven by the LAG-3 PET assessments procedures:

- Cycle1 will start with the administration of the anti-PD1 treatment BI 754091 at Day1. The procedures for baseline LAG-3 PET assessment will start with the injection of the tracer [^{89}Zr]Zr-BI 754111 that should be done no later than Day8, followed by the PET/CT scans.
- Cycle2 will start with the first administration of the anti-LAG-3 treatment BI 754111 in combination with BI 754091 at Day1. The procedures for on-treatment LAG-3 PET assessment will start with the injection of the tracer [^{89}Zr]Zr-BI 754111 that should be done at Day1 (after the infusion of BI 754091 and BI 754111) followed by the PET/CT scans.

After Cycle2, the visits will be 1-day visit at day 1 of each cycle. If a patient misses a scheduled visit, and reports to the Investigator between the missed visit and the next scheduled visit, the assessments for the missed visit must be done with the actual date and the reason must be given for the delayed visit. The next visit must then take place at the scheduled time after the first administration of the trial drug in the respective treatment cycle.

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

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

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

The procedures required at each trial visit in all portions of the trial are presented in the Flow Chart of this protocol. The key procedures required include:

- FDG-PET for assessment necrosis and tumor viability at screening
- PET scan for LAG-3 biodistribution and tumor uptake assessments
- Blood samples for PK concentration BI 754111
- Blood samples for radioactivity concentration *post [^{89}Zr]Zr-BI 754111 injection and* at LAG-3 PET assessments
- Reporting of all AEs occurring after the ICF has been signed
- Baseline and on-treatment blood samplings for biomarker and immunogenicity assessments

- Tumor biopsy for assessment of LAG-3 expression at screening
- Tumor tissue (5 slices) from tumor biopsy taken prior to the anti-PD-1/PD-L1 treatment, if available
- *Optional tumor biopsies for autoradiography and Flow cytometry at C1*
- Tumor assessments (based on CT/PET and/or MRI scan) according to RECIST Version 1.1 and iRECIST must be performed once every 2 Cycles (meaning every 6 weeks if there are no delays in cycles but as close as possible to the end of the second of the 2 cycles of treatment if there was a delay) after the start of the anti-LAG-3 treatment BI 754111 for the first 6 months, and then every 3 Cycles (9 weeks) thereafter. The baseline tumor assessment must be performed within 28 days prior to the start of the anti-LAG-3 treatment BI 754111.

6.2.1 Screening period

The screening period may occur over a period of 15 days (period within the trial and before the first administration of BI 754091). For the detailed description of the tests to be performed during this period and their timing, please refer to the Flow Chart.

6.2.1.1 Baseline Conditions

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

6.2.1.2 Medical History

6.2.1.2.1 Medical history of cancer

History of the patient's cancer will be obtained. The type of cancer, the date of the first histological diagnosis (month and year may be sufficient), and the primary tumor 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 tumor, (lymph) node, and metastasis (TNM Classification of Malignant Tumours (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 tumor progression after previous lines of treatment will be recorded, if known.

6.2.1.2.2 Other medical history

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

6.2.1.3 Concomitant medications

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

6.2.2 Treatment period(s)

Please refer to the Flow Chart for a detailed presentation of each visit during the treatment period.

6.2.3 Follow up period and trial completion

6.2.3.1 End-of-treatment visit

The EOT visit will be performed as soon as possible but no later than 7 days after permanent discontinuation of the trial medications (BI 754091 and BI 754111) for any reason or e.g. when the Investigator decided with the patient to permanently discontinue the trial medications or became aware that the trial medications 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, tumor assessment/imaging must be performed at the time of EOT, unless it has been done within the past 4 weeks.

6.2.3.2 30-day safety follow-up visit

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

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

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN - MODEL

This is an open-label, non-randomised study consisting of two Parts. The main objective of this study is to determine the tumor accumulation of [^{89}Zr]Zr-BI 754111 at baseline and its change upon treatment doses.

The primary endpoints are specified in Section 2.1.2. Further endpoints including pharmacokinetics (PK) are defined in Section 2.2.2. For both Parts of the study (Part 1 and Part 2) endpoints will be analysed by descriptive statistics. Inferential statistics is not planned (as explained in Section 7.2).

7.2 NULL AND ALTERNATIVE HYPOTHESES

It is not planned to test any statistical hypotheses in a confirmatory sense. All statistical analyses are exploratory even if they use confirmatory methods. Confidence intervals (CI) will be computed and will be interpreted in terms of the exploratory character of the study, i.e. confidence intervals are considered as interval estimates for effects.

7.3 PLANNED ANALYSES

All individual data will be listed. Adherence to the protocol will be checked. Important protocol violations (IPVs) will be identified no later than in the Report Planning Meeting and provided in the trial statistical analysis plan (TSAP).

7.3.1 Primary endpoint analyses

The primary endpoint will be evaluated descriptively.

All evaluations will be based on the treated set (TS), unless otherwise stated. Patients who might not be evaluable for the baseline assessment of [^{89}Zr]Zr-BI 754111 will be excluded from the primary endpoint analysis (to be decided no later than in the Report Planning Meeting). Exclusion of a subject's data will be documented in the clinical trial report (CTR).

Association between tumor uptake and other imaging/efficacy or biomarker assessments will be investigated using generalized linear models. In addition, parameter-free correlation techniques, e.g. Kendall tau, will be provided where applicable. These analyses will be based on all data collected in the study.

In Part 2, an exploratory analysis might be performed to model the association between BI 754111 treatment dose vs. SUVs. These evaluations will be performed only if at least 3 different BI 754111 doses are investigated with a sufficient number of patients per dose (minimum of 3 patients per dose cohort).

The details of all aforementioned analyses will be provided in the TSAP.

[redacted]

7.3.3 Safety analyses

Adverse events will be coded using the Medical Dictionary for Drug Regulatory Activities (MedDRA). Standard BI summary tables and listings will be produced. All adverse events with an onset between start of treatment (i.e. 1st administration of anti-PD-1 treatment BI 754091 at Cycle1 Day1) and the safety follow-up (FU) 30 days after the last dose of trial medications, will be assigned to the on-treatment period for evaluation. Statistical analysis and reporting of adverse events will concentrate on treatment-emergent adverse events, i.e. all adverse events occurring between start of treatment and end of the residual effect period. Adverse events that start before first drug intake and deteriorate under treatment will also be considered as 'treatment-emergent'.

All treated patients will be included in the safety analysis. In general, safety analyses will be descriptive in nature and will be based on BI standards. No hypothesis testing is planned.

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

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

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

7.3.4 Pharmacokinetic and pharmacodynamic analyses

Pharmacokinetic parameters as described in Section 2.2.2 will be calculated by means of noncomPartmental analysis. The derivation of PK parameters is described in BI internal SOP (001-MCS-36-472).

Further details on analysis will be described in the TSAP.

7.4 INTERIM ANALYSES

The sponsor will continuously monitor the safety. The design of the study foresees that the Sponsor and the SMC perform regular evaluations of all available data. These evaluations will be unblinded to dose.

Part 2 will commence based on SMC decision after review of all available data from Part 1.

7.5 HANDLING OF MISSING DATA

In general, no imputation will be performed on missing imaging/efficacy data.

Missing baseline laboratory values will be imputed by the respective values from the screening visit. For Partial or missing AE onset and/or end dates, BI internal rules will be followed (see SOP Reference Document 001-MCG-156_RD-01).

No other imputations will be performed on missing data although every effort will be made to obtain complete information on all imaging, PK/PD, safety and efficacy endpoints.

7.6 RANDOMISATION

No randomisation will be performed. Patients will be assigned to the different Parts of the study by order of admission into the trial.

In Part 2, patients tested positive for tumor LAG-3 expression will be assigned to various dose cohorts of BI 754111 by order of admission into the trial. Patients tested without LAG-3 expressing tumor will be offered the trial treatment as described in Section 3.1 or may opt to cancel their trial Participation.

7.7 DETERMINATION OF SAMPLE SIZE

Up to 40 patients (up to 5 patients for Part 1 and up to 35 patients for Part 2) are planned to be entered in this trial.
The planned sample size is not based on a power calculation but is judged to be adequate to fulfil the objectives and requirements of this exploratory trial. The exact number of patients entered in the each Part will be defined by the SMC, but it will not exceed the planned sample size.

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

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

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

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

The Boehringer Ingelheim transparency and publication policy can be found on the following web page: trials.boehringer-ingelheim.com. The rights of the investigator and of the sponsor with regard to publication of the results of this trial are described in the investigator contract. As a rule, no trial results should be published prior to finalization of the Clinical Trial Report. In exceptional cases, data may be published before the clinical trial report as long as this is discussed and agreed to by the investigators and the sponsor
The certificate of insurance cover is made available to the investigator and the patients, and is stored in the ISF.

8.1 TRIAL APPROVAL, PATIENT INFORMATION, INFORMED CONSENT

This trial will be initiated only after all required legal documentation has been reviewed and approved by the local Ethics Committee (Dutch: Medisch-Ethische Toetsingscommissies (METc)) and competent authority (CA) according to national and international regulations. The same applies for the implementation of changes introduced by amendments.

Prior to patient Participation in the trial, written informed consent must be obtained from each patient according to ICH/GCP and to the regulatory and legal requirements of the Participating country. Each signature must be personally dated by each signatory and the informed consent and any additional patient-information form retained by the investigator as Part of the trial records. A signed copy of the informed consent and any additional patient information must be given to each patient.
The investigator must give a full explanation to trial patients based on the patient information form. A language understandable to the patient should be chosen, technical terms and expressions avoided, if possible.

The patient must be given sufficient time to consider Participation in the trial. The investigator obtains written consent of the patient’s own free will with the informed consent form after confirming that the patient understands the contents. The investigator must sign (or

place a seal on) and date the informed consent form. If a trial collaborator has given a supplementary explanation, the trial collaborator also signs (or places a seal on) and dates the informed consent.

Re-consenting may become necessary when new relevant information becomes available and should be conducted according to the sponsor's instructions.
The consent and re-consenting process should be properly documented in the source documentation.

8.2 DATA QUALITY ASSURANCE

A risk-based approach is used for trial quality management. It is initiated by the assessment of critical data and processes for trial subject protection and reliability of the results as well as identification and assessment of associated risks. An Integrated Quality and Risk Management Plan documents the rationale and strategies for risk management during trial conduct including monitoring approaches, vendor management and other processes focusing on areas of greatest risk.
Continuous risk review and assessment may lead to adjustments in trial conduct, trial design or monitoring approaches.

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

8.3 RECORDS

CRFs for individual patients will be provided by the sponsor.
For drug accountability, refer to Section 4.1.8.

8.3.1 Source documents

In accordance with regulatory requirements the investigator should prepare and maintain adequate and accurate source documents and trial records that include all observations and other data pertinent to the investigation on each trial patient. Source data as well as reported data should follow the "ALCOA principles" and be **a**ttributable, **l**egible, **c**ontemporaneous, **o**riginal and **a**ccurate. Changes to the data should be traceable (audit trail).
Data reported on the CRF must be consistent with the source data or the discrepancies must be explained.
The current medical history of the patient may not be sufficient to confirm eligibility for the trial and the investigator may need to request previous medical histories and evidence of any diagnostic tests. In this case the investigator must make three documented attempts to retrieve previous medical records. If this fails a verbal history from the patient, documented in their medical records, would be acceptable.

Copies of tumor assessment scans will be collected by the sponsor for later Radiomics assessment. This could include CT/MRI/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. Before sending or uploading those copies, the investigator must ensure that all patient identifiers (e.g. patient's name, initials, address, phone number, social security number) have properly been removed or redacted from any copy of the patients' source documents before sending them to the sponsor.

If the patient is not compliant with the protocol, any corrective action e.g. re-training must be documented in the patient file.
For the CRF, data must be derived from source documents, for example:

- Patient identification: gender, year of birth (in accordance with local laws and regulations)
- Patient Participation in the trial (substance, trial number, patient number, date patient was informed)
- Dates of patient's visits, including dispensing of trial medication
- Medical history (including trial indication and concomitant diseases, if applicable)
- Medication history
- Adverse events and outcome events (onset date (mandatory), and end date (if available))
- Serious adverse events (onset date (mandatory), and end date (if available))
- Concomitant therapy (start date, changes)
- Originals or copies of laboratory results and other imaging or testing results, with proper documented medical evaluation (in validated electronic format, if available)
- Completion of patient's Participation in the trial" (end date; in case of premature discontinuation document the reason for it).
- Prior to allocation of a patient to a treatment into a clinical trial, there must be documented evidence in the source data (e.g. medical records) that the trial Participant meets all inclusion criteria and does not meet any exclusion criteria. The absence of records (either medical records, verbal documented feedback of the patient or testing conducted specific for a protocol) to support inclusion/exclusion criteria does not make the patient eligible for the clinical trial.
- Technical information collected on PK sampling days (e.g., PK sampling times, repeated vital signs linked with PK) may be collected on specific paper PK logs, which will be considered as source data for related entries in eCRF and are considered Part of the ISF.

8.3.2 Direct access to source data and documents

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

8.3.3 Storage period of records

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

8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

BI is responsible to fulfil their legal and regulatory reporting obligation in accordance with regulatory requirements.
Exemptions from expedited reporting are described in Section 5.2.6.2, if applicable.

8.5 STATEMENT OF CONFIDENTIALITY AND PATIENT PRIVACY

Individual patient data obtained as a result of this trial is considered confidential and disclosure to third Parties is prohibited with the exceptions noted in Section 8.7. 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 (WHO) GCP handbook.

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

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

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

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

8.6 TRIAL MILESTONES

The **start of the trial** is defined as the date when the first patient in the whole trial signs informed consent.
The end of the trial is defined as the date of the last visit of the last patient in the whole trial ("Last Patient Completed").
The "**Last Patient Drug Discontinuation"** (LPDD) date is defined as the date on which the last patient at the trial site ends trial medication (as scheduled per protocol or prematurely). Individual investigators will be notified of suspected unexpected serious adverse reactions (SUSARs) occurring with the trial medication until 30 days after LPDD. **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.
The IEC/CA in the member state will be notified about the trial milestones according to the local laws.
A final report of the clinical trial data will be written only after all patients have completed the trial to incorporate and consider all data in the report.
The sponsor will submit to the EU database a summary of the final trial results within one year from the end of a clinical trial.

8.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL

The trial is sponsored by Boehringer Ingelheim (BI).
The trial is conducted at a site specialized in conducting PET studies for biodistribution and tumor uptake of radiolabled drugs.
A Coordinating Investigator is responsible to coordinate investigators at the Participating site. Tasks and responsibilities are defined in a contract.

A SMC composed of members of the trial site and members of the BI trial team will be established to review individual and aggregated data at regular intervals to assess the feasibility/specificity of the process, to evaluate the appropriacy of further enrolment in a cohort or the move to the next cohort and to support the identification of the best dose based on PET results and possible associated biomarkers. The SMC will also review safety and efficacy data to support the overall determination of the safety profile and risk/benefit ratio of the treatment.
Details of the SMC responsibilities and procedures are described in the SMC plan.

Relevant documentation on the Participating (Principal) Investigators (e.g. their curricula vitae) will be filed in the ISF. The investigators will have access to the BI clinical trial portal (Clinergize) to facilitate document exchange and maintain electronic ISF.

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

- manage the trial in accordance with applicable regulations and internal SOPs,

- direct the clinical trial team in the preparation, conduct, and reporting of the trial,
- ensure appropriate training and information of Local Clinical Monitor (CML), Clinical Research Associates (CRAs), and investigators of Participating country.

The organisation of the trial in the Participating country will be performed by the respective local or regional BI-organisation (Operating Unit (OPU)) in accordance with applicable regulations and BI SOPs.

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

Tasks and functions assigned in order to organise, manage, and evaluate the trial are defined according to BI SOPs. A list of responsible persons and relevant local information can be found in the ISF.
External laboratory services will be used in this trial. Details will be provided in the Laboratory Manuals, available in the ISF.

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R18-3257 Central Committee on Research Involving Human Subjects (CCMO): starting page. http://www.ccmo.nl/en/ (access date: 25 October 2018); Central Committee on Research Involving Human Subjects (CCMO) 2018.

9.2 UNPUBLISHED REFERENCES

001-MCG-156_RD-01 Reference Document to Corporate Guideline: Handling of Missing and Incomplete AE Dates. Version 3.0

001-MCS-36-472 Corporate SOP: Standards and processes for analyses performed within Clinical Pharmacokinetics/ Pharmacodynamics. Version 3.0

10. APPENDICES

10.1 IMMUNE-RELATED ADVERSE EVENTS OF SPECIAL INTEREST

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

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

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

Table 10.1: 1 (con't) Immune-related adverse events of special interest

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

Table 10.1: 1 (con't) Immune-related adverse events of special interest

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

10.2 MANAGEMENT OF IMMUNE-RELATED ADVERSE EVENTS

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

- Pneumonitis:
  - For Grade 2 events, treat with systemic corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 28 days.
  - Add prophylactic antibiotics for opportunistic infections in the case of prolonged steroid administration.
  - For Grade 3-4 events immediately treat with i.v. steroids. Administer additional anti-inflammatory measures, as needed.
  - BI 754091 and BI 754111 should be permanently discontinued for Grade 3-4 pneumonitis, inability to taper steroids to 10 mg or less prednisone or equivalent within 12 weeks, or persistent Grade 2 AEs that do not recover to Grade 1 or less within 12 weeks.
- Diarrhea/Colitis:
  Subjects should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, 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 diarrhea/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 diarrhea, consider gastro-intestinal (GI) consultation and endoscopy to confirm or rule out colitis.
  - For Grade 2 diarrhea/colitis that persists greater than 3 days, administer oral corticosteroids.
  - For Grade 3 or 4 diarrhea that persists >1 week, treat with i.v. steroids followed by high-dose oral steroids.
  - For Grade 3 or 4 colitis, or recurrent colitis of any grade, permanently discontinue BI 754091 and BI 754111, and immediately treat with i.v. steroids followed by high-dose oral steroids.
  - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 28 days.
  - BI 754091 and BI 754111 should be permanently discontinued for Grade 3-4 or recurrent colitis of any grade, inability to taper steroids to 10 mg or less prednisone or equivalent within 12 weeks, or persistent Grade 2-3 AEs that do not recover to Grade 1 or less within 12 weeks.
- Type 1 diabetes mellitus (if new onset, including diabetic ketoacidosis) Grade 3, or ≥ Grade 3 hyperglycaemia, if associated with ketosis (ketonuria) or metabolic acidosis

  - For Type 1 diabetes mellitus Grade 3-4 or Grade 3-4 hyperglycaemia
    - Insulin replacement therapy is recommended for Type I diabetes mellitus and for Grade 3-4 hyperglycaemia associated with metabolic acidosis or ketonuria.
    - Evaluate subjects with serum glucose and a metabolic panel, urine ketones, glycosylated haemoglobin, and C-peptide.
  - BI 754091 and BI 754111 should be permanently discontinued for Grade 4 diabetes mellitus, any recurrent Grade 3 AE or persistent Grade 2-3 AE that does not recover to Grade 1 or less within 12 weeks.
- Hypophysitis:
  - For Grade 2 events, treat with corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 28 days. Replacement of appropriate hormones may be required as the steroid dose is tapered.
  - For Grade 3 events, treat with an initial dose of *i.v.* corticosteroids followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 28 days. Replacement of appropriate hormones may be required as the steroid dose is tapered.
  - For Grade 4 events, permanently discontinue BI 754091 and BI 754111, and treat with an initial dose of i.v. corticosteroids followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 28 days. Replacement of appropriate hormones may be required as the steroid dose is tapered.
  - BI 754091 and BI 754111 should be permanently discontinued for Grade 4 hypophysitis, any recurrent Grade 3 AE, inability to taper steroids to 10 mg or less prednisone or equivalent within 12 weeks, or persistent Grade 2-3 AEs that do not recover to Grade 1 or less within 12 weeks.
- Hyperthyroidism or Hypothyroidism:
- Thyroid disorders can occur at any time during treatment. Monitor subjects for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders.
  - For Grade 2 hyperthyroidism events (and Grade 3-4 hypothyroidism):
    - In hyperthyroidism, nonselective beta-blockers (e.g., propranolol) are suggested as initial therapy.
    - In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyronine, is indicated per standard of care.
  - For Grade 3-4 hyperthyroidism
    - Treat with an initial dose of i.v. corticosteroid followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 28 days. Replacement of appropriate hormones may be required as the steroid dose is tapered.
  - BI 754091 and BI 754111 should be permanently discontinued for any recurrent Grade 3-4 AE, inability to taper steroids to 10 mg or less prednisone or equivalent within 12 weeks, or persistent Grade 2-3 AEs that do not recover to Grade 1 or less within 12 weeks.

- Hepatic:
  - For Grade 2 events, monitor liver function tests more frequently until returned to baseline values (consider weekly).
    - Treat with *i.v.* or oral corticosteroids
  - For Grade 3-4 events, treat with i.v. corticosteroids for 24 to 48 hours.
  - When symptoms improve to Grade 1 or less, a steroid taper should be started and continued over no less than 28 days.
  - BI 754091 and BI 754111 should be permanently discontinued for any recurrent Grade 3-4 AE, transaminase increases >5 times ULN or total bilirubin >3 times ULN (unless unequivocally attributably to another cause), inability to taper steroids to 10 mg or less prednisone or equivalent within 12 weeks, or persistent Grade 2-3 AEs that do not recover to Grade 1 or less within 12 weeks.
- Renal failure or nephritis:
  - For Grade 2 events, treat with corticosteroids.
  - For Grade 3-4 events, treat with systemic corticosteroids.
  - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 28 days.
  - BI 754091 and BI 754111 should be permanently discontinued for any recurrent Grade 3-4 AE, inability to taper steroids to 10 mg or less prednisone or equivalent within 12 weeks, or persistent Grade 2-3 AEs that do not recover to Grade 1 or less within 12 weeks.
- Adrenal insufficiency:
  - BI 754091 and BI 754111 should be permanently discontinued for Grade 3-4 adrenal insufficiency or persistent Grade 2 AEs that do not recover to Grade 1 or less within 12 weeks.
- Rash:
  - BI 754091 and BI 754111 should be permanently discontinued for Grade 4 rash, any recurrent Grade 3 AE or persistent Grade 2-3 AEs that do not recover to Grade 1 or less within 12 weeks.
- Encephalitis:
  - BI 754091 and BI 754111 should be permanently discontinued for any grade encephalitis.
- Infusion reactions:
  Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion.
  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 IRECIST

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

Confirming progression

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

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

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

New lesions

New lesions should be assessed and measured as they appear using RECIST 1.1 criteria (maximum of 5 lesions, no more than 2 per site, at least 10 mm in long axis (or 15 mm in short axis for nodal lesions), and recorded as New Lesions-Target (NLT) and New Lesion-Non-Target (NLNT) to allow clear differentiation from baseline target and non-target lesions. New lesions may either meet the criteria of NLT or NLNT to drive iUPD (or iCPD). However, the measurements of target lesions should NOT be included in the sum of measures of original target lesions identified at baseline. Rather, these measurements will be collected on a separate table in the case record form.
PD is confirmed in the New Lesion category if the next imaging assessment, conducted at least 4 weeks (but not more than 8 weeks) after iUPD confirms further progression from iUPD with either an increase of at least 5 mm in the absolute value of the sum of NLT OR an

increase (but not necessarily unequivocal increase) in the size of NLNT lesions OR the appearance of additional new lesions

Table 10.3: 1 Time-point (TP) iResponse

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

* Using RECIST 1.1 principles. If no PSPD occurs, RECIST 1.1 and iRECIST categories for CR, PR and SD would be the same.

** in any lesion category.

*** previously identified in assessment immediately prior to this TP.

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

Table 10.3: 2 iRECIST Best Overall Response (iBOR)

TPR1	TPR2	TPR3	TPR4	TPR5	iBOR
iCR	iCR	iCR, iPR, iUPD, NE	iUPD	iCPD	iCR
iUPD	iPR, iSD, NE	iCR	iCR	iCR, iPR, iSD, iUPD, NE	iCR
iUPD	iPR	iPR	iPR, iSD, iUPD, NE	iPR, iSD, iUPD, NE, iCPD	iPR
iUPD	iSD, NE	iPR	iPR	iPR, iSD, iUPD, NE	iPR
iUPD	iSD	iSD, iUPD, NE	iSD, iUPD, iCPD, NE	iSD, iUPD, iCPD, NE	iSD
iUPD	iCPD	Anything	Anything	Anything	iCPD
iUPD	iUPD	iCPD	Anything	Anything	iCPD
iUPD	NE	NE	NE	NE	iUPD

- NE = not evaluable that cycle.
- Designation “I” for BOR can be used to indicate prior iUPD to aid in data interpretation.
- For patients with non-target disease only at baseline, only CR or non-CR/non-PD can be assigned at each TPR but is not shown in the table for ease of presentation.

10.4 SPECIFIC COUNTRY ADAPTIONS

Ethical conduct of the study (addendum to Section 8)
This study will be conducted according to the principles of the Declaration of Helsinki (adopted by the 18th World Medical Association (WMA) General Assembly, Helsinki, Finland, June 1964 and last amended by the 64th WMA General Assembly, Fortaleza, Brazil, October 2013and are consistent with ICH/Good Clinical Practice, and applicable regulatory requirements subject data protection.

Public disclosure and publication policy (addendum to Section 8)
Public disclosure and publication policy will follow Centrale Commissie Mensgebonden Onderzoek (CCMO) requirements and is available on website of CCMO (R18_3257).

Compensation for injury (addendum to Section 8)
The sponsor/investigator has a liability insurance which is in accordance with article 7, subsection 9 of the WMO.
The sponsor (also) has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO and the Measure regarding Compulsory Insurance for Clinical Research in Humans of 23th June 2003). This insurance provides cover for damage to research subjects through injury or death caused by the study.

Use and storage of data / body material (addendum to Section 8.3.3)
All coded data will be kept by the sponsor. This link will remain at the trial site for a maximum of 30 years

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 investigations. The trial samples will be discarded not later than 5 years after the final trial report has been signed (see Section 5.3.2).

Biobanking for remainders (leftover) from mandatory tumor samples collected for the purposes of the clinical trial, which would otherwise be discarded, can be stored in a biobank for up to 30 years for future research.

Study updates (addendum to Section 8.6)
Start and end date of the study as well as annual progress reports and notification of (early) termination study will be passed on to the Ethics Committee (METc).

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

11.1 GLOBAL AMENDMENT 1

Date of amendment		30 Oct 2018
EudraCT number **EU number**		2017-005046-30
BI Trial number		1381-0003
BI Investigational Product(s)		[^{89}Zr]Zr-BI 754111, BI 754091 and BI 754111
Title of protocol		An open label Phase I PET imaging study to investigate the bio-distribution and tumor uptake of [^{89}Zr]Zr-BI 754111 in patients with advanced non-small cell lung cancer and head and neck squamous cell carcinoma treated with BI 754111 in combination with BI 754091
To be implemented only after approval of the IRB / IEC / Competent Authorities		☒
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		☐
Section to be changed		1. Section 1.4 2. Section 8.1 3. Section 9.1 4. Section 10.4
Description of change		1. Change regarding risk due to radiation burden 2. Deletion of wording refering to legal representative and addition of local Ethics Committee reference 3. Deletion of obsolete unpublished reference 4. New section
Rationale for change		1. Text adapted to better describe the risk due to radiation exposure and to correctly describe the risk category. 2. Ethics committee requirement 3. Section to address country specific requirements

11.2 GLOBAL AMENDMENT 2

Date of amendment		27 Jan 2020
EudraCT number **EU number**		2017-005046-30
BI Trial number		1381-0003
BI Investigational Product(s)		[^{89}Zr]Zr-BI 754111, BI 754091 and BI 754111
Title of protocol		An open label Phase I PET imaging study to investigate the bio-distribution and tumor uptake of [^{89}Zr]Zr-BI 754111 in patients with advanced non-small cell lung cancer and head and neck squamous cell carcinoma treated with BI 754111 in combination with BI 754091
To be implemented only after approval of the IRB / IEC / Competent Authorities		☒
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		☐
Section to be changed		1. Flow chart 2. Blood sample flow chart 3. Section 1.4 4. [redacted] 5. Section 3.1 6. Section 4.2.1 7. Section 5.1 8. Section 5.2.3 9. Section 5.2.6.1.4 10. Section 5.2.6.2.5 11. Section 5.4.1 12. Section 5.4.2 13. Section 5.6.2 14. Section 6.2 15. Section 9.1 16. Section 10.2 (Appendix)
Description of change		1. Table and footnotes adapted for considering: **a)** "administration of pre-treatment medication",

		b) optional biopsy at Cycle 1 **c)** changed timepoints for blood sampling, **d)** changed timepoints for PET imaging 2. Table adapted for considering changed timepoints for PK radioactivity sampling, BI754111 PK sampling and PET scan time points in cycles 1 and 2 3. Update on safety and efficacy information 4. [redacted] 5. Adapted design for part 2 6. Change in pre-medication information 7. Correction 8. Additional information in case of criteria for hepatic injury are fulfilled 9. Text related to AESI adapted for potential DILI events/hepatic injury and for infusion-related reactions 10. Title correction and clarification on exempted events 11. Addition of optional biopsy at Cycle 1 12. Correction 13. Adaptation 14. Adaptation 15. Correction 16. Update
Rationale for change		1. Adaptations for considering: **a)** Prophylactic treatment to reduce the risk of infusion-related reaction – **b)** Optional biopsies added to allow for [redacted] **c)** Revised blood sampling time points: To better determine initial clearance, potential non-linearity due to major sink or internalization of [^{89}Zr]Zr-BI 754111 to determine if radioactivity concentration in blood correlates well with the image derived input function and the concentration of BI 754111. **d)** Change in PET scan timepoints has been made to

		support kinetic based modelling of drug uptake in tumor lesions and organs/ tissues 2. See rational **c)** above 3. 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 4. [redacted] 5. Adapted design to consider the additional PET timepoints and the optional biopsy 6. 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 7. To correct erroneous reference 8. 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. 9. Language about hepatic injury and potential DILI case has been updated to clarify the criteria for liver abnormalities which prompt reporting as AESI and completion of potential DILI checklist. In addition, text has been added for pre-treatment medication prior to administration of the study treatment in order to reduce the risk of infusion related reactions and more detail has been provided on what to do in the event of a Grade 3 or higher infusion related reaction. 10. Clarification that hepatic injury does not apply for PD reporting exemption 11. Optional biopsy: same rational as above (1, **b)**) 12. Text related to cytokines measurement has been deleted as this does not apply in this trial 13. Adaptation for considering changed timepoints for PK radioactivity sampling in cycles 1 and 2 14. Adaptation for considering optional biopsy in C1 and changed timepoints for PK radioactivity sampling in C1 and C2 15. To correct for actual reference for iRECIST 16. To provide more detail on what to do in the event of an infusion related reaction

APPROVAL / SIGNATURE PAGE

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

Title: An open label Phase I PET imaging study to investigate the bio-distribution and tumor uptake of [89Zr]Zr-BI 754111 in patients with advanced non-small cell lung cancer and head and neck squamous cell carcinoma treated with BI 754111 in combination with BI 754091

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval-Therapeutic Area [redacted]	[redacted]	27 Jan 2020 12:39 CET
Approval-Biostatistics		27 Jan 2020 13:42 CET
Approval-Clinical Trial Leader		27 Jan 2020 14:36 CET
Approval-Clinical Pharmacokinetics		27 Jan 2020 16:05 CET
Approval-Team Member Medicine		27 Jan 2020 16:21 CET
Verification-Paper Signature Completion		29 Jan 2020 15:57 CET

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed