Clinical Trial Protocol

	Document Number:	**c16151514-12**
EudraCT No.: **EU Trial No:**	2017-001378-41	
BI Trial No.:	1336-0011	
BI Investigational Product(s):	BI 836880 (anti-VEGF/Ang2) Ezabenlimab (BI 754091 [anti-PD-1])	
Title:	An open label phase Ib dose finding study of BI 836880 in combination with ezabenlimab to characterize safety, tolerability, pharmacokinetics, pharmacodynamics and efficacy in patients with locally advanced or metastatic non-squamous Non-Small Cell Lung Cancer and in other solid tumors	
Lay Title:	A study to test different doses of BI 836880 combined with ezabenlimab in patients with advanced non-small cell lung cancer followed by other types of advanced solid tumours	
Clinical Phase:	Phase Ib	
Trial Clinical Monitor:	[redacted] Phone: [redacted] Fax: [redacted]	
Coordinating Investigator:	[redacted] Phone: [redacted] Fax: [redacted]	
Status:	Final Protocol (Revised Protocol (based on global amendment 8)	
Version and Date:	Version: 9.0	Date 18 May 2023

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Finished product name	Not applicable
Active ingredient name:	BI 836880 and BI 754091 (ezabenlimab)
Protocol date	19 Jan 2018
Revision date	18 May 2023
Trial number	1336-0011
Title of trial:	An open label phase Ib dose finding study of BI 836880 in combination with ezabenlimab to characterize safety, tolerability, pharmacokinetics, pharmacodynamics and efficacy in patients with locally advanced or metastatic non-squamous Non-Small Cell Lung Cancer and in other solid tumors
Coordinating Investigator	[redacted] Phone: [redacted] Fax: [redacted]
Trial site(s):	Multinational and multicentre study
Clinical phase:	Phase 1b
Study Design	This is a Phase Ib study, containing two parts; Part 1 (dose escalation of BI 836880 in combination with ezabenlimab) and Part 2 (expansion phase in 8 cohorts). **Part 1**: Dose escalation of BI 836880 in combination with ezabenlimab in check point inhibitor naïve or previously treated patients with locally advanced or metastatic non-squamous NSCLC who progressed during or after completion of at least 2 cycles first line (in case of checkpoint inhibitor naïve patients) platinum-based therapy and patients who progressed during or relapsed after completion of at least 2 cycles (in case of checkpoint inhibitor relapsing patients) of platinum-based chemotherapy and a checkpoint inhibitor treatment (monotherapy or in combination with chemotherapy). **Part 2**: Open label, non-randomized expansion phase to assess efficacy and safety of BI 836880 in combination with ezabenlimab:

	Cohort A (NSCLC): Patient with pathologically confirmed locally advanced or metastatic non-squamous NSCLC who progressed during or after **check-point inhibitor monotherapy treatment**. Patient must also have received treatment with a platinum-based chemotherapy regimen and have progressed or be intolerant, or ineligible, as per applicable local practice. **Cohort B (NSCLC):** Patient with pathologically confirmed locally advanced or metastatic non-squamous NSCLC who progressed during or after **platinum-based chemotherapy and a check-point inhibitor (CPI) combination treatment as the** most recent anticancer treatment. **Cohort C (SCLC):** Patient with pathologically confirmed locally advanced or metastatic Small Cell Lung Cancer (SCLC) with documented intolerance to platinum-based chemotherapy or refractory to platinum-based chemotherapy (progression during treatment or during < 90 days of the last dose of platinum-based chemotherapy). Patients who are platinum-sensitive (progression ≥ 90 days of the last dose of platinum-based chemotherapy) must also have received one additional prior line of platinum-based chemotherapy, if eligible, with or without combination with CPI as per applicable local treatment country guidelines. **Cohort D (Glioblastoma):** Patient with histologically confirmed recurrent glioblastoma with **no more than two previous lines of chemotherapy** (concurrent and adjuvant temozolomide based chemotherapy including in combination with another investigational agent is considered one line of chemotherapy). **Cohort E (Melanoma):** Patient with histologically confirmed, unresectable, Stage IV metastatic melanoma who progressed during or after CPI based regimen. Patients with a BRAF mutation must have received targeted treatment, or were not eligible, with a BRAF and MEK inhibitor as per applicable local country guidelines. **Cohort F (2nd line Hepatocellular Carcinoma):** Patient with locally advanced or metastatic and/or unresectable Hepatocellular Carcinoma (HCC) who were intolerant or progressed during 1st line sorafenib or lenvatinib treatment. **Cohort G (1st line Hepatocellular Carcinoma):**

	Patient with locally advanced or metastatic and/or unresectable HCC with no prior systemic treatment. This will be implemented only in countries where this cohort is approved. **Cohort H (2nd line Hepatocellular Carcinoma – atezolizumab in combination with bevacizumab failures):** Patient with locally advanced or metastatic and/or unresectable Hepatocellular Carcinoma (HCC) who were intolerant or progressed during 1st line treatment with atezolizumab in combination with bevacizumab. This will be implemented only in countries where this cohort is approved.
Objective(s):	**PART 1:** **Primary objective:** • To determine the Recommended Phase 2 Dose (RP2D) of BI 836880 in combination with ezabenlimab in check point inhibitor naïve or previously treated patients with locally advanced or metastatic non-squamous NSCLC who progressed during or after first line platinum-based chemotherapy **Secondary objective:** • To provide safety data • To evaluate the basic pharmacokinetics of BI 836880 and ezabenlimab during combination therapy after the first and fourth infusion cycle. [redacted] **PART 2:** **Primary objective:** • To assess anti-tumor activity of BI 836880 in combination with ezabenlimab in patients with locally advanced or metastatic non-squamous NSCLC and other solid tumors **Secondary objective**: • To provide safety data and further investigate clinical efficacy including disease control (DC), duration of objective

	response (DoR), progression free survival (PFS), and tumor shrinkage. • To evaluate the basic pharmacokinetics of BI 836880 and ezabenlimab during combination therapy after the first infusion cycle [redacted]
Endpoints	Primary endpoints: **PART 1:** • The primary endpoint is the number of patients with dose limiting toxicity (DLT) within the first cycle of treatment (3 weeks). **PART 2:** • The primary endpoint is Objective Response (OR) defined as best overall response (RECIST 1.1) of complete response (CR) or partial response (PR) from first treatment infusion until the earliest of disease progression, death or last evaluable tumor assessment before start of subsequent anti-cancer therapy, lost to follow-up, or withdrawal of consent. In case of recurrent glioblastoma (GBM), assessment will be based on RANO (Response Assessment in Neuro-Oncology) criteria. **Secondary endpoint(s):** **PART 1:** • Adverse events (AEs), drug related AEs, drug related AEs leading to dose reduction or discontinuation during treatment period. • Pharmacokinetic parameters C_{max}, t_{max}, $AUC_{0\text{-}504h}$ after the first and fourth infusion cycle. **PART 2:**

	• Adverse events (AEs), drug related AEs, drug related AEs leading to dose reduction or discontinuation during treatment period • Disease control (DC), defined as best overall response of CR, PR, or stable disease (SD) (RANO for GBM & RECIST1.1 for all other cohorts) from first treatment infusion until the earliest of disease progression, death or last evaluable tumor assessment before start of subsequent anti-cancer therapy, lost to follow-up or withdrawal of consent. • Duration of objective response (DoR), defined as the time from first documented CR or PR (RANO for GBM & RECIST1.1 for all other cohorts) until the earliest of disease progression or death among patients with OR. • Progression-free survival (PFS) (RANO for GBM & RECIST1.1 for all other cohorts), defined as the time from first treatment infusion until disease progression or death from any cause, whichever occurs earlier. Tumour shrinkage (in millimeters), defined as the difference between the minimum post-baseline sum of diameters of target lesions (longest for non-nodal lesions, short axis for nodal lesions) and the baseline sum of diameters of the same set of target lesions in case of RECIST. In GBM, using RANO criteria, tumor shrinkage will be calculated based on the difference between the post-baseline and baseline measurements of the sum of product of the largest bi-dimensional measurements for all target lesions. • Pharmacokinetic parameters C_{max}, t_{max}, $AUC_{0\text{-}504h}$ after the first infusion cycle.
Number of patients entered:	A total of approximately 420 patients (22 in Part 1 plus 398 in Part 2) will be entered.
Number of patients on each treatment:	Part 1: 12 to 18 evaluable patients Part 2: 80 evaluable locally advanced or metastatic non-squamous NSCLC patients (Cohort A and B; 40 patients per cohort); 60 evaluable patients in cohort F and 30 evaluable patients in each of the other 5 cohorts for a total of 290 patients.
Diagnosis:	Part 1: Naïve or previously checkpoint inhibitor treated patients with locally advanced or metastatic non-squamous NSCLC who progressed during or after first line (in case of checkpoint inhibitor naïve patients) platinum-based therapy and patients who progressed during or relapsed after completion of at least 2 cycles (in case of checkpoint inhibitor relapsing patients) of platinum-based

	chemotherapy and a checkpoint inhibitor treatment (monotherapy or in combination with chemotherapy). Part 2: Cohort A and B: Patients with locally advanced or metastatic non-squamous NSCLC who progressed or relapsed during or after a CPI based treatment as monotherapy or in combination with platinum-based chemotherapy. Cohort C: Patients with metastatic SCLC Cohort D: Patients with recurrent glioblastoma Cohort E: Patients with metastatic melanoma Cohort F: Patients with 2nd line hepatocellular carcinoma Cohort G: Patients with 1st line hepatocellular carcinoma (This will be implemented only in countries where this cohort is approved.) Cohort H: Patients with 2nd line hepatocellular carcinoma – atezolizumab + bevacizumab failures (This will be implemented only in countries where this cohort is approved.)
Main in- and exclusion criteria	**Inclusion Criteria:** <u>For Part 1:</u> 1. Age ≥ 18 years 2. Pathologically confirmed diagnosis of non-squamous NSCLC 3. Locally advanced (stage IIIb) or metastatic (stage IV) NSCLC 4. Documented disease progression or relapse (based on investigator's assessment) during or after completion of at least 2 cycles of platinum-based chemotherapy as first line treatment of Stage IIIB/IV non- squamous NSCLC or for checkpoint inhibitor experienced patients during or after completion of at least 2 cycles of platinum-based chemotherapy and a checkpoint inhibitor treatment (monotherapy or in combination with chemotherapy). This includes patients relapsing within 6 months of completing (neo)adjuvant/curative-intent chemotherapy/CPI or chemoradiotherapy. 5. At least one target lesion (outside the brain), that can be accurately measured per RECIST v 1.1 6. Availability and willingness to provide a fresh tumour tissue sample obtained after relapse or progression on or after prior therapy. 7. ECOG performance status of 0 or 1 8. Adequate hepatic, renal and bone marrow functions

For Part 2:

1. Of full age (according to local legislation, usually ≥ 18 years) at screening
2. At least one measurable target lesion outside the brain (excluding the glioblastoma patients), that can be accurately measured per RECIST v 1.1
3. ECOG performance status ≤ 1 (Karnofsky status for GBM)

Inclusion for:

Cohort A (NSCLC):

- Pathologically confirmed locally advanced or metastatic non-squamous NSCLC
- **Prior Check-point inhibitor monotherapy either as 1st or 2nd line. Patient must also have received treatment with a platinum-based chemotherapy regimen and have progressed or be intolerant, or ineligible, as per applicable local practice.**
- Approximately 10 patients will be recruited who have primary resistance to CPI based therapy which is defined as those advanced or metastatic IIIB/IV non-squamous NSCLC patients who previously received at least 2 cycles of CPI treatment and progressed without achieving benefit (SD <4 months or progressive disease in <4 months).
- Approximately 30 patients will be recruited who have secondary resistance to CPI based therapy which is defined as those advanced or metastatic IIIB/IV non-squamous NSCLC patients who had a documented minimum duration of benefit of (minimum of stable disease) 4 months and minimum treatment duration of 2 cycles on the previous CPI treatment without experiencing disease progression during that period.

  Patients with NSCLC known to harbor an ALK rearrangement, or EGFR mutation, or other genomic aberrations (e.g., ROS rearrangement, BRAF V600E mutation), are only eligible after experiencing disease progression (during or after treatment) or intolerance to approved targeted therapy for respective genomic aberrations, as applicable per local country guidelines.
- No more than one prior line of targeted therapy or chemotherapy regimen is allowed.

Cohort B (NSCLC):

	- Pathologically confirmed locally advanced or metastatic non-squamous NSCLC - **1st line Platinum-based chemotherapy and a check-point inhibitor combination treatment** as the most recent therapy before entering trial - Approximately 10 patients will be recruited who have primary resistance to the combination therapy which is defined as those advanced or metastatic IIIB/IV non-squamous NSCLC patients who previously received at least 2 cycles of platinum-based chemotherapy and CPI treatment and progressed without achieving benefit (SD < 4 months or progressive disease in < 4 months). - Approximately 30 patients will be recruited who have secondary resistance to CPI based therapy which is defined as those advanced or metastatic IIIB/IV non-squamous NSCLC patients who had a documented minimum duration of benefit (minimum of stable disease) of 4 months when previously treated with at least 2 cycles of the CPI and platinum-based chemotherapy in a first line setting without experiencing disease progression during that period. - Patients with NSCLC known to harbor an ALK rearrangement, or EGFR mutation, or other genomic aberrations (e.g., ROS rearrangement, BRAF V600E mutation), are only eligible after experiencing disease progression (during or after treatment) or intolerance to approved targeted therapy for respective genomic aberrations, as applicable per local country guidelines. No more than one line of targeted therapy is allowed.
	Cohort C (SCLC): - Pathologically confirmed locally advanced or metastatic SCLC - Documented intolerance to platinum-based chemotherapy or refractory to platinum-based chemotherapy (progression during treatment or during < 90 days of the last dose of platinum-based chemotherapy). Patients who are platinum-sensitive (progression ≥ 90 days of the last dose of platinum-based chemotherapy) must also have received one additional prior line of platinum-based chemotherapy, if eligible, with or without combination with CPI as per applicable local treatment country guidelines.
	Cohort D (recurrent glioblastoma): - Histologically confirmed de novo glioblastoma (primary) at first or second recurrence after initial standard, control or experimental therapy that includes at a minimum RT.

	- Unequivocal evidence of progressive disease on contrast-enhanced brain CT or MRI as defined by RANO Criteria, or have documented recurrent glioblastoma on diagnostic biopsy. - **No more than two lines of prior chemotherapy** (concurrent and adjuvant temozolomide based chemotherapy including in combination with another investigational agent is considered one line of chemotherapy). - Only first and second recurrences of GBM are eligible - An interval of at least 12 weeks from the completion of radiation therapy to start of study drug unless there is a new area of enhancement consistent with recurrent tumor outside the radiation field or there is unequivocal histologic confirmation of tumor progression - Patient may have been operated for recurrence. If operated: residual and measurable disease after surgery is required; surgical site must be adequately healed free of drainage or cellulitis, and the underlying cranioplasty must appear intact at the time of randomization - Karnofsky performance status (KPS) ≥ 70 - MRI within 14 days prior to start of study drug - Patients should be immunocompetent (i.e. no concomitant treatment with dexamethasone (or equivalent), or receive stable/decreasing steroid levels not exceeding 2 mg/day dexamethasone (or equivalent) during the last 3 days prior to clinical screening; no severe lymphopenia).
	Cohort E (Melanoma): - Histologically confirmed, unresectable, Stage IV metastatic melanoma. - Patients with a BRAF mutation must have received targeted treatment, or were not eligible, with a BRAF and MEK inhibitor as per applicable local country guidelines. In such a case no more than one line of targeted therapy is allowed. - **At least one line of any kind of CPI based regimen as last treatment before entering the study** - Documented progression during or after CPI therapy based regimen.
	Cohort F (2nd line Hepatocellular Carcinoma): - Patients must have diagnosis of locally advanced or metastatic and/or unresectable histologically confirmed advanced hepatocellular carcinoma, not eligible for surgical and/or locoregional therapies.

	- Patients should have progressed on or after first line treatment with sorafenib or lenvatinib or discontinued sorafenib or lenvatinib due to lack of tolerability after receiving at least two weeks of treatment. Reason for discontinuation must be documented. - Documented virology status of hepatitis, as confirmed by screening hepatitis B surface antigen (HBsAg), antibody to hepatitis B core antigen (anti-HBc), HBV DNA, anti-hepatitis C virus (anti-HCV) and HCV RNA as applicable. - Child-Pugh score class A. - Anti-viral therapy per local standard-of-care if active hepatitis B virus (HBV). HBV DNA to be <500IU/ml and patients on anti HBV therapy for >4 weeks before entering the study.
	Cohort G (1st line Hepatocellular Carcinoma): (To be implemented only in countries where this cohort is approved.) - The subject should have diagnosis of locally advanced or metastatic and/or unresectable histologically confirmed advanced hepatocellular carcinoma that is not amenable to a curative treatment approach (e.g., transplant, surgery, ablation therapy) or locoregional therapy (e.g., TACE). - No prior systemic therapy for HCC. Previous use of herbal therapies/traditional Chinese medicines with anti-cancer activity included in the label is allowed, provided that these medications are discontinued prior to randomization. - Child-Pugh Score of A. - Documented virology status of hepatitis, as confirmed by screening hepatitis B surface antigen (HBsAg), antibody to hepatitis B core antigen (anti-HBc), HBV DNA, anti-hepatitis C virus (anti-HCV) and HCV RNA as applicable. - Anti-viral therapy per local standard-of-care if active hepatitis B virus (HBV). HBV DNA to be <500IU/ml and patients on anti HBV therapy for >4 weeks before entering the study.
	Cohort H (2nd line Hepatocellular Carcinoma – atezolizumab + bevacizumab failures): (To be implemented only in countries where this cohort is approved.) - Patients must have diagnosis of locally advanced or metastatic and/or unresectable histologically confirmed advanced hepatocellular carcinoma, not eligible for surgical and/or locoregional therapies.

- Patients should have progressed on or after first line treatment with atezolizumab in combination with bevacizumab or discontinued treatment due to lack of tolerability after receiving at least two cycles of treatment. Reason for discontinuation must be documented.
- Documented virology status of hepatitis, as confirmed by screening hepatitis B surface antigen (HBsAg), antibody to hepatitis B core antigen (anti-HBc), HBV DNA, anti-hepatitis C virus (anti-HCV) and HCV RNA as applicable.
- Child-Pugh score class A.

  Anti-viral therapy per local standard-of-care if active hepatitis B virus (HBV). HBV DNA to be <500IU/ml and patients on anti HBV therapy for >4 weeks before entering the study.

4. Adequate hepatic, renal and bone marrow functions
5. Availability and willingness to provide a fresh tumor tissue sample obtained after relapse or progression on or after prior therapy. In case a fresh biopsy cannot be obtained (e.g. inaccessible lesions or patient safety concern), an archived specimen obtained up to 6 months prior to cycle 1, visit 1 (C1V1) may be submitted in case no systemic antineoplastic therapy has been administered between the biopsy and C1V1 (except for cohort D). For cohorts E, F and G, a fresh on-treatment biopsy is mandatory at C3D1, if possible from the same lesion as the pre-treatment biopsy.
6. Life expectancy ≥ 3 months after start of the treatment in the opinion of the investigator.

Exclusion Criteria:

<u>Part 2:</u>

1 Not more than one CPI based treatment regimen prior to entering study (e.g., anti-Programmed Death receptor-1 (PD-1), anti-Programmed Death-1 ligand-1 (PD-L1), anti-PD-L2, or anti-cytotoxic T lymphocyte associated antigen-4 (anti-CTLA-4) antibody). In case of CPIs combination, they need to be approved by the local regulatory agencies (e.g., Melanoma cohort (Cohort E)).

2 Active hepatitis B virus (HBV) or hepatitis C virus (HCV) infection (exception for patients in HCC cohorts; Cohort F, G & cohort H).

3 Prior treatment with any antiangiogenic treatment (e.g. bevacizumab, cediranib, aflibercept, vandetanib, XL-184, sunitinib, etc) except for prior sorafenib or lenvatinib treatment in 2nd line HCC cohort (Cohort F) and for prior

	treatment with atezolizumab in combination with bevacizumab in Cohort H. 4 Patients with known active second malignancy other than non-melanoma skin cancers, non-metastatic prostate cancer, in situ cervical cancer, and ductal or lobular carcinoma in situ of the breast. Patients are not considered to have a currently active malignancy if they have completed anticancer therapy and have been disease free for greater than 2 years prior to screening <u>Further exclusion criteria:</u> Exclusion criteria for Glioblastoma cohort (Cohort D): 5 Tumor primarily localized to the brainstem or spinal cord. 6 Presence of diffuse leptomeningeal disease or extracranial disease. 7 Is known to have IDH mutant variety of recurrent glioblastoma. 8 Any prior treatment with prolifeprospan 20 with carmustine wafer. 9 Any prior treatment with an intracerebral agent. Exclusion criteria for Melanoma cohort (Cohort E): 10 Uveal or ocular melanoma. Exclusion criteria for HCC cohorts (Cohorts F, G & H): 11 Co-infection with HBV and HCV or HBV and hepatitis D virus (HDV) 12 Known fibrolamellar HCC, sarcomatoid HCC, or mixed cholangiocarcinoma and HCC 13 History of hepatic encephalopathy 14 Untreated or incompletely treated varices with bleeding or high-risk for bleeding 15 Untreated active Hepatitis B virus (HBV) 16 Treatment with any HCV anti-viral therapy within 4 weeks prior to Cycle 1 Day 1
Test product(s):	BI 836880; Ezabenlimab (BI 754091)
dose:	**Part 1**: BI 836880: starting dose 360mg Ezabenlimab: 240mg

	Part 2: RP2D of BI 836880 and Ezabenlimab BI 836880: 720 mg Ezabenlimab: 240 mg
Comparator products:	Not applicable
dose:	Not applicable
mode of administration:	Intravenous infusion
Duration of treatment:	Treatment may continue until disease progression, undue toxicity, withdrawal of patient consent, or 53 cycles [approximately 3 years] from the start of first treatment administration, whichever occurs first. Patients will be allowed to stay on treatment also in the case of initial radiological PD, until progression is confirmed or up to 53 cycles from the start of first treatment administration if the investigator considers that the treatment is beneficial for the patient.
Safety criteria:	Incidence and severity of adverse events graded according to the common terminology criteria for adverse events (CTCAE, version 5.0), incidence of dose limiting toxicities; laboratory parameters, vital signs, ECG
Statistical methods:	**Part 1:** Dose escalation will be guided by Bayesian Logistic Regression Models (BLRMs) with overdose control that will be fitted to binary toxicity outcomes. The estimate of parameters will be updated as data are accumulated using BLRM. At the end of dose escalation, the toxicity probability at each dose (combination) level will be calculated to guide an estimate of the MTD and/or RP2D of the combination of BI 836880 plus ezabenlimab. **Part 2**: Objective response rate as primary endpoints will be estimated by Bayesian hierarchical model (BHM) approach, which assumes full exchangeability of model parameters and allows borrowing information across patients' cohorts. Other efficacy endpoints and safety related data will be summarized descriptively. For PFS and duration of response, the median and 95% two-sided confidence interval will be presented using the Kaplan-Meier method. No hypothesis testing is planned in this trial.

FLOW CHART (PART 1)

Trial Periods	**Screen**	**Treatment cycles**								**EOT**	**EoR**	**FU / EoFU**
Cycle		1, 2, 3, 4					5, 6		7-53			
Week		w1			w2	w3	w1	w2	w1			
Visit	Screen	V1			V2	V3	V1	V2	V1			
Day; visit window [days]	-21 to -1	d 1	d2	d3; +1d (1,2)*	d8; -1/+2d	d15; -1/+2d	d1	d8; -1d/ +2d	d1	EoT (when defined)	Last admin +42d; (+3d)	every 6 weeks (+/- 3d) until PD
Informed consent / IRT call	X											
Demographics	X											
Medical history	X											
Review of in-/ exclusion criteria	X											
Height	X											
Weight	X	X					X		X	X		
ECOG performance status	X	X					X		X	X		
body temperature	X	X			X (1,2)*		X		X	X		
Blood pressure, heart rate [1]	X	X	X	X	X	X	X	X	X	X	X	
12-lead ECG [2]	X	X	X (1,2)*				X		X	X		
Echocardiography [3]	X	if clinically indicated								X		
General safety laboratory parameters [4]	X	X		X	X	X	X	X	X	X		
Serum pregnancy test	X	X					X		X	X		
Concomitant therapy	X	X	X	X	X	X	X	X	X	X	X	
Physical examination [5]	X	X	X	X	X	X	X	X	X	X	X	
Adverse events [6]	X	X	X	X	X	X	X	X	X	X	X	X
Eligibility for treatment / IRT call [7]		X					X		X			
Admin of ezabenlimab/ BI 836880		X					X		X			
Disease / response assessment (clinical/imaging) [8]	X						X					
Pharmacokinetics [9]		X	X (1,4) *		X (1,4)*	X (1,4)*	X					
[redacted]		[redacted]					[redacted]					

Trial Periods	**Screen**	**Treatment cycles**								**EOT**	**EoR**	**FU / EoFU**
Cycle *		1, 2, 3, 4					5,6		7-53			
Week		w1			w2	w3	w1	w2	w1			
Visit	Screen	V1			V2	V3	V1	V2	V1			
Day; visit window [days]	-21 to -1	d 1	d2	d3; +1d (1,2)*	d8; -1/+2d	d15; -1/+2d	d1	d8; -1/+2d	d1	EoT (when defined)	Last admin +42d; (+3d)	every 6 weeks (+/- 3d) until PD
[redacted]		[redacted]			[redacted]		[redacted]					
					X (1)	X (1)						
		[redacted]										
	[redacted]			[redacted]								
Reason for treatment discontinuation										X		
Patients status											X	X
Next line of anti-cancer therapy											X	X

* number in brackets indicate the cycle this visit/assessment is applicable
EoC = End of Cycle; FU1 = 1st Follow-up visit

1 See Appendix 10.2
2 ECG for all patients according to flowchart schedule.
3 Echocardiography to be done within 7 days before treatment start and at EOT.
4 Safety lab to be done at local lab according to the Flowchart but should be more frequent in case of relevant findings based on medical opinion of the investigator.(Section 5.2.3)
5 Complete physical examination must be performed at screening and before start of treatment and EoT and EoR. For further time points, at minimum the actual health status of the patient should be assessed (see Section 5.2.1).
6 More details about AEs are provided in Section 5.2.7.

7 For medication number allocation, it's possible to conduct IRT call ahead of the planned visit (= day of administration).
Start with administration of ezabenlimab and 15 min after the end of this infusion, BI 836880 should be administered (***see Instructions for Pharmacist provided in the ISF***)

8 The same method of assessment / same technique should be used also in follow up of identified and reported lesions. Baseline evaluation must be performed as close as possible to the treatment start and no more than 28 days before start of treatment. Tumour assessment can be performed according to institutional practices and SOC from the data cut-off date for interim database lock forward, starting from first trial medication infusion.

9, 10 and 11: see Appendix 10.5 Table 10.5.1: 1

[redacted]

FLOW CHART (PART 2)

Trial Periods	**Screen**	**Treatment cycles**					**EOT**	**Safety Follow-up**	**FU / EoFU**
Cycle		1				2 - 53			
Week		w1		w2	w3	w1			
Visit	Screen	V1		V2	V3	V1			
Day; visit window [days]	-21 to -1	d1	d2	d8; (-1/+2d)	d15; (-1/+2d)	d1; (+2d)for cycle 2; ongoing cycles (-1/+2d)	EoT (when defined)	Last admin +42d;(+3d)	every 6 weeks (+/- 3d) until PD
Informed consent / IRT call	X								
Demographics	X								
Medical history	X								
Review of in-/ exclusion criteria	X								
Height	X								
Weight	X	X				X	X	X	
ECOG / Karnofsky performance status[@]	X	X				X	X	X	
Body temperature	X	X		X		X	X		
Blood pressure, heart rate [1]	X	X	X	X	X	X	X	X	
12-lead ECG [2]	X	X				X (2,3,4,6, 8, 10,12..)*	X		
Echocardiography [3]	X	if clinically indicated					X		
Infectious Screen[$]	X								
General safety laboratory parameters [4]	X	X		X	X	X	X		
Pregnancy test[§]	X	X				X	X		
Concomitant therapy	X	X	X	X	X	X	X	X	
Physical examination [5]	X	X	X	X	X	X	X	X	
Adverse events [6]	X	X	X	X	X	X	X	X	X
Eligibility for treatment / IRT call [7]		X				X			
Admin of ezabenlimab/ BI 836880		X				X			
Disease / response assessment (clinical/imaging) [8]	X	X							

Trial Periods	**Screen**	**Treatment cycles**					**EOT**	**Safety Follow-up**	**FU / EoFU**
Cycle		1				2 - 53			
Week		w1		w2	w3	w1			
Visit	Screen	V1		V2	V3	V1			
Day; visit window [days]	-21 to -1	d1	d2	d8; (-1/+2d)	d15; (-1/+2d)	d1; (+2d) for cycle 2; ongoing cycles (1/+2d)	EoT (when defined)	Last admin +42d; (+3d)	every 6 weeks (+/- 3d) until PD
Pharmacokinetics [9]		X	X	X	X				
[redacted]									

* number in brackets indicate the cycle this visit/assessment is applicable
EoC = End of Cycle; FU1 = 1st Follow-up visit

1 See Appendix 10.2 for BP and HR should be measured before and after study drugs have been administered. Please follow the BP monitoring and study drug administration guidelines in Appendix 10.2.1.
2 ECG for all patients according to flowchart schedule.- Cycle 1 to 4 pre and post treatment (within 60 min after completion of administration of BI 836880) and thereafter ECG at pre- and post treatment of BI 836880 performed every second cycle (cycle 6,8, 10…etc

3 Echocardiography to be done within 21 days before treatment start and at EOT.
4 Safety lab to be done at local lab according to the Flowchart (up to 72 hours before treatment start) but should be more frequent in case of relevant findings based on medical opinion of the investigator.(Section 5.2.3~~).~~
5 Complete physical examination must be performed at screening and before start of treatment and EoT andSafety Follow-up visit. For further time points, at minimum the actual health status of the patient should be assessed (see Section 5.2.1).
6 more details about AE are provided in Section 5.2.7
7 For medication number allocation it's possible to conduct IRT call ahead of the planned visit (= day of administration).
Start with administration of ezabenlimab and 15 min (+/- 10 min) after the end of this infusion, BI836880 should be administered (***see Instructions for Pharmacist provided in the ISF***)
8 Tumour assessments should be done according to RECIST v1.1 and iRECIST for all cohorts except GBM. RANO/iRANO criteria to be followed for GBM cohort. Assessments should include computed tomography (CT) scans of the chest and abdomen only, if clinically indicated, imaging of any other known or suspected sites of disease (e.g., pelvis, brain) using an appropriate method (CT scan or magnetic resonance imaging [MRI]). The same radiographic procedure must be used throughout the trial. Baseline evaluation must be performed as close as possible to the treatment start and no more than 28 days before start of treatment (For GBM – 14 days prior to treatment). Tumour assessment can be performed according to institutional practices and SOC from data cut-off date interim database lock forward. Assessments are always done prior to the start of the new treatment cycle.
9, 10 and 11: see Appendix 10.5 Table 10.5.1: 2
12 Cohorts F, G & H (HCC cohorts): only C1D1 sample to be collected. NO on-treatment samples.
13 ONLY Cohort F, G & H (HCC) cohorts
14 Cohorts F, G & H (HCC) cohorts: NO samples collected
From December 2021, no further blood samples should be obtained for central lab shipments.

§ Women of child-bearing potential must have a serum beta human chorionic gonadotropin (β-HCG) pregnancy test at screening. Thereafter, this test can be done in either serum or urine for all patients. as per Day 1 of each cycle, and at the EOT visit. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
$ Hepatitis B surface antigen (HBsAg; qualitative), hepatitis B core antibody (anti-HBc; qualitative), Hep B DNA, hepatitis C antibodies (Anti-HCV; qualitative), Hep C RNA, hepatitis D antibodies (Anti-HDV; qualitative) human immunodeficiency virus (HIV)-1 and HIV-2 antibody (at the discretion of the Investigator where clinically indicated) will be performed. For HCC cohorts (cohorts F & G) additional tests may include HBV DNA (if needed), HCV RNA (if needed) and Hepatitis D (anti-HDV qualitative).

@ Karnofsky performance status (KPS) to be implemented for GBM cohort

- [a] **Part 2/ Tumour biopsy**
    - **Mandatory pretreatment biopsy for cohort A, B, C, E, F, G and H:** - The equivalent of 2 14 -16 G (or-I: 4 18 G) needle biopsies should be freshly taken during screening after IC signed and before first trial medication administration, In case a fresh baseline biopsy cannot be obtained (e.g. inaccessible lesions or patient safety concern), 20 archival 4 µm sections from an archival block, taken within 6 months of trial start with no intermediate therapy have to be provided.
    - **Mandatory for cohorts E, F, G and H a fresh on-treatment biopsy**: - The equivalent of 2 14-16 G (or 4 18G) needle biopsies at C3D1 (-/+ 7 days) if possible from the same lesion as the pre-treatment biopsy. Treatment to be initiated only after ensuring patient is stable and bleeding has stopped completely after biopsy.
    - **Optional for cohorts A-C:** - The equivalent of 4 18 G needle biopsies on treatment before start of Cycle 3 (-/+ 7 days, 6 weeks after treatment start)

Note for on treatment biopsies: Biopsy to be performed on a lesion different than target lesion and if there is only one lesion than biopsy may be skipped in that patient.

From December 2021, no further biopsies should be performed.

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ABBREVIATIONS

ABPM	Ambulatory Blood Pressure Measurement
[redacted]	
AE	Adverse Event
AESI	Adverse Event of Special Interest
AFP	Alpha-Fetoprotein
AP	Alkaline Phosphate
ANG2	Angiopoietin-2
aPTT	Activated Partial Thromboplastin Time
AUC	Area under the Curve
b.i.d.	bis in die (twice daily dosing)
BHM	Bayesian Hierarchical Model
BLRM	Bayesian Logistic Regression Model
CBPM	Conventional Blood Pressure Measurement
CCDS	Company Core Data Sheet
CI	Confidence Interval
CML	Clinical Monitor Local
CPI	Check Point Inhibitor
CR	Complete Response
CrCl	Creatinine Clearance
CRA	Clinical Research Associate
CRF	Case Report Form, paper or electronic (sometimes referred to as “eCRF”)
CTCAE	Common Terminology Criteria for Adverse Events
CT/MRI	Computed Tomography scan/ Magnetic Resonance Imaging
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
DC	Disease Control
[redacted]	
DCR	Disease Control Rate
DILI	Drug Induced Liver Injury
DLT	Dose Limiting Toxicity
DoR	Duration of Objective Response
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic Data Capture
eCRF	Electronic Case Report Form
EMA	European Medicines Agency
EOT	End of Treatment
EOR	End of Residual Effect Period
EudraCT	European Clinical Trials Database
EWOC	Escalation With Overdose Control
FAS	Full Analysis Set
FC	Flow Chart
FDA	Food and Drug Administration
GBM	Glioblastoma
GCP	Good Clinical Practice

GFR	Glomerular Filtration Rate
HPC	Human Pharmacology Centre
IB	Investigator's Brochure
iCPD	Immune Confirmed Progression Disease
IEC	Independent Ethics Committee
INR	International Normalised Ratio
iRANO	immunotherapy Response Assessment for Neuro-Oncology
IRB	Institutional Review Board
iRECIST	Immunotherapy Response Evaluation Criteria In Solid Tumours
IRT	Interactive Response Technology
ISF	Investigator Site File
i.v.	Intravenous
iUPD	Immune Unconfirmed Progression Disease
KPS	Karnofsky Performance Status
LDH	Lactate Dehydrogenase
LPDD	Last Patient Drug Discontinuation
LoEE	List of Essential Element
LMWH	Low-Molecular-Weight Heparin
LVEF	Left Ventricular Ejection Fraction
MedDRA	Medical Dictionary for Drug Regulatory Activities
MDSC	Myeloid-derived suppressor cells
MST	Medical Sub Team
MTD	Maximum Tolerated Dose
NS NSCLC	Non Squamous Non-Small Cell Lung Cancer
NSCLC	Non-Small Cell Lung Cancer
NSAID	Nonsteroidal anti-inflammatory drugs
OPU	Operative Unit
OR	Objective Response
ORR	Overall Response Rate
OS	Overall Survival
PD	Pharmacodynamics
PD-1	Programmed death 1
PDL-1	Programmed death-ligand 1
PK	Pharmacokinetics
PLT	Platelets
p.o.	per os (oral)
PR	Partial Response
PT	Prothrombin Time
RANO	Response Assessment for Neuro-Oncology
RECIST	Response Evaluation Criteria In Solid Tumours
q.d.	quaque die (once a day)
eDC	electronic Data Capturing
REP	Residual Effect Period
SAE	Serious Adverse Event
s.c.	Subcutaneous
SCLC	Small Cell Lung Cancer
SD	Stable disease

SMC	Safety Monitoring Committee
SmPC	Summary of Product Characteristics
SOC	Standard of Care
SUSAR	Suspected Unexpected Serious Adverse Reactions
TCM	Trial Clinical Monitor
TDMAP	Trial Data Management and Analysis Plan
t.i.d.	ter in die (3 times a day)
TMF	Trial Master File
TSAP	Trial Statistical Analysis Plan
ULN	Upper Limit of Normal
UPCR	Urine Protein to Creatinine Ratio
VEGF	Vascular endothelial growth factor
WBC	White Blood Cells Count
WHO	World Health Organization
WOCBP	Woman of childbearing potential

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Angiogenesis is the formation of new blood vessels from pre-existing vasculature and is a key process in tumor growth. The Ang2/Tie2 and the VEGF/VEGFR2 pathways have been identified as key pathways mediating tumor angiogenesis (R13-0448). Multiple studies have described increased VEGF levels in a variety of human cancers and the VEGF expression levels have been correlated with poor survival (R15-1720). The VEGF neutralizing monoclonal antibody bevacizumab has demonstrated anti-tumor activity in clinical trials and is currently approved for several indications and setting, mainly in combination with standard chemotherapy regimens (R15-1222).

Studies in mice have shown that Ang2, a ligand of the Tie2 receptor, controls vascular remodeling by enabling the functions of other angiogenic factors, such as VEGF (R12-3593). Ang2 is primarily expressed by endothelial cells, strongly induced by hypoxia and other angiogenic factors and has been demonstrated to regulate tumor vessel plasticity, allowing vessels to respond to VEGF and FGF2 (R12-3834).

The normal role of the immune system is to protect the body against the invasion of foreign agents such us 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 treat, the immune system deploys the immune system checkpoint program to dampen the immune response and minimize collateral immune-mediated damage to healthy tissue. The programmed-cell-death (PD-1, CD279) receptor and its ligands, programmed-cell-death ligand 1 (PD-L1, B7-H1; CD274) and programmed-cell-death ligand 2 (PDL-2; B7-DC; CD273) are the major immune checkpoint master switches. The expression of PD-1 on immune cells, including T and B lymphocytes, natural killer (NK) cells and antigen presenting cells is upregulated in response to inflammation in peripheral tissue. As with PD-1 level, the expression of PD-L1 is also induced as a result of peripheral tissue inflammation. The interaction of PD-1 and PD-L1 in an inhibitory signal that interferes with antigen receptor signaling, marked changes in the cytokine profile decreased T-cell activation, increased activation of regulatory T-cells and increase in cytotoxic T-cell apoptosis. Collectively, these events lead to an immune suppressive environment and dampening of the immune response. Tumor immune evasion is achieved when PD-L1 within the tumour microenvironment engages PD-1 expressed on activated tumour infiltration T-cells and initiates the immune suppressive tumor microenvironment in which activated cytotoxic T-cells are inactivated and some are sent down an apoptotic pathway.

VEGF-A induces accumulation of Myeloid-derived suppressor cells (MDSCs), immature DC, Treg and tumour-associated macrophage. MDSC are able to control activation of T-cell and NK cells. Anti-VEGF treatment significantly enhances dendritic cell maturation. (R17-4036 R17-4037), decrease Treg either by inhibiting the accumulation of MDSCs and immature DC in tumor environment or directly through VEGF/VEGFR pathway inhibition of Treg. (R17-4038, R17-4039).

Preclinical evidence of interaction between these 2 pathways was shown as well as encouraging antitumor activity of the combination of VEGF blockade and PD-1/PD-L1 blockade.

During the last decade, notable changes occurred in the treatment of NSCLC resulting in a paradigm shift. The current treatment approach of NSCLC incorporates important predictive markers of benefit from specific agents such us pathology subtype (histology) and molecular genotype (EGFR mutation and EML4-ALK fusion gene). More recently immunotherapy treatments (checkpoint inhibitors) have changed the treatment strategy in NSCLC.

First line treatment of advanced stage NSCLC has more recently been markedly transformed by the introduction anti PD-1/anti-PD-L1 immune checkpoint inhibitor (CPI) mAbs. Pembrolizumab is currently indicated for first line treatment of both squamous and non-squamous NSCLC. The use of pembrolizumab is currently restricted to patients whose tumors express high levels of PD-L1 (>50% of tumor cells being PD-L1 positive using IHC).

For patient with low PD-L1 expressing tumors (1-49% of tumor cells being PD-L1 positive), first line treatment consists of a platinum-based chemotherapy (platinum plus gemcitabine or pemetrexed or taxane). Several platinum-based chemotherapy doublets have shown comparable efficacy with a higher response rate for cisplatin combinations compared to carboplatin combinations. Based on randomized phase III trials results, pemetrexed is preferred to gemcitabine in non-squamous tumors. Platinum-based chemotherapy doublets, excluding pemetrexed are also indicated in squamous tumors.

The first-line treatment for patients with tumors harboring specific gene alterations that are key oncogenic events (EGFR mutation or EML4-ALK fusion gene), consists of a specific targeted therapy: EGFR TKI (e.g. erlotinib) for EGF-mutated patients and ALK inhibitor (e.g. crizotinib for ALK amplified patients). (R15-3759, R14-5319) Such treatment offers the possibility of a highly specific treatment of these molecularly defined NSCLC subtypes. The clinical benefit of adding bevacizumab in first line treatment to platinum-based chemotherapy is controversial with a benefit in terms of PFS and ORR. This improvement did not translate into a benefit in OS.

Maintenance therapy is indicated in patients who did not progress after completion of first line chemotherapy (4-6 cycles). Pemetrexed is indicated in non-progressive patients with non-squamous tumors (P13-07693), whilst EGFR TKIs can be used in patients with EGFR mutations (squamous and non-squamous tumors) with stable disease after induction therapy (R11-1185).

Platinum-based chemotherapy is indicated for the second line treatment of patients who received prior systemic targeted therapy (EGFR TKI or ALK inhibitor). For patients previously treated with platinum doublet chemotherapy, single agent docetaxel, (R14-5321) pemetrexed or EGFR inhibitor should be used.

More recently, three PD-1/anti-PD-L1 immune CPI have been approved for second line NSCLC treatment. All three compounds (nivolumab, pembrolizumab and atezolizumab) are currently approved for second line treatment of both squamous and non-squamous NSCLC.

The use of pembrolizumab is currently restricted to patients whose tumors express PD-L1 (>1% of tumor cells being PD-L1 positive using IHC) where as nivolumab and atezolizumab's use is open to patients regardless of PD-L1 expression levels.

Previously, based on positive Phase III trial in advanced/metastatic NSCLC on (KEYNOTE 024 trial) showing PFS and OS improvement in pembrolizumab monotherapy arm (versus standard chemotherapy) (R16-4783), Pembrolizumab has been approved for 1st line treatment in patients with tumors expressing PD-L1 in ≥ 50% of tumor cells. FDA based on KEYNOTE-042 (NCT02220894) trial approved pembrolizumab monotherapy for the first-line treatment of patients with stage III NSCLC who are not candidates for surgical resection or definitive chemoradiation or metastatic NSCLC. Patients' tumors must have no EGFR or ALK genomic aberrations and express PD-L1 (Tumor Proportion Score [TPS] ≥1%) determined by an FDA-approved test.

Atezolizumab in combination with bevacizumab, paclitaxel, and carboplatin, is also indicated for the first-line treatment of patients with metastatic NSCLC with no EGFR or ALK genomic tumor aberrations.

Small cell lung cancer (SCLC) is a neuroendocrine tumor that represents about 15 percent of all lung cancers. SCLC occurs predominantly in smokers and is distinguished clinically from most types of non-small cell lung cancer (NSCLC) by its rapid doubling time, high growth fraction, and the early development of metastases. SCLC usually presents with disseminated disease, and treatment strategies have focused on systemic therapy. Although SCLC is highly responsive to both chemotherapy and radiotherapy (RT), it commonly relapses within months despite treatment. SCLC is usually staged as either limited or extensive. The standard treatment in limited SCLC is chemoradiation. The chemo drugs used are usually etoposide or irinotecan plus either cisplatin or carboplatin. Atezolizumab is approved as a first line treatment for extensive SCLC. The addition of atezolizumab to chemotherapy in the first-line treatment of extensive-stage small-cell lung cancer resulted in significantly longer overall survival and progression-free survival than chemotherapy alone (IMpower 133). (R19-1714) Nivolumab is approved for metastatic small cell lung cancer with progression after platinum based chemotherapy and at least one other line of therapy. Nivolumab monotherapy provided durable responses and was well tolerated as a third- or later-line treatment for recurrent SCLC (CHECKMATE 032). (R19-1713)

High-grade gliomas are malignant and often rapidly progressive brain tumors that are divided into anaplastic gliomas (anaplastic astrocytoma, anaplastic oligodendroglioma) and glioblastoma based upon their histopathologic and molecular features. Despite the survival benefit associated with adjuvant radiation and chemotherapy, the majority of patients relapse following initial therapy. The most commonly used systemic agents in recurrent or progressive high-grade gliomas are bevacizumab, nitrosoureas, and temozolomide rechallenge (since the majority of patients will have received temozolomide at part of initial therapy). In the largest randomized trial to test whether combination therapy is superior to single-agent therapy, the addition of bevacizumab to lomustine improved progression-free but not overall survival compared with lomustine alone. Early experience with CPIs such as pembrolizumab and nivolumab in unselected patients with recurrent high-grade glioma has shown only modest activity. Preliminary results of a phase III trial of nivolumab versus

bevacizumab in recurrent glioblastoma found no difference in overall survival (CHECKMATE 143).

Most cases of malignant melanoma diagnosed at an early stage and surgical excision can be curative. However, a few patients have metastatic disease at presentation, and some develop metastases after their initial definitive treatment. High-dose interleukin-2 (IL-2) was the first treatment to modify the natural history of patients with metastatic melanoma resulting in cure in a small fraction of patients. However, its severe toxicity has limited its application to carefully selected patients treated at centers with experience in managing the side effects of treatment. Immunotherapy is an important systemic treatment modality for metastatic melanoma. Checkpoint inhibition with an anti-programmed cell death 1 (PD-1) antibody (pembrolizumab, nivolumab) in combination with the anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) antibody ipilimumab has better efficacy (response rates, progression-free survival) than single-agent anti-PD-1 therapy in patients with advanced melanoma who are candidates for systemic therapy. Survival data from phase III trials suggest that 50 percent of patients receiving nivolumab (CHECKMATE-066) and 50 to 60 percent of patients receiving the combination of nivolumab and ipilimumab (CHECKMATE-067) will remain alive at three years. In the phase III KEYNOTE-006 trial, pembrolizumab demonstrated significantly longer PFS and improved overall survival compared with ipilimumab in patients with advanced melanoma. Overall survival was significantly prolonged with pembrolizumab compared with ipilimumab (four-year overall survival rate 41.7 versus 34.1 percent; HR 0.73, 95% CI 0.61-0.89).

Hepatocellular carcinoma (HCC) typically diagnosed late in its course is an aggressive tumor that often occurs in the setting of chronic liver disease and cirrhosis. Although the mainstay of therapy is surgical resection, the majority of patients are not eligible because of tumor extent or underlying liver dysfunction. There has been a resurgence of interest and enthusiasm for systemic therapy of HCC with the emergence of data showing that the molecularly targeted agents sorafenib, levatinib and regorafenib improve survival versus best supportive care alone. (R12-0948) Both sorafenib and levatinib have been for the first-line treatment of patients with unresectable HCC. Sorafenib HCC Assessment Randomized Protocol (SHARP) trial demonstrated that angiogenesis biomarkers Ang2 and VEGF were independent predictors of survival in patients with advanced HCC but not were predictive of response to sorafenib. Subsequently, a survival benefit has also been shown in the second-line setting patients for HCC who had disease progression on or after sorafenib or were intolerant to sorafenib in nivolumab (CHECKMATE-040) and pembrolizumab (KEYNOTE-224; NCT02702414) trials. Currently multiple phase III studies of CPI in combination with anti-angiogenics is being conducted in 1st line HCC. Atezolizumab in combination with bevacizumab received regulatory approval from the US Food and Drug Administration (FDA) in May 2020 and European Medical Agency (EMA) in Sep 2020 for the frontline treatment of patients with unresectable or metastatic HCC based on findings from the phase 3 IMbrave150 trial. In the trial, the combination led to a 42% reduction in the risk of death compared with sorafenib. Based on the superior efficacy it is expected that atezolizumab in combination with bevacizumab or similar such combinations is expected to be the standard of care. It is important that further options for progressors on this first line treatment options be explored.

The planned inclusion of a cohort of patients with locally advanced or metastatic and/or unresectable hepatocellular carcinoma (HCC) with no prior systemic treatment is based on an understanding of the mechanisms involved in the proposed combination therapy, and the available evidence supporting the expectation of enhanced activity with the added inhibition of Ang2 signaling. Hepatocellular carcinoma (HCC) is a vascular tumor and angiogenesis is believed to play an important role in its progression. The role of anti-VEGF is well established in HCC.
Multikinase inhibitors targeting VEGFR like sorafenib and lenvatinib have been approved as a first-line treatment in HCC. Given its high immunogenicity, immune checkpoint inhibitors (ICI), targeting the programmed cell death-1 (PD-1) axis have been approved either as monotherapies or in combination with other ICI, such as cytotoxic T lymphocyte antigen-4 (CTLA-4).

Combination therapies involving antiangiogenics and ICI show improved response over antiangiogenic monotherapy (IMbrave150 trial). It is hypothesized that this is due to the complementary mechanisms involved.
The phase III IMbrave150 study conducted in the previously untreated HCC patients supported the combination of atezolizumab (anti-PDL1) with bevacizumab (anti-VEGF). Overall response rate was 27% with atezolizumab plus bevacizumab vs 12% compared to sorafenib based on independent assessment using RECIST 1.1 criteria. Median progression-free survival (PFS) was also significantly increased (median 6.8 vs 4.3 months, HR = 0.59; 95% CI = 0.47– 0.76, P < .0001).

The combination therapy being investigated in this trial addresses both mechanisms described above. It combines an anti-PD-1 agent (ezabenlimab) with a bispecific nanobody (BI 836880) that blocks VEGF and in addition Ang2. Data suggests that this added activity against Ang2 may add to the overall response seen with the combination of ICI and anti-VEGF alone. The rationale for this is described below. Ang2 leads to immune suppression by distinct mechanisms compared to VEGF. VEGF plays a key role in suppressing tumor immune response by negatively affecting the antigen presenting cells (APCs) (R20-2104) and effector T-cells (R20-2103, R20-2106) while augmenting the effects of immune suppressive cells such as T-regulatory cells (T-regs) (R20-2107) and myeloid derived suppressor cells (MDSCs) (R20-2102).

Ang-2 increases the neutrophil recruitment and adhesion of both neutrophils and TEMs to endothelium (R16-5098) and increases the conversion to M2-like macrophage phenotype (R20-2101). Ang-2 further can stimulate TEMs to secrete IL-10, which can promote the expansion of T-regs and the inhibition of effector T-cells. The Sorafenib HCC Assessment Randomized Protocol (SHARP) trial demonstrated that angiogenesis biomarkers Ang2 and VEGF were independent predictors of survival in patients with advanced HCC (R12-0948). Furthermore, patients with high pre-treatment serum Ang-2 levels were found to respond poorly to CTLA-4 and PD-1 ICIs. Also, treatment with ICIs can lead to elevated Ang-2 levels, resulting, again, in poor prognosis (R19-1712). In the Keynote-524 study evaluating the combination of pembrolizumab and lenvatinib in 1st line HCC patients it was observed that reduced decrease of Ang-2 was associated with a decrease in PFS suggesting a role for Ang-2in treatment resistance (R21-2811). Preclinical evidence also suggests a role of Ang-2 in mediating resistance to VEGF signaling blockade (R15-5149)

Based on the distinct role of Ang-2 in immune suppression of the tumor microenvironment and its role in conferring resistance to therapy targeting only VEGF, we believe selective triple inhibition of anti-VEGF, anti-Ang2 and PD-1 may confer a distinct advantage in the treatment of HCC patients. This is supported by preclinical data from a LL/2 (lewis lung) syngeneic tumour pre-clinical study (please refer to section 5.1.1.4 "Combining BI 836880 with immune checkpoint inhibition" of the IB), as well as a study that investigated a combination of a PD1 antibody with a bispecific Ang-2/VEGFa antibody in multiple mouse in vivo models (R20-2105).

As of January 2022, a total of 252 patients have been treated in this ongoing Phase Ib study evaluating BI 836880 and ezabenlimab in patients with advanced or metastatic solid tumours. Clinical activity was observed across all cohorts. A total of 44 patients remain on treatment and continue to be followed up.

1.2 DRUG PROFILE

1.2.1 BI 836880

BI 836880 is a genetic fusion protein of one VEGF-A-binding and one Ang2-binding single domain antibodies (V_{HH}, Nanobody®). The two single domain antibody moieties are linked via a human serum albumin-binding Alb11 domain, serving as half-life extension, and glycine-serine linkers between the domains. The protein has a molecular mass of 40.7 kDa (c02353883-09). The Nanobody® technology was originally developed following the discovery that camelidae (camels and llamas) possess fully functional antibodies that lack light chains. These heavy chain antibodies contain a single variable domain (V_{HH}) and two constant domains CH3). The cloned and isolated V_{HH} domain is a stable polypeptide harbouring the full antigen-binding capacity of the original heavy-chain antibody. These newly discovered V_{HH} domains form the basis of a new generation of therapeutic antibodies named Nanobodies (R15-1719).

BI 836880 is highly selective for VEGF-A and Ang2, as he molecule did not bind to the related growth factors VEGF-B, -C, -D, placental growth factor (P1GF), and angiopoietin 1 (Ang1). BI 836880 is highly potent and showed in vivo monotherapy efficacy (tumor growth inhibition) in several tumor xenograft representing colon cancer (CXF 243), non-small cell lung cancer (LXFE 211, LXFE 1422), mammary cancer (MAXF 401), ovarian cancer (OVXF 1353), pancreatic cancer (PAXF 546) and renal cell cancer (RXF 1220).

A 13-week repeat dose administration of BI 836880 was performed in cynomolgus monkeys. BI 836880 was well tolerated up to the highest dose of 60 mg/kg. No mortality was attributed directly to BI 836880 administration. BI 836880 did not demonstrate any effects on neurological, renal, or cardiovascular functions including electrocardiograms (ECGs). In a monkey presenting the immunogenic reaction, membrano-proliferative glomerulopathy in the kidney was observed. This finding was considered a secondary response to immune complex deposition in the glomeruli and not directly related to BI 836880 administration.

At the time of data cut off for IB version (17 Aug 2021), 421 patients had been treated with BI 836880 in 5 clinical trials, either as a monotherapy (n = 62) or in a combination therapy (n = 359). The combination therapy trials evaluate BI 836880 in combination with ezabenlimab, an anti-PD-1 monoclonal antibody, administered every 3 weeks (1336-0011, 1336-0012 Part 2, 1381-0009 Module C). Of the 359 patients exposed to combination therapy so far, 347 patients have been treated with the recommended Phase II dose (RP2D).

The most frequent adverse events (AEs) in patients treated with BI 836880 monotherapy were hypertension (54.8%), asthenia (48.4%), vomiting (29.0%), nausea (27.4%), diarrhoea (25.8%), and constipation (25.8%). One patient (1.6%) was reported with an AE requiring dose reduction and 13 patients (21.0%) with AEs leading to treatment discontinuation. There were 43.5% of patients with on-treatment SAEs; hypertension and pleural effusion (3 patients [4.8%] each) were the only SAEs reported for more than 2 patients.

After evaluating all available PK, PD, efficacy, and safety data, the dose of 720 mg BI 836880 every 3 weeks (q3w) was determined as a RP2D. The most common AEs reported for this dosing regimen were hypertension (73.9%), asthenia (43.5%), vomiting (34.8%), and nausea (39.1%). Hypertension (34.8%) was also the most frequently reported Grade 3 event. Two patients (8.7%) were reported with a Grade 4 AE; these AEs were neutropenia and dyspnoea. One patient in this dose group was reported with fatal AEs resulting from disease progression: metastases to liver and hepatic failure.

Data pooled from the combination trials showed that 326 patients (90.8%) treated so far have been reported with at least 1 AE. The most common individual AE (by preferred term) has been hypertension (20.3%), followed by asthenia (17.5%), diarrhoea (17.3%), nausea (16.7%), fatigue (15.3%), decreased appetite (12.8%), peripheral oedema (12.3%), and vomiting (10.3%). Six patients (1.7%) have been reported with AEs requiring dose changes; 25 patients (7.0%) had an AE leading to treatment discontinuation. Hypertension (8.4%) has been the most frequently reported Grade 3 event. Adverse events of Grade 4 have been reported for 13 patients (3.6%); each Grade 4 AE has been reported for a single patient. There have been 22 patients (6.1%) with AEs resulting in death; sepsis and general physical health deterioration (3 patients each, 0.8%) as well as respiratory failure (2 patients, 0.6%) have been the only fatal AEs reported for more than 1 patient. Adverse events under the SMQ haemorrhages occurred in 28 patients (7.8%), with 4 patients (1.1%) presenting AEs of Grade 3 and 3 patients (0.8%) presenting a Grade 5 AE. There have been 59 patients (16.4%) reported with immune-related AEs according to investigator’ s judgement; 7 patients (1.9%) had Grade 3 AEs and 6 patients (1.7%) had Grade 4 AEs.

Laboratory values from all conducted trials did not show any event that met Hy’s law criteria.

The pharmacokinetics, pharmacodynamics and immunogenicity of BI 836880 were investigated based on data from the monotherapy Phase I studies.

Maximum plasma concentrations were reached shortly after the end of infusion. BI 836880 plasma concentration remained around the maximum for up to 8 h and started to decline afterwards slowly. Cmax and AUC increased in a dose-proportional manner over the entire dose range. As expected for a nanobody, the clearance was low, resulting in a terminal half-

life of ~11 days. The volume of distribution was also low and in the range of the average blood volume. An accumulation ratio of 1.20 to 1.92 was observed, showing slight accumulation of BI 836880 after multiple dosing. No pharmacokinetic interaction between BI 836880 and ezabenlimab was detected as the PK parameter were comparable between administration alone and in combination.

For a more detailed description of the drug profile refer to the current Investigator's Brochures (IB).

1.2.2 BI 754091 (Ezabenlimab)

Ezabenlimab is a humanized IgG4 pro-monoclonal antibody showing potent and selective binding to human PD-1(c07895879-06). Ezabenlimab has highly human frameworks and a low predicted immunogenicity score. The ezabenlimab molecule has a molecular weight approximately 148 kilo Daltons. The antibody is composed of 2 heavy chains (446 amino acids each) and 2 light chains (218 amino acids each). The 4 polypeptide chains of the antibody are linked together by disulfide bonds. Each heavy chain contains one consensus sequence for N-linked glycosylation.

Ezabenlimab shows anti-tumor effects in *vivo* several mice model including in the syngenic MC-38 mouse model.

A 13-week repeat dose administration of ezabenlimab was performed in cynomolgus monkeys. Ezabenlimab was well tolerated and no related mortality or clinical signs, or changes to body weight, food consumption, respiratory rate or electrocardiogram were observed.

Ezabenlimab exposure increased dose-proportionally and accumulated with repeat dosing for all tested dose levels. Ezabenlimab was still detectable after 4 week recovery period in the highest dose level (100 mg/kg). Engagement of ezabenlimab with target was assessed by measuring available ezabenlimab-free PD-1 on $CD3^+/CD95^+$ T cells. After 13 weeks of

dosing ezabenlimab resulted in in vivo target engagement at all dose levels. After 4 week recovery period; available PD-1 remained decreased in the 100 mg dose group demonstrating sustained target engagement throughout the recovery period.

As of November 1st 2021, 117 patients with advanced/metastatic solid tumours have been treated with single agent ezabenlimab, 111 of these patients were treated with the 240 mg q3w recommended phase II dose (RP2D). Additionally, 881 patients have been treated with the RP2D of ezabenlimab in combination with other agents. Three hundred and ninety four patients treated in combination with BI754111 (anti-LAG-3 mAb), 381 patients were treated in combination with BI 836880 (VEGF/Ang-2 inhibitor), 37 patients were treated in combination with BI 891065 (SMAC mimetic) and 11 patients were treated in combination with BI 754111 and BI 907828 (MDM2-p53 antagonist). 6 patients were treated with the combination of ezabenlimab and BI 907828 (MDM2 inhibitor), 5 patients were treated with the combination of ezabenlimab and BI 1387446 (STING agonist), 20 patients were treated with the combination of ezabenlimab plus BI 765063 (SIRP α antagonist), and 27 patients were treated with the combination of ezabenlimab plus BI 3018078 (anti-tumor vaccine).

The currently available ezabenlimab clinical data demonstrate that it is well tolerated. The most common AEs reported in patients treated with ezabenlimab monotherapy were fatigue (39.3%), nausea (29.9%) and decreased appetite (21.4%). There were no Grade 5 or treatment related Grade 4 events reported in patients treated with ezabenlimab monotherapy. Immunerelated AEs (irAEs) were reported in 32 patients (27.4%) on ezabenlimab monotherapy, the vast majority were Grade 1 and 2. There were no Grade 4 or Grade 5 irAEs and no infusion related reaction of any grade reported in patients treated with ezabenlimab monotherapy.

Preliminary efficacy analysis shows overall objective response rate ezabenlimab monotherapy of 16.2% across all cohorts (15 patients with confirmed partial response [PR] and 3 patients with complete responses [CR]) (95% CI 9.4, 23.2). All 3 patients with CRs and 8 of the 15 patients with PR were still on treatment at the time of last data cut-off. Tumor responses were seen in diverse cancer types.

The available PK data show that ezabenlimab has a (at least) bi-phasic distribution. The volume of distribution ranged between 4.63 L and 5.88 L. The systemic clearance of ezeabenlimab ranged between 0.00971 L/h (80mg dose) and 0.0119 L/h (400mg dose) (i.e. approx. 0.0237 - 0.0286 L/day) resulting in gMean half-life estimates of 13.8 to 17.8 days. Volume of distribution ranged from 4.63L to 5.88 L. The small total volume of distribution is consistent with a limited extravascular disposition as expected for a therapeutic antibody

For a more detailed description of the ezabenlimab profile, please refer to the current Investigator's Brochures (IB).

1.3 RATIONALE FOR PERFORMING THE TRIAL

Check point (PD-1 and PD-L1) inhibition and angiogenesis inhibition (VEGF, Ang-2) demonstrated antitumor activity with a clinical benefit in several tumor types. Despite this effect, an important number of patients will not respond to such therapy and most of patients

who benefit from treatment will relapse and die from their disease. Defining novel therapeutic strategy is needed to improve survival in patients with NSCLC patient and other solid tumors.

It is well established that pro-angiogenic factors (e.g. VEGF-A) have an immunosuppressive effect in the tumour microenvironment. Preclinical data showed modulation of immunosuppressive cells by an anti-VEGF treatment and enhancement of antitumor effect of the combination of VEGF and PD-1 inhibition. Furthermore, internal BI preclinical data showed an additive effect of the angiopoietin inhibition on the top of the dual VEGF and PD-1 inhibition (BI 836880 IB).

This scientific rationale and preclinical data support a combination trial of the triple inhibition of VEGF, Ang-2 and PD-1 inhibition. This trial will evaluate the tolerability of the combination of BI836880 and ezabenlimab and the effect of the triple inhibition in 2 populations of patients with NSCLC, according to previous PD-1 / PD-L1 inhibitor treatment. This combination will also be tested in other unmet need indications as exploratory expansion cohorts in which either a high baseline Ang-2 or increase of Ang-2 at recurrence has been reported. Ang2 and VEGF have been reported as independent predictors of survival in patients with advanced HCC. Similarly, Ang2 and VEGF have also been reported as predictors of outcome for some CPI therapy in metastatic melanoma and supporting a rational combinatorial approach to improve the efficacy of immune therapy (R19-1712).

As of January 2022, a total of 252 patients have been treated in this ongoing Phase Ib study. Clinical activity was observed across all cohorts.

DECISION TO TERMINATE THE TRIAL

Although a preliminary assessment of the available data from the ongoing clinical program for the ezabenlimab + BI 836880 combination exhibit signs of antitumor activity and a manageable safety profile for an overall positive benefit risk ratio, careful review of the full data set performed in the context of the current standards of care for the indications under study has led to the decision taken by the sponsor in December 2021 to discontinue recruitment in study 1336.11, and terminate further expansion of the study.

An important consideration in the review process was whether the investigational combination treatment under study, namely BI 836880 plus ezabenlimab, had demonstrated benefit that delivered clear improvement over the current standards of care, some of which had evolved over the course of the study. The measure used to evaluate efficacy was the Objective Response Rate (ORR) which was the primary efficacy endpoint of the trial. It is important to note that at the time of this evaluation all cohorts had completed planned enrolment, and sufficient data had been collected to support a well-informed decision. Based on this evaluation, the efficacy observed in the different indications did not show clear improvement over the standards of care relative to published efficacy results in the different indications, with the one possible promising result in the 2L HCC cohort. This finding, however, was confounded by the population studied. The 2L HCC cohort enrolled patients that had received prior 1L treatment with monotherapy anti-angiogenic TKi (i.e., either sorafenib or lenvatinib). Given the evolution

of the standard of care for 1L HCC, from monotherapy anti-angiogenic TKi treatment to combination treatment with immune checkpoint inhibitor plus an anti-angiogenic agent, it was determined that this cohort was not representative of what is expected to be the 2L HCC patient population moving forward. Based on this evaluation, the decision was taken to terminate the trial.

As a part of this decision, for patients still under active treatment, treatment with BI 836880 plus ezabenlimab may continue until disease progression, undue toxicity, withdrawal of patient consent, or 53 cycles [approximately 3 years] from the start of first treatment administration, whichever occurs first (see Section 4.1.4, “Treatment duration” for full details).

1.4 BENEFIT - RISK ASSESSMENT

Both BI 836880 and ezabenlimab are currently tested in early phase clinical trials. At the time of data cut-off for this IB version (17 Aug 2020) 62 patients with solid tumours had been treated with BI 836880 monotherapy in 3 Phase I clinical trials testing either an every-3-week schedule (1336.1, 1336-0012 Part 1) or a weekly schedule (1336.6). Additional 81 patients with solid tumours received BI 836880 in combination with a checkpoint inhibitor Ezabenlimab in a Phase Ib trial (1336-0011) and in Part 2 of a Phase I trial (1336-0012). RP2D for both monotherapy and combination trials was determined to be 720 mg Q3W.

After completing a dose escalation phase and determination of RP2D of ezabenlimab is currently used in an expansion phase evaluating the preliminary efficacy of the compound in several tumor types including NSCLC. Three doses of ezabenlimab (80, 240 and 400 mg) were tested in the dose escalation part of the phase I trial in 9 patients with solid tumors. No DLTs drug related serious AEs were observed during the MTD evaluation period at any dose level. The most common reported AEs are nausea, fatigue, decrease appetite, constipation and arthralgia. Based on this dose escalation data, the dose of 240 mg is recommended for further development in monotherapy or as a starting dose in combination trials.

The combination of an immune CPI with a VEGF blocker has previously been tested in multiple phase I, phase II and phase III trial combining atezolizumab with bevacizumab in patients with advanced solid tumors. The safety of TECENTRIQ with bevacizumab, paclitaxel and carboplatin was evaluated in IMpower150 in metastatic NSCLC. This combination was well tolerated with most AEs being mild or moderate in severity. The only grade 3-4 events were hypertension. AEs included check-point inhibitor related events such as fatigue, chills, diarrhea, rash and pruritus and other AEs related to VEGF blockade (fatigue, hypertension, and epistaxis).

Based on the mode of action of ezabenlimab and BI 836880, published and internal preclinical data and available clinical data, it is expected that the combination will increase the anti-tumor efficacy resulting in an increase in response rate with prolonged duration of response as compared to each monotherapy.

Despite the good safety profile reported for both drugs, patients should be advised of the potential risk of side effects from these investigational drugs. In Part 1, due to observed hypertension and potential infusion reactions, a 48-hour hospitalization was required after first administration of trial medications for closer observation with access to intensive care for ensuring patient safety.

In Part 2, hospitalization is optional. The period of surveillance after study drug administration depends on the medical assessment of the investigator and is at the investigator's discretion. Please refer to Sections 5.2.1, 5.2.2, and 5.2.3.

Patients enrolled in Part 2 will continue to be excluded if they have uncontrolled hypertension (defined as BP > 140/90 mmHg) at baseline, and/or a history of severe haemorrhage or thromboembolism. The most frequent AEs in patients treated in the combination therapy trials were hypertension (19.8%, including 8.6% of Grade 3), followed by nausea (12.3%, no AEs of Grade ≥3), and cough and diarrhoea (11.1%, no AEs of Grade ≥3). No patients were reported with AEs requiring dose changes; 3 patients (3.7%) had an AE leading to treatment discontinuation. Infusion-related reactions and corresponding symptoms were reported in 8 patients (9.9%), with no AEs being higher than Grade 3. Adverse events under the SMQ haemorrhages occurred in 4 patients (4.9%), with 2 patients (2.5%) presenting AEs of Grade 3 and 1 patient presenting a Grade 5 AE. Eleven patients (13.6%) were reported with immune-related AEs according to investigator's judgement; 1 AE was of Grade 3 and 1 was of Grade 4.

Other side effects 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. In summary, considering the unmet medical need for new treatment armamentarium in patients with advanced or metastatic NSCLC who are progressing during or after prior PD-1 /PD-L1 based therapy and other solid tumours, the anti-tumour activity of VEGF blockade or PD-1 inhibition and the good safety profiles of BI836880 and ezabenlimab monotherapy and the existing data suggesting that a combination of PD-1 blockade with VEGF blockade is a promising therapeutic strategy, the benefit risk assessment for patients included into this trial is considered to be favorable.

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.

1.4.1 Benefit-Risk Assessment in context of COVID-19 pandemic for patients participating in clinical trials investigating BI 836880 in combination with ezabenlimab

Considering the mechanism of action of VEGF/Ang2 inhibition and PD-1receptor blockade, there is no evidence to suggest an increased risk of infection. Based on available data, treatment with BI 836880 alone and in combination with a PD-1 inhibitor is not anticipated to pose a higher risk of acquiring a COVID-19 infection in cancer patients. Overlapping

toxicity with VEGF/Ang2 combined with PD1 with an increased risk of infection has not been observed.

Considerations around drug-drug interactions are not included in this benefit-risk assessment – this information is provided in the protocol, Investigator's Brochure and the most recent label of the respective medication(s) used for treatment of COVID-19 infection.

BENEFITS AND RISKS CONCLUSIONS AND RECOMMENDATIONS

Patients in clinical trials with BI 836880 and ezabenlimab have advanced late stage cancer with limited treatment options. Given the life threatening nature of the underlying disease, the approach recommended by professional oncology organizations (e.g. ASCO, ESMO) remains to treat patients with cancer as under normal circumstances. No consensus on recommendations exist regarding holding chemotherapy or immunotherapy or delaying adjuvant therapy or radiotherapy treatment in cancer patients with no signs of a COVID-19 infection. Withdrawing treatment in a cancer patient who may have few or any alternative treatment options requires a careful, individual evaluation.

To date, there is no evidence suggesting a link between susceptibility to COVID-19 infections and the inhibition of VEGF-A and Ang2 targeted by BI 836880. Also, there is no evidence suggesting a link between susceptibility to COVID-19 infections and the inhibition of PD-1/PDL-1. Available non-clinical and clinical data from completed clinical trials have not shown an increased risk of infections with BI 836880 and ezabenlimab.

Considering the limited and sparse data on immune activation and the role of inflammation as well as other underlying factors that may increase the severity and mortality from COVID-19 infection, there may be some factors representing the risk for using VEGF/Ang2 or PD1 that are currently still unknown. The information about the risk factors, the severity and the activity of immune response in patient with COVID-19 infections will be constantly monitored as it evolves.

All up-to-date information about the investigational compounds (preclinical, clinical, clinical pharmacology) is included in the trial documentation, including IB, clinical trial protocol for the guidance of the investigator. The latter also outlines the pre-cautionary eligibility criteria, measures for management of associated AEs, required dose reductions etc. The protocol-defined trial procedures themselves do not impose any increased risk to study participants in developing COVID-19 infection. The risk mitigation measures currently in place within the clinical trial protocols are a sufficient safeguard, as patients are frequently monitored with comprehensive safety evaluations. Based on laboratory data and any adverse event that may occur, clinical trial protocols include guidance for the continuation, interruption, dose reduction, and discontinuation of study drugs.

Therefore, assuming the protocol-defined requirements for continued study drug administration are met, the decision about concomitant use of experimental anti-cancer therapy with VEGF/Ang2 and PD1 with COVID-19 treatment in case of contracted COVID-19 infection will be left to the investigator's benefit-risk assessment on a case-by-case basis.

The investigators will take the totality of information related to each single patient and the local COVID-19 situation into consideration when performing the individual benefit-risk assessment on a case-by-case basis. Considering all aspects, the investigator will decide upon each patient's (continued) participation in the planned trials. BI as the sponsor, recommend to adhere to the trial protocol and where required, will support the investigator in their decision finding, where this protects the safety, wellbeing and/or is in the best interest of the patient.

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

2.1.1 Main objectives

PART 1:

Primary objective:

To determine the Recommended Phase 2 Dose (RP2D) of BI 836880 in combination with ezabenlimab in patients with locally advanced or metastatic non-squamous NSCLC who progressed during or after first line (in case of checkpoint inhibitor naïve patients) platinum-based therapy and patients who relapsed after completion of at least 2 cycles (in case of checkpoint inhibitor relapsing patients) of platinum-based chemotherapy and a checkpoint inhibitor treatment (monotherapy or in combination with chemotherapy).

Secondary objective:

- To provide safety data
- To evaluate the basic pharmacokinetics of BI 836880 and ezabenlimab during combination therapy after the first and fourth infusion cycle.

PART 2:

Primary objective:

- To assess anti-tumour activity of BI 836880 in combination with ezabenlimab in patients with locally advanced or metastatic non-squamous NSCLC and other solid tumors

Secondary objective:

- To provide safety data and further investigate clinical efficacy including disease control (DC), duration of objective response (DoR), progression free survival (PFS), and tumour shrinkage
- To evaluate the basic pharmacokinetics of BI 836880 and ezabenlimab during combination therapy after the first infusion cycle.

2.1.2 Primary endpoint(s)

PART 1:

The primary endpoint is the number of patients with DLTs within the first cycle of treatment, which will be assessed for dose escalation in order to meet the objective of determination of the MTD of the combination BI 836880 and ezabenlimab in patients with locally advanced or metastatic non-squamous NSCLC.

PART 2:

The primary endpoint is Objective Response (OR) defined as best overall response (RECIST 1.1) of complete response (CR) or partial response (PR) from first treatment infusion until the earliest of disease progression, death or last evaluable tumour assessment before start of subsequent anti-cancer therapy, lost to follow-up, or withdrawal of consent. In case of recurrent glioblastoma (GBM), assessment will be based on RANO (Response Assessment in Neuro-Oncology) criteria.

2.1.3 Secondary endpoint(s)

PART 1:

- Adverse events (AEs), drug related AEs, drug related AEs leading to discontinuation during treatment period.
- Pharmacokinetic parameters Cmax, tmax, and AUC0-504h after the first and fourth infusion cycle.

PART 2:

- Adverse events (AEs), drug related AEs, drug related AEs leading to discontinuation during treatment period.
- Disease control (DC), defined as best overall response of CR, PR, or stable disease (SD) by RECIST 1.1 (RANO for the GBM cohort) from first treatment infusion until the earliest of disease progression, death or last evaluable tumour assessment before start of subsequent anti-cancer therapy, lost to follow-up or withdrawal of consent.
- Duration of objective response (DoR), defined as the time from first documented CR or PR by RECIST 1.1 (RANO for the GBM cohort) until the earliest of disease progression or death among patients with OR.
- Progression-free survival (PFS) (RANO for the GBM cohort & RECIST 1.1 for all other cohorts) , defined as the time from first treatment infusion until disease progression or death from any cause, whichever occurs earlier.
- Tumour shrinkage (in millimeters), defined as the difference between the minimum post-baseline sum of diameters of target lesions (longest for non-nodal lesions, short axis for nodal lesions) and the baseline sum of diameters of the same set of target lesions. In GBM, using RANO criteria, tumor shrinkage will be calculated based on the difference between the post-baseline and baseline measurements of the sum of product of the largest bi-dimensional measurements for all target lesions.
- Pharmacokinetic parameters C_{max}, t_{max}, $AUC_{0\text{-}504h}$ after the first infusion cycle.

[redacted]

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

This is a Phase I, non-randomized, uncontrolled, open-label, dose escalating study of BI 836880 administered in combination with ezabenlimab intravenously every 3 weeks. The eligible patient population will be CPI naïve and experienced patients with locally advanced or metastatic non - squamous NSCLC who progressed during or after first line platinum-based chemotherapy or CPI monotherapy treatment or the combination of CPI and chemotherapy in Part 1. Part 2 will have additional expansion cohorts.

Part 1:

Dose escalation of BI 836880 in combination with ezabenlimab in patients with locally advanced or metastatic non-squamous NSCLC who progressed during or after first line (in case of checkpoint inhibitor naïve patients) platinum-based therapy or relapsed after completion of at least 2 cycles (in case of checkpoint inhibitor relapsing patients) of platinum-based chemotherapy and a checkpoint inhibitor treatment (monotherapy or in combination with chemotherapy).

Dose escalation will start at combination of BI 836880 360mg and ezabenlimab 240mg and will be guided by Bayesian Logistic Regression Model (BLRM) Section 7.

At the first dose level, the first patient will be treated and observed for at least 15 days before allowing the second patient to receive BI 836880 and ezabenlimab infusions.

A safety monitoring committee (SMC) meeting will be held to decide if the 2nd patient can be enrolled to the study. Subsequent enrollment at all dose levels within dose escalation, each patient in a given cohort (dose level) will be observed for a minimum of 48 hours after first BI 836880 and ezabenlimab application for acute reaction monitoring before allowing treatment for subsequent patient in the same cohort. As described in Section 6.1 of the protocol, during the treatment phase, after administration of BI 836880 and ezabenlimab, patients are required to be hospitalized under close surveillance with access to intensive care for at least 48 hours after administration of trial medication to allow close monitoring for infusion-related reactions or other adverse events and availability of patients for PK visits. The sponsor will contact the investigator to verify if any acute reaction was investigated before allowing treatment for subsequent patient in the same cohort. For any dose-escalation cohort, at least 2 patients will be required. After all patients in a cohort have either experienced a DLT or have been observed for at least one cycle (1 cycle is defined as 3 weeks) without a DLT, the BLRM will be updated with the newly accumulated data. The overdose risk will then be calculated for each dose, and escalation will be permitted to all doses which fulfil the EWOC criterion and dose escalation rules according to Section 4.1.3. Decision on further recruitment (dose escalation, de-escalation or cohort expansion) will be made by a Safety Monitoring Committee (SMC) based on the collected safety data as well as other data (e.g. PK/PD data) when available.

If DLTs are observed in the first 2 consecutive patients of a previously untested dose level, subsequent enrolment to that cohort will be stopped. The BLRM will be re-run to confirm

that the dose-level still fulfils the EWOC criterion. Decision will be made whether the next patients will be enrolled on the same dose level, or if they will be enrolled to a lower dose level.

Part 2:

It is foreseen to treat up to 290 patients of full age (according to local legislation, usually ≥ 18 years) at screening in different indications: patients with locally advanced or metastatic 2nd or 3rd line CPI resistant non-squamous Non-Small Cell Lung Cancer (NSCLC), ≥2nd line Small Cell Lung Cancer (SCLC), recurrent glioblastoma, IO failure metastatic melanoma, 1st line HCC patients (cohort G), HCC patients who were intolerant or progressed during or after standard first line treatment with sorafenib or lenvatinib (cohort F) and HCC patients who were intolerant or progressed during or after standard first line treatment with atezolizumab in combination with bevacizumab (cohort H). **Please note that the cohorts will run in parallel, not sequentially** (see Figure 3.1: 1). The HCC cohorts (cohorts F, G, and H) will be implemented only in countries where these cohorts are approved.

Notes and justification of enrolling additional patients in cohort F (2nd line HCC patients pre-treated with sorafenib or lenvatinib):

At the time of protocol version 7, 30 patients in cohort F were treated and 40% confirmed responses (naïve estimate for observed complete or partial responses) with durable duration were observed among the second line HCC patients who were pre-treated with sorafenib and lenvatinib. Response rates of currently approved non-immuno-oncology treatments (e.g. Cabozatinib, Regorafenib, Ramucirumab) were reported from 4%-7% (R20-3048, R20-3049, R20-3057) in sorafenib pre-treated patients only. Among immuno-oncology treatments, 18% and 32.2% response rates were reported for pembrolizumab (R21-2759) and for combination treatment of nivolumab and ipilimumab (R21-2758) in sorafenib pre-treated patients. The efficacy results so far observed in cohort F are very promising and warrant further investigation. 30 additional patients are thus planned to be enrolled in cohort F.

In particular, the patients in cohort F with treatment start date before 15-Jul-2021 are considered as stage I patients whereas patients starting treatment after 15-Jul-2021 (in accordance with protocol version 7) will be considered as stage II. An analysis is planned at the end of stage II, incorporating data from both stages, using a Bayesian method. An amendment may be made to further expand this cohort depending on the end of stage II result. The decision criterion as well as details of the statistical model are specified in Section 7.1.2.
Based on the current clinical evidence observed in cohort F of the ongoing trial and the documented role of Ang-2 across other HCC studies, we would like to further explore this combination in 30 patients who have progressed with atezolizumab in combination with bevacizumab in the 1st line setting (cohort H).

As of the decision of Boehringer Ingelheim in Dec 2021 no additional patients will be further included to the trial.

Figure 3.1:1 Cohorts in the expansion phase (Part 2) of the study

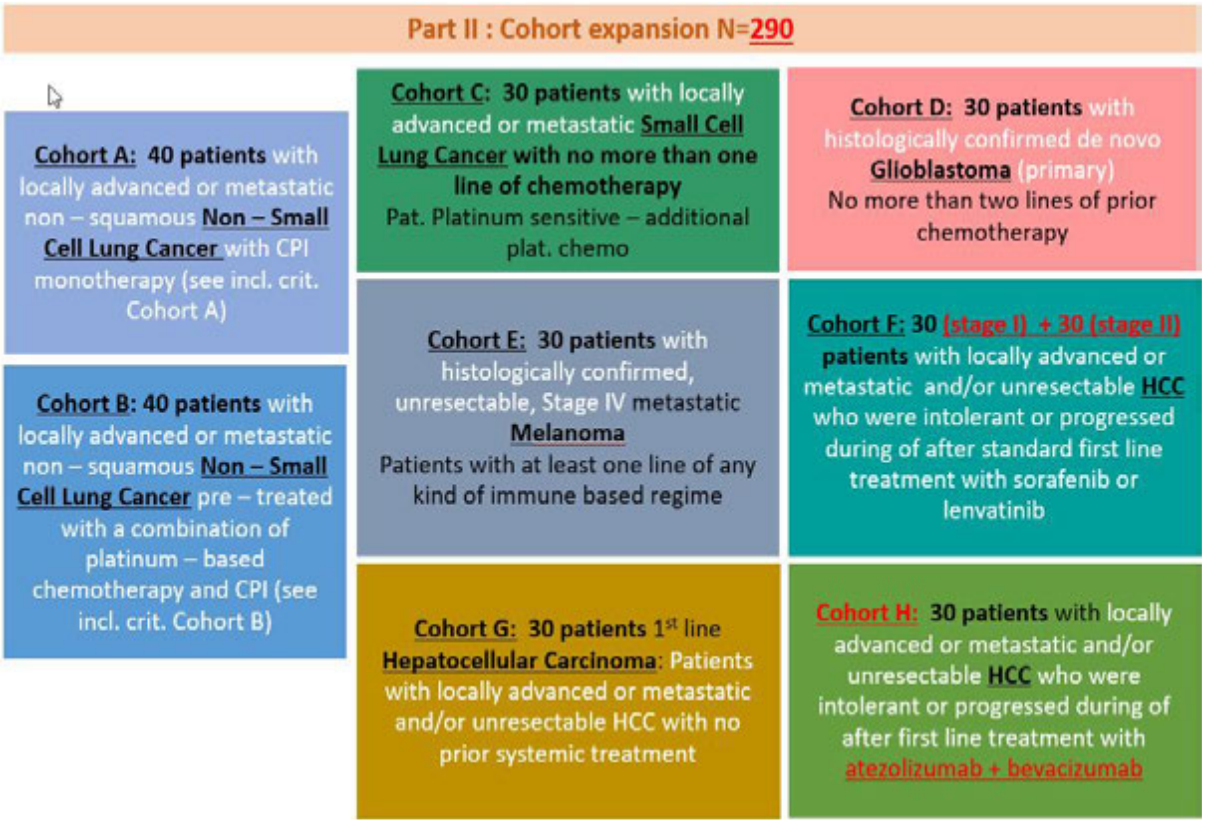
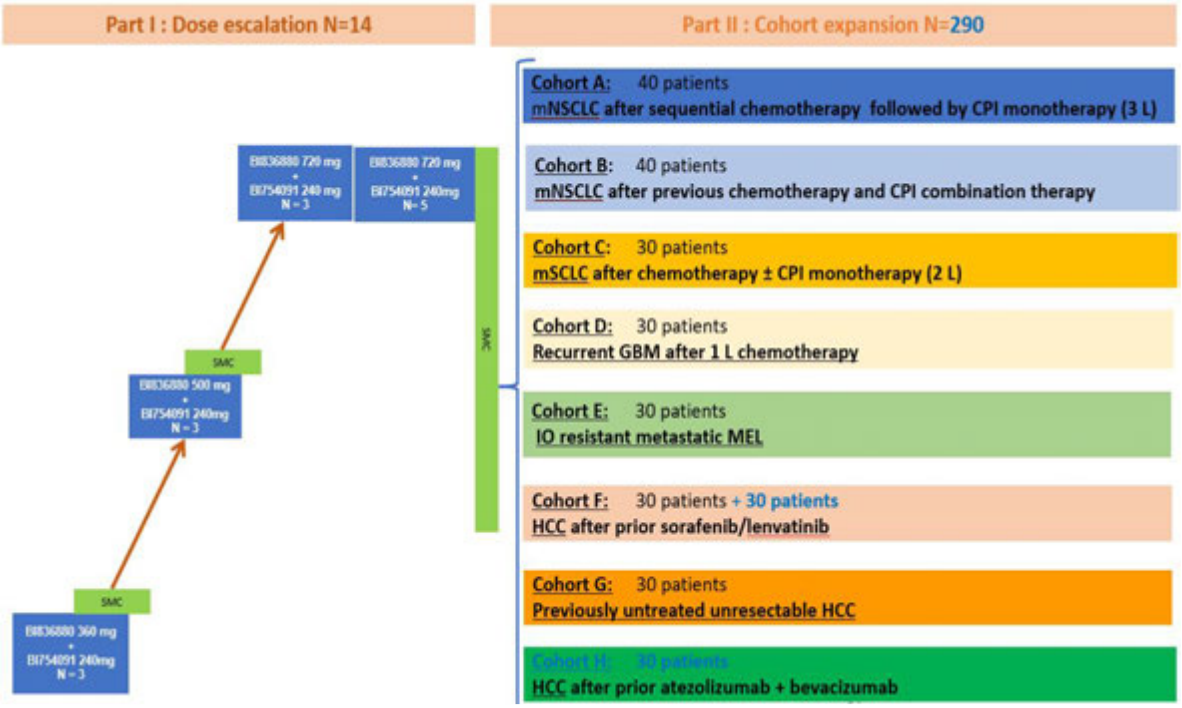


Figure 3.1:2 Study design



Doses and number of patients per cohort are given as examples and can be different based on the occurrence of DLTs and BLRM.

Routine safety laboratory exams will be performed by local laboratories. All trial relevant documentation will be stored in the Trial Master File (TMF) at Boehringer Ingelheim. In addition, each site will have an ISF containing all trial documents relevant for the site.
As described in Section 6.1 of the protocol, the period of surveillance during the treatment phase after administration of BI 836880 and ezabenlimab is at the investigator's discretion. Management guidelines have been provided for infusion related reactions (Section 5.2.7.1) and hypertension episodes (Appendix 10.2.1).

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

Part 1 is a Phase I, non-randomized, uncontrolled, open-label, dose escalating study of BI 836880 administered in combination with ezabenlimab intravenously. The eligible patients are patients with locally advanced or metastatic non - squamous NSCLC who progressed during or after first line (in case of naïve patients) of platinum-based therapy. Additional we include patients who relapsed after completion of at least 2 cycles (in case of relapsed patients) of platinum-based chemotherapy and a checkpoint inhibitor treatment (monotherapy or in combination with chemotherapy). Dose escalation will be guided by a Bayesian logistic regression model (details refer to Section 7.1).

Part 2 is an open-label expansion phase to assess efficacy and safety of BI 836880 in combination with ezabenlimab in pretreated or naïve check point inhibitor patients with

locally advanced or metastatic non-squamous NSCLC, small cell lung cancer, recurrent glioblastoma, malignant melanoma and 1st and 2nd line hepatocellular carcinoma.
Once RP2D is determined in Part 1, it is planned to enroll 320 patients as described in Section 3.1 for Part 2.
As of the decision of Boehringer Ingelheim in Dec 2021 no additional patients will be further included to the trial and the number of total enrolled patients will not be reached.

3.3 SELECTION OF TRIAL POPULATION

Eligible patients for Part 1 are patients with locally advanced or metastatic non-squamous NSCLC which progressed during or after first line (in case of naïve patients) of platinum-based therapy and patients who relapsed after completion of at least 2 cycles (in case of relapsed patients) of platinum-based chemotherapy and a checkpoint inhibitor treatment (monotherapy or in combination with chemotherapy). In Part 2, CPI pretreated or naïve patients with locally advanced or metastatic non-squamous NSCLC, small cell lung cancer, recurrent glioblastoma, malignant melanoma and hepatocellular carcinoma will be enrolled. This study is planned to be conducted in approximately 50 sites. These sites will be located in in Australia, Asia (incl. China, South Korea, Japan), North America (incl. US) EU (incl. Germany, France, Spain, UK, Russia, Poland, Ukraine). Approximately 80 patients will be enrolled in the NSCLC cohort and 30 patients each in the SCLC, metastatic melanoma, recurrent glioblastoma, 1st and 2nd line HCC cohorts (Cohorts F and G). In addition, as of protocol version 7, 30 patients will be added to cohort F, and a new cohort H will start with 30 patients to be enrolled. HCC cohorts will be implemented only in countries where this cohort is approved. In France and Germany, the 1st line HCC cohorts will not be submitted for approval. As of the decision of Boehringer Ingelheim in December 2021, no additional patients will be further included to the trial.

Recruitment of patients in this trial is competitive, i.e. screening for the trial will stop once the planned number of patients has been screened and entered. Investigators will be notified about screening completion and will then not be allowed to screen additional patients for this trial.

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

3.3.1 Main diagnosis for trial entry

In Part 1, the following patients are allowed for trial entry: patients with advanced/metastatic non squamous NSCLC who have progressed during or after first line (in case of naïve patients) of platinum-based therapy and patients who relapsed after completion of at least 2 cycles (in case of relapsed patients) of a CPI treatment alone or in combination with platinum-based chemotherapy (monotherapy or in combination with chemotherapy). Patients included in Part 1 are not eligible to participate in Part 2.

In Part 2, the following patients are allowed for trial entry: patients with locally advanced or metastatic as 2nd and 3rd line CPI resistant NSCLC and 2nd line SCLC, recurrent glioblastoma,

IO failure metastatic melanoma, 1st line HCC patients and HCC patients who are intolerant or failed the first line treatment with sorafenib or lenvatinib or with combination of atezolizumab and bevacizumab.

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 PART 1:

1. Of full age (according to local legislation, usually ≥ 18 years) at screening.

2. Pathologically confirmed locally advanced or metastatic non-squamous NSCLC with PDL-1 expression available and >1% by IHC (*as defined by the Pembrolizumab companion diagnostic test*, determined by appropriate local pathology lab.

3. No previous treatment with check-point inhibitor. Or patients with checkpoint inhibitor based treatment as last therapy before entering the trial.

4. Documented disease progression or relapse (based on investigator's assessment) during or after completion of at least 2 cycles of platinum-based chemotherapy as first line treatment of Stage IIIB/IV non- squamous NSCLC or for checkpoint inhibitor experienced patients during or after completion of at least 2 cycles of platinum-based chemotherapy and a checkpoint inhibitor treatment (monotherapy or in combination with chemotherapy). This includes patients relapsing within 6 months of completing (neo)adjuvant/curative-intent chemotherapy/CPI or chemoradiotherapy.

5. At least one target lesion (outside the brain) that can be accurately measured per Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1.

6. Lesion with a diameter ≥ 2cm assessed by radiologist as suitable for DCE-MRI evaluation (Mandatory in Part 1, optional in Part 2).

7. Eastern Cooperative Oncology Group (ECOG) performance status ≤ 1.

8. Life expectancy ≥ 3 months after start of the treatment in the opinion of the investigator.

9. Recovery from all reversible adverse events of previous anti-cancer therapies to baseline or CTCAE grade 1, except for alopecia (any grade), sensory peripheral neuropathy, must be ≤ CTCAE grade 2 or considered not clinically significant.

10. Signed and dated written informed consent in accordance with ICH-GCP and local legislation prior to admission to the trial.

11. Availability and willingness to provide a fresh tumour tissue sample obtained at baseline, and after 2 cycles of treatment.

12. Adequate organ function defined as all of the following (all screening labs (see Table 3.3.2: 1) should be performed at local lab within 10 days prior to treatment initiation):

Table 3.3.2: 1 Laboratory parameters

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1.5 x 10^9/L.
Platelets	≥75 x 10^9/L.
Hemoglobin	≥9.0 g/dL or ≥5.6 mmol/L.
Renal	
Creatinine **OR** Measured or calculated[a] creatinine clearance (Glomerular Filtration Rate (GFR) can also be used in place of creatinine or CrCl)	≤ 1.5 x ULN **OR** ≥50 mL/min for patients with creatinine levels >1.5x ULN.
Hepatic	
Total bilirubin	≤1.5 times the upper limit of normal (ULN).
AST (SGOT) and ALT (SGPT)	≤2.5 x ULN **OR** ≤5 x ULN for patients with liver metastases.
Coagulation	
International Normalised Ratio (INR) or Prothrombin Time (PT)	≤1.5xULN unless patient is receiving anticoagulant therapy as long as PT is within therapeutic range of intended use of anticoagulants.
Activated Partial Thromboplastin Time (aPTT)	≤1.5xULN unless patient is receiving anticoagulant therapy as long as PTT is within therapeutic range of intended use of anticoagulants.
[a] Creatinine clearance should be calculated per institutional standard.	

13. 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 ICH M3 (R2) that result in a low failure rate of less than 1% per year when used consistently and correctly, starting with the screening visit and through 6 months after the last dose of BI 836880 and ezabenlimab treatment, respectively. A list of contraception methods meeting these criteria is provided in the patient information. For further detail refer to Section 4.2.2.3.

    Note: Female patients of childbearing potential must have a negative serum pregnancy test within 72 hours prior to taking study medication during the screening period. At the following visits according to the flowchart a urine and/or serum pregnancy test is required. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required. The serum pregnancy test must be negative for the patient to be eligible.

[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.

For PART 2:

Main Inclusion Criteria for all cohorts

1. Of full age (according to local legislation, usually ≥ 18 years) at screening.

2. At least one measurable target lesion outside the brain (excluding the glioblastoma patients where brain lesions are allowed), that can be accurately measured per RECIST v 1.1 or RANO.

3. ECOG performance status ≤ 1 (For glioblastoma cohort, Karnofsky status is applicable; see below).

4. Adequate organ function as all of the following (all screening labs should be performed at local lab within approximately 72 hours prior to treatment initiation):

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1.5 x 10^9/L.
Platelets	≥75 x 10^9/L.
Hemoglobin	≥9.0 g/dL or ≥5.6 mmol/L.
Renal	
Creatinine **OR** Measured or calculated[a] creatinine clearance (Glomerular Filtration Rate (GFR) can also be used in place of creatinine or CrCl)	≤ 1.5 x ULN **OR** ≥50 mL/min for patients with creatinine levels >1.5x ULN.
Hepatic	
Total bilirubin	≤1.5 times the upper limit of normal (ULN).
AST (SGOT) and ALT (SGPT)	≤2.5 x ULN **OR** ≤5 x ULN for patients with liver metastases.
Coagulation	
International Normalised Ratio (INR) or Prothrombin Time (PT)	≤1.5xULN, unless patient is receiving anticoagulant therapy as long as PT/INR is within therapeutic range of intended use of anticoagulants.

	Activated Partial Thromboplastin Time (aPTT)	≤1.5xULN, unless patient is receiving anticoagulant therapy as long as PTT is within therapeutic range of intended use of anticoagulants.
	[a] Creatinine clearance should be calculated per institutional standard.	

5. Availability and willingness to provide a fresh tumor tissue sample obtained after relapse or progression on or after prior therapy. For Part 2, In case a fresh biopsy cannot be obtained (e.g. inaccessible lesions or patient safety concern), an archived specimen obtained up to 6 months prior to cycle 1, visit 1 (C1V1) may be submitted in case no systemic antineoplastic therapy has been administered between the biopsy and C1V1 (except for cohort D). For cohorts E, F and G, a fresh on-treatment biopsy is mandatory at C3D1, if possible from the same lesion as the pre-treatment biopsy.

6. Life expectancy ≥ 3 months after start of the treatment in the opinion of the investigator.

7. Recovery from all reversible adverse events of previous anti-cancer therapies to baseline or CTCAE grade 1, except for alopecia (any grade), sensory peripheral neuropathy, must be ≤ CTCAE grade 2 or considered not clinically significant.

8. Signed and dated written informed consent in accordance with ICH-GCP and local legislation prior to admission to the trial.

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 ICH M3 (R2) that result in a low failure rate of less than 1% per year when used consistently and correctly, for the entire duration of the trial treatment intake and for 6 months after the end of the trial treatment. A list of contraception methods meeting these criteria is provided in the patient information. For further detail refer to Section 4.2.2.3.

   Note: Female patients of childbearing potential must have a negative serum pregnancy test within 72 hours during the screening period. At the following visits according to the flowchart, a urine and/or serum pregnancy test is required. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required. The serum pregnancy test must be negative for the patient to be eligible.

Inclusion for:

Cohort A (NSCLC):

- Pathologically confirmed locally advanced or metastatic IIIB/IV non-squamous NSCLC
- Prior Check-point inhibitor monotherapy either as 1st or 2nd line. Patient must also have received treatment with a platinum-based chemotherapy regimen and have progressed or be intolerant, or ineligible, as per applicable local practice.
- Approximately 10 patients will be recruited who have primary resistance to CPI based therapy which is defined as those advanced or metastatic IIIB/IV non-

squamous NSCLC patients who previously received at least 2 cycles of CPI treatment and progressed without achieving benefit (RECIST v1.1 SD <4 months

[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.

or progressive disease in <4 months). Approximately 30 patients will be recruited who have secondary resistance to CPI based therapy which is defined as those advanced or metastatic IIIB/IV non-squamous NSCLC patients who had a documented minimum duration of benefit of (minimum of stable disease) 4 months and minimum treatment duration of 2 cycles on the previous CPI treatment without experiencing disease progression during that period. - Patients with NSCLC known to harbor an ALK rearrangement, or EGFR mutation, or other genomic aberrations (e.g., ROS rearrangement, BRAF V600E mutation), are only eligible after experiencing disease progression (during or after treatment) or intolerance to approved targeted therapy for respective genomic aberrations, as applicable per local country guidelines. - No more than one prior line of targeted therapy or chemotherapy regimen is allowed.
- **Cohort B (NSCLC):** - Pathologically confirmed locally advanced or metastatic IIIB/IV non-squamous NSCLC - **1st line Platinum-based chemotherapy and a check-point inhibitor combination treatment** as the most recent therapy before entering trial - Approximately 10 patients will be recruited who have primary resistance to the combination therapy which is defined as those advanced or metastatic IIIB/IV non-squamous NSCLC patients who previously received at least 2 cycles of platinum-based chemotherapy and CPI treatment and progressed without achieving benefit (RECIST v1.1 SD < 4 months or progressive disease in < 4 months). - Approximately 30 patients will be recruited who have secondary resistance to CPI based therapy which is defined as those advanced or metastatic IIIB/IV non-squamous NSCLC patients who had a documented minimum duration of benefit (minimum of stable disease) of 4 months when previously treated with at least 2 cycles of the CPI and platinum-based chemotherapy in a first line setting without experiencing disease progression during that period. - Patients with NSCLC known to harbor an ALK rearrangement, or EGFR mutation, or other genomic aberrations (e.g., ROS rearrangement, BRAF V600E mutation), are only eligible after experiencing disease progression (during or after treatment) or intolerance to approved targeted therapy for respective genomic aberrations, as applicable per local country guidelines. No more than one line of targeted therapy is allowed.

Cohort C (SCLC):

- Pathologically confirmed locally advanced or metastatic SCLC.
- Documented intolerance to platinum-based chemotherapy or refractory to platinum-based chemotherapy (progression during treatment or during < 90 days of the last dose of platinum-based chemotherapy). Patients who are platinum-sensitive (progression ≥ 90 days of the last dose of platinum-based chemotherapy) must also have received one additional prior line of platinum-based chemotherapy, if eligible, with or without combination with CPI as per applicable local treatment country guidelines.

Cohort D (recurrent glioblastoma):

- Histologically confirmed denovo glioblastoma (primary) at first or second recurrence after initial standard, control or experimental therapy that includes at a minimum RT.
- Unequivocal evidence of progressive disease on contrast-enhanced brain CT or MRI as defined by RANO Criteria, or have documented recurrent glioblastoma on diagnostic biopsy.
- **No more than two lines of prior chemotherapy** (concurrent and adjuvant temozolomide based chemotherapy including in combination with another investigational agent is considered one line of chemotherapy).
- Only first and second recurrences of GBM are eligible.
- An interval of at least 12 weeks from the completion of radiation therapy to start of study drug unless there is a new area of enhancement consistent with recurrent tumor outside the radiation field or there is unequivocal histologic confirmation of tumor progression.
- Patient may have been operated for recurrence. If operated: residual and measurable disease after surgery is required; surgical site must be adequately healed free of drainage or cellulitis, and the underlying cranioplasty must appear intact at the time of randomization.
- Karnofsky performance status ≥ 70.
- MRI within 14 days prior to start of study drug.
- Patients should be immunocompetent (i.e. no concomitant treatment with dexamethasone (or equivalent), or receive stable/decreasing steroid levels not exceeding 2 mg/day dexamethasone (or equivalent) during the last 3 days prior to clinical screening; no severe lymphopenia).

Cohort E (Melanoma):

- Histologically confirmed, unresectable, Stage IV metastatic melanoma
- Patients with a BRAF mutation must have received targeted treatment, or were not eligible, with a BRAF and MEK inhibitor as per applicable local country guidelines. In such a case no more than one line of targeted therapy is allowed.
- At least one line of any kind of CPI based regimen as last treatment before entering the study
- Documented progression during or after CPI therapy based regimen

Cohort F (2nd line HepatocellularCarcinoma):

- Patients must have diagnosis of locally advanced or metastatic and/or unresectable histologically confirmed advanced hepatocellular carcinoma, not eligible for surgical and/or locoregional therapies
- Patients should have progressed on or after first line treatment with sorafenib or lenvatinib or discontinued sorafenib or lenvatinib due to lack of tolerability after receiving at least two weeks of treatment. Reason for discontinuation must be documented.
- Documented virology status of hepatitis, as confirmed by screening hepatitis B surface antigen (HBsAg), antibody to hepatitis B core antigen (anti-HBc), HBV DNA, anti-hepatitis C virus (anti-HCV) and HCV RNA as applicable.
- Child-Pugh score class A
- Anti-viral therapy per local standard-of-care if active hepatitis B virus (HBV). HBV DNA to be <500IU/ml and patients on anti HBV therapy for >4 weeks before entering the study.

Cohort G (1st line Hepatocellular Carcinoma): To be implemented only in countries where this cohort is approved.

- The subject should have have diagnosis of locally advanced or metastatic and/or unresectable histologically confirmed advanced hepatocellular carcinoma that is not amenable to a curative treatment approach (eg, transplant, surgery, ablation therapy) or locoregional therapy (eg, TACE).
- No prior systemic therapy for HCC. Previous use of herbal therapies/traditional Chinese medicines with anti-cancer activity included in the label is allowed, provided that these medications are discontinued prior to randomization.
- Child-Pugh Score of A.
- Documented virology status of hepatitis, as confirmed by screening hepatitis B surface antigen (HBsAg), antibody to hepatitis B core antigen (anti-HBc), HBV DNA, anti-hepatitis C virus (anti-HCV) and HCV RNA as applicable.
- Anti-viral therapy per local standard-of-care if active hepatitis B virus (HBV). HBV DNA to be <500IU/ml and patients on anti HBV therapy for >4 weeks before entering the study.

Cohort H (2nd line Hepatocellular Carcinoma - atezolizumab + bevacizumab failures): To be implemented only in countries where this cohort is approved.

- Patients must have diagnosis of locally advanced or metastatic and/or unresectable histologically confirmed advanced hepatocellular carcinoma, not eligible for surgical and/or locoregional therapies
- Patients should have progressed on or after first line treatment with atezolizumab in combination with bevacizumab or discontinued due to lack of tolerability after receiving at least two cycles of treatment. Reason for discontinuation must be documented.
- Documented virology status of hepatitis, as confirmed by screening hepatitis B surface antigen (HBsAg), antibody to hepatitis B core antigen (anti-HBc), HBV DNA, anti-hepatitis C virus (anti-HCV) and HCV RNA as applicable.

- Child-Pugh score class A
- Anti-viral therapy per local standard-of-care if active hepatitis B virus (HBV). HBV DNA to be <500IU/ml and patients on anti HBV therapy for >4 weeks before entering the study.

3.3.3 Exclusion criteria

For PART 1:

1. Known hypersensitivity to the trial drugs or their excipients or risk of allergic of anaphylactic reaction to drug product according to Investigator judgement (e.g. patient with history of anaphylactic reaction or autoimmune disease that is not controlled by nonsteroidal anti-inflammatory drugs (NSAIDs), inhaled corticosteroids, or the equivalent of </= 10 mg/day prednisone).

2. Known immunodeficiency virus infection or an active hepatitis B or C virus infection.

3. History of severe hypersensitivity reactions to other mAbs.

4. Immunosuppressive corticosteroid doses (> 10 mg prednisone daily or equivalent) within 4 weeks prior to the first dose of trial medication.

5. Current or prior treatment with any systemic anti-cancer therapy either within 28 days or a minimum of 5 half-lives, whichever is shorter before start of treatment.

6. Serious concomitant disease, especially those affecting compliance with trial requirements or which are considered relevant for the evaluation of the endpoints of the trial drug, such as neurologic, psychiatric, infectious disease or active ulcers (gastrointestinal tract, skin) or laboratory abnormality that may increase the risk associated with trial participation or trial drug administration, and in the judgment of the investigator would make the patient inappropriate for entry into the trial.

7. Major injuries and/or surgery or bone fracture within 4 weeks of start of treatment, or planned surgical procedures during the trial period.

8. Patients with personal or family history of QT prolongation and/or long QT syndrome, or prolonged QTcF at baseline (> 480 ms).

9. Significant cardiovascular/cerebrovascular diseases (i.e. uncontrolled hypertension, unstable angina, history of infarction within past 6 months, congestive heart failure > NYHA II).
   Uncontrolled hypertension defined as: Blood pressure in rested and relaxed condition >= 140 mmHg, systolic or >= 90 mmHg diastolic (with or without medication), measured according to Appendix 10.2.

10. LVEF < 50%

11. History of severe hemorrhagic or thromboembolic event in the past 12 months (excluding central venous catheter thrombosis and peripheral deep vein thrombosis).

12. Known inherited predisposition to bleeding or to thrombosis in the opinion of the investigator.

13. Patient with brain metastases that are symptomatic and/or require therapy.

14. Patients who require full-dose anticoagulation (according to local guidelines). No Vitamin K antagonist and other anticoagulation allowed; LMWH allowed only for prevention not for curative treatment.

15. History of pneumonitis within the last 5 years.

16. Patients who are under judicial protection and patients who are legally institutionalized.

17. Patients unable or unwilling to comply with protocol

18. Previous enrolment in this trial (Part 1 or Part 2).

19. Chronic alcohol or drug abuse or any condition that, in the investigator's opinion, makes them an unreliable trial patient or unlikely to complete the trial.

20. Women who are pregnant, nursing, or who plan to become pregnant in the trial

For PART 2:

1. Known hypersensitivity to the trial drugs or their excipients or risk of allergic of anaphylactic reaction to drug product according to Investigator judgement (e.g. patient with history of anaphylactic reaction or autoimmune disease that is not controlled by nonsteroidal anti-inflammatory drugs (NSAIDs), inhaled corticosteroids, or the equivalent of </= 10 mg/day prednisone).

2. Not more than one CPI based treatment regimen prior to entering study (eg. anti-Programmed Death receptor-1 (PD-1), anti-Programmed Death-1 ligand-1 (PD-L1), anti-PD-L2, or anti-cytotoxic T lymphocyte associated antigen-4 (anti-CTLA-4) antibody).In case of CPIs combination, they need to be approved by the local regulatory agencies; for e.g., Melanoma cohort (Cohort E).

3. Known HIV infection

4. Active hepatitis B virus (HBV) or hepatitis C virus (HCV) infection (exception for patients in HCC cohorts; Cohorts F, G & H).

5. History of severe hypersensitivity reactions to other mAbs.

6. Immunosuppressive corticosteroid doses (> 10 mg prednisone daily or equivalent) within 4 weeks prior to the first dose of trial medication except for control of cerebral edema in case of recurrent glioblastoma (Cohort D).

7. Current or prior treatment with any systemic anti-cancer therapy (including radiotherapy) either within 28 days or a minimum of 5 half-lives, whichever is shorter before start of treatment.

8. Serious concomitant disease, especially those affecting compliance with trial requirements or which are considered relevant for the evaluation of the endpoints of the trial drug, such as neurologic, psychiatric, infectious disease or active ulcers (gastrointestinal tract, skin) or laboratory abnormality that may increase the risk associated with trial participation or trial drug administration, and in the judgment of the investigator would make the patient inappropriate for entry into the trial.

9. Major injuries and/or surgery or bone fracture within 4 weeks of start of treatment, or planned surgical procedures during the trial period.

10. Patients with personal or family history of QT prolongation and/or long QT syndrome, or prolonged QTcF at baseline (> 480 ms).

11. Significant cardiovascular/cerebrovascular diseases (i.e. uncontrolled hypertension, unstable angina, history of infarction within past 6 months, congestive heart failure > NYHA II).
    Uncontrolled hypertension defined as: Blood pressure in rested and relaxed condition >= 140 mmHg, systolic or >= 90 mmHg diastolic (with or without medication), measured according to Appendix 10.2.

12. LVEF < 50%

13. History of severe hemorrhagic or thromboembolic event in the past 12 months (excluding central venous catheter thrombosis and peripheral deep vein thrombosis).

14. Known inherited predisposition to bleeding or to thrombosis in the opinion of the investigator.

15. Patient with brain metastases that are symptomatic and/or require therapy.

16. Patients who require full-dose anticoagulation (according to local guidelines). No Vitamin K antagonist and other anticoagulation allowed; LMWH allowed only for prevention not for curative treatment.

17. History of pneumonitis (non-infectious) within the last 5 years

18. Patients who are under judicial protection and patients who are legally institutionalized.

19. Patients unable or unwilling to comply with protocol

20. Previous enrolment in this trial.

21. Chronic alcohol or drug abuse or any condition that, in the investigator's opinion, makes them an unreliable trial patient or unlikely to complete the trial.

22. Women who are pregnant, nursing, or who plan to become pregnant in the trial

23. Symptomatic pleural effusion, pericardial effusion, or ascites

24. Prior treatment with any antiangiogenic treatment (e.g. bevacizumab, cediranib, aflibercept, vandetanib, XL-184, sunitinib, etc) except for prior sorafenib or lenvatinib treatment in 2nd line HCC cohort (Cohort F) and for prior treatment with atezolizumab in combination with bevacizumab in Cohort H.

25. Has received a live vaccine within 30 days prior to the first dose of study drug

26. Patients with known active second malignancy other than non-melanoma skin cancers, non-metastatic prostate cancer, in situ cervical cancer, and ductal or lobular carcinoma in situ of the breast. Patients are not considered to have a currently active malignancy if they have completed anticancer therapy and have been disease free for greater than 2 years prior to screening

Further exclusion criteria:

Exclusion criteria for Glioblastoma cohort:

1. Has tumor primarily localized to the brainstem or spinal cord.

2. Has presence of diffuse leptomeningeal disease or extracranial disease.

3. Is known to have IDH mutant variety of recurrent glioblastoma.

4. Any prior treatment with prolifeprosan 20 with carmustine wafer.

5. Any prior treatment with an intracerebral agent.

Exclusion criteria for Melanoma cohort:

1. Uveal or ocular melanoma

Exclusion criteria for HCC cohorts (cohorts F, G & H):

1. Co-infection with HBV and HCV or HBV and hepatitis D virus (HDV)

2. Known fibrolamellar HCC, sarcomatoid HCC, or mixed cholangiocarcinoma and HCC

3. Untreated active Hepatitis B virus (HBV)

4. History of hepatic encephalopathy

5. Participants with untreated or incompletely treated varices with bleeding or high-risk for bleeding

6. Treatment with any HCV anti-viral therapy within 4 weeks prior to Cycle 1 Day 1

3.3.4 Withdrawal of patients from therapy or assessments

Patients may potentially be withdrawn from trial treatment or from the trial as a whole ("withdrawal of consent") with very different implications, please see Sections 3.3.4.1 and 3.3.4.2 below.

Every effort should be made to keep entered 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 patient's participation, 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 eCRF.

3.3.4.1 Withdrawal from trial treatment

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

- The patient wants to withdraw from trial treatment, without the need to justify the decision.
- The patient needs to take concomitant drugs that interfere with the investigational product or other trial medication.
- The patient can no longer be treated with trial medication for other medical reasons (such as surgery, adverse events, other diseases, or pregnancy).
- The patient can no longer be treated with trial drug after a drug related Adverse Event CTCAE Grade 4.
- The patient can no longer be treated with trial drug after a DLT, which did not recover to CTCAE Grade 1 or pre-treatment values within 2 weeks (not applicable for part 2)
- The patient has repeatedly shown to be non-compliant with important trial procedures and, in the opinion of both, the investigator and sponsor representative, is not willing or able to stick to the trial requirements in the future.

Given the patient's agreement, the patient will undergo the procedures for early treatment discontinuation and 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. adverse events) must be recorded in the eCRF. These data will be included in the trial database and reported.

3.3.4.2 Withdrawal of consent for trial participation

Patients may withdraw their consent for trial participation at any time without the need to justify the decision.

This will however mean that no further information may be collected for the purpose of the trial and negative implications for the scientific value may be the consequence. Furthermore, it may mean that further patient follow up on safety cannot occur.

If a patient wants to withdraw consent, the investigator should explain the difference between treatment withdrawal and withdrawal of consent for trial participation and explain the options for continued follow up after withdrawal from trial treatment, please see Section 3.3.4.1 above.

3.3.4.3 Discontinuation of the trial by the sponsor

Boehringer Ingelheim reserves the right to discontinue the trial overall or at a particular trial site at any time for the following reasons:

1. Failure to meet expected enrolment goals overall or at a particular trial site
2. Emergence of any efficacy/safety information invalidating the earlier positive benefit-risk-assessment that could significantly affect the continuation of the trial
3. Violation of GCP, the trial protocol, or the contract impairing the appropriate conduct of the trial
4. Termination of the development of the compound in this indication.

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

In this trial, the IMP BI 836880 will be switched to a new pharmaceutical formulation which is diluted in a standard 5% Glucose/Dextrose solution. The new formulation will be made available in this trial at the latest before expiry of the old formulation prepared with a drug specific Diluent. Details of the trial medications, BI 836880, ezabenlimab, and respective diluents, are presented in Tables 4.1.1: 1 and 4.1.1: 2, in the IBs for BI 836880 and ezabenlimab as well as in the Instruction for the Pharmacist (IfP).

Table 4.1.1: 1 BI 836880

Substance:	BI 836880
Pharmaceutical formulation:	Solution for infusion
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	10 mg/ml (vials with 10 ml)
Posology	rate controlled infusion on Day 1 of each 3-week cycle
Route of administration:	i.v.
Duration of use:	until progression, unacceptable toxicity, or up to a maximum of 53 cycles

Table 4.1.1: 2 Ezabenlimab (BI 754091)

Substance:	Ezabenlimab (BI 754091)
Pharmaceutical formulation:	Solution for Infusion or Concentrate for solution for infusion
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	20 mg /mL (15 mL vial) or 20 mg /mL (12 mL vial)
Posology	rate controlled infusion on Day 1 of each 3-week cycle
Route of administration:	i.v.
Duration of use:	until progression, unacceptable toxicity, or up to a maximum of 53 cycles

4.1.2 Selection of doses in the trial

4.1.2.1 Part 1

BI 836880 is currently tested as monotherapy in 2 phase I trials. 29 and 24 patients received BI 836880 in trial 1336.1 (every 3 week schedule) and in trial 1336.6 (weekly schedule), respectively. Dose levels between 40 mg and 1000 mg of BI 836880 were tested in the every 3 week trial. Most commonly reported adverse events were hypertension, asthenia, nausea, vomiting, diarrhea and constipation. 5 DLTs occurred in the two studies (pulmonary embolism, proteinuria, hypertension, respiratory distress). Other relevant adverse events (mode of action related) include peripheral edema and bleeding (epistaxis).

Based on safety data as well as PK and PD analysis, the dose of 720 mg is selected as recommended phase 2 dose (RP2D). This dose will be the highest dose that can be tested in combination with ezabenlimab. The dose below this dose tested in monotherapy trial (360 mg) is safe and showed complete inhibition of systemic targets, and will used as starting dose for the combination with ezabenlimab. However because of the important safety difference between 360 and 720 mg (mainly occurrence and severity of hypertension), a BI 836880 intermediate dose of 500 mg will be tested. The highest tested dose levels will be expanded before selection of BI 836880 dose to be used for Part 2 of the trial.

In the monotherapy phase I trial (1381.1), a total of 9 patients received ezabenlimab at 3 dose levels (80 mg, 240 mg and 400 mg) in the dose escalation cohorts. There were no DLTs or drug-related SAE reported in any cohort. The most common reported AEs were nausea, fatigue, decreased appetite, constipation and arthralgia. Eight additional patients have been treated at dose of 240 mg in the expansion part of this trial. No grade 4, Grade 5 AE or DLT was reported.

The exploratory analysis of biomarker performed in these 9 patients shows 100% PD-1 receptor occupancy in peripheral blood in all on-treatment patient samples compared to baseline throughout one treatment cycle.

Plasma concentration of ezabenlimab appears to increase linearly (based on AUC0-504h Cmax and Cpre). Furthermore, the observed ezabenlimab PK was compared with model simulated pembrolizumab PK (R17-2460). Observed ezabenlimab PK profiles overlap with those simulated for pembrolizumab at a dose of 200 mg.

The dose of 240 mg of ezabenlimab once every 3 weeks was chosen to be further explored in monotherapy trials and is recommended as a starting dose in combination trials. The dose level of ezabenlimab will likely be fixed in this study unless safety signals suggest a dose adjustment.

4.1.2.2 Part 2

Once at least 6 patients have received at least 1 cycle at the maximum dose level in Part 1, a safety evaluation of all patients treated in Part 1 will be performed. Based on all available data, the SMC may approve the selected BI 836880 dose (RP2D) to be used in combination

with ezabenlimab for Part 2 of the trial. The RP2D assessment will be supported with the PK and PD analysis of at least 3 patients in each dose cohort.

Update after SMC decision:
The SMC selected the dose BI 836880 720 mg and for ezabenlimab 240 mg as dose for the Part 2 of this trial.

4.1.3 Method of assigning patients to treatment groups

After assessment of all in- and exclusion criteria, each eligible patient will be entered to treatment groups and 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

Medication will be assigned via Interactive Response Technology (IRT) for each treatment cycle. Each medication box does have a unique medication number. To facilitate the use of the IRT, the Investigator will receive all necessary instructions.

The study drug will be prepared and handled according to "Instruction for Pharmacists" which will be filed in ISF. Upon notification a patient entered the study; the pharmacy will prepare the study drug in the assigned dosage for administration to the patient.

Ezabenlimab and BI 836880 will be given every 3 weeks as 2 separate consecutive intravenous infusions by authorized site staff in a specialized unit where emergency care can be provided (e.g. intensive care unit available, medical personal trained in advanced live support) according to "Instruction for Pharmacists".

The expected infusion time is 60 minutes for ezabenlimab and same for BI 836880; ezabenlimab will be administered first, then 15 minutes (+/- 10 min) after the end of this infusion BI 836880 will be administered.

In case of technical issues or complications during infusion, the total infusion time (including stop time and flushing) for BI836880 should not exceed 360 minutes.

For ezabenlimab, in case of technical issues or complications during infusion, the total infusion time (including stop time) should not exceed 180 minutes.

Appropriate drugs and medical equipment to treat anaphylactic reactions must be immediately available, and study personnel must be trained to recognize and treat anaphylaxis.

In the event of an infusion-related reaction $\leqslant$ Grade 2, the infusion rate of ezabenlimab 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 $\leqslant$ Grade 2, subsequent infusions may be administered at 50% of the initial rate. Depending

on the time of occurrence and the severity of the reaction, the investigator may consider administering additional supportive medication, e.g. corticosteroids for re-introduction. Infusion rate and premedication for further treatment cycles should be adapted according to Investigator decision, but adaption of administration scheme need to be agreed with sponsor. If an infusion related reaction is Grade 3 or higher in severity at any point during the study, treatment with ezabenlimab has to be permanently discontinued.

Premedication:
No premedication will be required for BI 836880 IV or ezabenlimab infusion. If a patient expressed sign of infusion reaction at any BI 836880 treatment, a premedication will be considered for all subsequent treatment infusions (dosage and schedule according investigator's decision) comparable to following scheme:

- Acetaminophen/Paracetamol 650 mg - 1000 mg p.o., or equivalent
- Antihistamine p.o. or i.v., equivalent to Diphenhydramine 50 mg i.v.

Drug re-administration criteria after the first cycle has been completed for Part 1:
Before initiating a new treatment cycle the actual health status will be assessed according to Flow Chart and described in Section 5.2.5. To continue treatment with further cycles, all of the following criteria must be met:

- No uncontrolled hypertension (according to Exclusion-Criterion #9)
- QTcF <=480 ms (according to Exclusion-Criterion #8)
- Acceptable tolerability (in case of an adverse event at the planned start of a treatment cycle patients may continue therapy only after recovery to a level which would allow further therapy; i.e. CTCAE grade 1 or pre-treatment value or considered not clinically significant)

In case one of the above mentioned criteria is not fulfilled the patient should be re-evaluated for up to 2 weeks. Any case of a delay in treatment cycle should be communicated to the Clinical Monitor at Boehringer Ingelheim. The investigator in agreement with the Clinical Monitor will decide about further treatment of individual patient, based on known risk/benefit of BI 836880 and ezabenlimab.

Rescreening is generally not allowed. In individual cases, rescreening can be considered in alliance with the sponsor.

In case of a DLT (drug related AEs CTCAE Grade 3, 4 according to Table 5.2.6.1: 1), the patient will discontinue treatment.

Once a DLT has recovered to CTCAE grade 1 or pre-treatment values, the study drugs may be re-started at a lower dose level in case the patients benefit from the study drug after discussion between investigator and Clinical Monitor at Boehringer Ingelheim.

Drug re-administration criteria after the first cycle has been completed in Part 2:
Before initiating a new treatment cycle the current health status of the patient will be assessed according to the Flow Chart.

To continue treatment with further cycles, all of the following criteria must be met:

1. Pre-infusion SBP should be < 160 mmHg and pre-infusion DBP should be < 100 mmHg; study drug administration of both study drugs should be temporarily delayed until BP < 160/100. Please see Table 10.2.1: 1 in Appendix 10.2.1, which describes the guidelines for BP management and study drug administration.

2. QTcF <=480 ms (according to Exclusion-Criterion #8)

3. Echocardiography if clinically indicated (based on investigators judgment) with Left Ventricular Ejection Fraction (LVEF) ≥ 50%

4. Acceptable tolerability (in case of an adverse event at the planned start of a treatment cycle patients may continue therapy only after recovery to a level which would allow further therapy in the opinion of investigator).

In case the above mentioned criteria 2, 3, and 4 are not fulfilled, the patient should be re-evaluated as needed. Any case of a delay in treatment cycle should be communicated to the Clinical Monitor at Boehringer Ingelheim. The investigator in agreement with the Clinical Monitor will decide about further treatment of individual patient, based on known risk/benefit of BI 836880 and ezabenlimab.

Dose reduction guidelines

Part 1:

Administration of trial drugs has to be stopped temporarily in case of a DLT (see Section 5.2.6.1). Patients may continue therapy only after recovery from DLT to at least fulfil retreatment criteria. The future dose of BI 836880 must be a tested dose which is one dose level below the dose received by the patient (Table 4.1.4: 1 and 4.1.4: 2 below) Treatment has to be discontinued in case the DLT is not reversible.

Table 4.1.4: 1 Dose reduction recommendations for BI 836880 in Part I

BI 836880 received dose	BI 836880 reduced dose
720 mg	500 mg
500 mg	360 mg
360 mg	Stop BI 836880

In case of AEs (DLTs) that can be definitely characterized as ezabenlimab related, dose can be reduced.

Table 4.1.4: 2 Dose reduction recommendations for ezabenlimab in Part I

Ezabenlimab received dose	Ezabenlimab reduced dose
240 mg	80 mg

For each drug, only one dose reduction will be allowed per patient.

Part 2:

Dose reductions or escalations are not allowed for ezabenlimab in any patient.

In the dose expansion study, only dose reductions/re-escalations are allowed for BI 836880.

Table 4.1.4: 3 Dose reduction recommendations for BI 836880 in Part 2

BI 836880 received dose	BI 836880 reduced dose
720 mg	480 mg

A dose reduction of BI 836880 from 720 mg to 480 mg is allowed, if investigator can attribute the AE unequivocally to the BI 836880 (for e.g., hypertension). If the reduced dose is still intolerable, the dose maybe delayed (please see below the sub-section "Delay of treatment"). If the reduced dose is tolerable, and where deemed in the best interest of the patient, the investigator should re-escalate to the originally assigned dose of 720 mg of BI 836880 as soon as deemed clinically appropriate.

Delay of treatment:

During combination therapy, if treatment is held or discontinued due to an AE(s), both BI 836880 and ezabenlimab will be held or discontinued together. If treatment is to be restarted after resolution (≤ Grade 1 or baseline) of the AE, preferably both BI 836880 and ezabenlimab must be started together.

In some cases, in discussions with the Sponsor, treatment with one of the two investigational drugs can be allowed if there is an AE reported which can be clearly attributed to one of the two drugs and further warrants a temporary discontinuation of this drug in the interest of the patient.

Treatment duration:

Treatment with BI 836880 plus ezabenlimab may continue until disease progression, undue toxicity, withdrawal of patient consent, or 53 cycles [approximately 3 years] from the start of first treatment administration, whichever occurs first. Patients will be allowed to stay on treatment also in the case of initial radiological PD, until progression is confirmed or up to 53 cycles from the start of first treatment administration if the investigator considers that the treatment is beneficial for the patient.

Investigators may consider discontinuing BI 836880 and continue therapy with ezabenlimab for up to 53 cycles from the start of the first treatment administration if the patient has been on therapy ≥ 6 months, has achieved at least SD by RECIST 1.1 and can tolerate the therapy, and if the investigator considers this to be in the best interest of the patient.

For any patient still on treatment with the investigational combination of BI 836880 plus ezabenlimab 53 cycles from the start of the first treatment administration, treatment extension will be considered on a case-by-case basis upon request by the investigator for a maximum additional 6 cycles, to complete no later than 30 April 2025, if the investigator considers this to be in the best interest of the patient. After this date treatment with the investigational combination BI 836880 plus ezabenlimab will no longer be available.

Investigators are requested to prepare for discontinuation of patients from the current investigational treatment of BI 836880 plus ezabenlimab and to switch them to alternative available treatment options outside of the current protocol no later than by the final availability date of 30 April 2025.

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

Not applicable, as this is an open-label study.

4.1.5.2 Unblinding and breaking the code

Not applicable.

4.1.6 Packaging, labelling, and re-supply

The investigational products will be provided by BI or a designated CRO. They will be packaged and labelled in accordance with the principles of Good Manufacturing Practice (GMP). Re-supply to the sites will be managed via an IRT system, which will also monitor expiry dates of supplies available at the sites.

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

4.1.7 Storage conditions

BI 836880 vials (old and new formulation) and ezabenlimab vials (solution and concentrate for solution) must be stored in their original packaging. The study product must be stored according to the instructions on the label (in a refrigerator at 2-8°C). The Investigator, the Pharmacist, or other personnel is allowed to store and dispense investigational product. They will be responsible for ensuring that the investigational product used in the study is securely maintained as specified by the sponsor and in accordance with the applicable regulatory requirements.

A temperature log must be maintained to make certain that the drug supplies are stored at the correct temperature.

In-use-stability of ready to use solution refers to “Instructions for Pharmacists” as described in Section 4.1.4.

Drug supplies will be kept in their original packaging and in a secure limited access storage area according to the recommended storage conditions on the medication label. A temperature log must be maintained for documentation. If the storage conditions are found to be outside the specified range, the CML (as provided in the list of contacts) must be contacted immediately.

4.1.8 Drug accountability

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

- Approval of the clinical trial protocol by the IRB / ethics committee,
- Availability of a signed and dated clinical trial contract between the sponsor and the investigational site,
- Approval/notification of the regulatory authority, e.g. competent authority,
- Availability of the curriculum vitae of the Principal Investigator,
- Availability of a signed and dated clinical trial protocol,
- Availability of the proof of a medical license for the Principal Investigator,
- Availability of FDA Form 1572 (if applicable).

Investigational drugs are not allowed to be used outside the context of this protocol. They must not be forwarded to other investigators or clinics. Patients should be instructed to return unused investigational drug.

The investigator < and/or > pharmacist < and/or > investigational drug storage manager must maintain records of the product’s delivery to the trial site, the inventory at the site, the use by each patient, and the return to the sponsor or warehouse / drug distribution center or alternative disposal of unused products. If applicable, the sponsor or warehouse / drug distribution center will maintain records of the disposal.

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

4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

Concomitant (non-oncological) therapies starting or changing during the cycle of the trial should be recorded in the electronic case report form (eCRF). 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 42-day follow up, only concomitant therapy indicated for treatment of a related AE has to be reported. If a new anti-cancer treatment is started, it will be documented in the eCRF.

4.2.1 Other treatments and emergency procedures

Potential side effects of BI 836880 or ezabenlimab have to be treated symptomatically. Symptomatic treatments of side effects or tumor-associated symptoms are allowed.

Concomitant medications, or therapy to provide adequate care, may be given as clinically necessary. There are no special emergency procedures to be followed.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

- Previous anti-cancer therapy must have been discontinued before first administration of trial drug and the patient must have recovered from all clinically relevant reversible toxicities (see Exclusion Criteria Section 3.3.3 for further details).

- Concomitant anti-cancer therapy is not allowed. Radiotherapy for local symptom control of non-target lesions can be allowed after consulting the investigator and sponsor. Palliative radiotherapy will not be allowed during the first cycle for any lesion. Palliative radiotherapy is allowed only for non-target lesions, following discussion with the Medical Monitor, provided that the reason for radiotherapy does not reflect PD and does not interfere with response assessment. Lesions that have been exposed to radiotherapy are no longer evaluable, and may not be included in the assessment of the non-target lesions and the overall assessment. Unless in emergency situations, the Medical Monitor should be contacted prior to the administration of palliative radiotherapy in the expansion phase.

- Immunosuppressive medications including, but not limited to systemic corticosteroids at doses exceeding 10 mg/day of prednisone or equivalent, methotrexate, azathioprine, and tumour necrosis factor-alpha blockers are prohibited. Use of immunosuppressive medications for the management of investigational product-related AEs or in patients with contrast allergies is acceptable, and does not necessarily warrant immediate treatment discontinuation. In addition, use of inhaled, topical, intranasal corticosteroids or local steroid injections (e.g., intra-articular injection) is permitted. Temporary uses of corticosteroids for concurrent illnesses (e.g., food allergies, computed tomography (CT) scan contrast hypersensitivity) are acceptable upon discussion with the Medical Monitor. For patients in the cohort D (Glioblastoma)

higher doses of corticosteroids may be allowed as defined in the cohort-specific eligibility criteria.

- 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.

- Full-dose anticoagulation (according to local guidelines) with Vitamin K antagonist and other anticoagulation is not allowed during the trial conduct; LMWH is allowed only for prevention not for curative treatment.

- Any planned surgeries are not allowed (see Exclusion Criteria Section 3.3.3 for further details). Unplanned surgeries should be postponed whenever possible four weeks after stop of treatment. For urgent interventions patients should not be further treated and should be intensely monitored regarding wound healing and post-operative complications.

4.2.2.2 Restrictions on diet and life style

No restriction.

4.2.2.3 Restrictions regarding women of childbearing potential

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

Highly-effective methods of contraception include:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation, Oral, intravaginal, transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation: oral, injectable, implantable
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion

- Vasectomised partner o provided that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomised partner has received medical assessment of the surgical success.
- Sexual abstinence - defined as refraining from heterosexual intercourse during the entire period (stated above) of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

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

Male patients with partners of childbearing potential must agree to use condoms and ensure their partner is using an additional highly-effective method of birth control, during the trial and until at least 6 months after the end of the trial treatment.

4.3 TREATMENT COMPLIANCE

BI 836880 and ezabenlimab 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 methods of collecting dosing information assure that total exposure can be calculated programmatically taken into account any missing doses.

5. ASSESSMENTS

5.1 ASSESSMENT OF EFFICACY

The same method of assessment and the same technique should be used also in follow up of identified and reported lesions. Lesions in previously irradiated areas may not be used as target lesions (except recurrent glioblastoma after a period of 12 weeks). Baseline evaluation must be performed as close as possible to the treatment start and no more than 28 days before start of treatment.

Efficacy endpoints will be assessed according to institutional practices and SOC from data cut-off date for interim database lock (iDBL) forward as specified in the flowchart.

All tumor imaging performed in this trial will be collected by authorized CRO and stored until shipment to Boehringer Ingelheim. The CRO will not be implicated in tumor response evaluation. This collected data might be considered for central review at a later time point.

5.1.1 Tumor response assessments using RECIST 1.1

The tumor response will be evaluated according to Response evaluation criteria in solid tumors (RECIST) Version 1.1 (R09-0262) and iRECIST (R17-0923) for all cohorts except cohort D (GBM). Complete response/immune complete response (CR/iCR), Partial response/immune partial response (PR/iPR), stable disease/immune stable disease (SD/iSD) or progressive disease/immune unconfirmed progressive disease/immune confirmed progressive disease (PD/iUPD/iCPD) will be assessed by the Investigator. The images should include all known or suspected sites of disease using an appropriate method.

Best overall response will be assessed by tumor measurements according to RECIST version 1.1, and is defined as the best response recorded at any time from the date of first administration of study drug until progression.

5.1.2 Tumor response assessments using RANO

If there are multiple contrast-enhancing lesions, a minimum of the two largest lesions should be measured, and the sum of the products of the perpendicular diameters of these lesions should be determined, similar to the criteria proposed for systemic tumors in RECIST version 1.1. However, given the heterogeneity of high-grade gliomas and the difficulty in measuring some lesions, a maximum of five of the largest lesions may be measured (R11-0753).

Evaluable for objective response: only those patients who have measurable disease present at baseline and have received at least one dose of therapy will be considered evaluable for response. These patients will have their response classified according to the definitions stated below.

Measurable disease: Bidimensionally, contrast-enhancing, measurable lesions with clearly defined margins by MRI scan, with a minimal diameter of 1 cm, and visible on 2 axial slices which are at least 5 mm apart with 0 mm skip. Measurement of tumor around a cyst or surgical cavity, if necessary, requires a minimum thickness of 3 mm.

Non-measurable evaluable disease: Unidimensionally measurable lesions, masses with margins not clearly defined, lesions with maximal diameter < 1 cm.

Response assessments in GBM will be performed according to institutional practices and SOC from data cut-off date for iDBL forwards using the objective status categories per RANO and iRANO criteria (R20-0571), which, in addition to radiographic scans, comprise elements of the neurological exam, KPS, and steroid use. Response assessments are to be derived from baseline or Best Response (see below).

Best Response:
This will be calculated from the sequence of objective status. For patients who are having all disease sites assessed at every evaluation period, the best response will be defined as the best objective status, measured according to RANO criteria described below. If the response does not persist at the next routinely scheduled scan, the response will still be recorded based on the prior scan, but will be designated as a non-sustained response. If the response is sustained, e.g. still present on the subsequent scan, it will be recorded as a sustained response, lasting until the time of tumor progression. Best response is unknown if the subject does not qualify for a best response or increasing disease and if all objective status determinations before progression are unknown.

Objective Status (per RANO Criteria):
Complete Response (CR). All of the following criteria must be met:

a. Complete disappearance of all enhancing measurable and non-measurable disease sustained for at least 4 weeks. In the absence of a confirming scan 4 weeks later, this scan will be considered only stable disease.
b. No new lesions
c. All measurable and non-measurable lesions must be assessed using the same techniques as baseline.
d. Patients must be on no steroids or on physiologic replacement doses only.
e. Stable or improved non-enhancing (T2/FLAIR) lesions
f. Stable or improved clinically, for clinical signs and symptoms present at baseline and recorded to be disease related.

Partial Response (PR). All of the following criteria must be met:

a. ≥ 50% decrease compared to baseline in the sum of products of perpendicular diameters of all measurable enhancing lesions sustained for at least 4 weeks. In the absence of a confirming scan 4 weeks later, this scan will be considered only stable disease.
b. No progression of non-measurable disease.
c. No new lesions.
d. All measurable and non-measurable lesions must be assessed using the same techniques as baseline.
e. The steroid dose at the time of the scan evaluation should be no greater than the dose at time of baseline scan.

f. Stable or improved non-enhancing (T2/FLAIR) lesions on same or lower dose of steroid compared to baseline scan.
g. Stable or improved clinically, for clinical signs and symptoms present at baseline and recorded to be disease related.

Progressive Disease (PD). The following criteria must be met:

a. 25% increase in sum of the products of perpendicular diameters of enhancing lesions (over best response or baseline if no decrease) on stable or increasing doses of steroids and/or one or more of the following:
b. Significant increase in T2/FLAIR non-enhancing lesion on stable or incrasing doses of steroids compared to baseline scan or best response following initiation of therapy, not due to co-morbid events (radiation therapy, demylination, ischemic injury, infection, seizures, post-operative changes, or other treatment effects).
c. Any new lesions
d. Clear clinical deterioration not attributable to other causes apart from the tumor (e.g. seizures, medication side effects, complications of therapy, cerebrovascular events, infection etc.). The definition of clinical deterioration is left to the discretion of the investigator but it is recommended that a decline in the KPS from 100 or 90 to 70 or less, a decline in KPS of at least 20 from 80 or less, or a decline in KPS from any baseline to 50 or less, for at least 7 days, be considered neurologic deterioration, unless attributable to co-morbid events or changes in steroid dose.
e. Failure to return for evaluation due to death or deteriorating condition.

Stable Disease (SD). All of the following criteria must be met:

a. Does not qualify for CR, PR, or PD.
b. All measurable and non-measurable sites must be assessed using the same techniques as baseline.
c. Stable non-enhancing (T2/FLAIR) lesions on same or lower dose of steroids compared to baseline scan. In the event that the steroid dose has been increased, the last scan considered to show stable disease will be the scan obtained when the steroid dose was equivalent to the baseline dose.
d. Stable clinically.

Unknown Response Status. Progressive disease has not been documented and one or more measurable or non-measurable lesions have not been assessed.

These RANO Response Criteria are also summarized in the following table.

Summary of the RANO Response Criteria				
	CR	**PR**	**SD**	**PD#**
T1-Gd+	None	≥ 50% decrease	< 50% decrease - < 25% increase	≥25% increase*

Summary of the RANO Response Criteria

	CR	**PR**	**SD**	**PD#**
T2/FLAIR	Stable or decrease	Stable or decrease	Stable or decrease	Increase*
New lesion	None	None	None	Present*
Corticosteroids	None	Stable or decrease	Stable or decrease	NA
Clinical Status	Stable or increase	Stable or increase	Stable or increase	Decrease*
Requirement for Response	All	All	All	Any*

Progression occurs when any of the criteria with * is present.

NA: Increase in corticosteroids alone will not be taken into account in determining progression in the absence of persistent clinical deterioration

iRANO:

Confirmation of progression on follow-up imaging 3 months after initial radiographic progression if:

1. No new or significantly worsened neurologic deficits not due to co-morbid event or concurrent medication AND

2. ≤ 6 months from initiation of immunotherapy

If follow-up imaging confirms progression, the date of actual progression should be back-dated to the date of initial radiographic progression

• Appearance of new lesions solely does not define progressive disease ≤ 6 months from initiation of immunotherapy. The lesions are added to the total lesion areas for follow-up assessments.

5.2 ASSESSMENT OF SAFETY

The safety of BI 836880 in combination with ezabenlimab will be assessed by a descriptive analysis of incidence and severity of adverse events graded according to CTCAE version 5.0, the incidence of DLT, laboratory data, and results of physical examinations.

5.2.1 Physical examination

A complete physical examination (including cardiac, neurological, dermatological, pulmonological etc.), record of height (only at screening visit), weight and ECOG /Karnofsky performance score will be performed at screening and before start of treatment and EoT and Safety Follow-up. At further time points specified in the FC not a complete PE must be done, but at minimum the actual health status of the patient should be assessed (incl. evaluation of BP, ECG, lab values, AE, Concomitant Treatments, ECOG/Karnofsky as applicable). During the physical examination, the patient should be assessed for possible AEs.

5.2.2 Vital signs

Vital signs (blood pressure, heart rate and body temperature) will be recorded at every visit indicated in the FC.

In Part 1, on days of study drug administration, blood pressure and heart rate will be evaluated at three time points:

1. Pre-dose (-60 min. to -5 min.) before infusion of ezabenlimab,
2. 5 to 10 minutes before infusion of BI 836880,
3. 5 to 10 minutes after infusion of BI 836880.

In case of an infusion-related reaction, the Investigator should decide whether to intensify or prolong monitoring of vital signs of the patient.

In Part 2, on days of study drug administration, blood pressure and heart rate will be evaluated at two time points:

1. Pre-dose (-60 min. to -5 min.), before infusion of ezabenlimab; the results should be assessed using the BP management and study drug administration guidelines in Appendix 10.3
2. 5 to 10 minutes after infusion of BI 836880.

In case of an infusion-related reaction, the Investigator should decide whether to intensify or prolong monitoring of vital signs of the patient.

Frequency of blood pressure measurements at each time point
Systolic and diastolic blood pressure as well as pulse rate (electronically or by palpation, count for 1 minute) will be measured after 5 minutes of rest in the seated position.

In Part 1, the blood pressure measurement should be performed three times at each time point and the values of these measurements will be entered in the eCRF. In Part 2, only a single blood pressure measurement is required at each time point.

Further details on the procedure for blood pressure measurements are given in Appendix 10.2.

Body temperature
Whenever possible the same method should be used for body temperature measurement in one patient. All methods used should deliver valid and reproducible results according to common clinical practice. Acceptable methods could be, but are not limited to: oral, rectal measurement with thermometer (digital, mercury or other fluid). Not preferred methods but accepted include: IR-measurement in ear, forehead or temple.

Body temperature measurements >= 38°C must be re-assessed after 1 hour, especially in cases were for febrile neutropenia is suspected (see CTCAE v. 5.0).

5.2.3 Safety laboratory parameters

Blood and urine samples for assessment of general safety laboratory examinations have to be collected at the time points specified in the Flow Chart, but should be more frequent in case of relevant findings, e.g. in case of grade 4 neutropenia, as any non-proven recovery within 7 days will be counted as DLT or proteinurea, for which determination of CTCAE grade 2 vs. grade 3 need to be done by quantitative measurement. Laboratory values planned for V1D1 (=day of administration) must be available before start of infusion in order to evaluate eligibility of patient to receive treatment. Therefore it's possible to take blood sample a valuable time ahead (usually the day before treatment but possible up to approximately 72 hours before). Safety laboratory examinations will include hematology, biochemistry, coagulation and urine analysis:

Hematology	Hemoglobin, white blood cell count (WBC) with differential, platelets (PLT)
Biochemistry inorganic	Glucose, sodium, potassium, calcium, magnesium, phosphate, creatinine, AST, ALT, alkaline phosphatase (AP), lactate dehydrogenase (LDH), bilirubin, serum urea nitrogen (or urea), thyroid panel [TSH, free T4, and free T3]), total protein, albumin, uric acid, CK, In case of pathological CK elevated, then CK-MB, additional troponin, and myoglobin as available should be reactively tested and the findings documented. Serum immunoglobulin levels (IgG, IgM, IgA; IgE) and direct antiglobulin test have to be measured at Screening and at occurrence of infusion related reactions.
Coagulation	Activated partial thromboplastin time (aPTT), prothrombin time (PT) or international normalised ratio (INR) where indicated (e.g. treatment with vitamin K antagonists)
Urine	pH, glucose, erythrocytes, leukocytes, protein, nitrite will be analyzed primarily qualitatively by dipstick. In case of clinically relevant findings, further evaluation should be performed and the findings documented. A positive urine dipstick for protein of ≥ 2+ (CTCAE gr 2) has to be followed by a determination of the ratio of urine protein to creatinine (UPCR) in a morning spot urine sample. In case of a ratio ≥ 0.5, a 24 hour urine collection for protein loss has to be performed. The 24 hour urine collection will be repeated every time the UPCR ratio is ≥ 0.5 as often as clinically indicated.
Pregnancy test	A pregnancy test needs to be obtained at the time points indicated in the Flow Chart in patients of child bearing potential. A beta human chorionic gonadotropin (β-

	HCG) pregnancy test in serum will be performed for women of childbearing potential (WOCBP) at screening. Thereafter, this test may be done in serum or urine on Day 1 of each cycle, at the EOT visit. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
Screening for Infections	HIV-1 and HIV-2 antibody (qualitative, as per applicable local regulations, at the discretion of the Investigator where clinically indicated). Hepatitis B serology (HBsAg, anti-HBc qualitative) and Hepatitis C serology (anti-HCV qualitative) for screening active Hepatitis B and Hepatitis C. For HCC cohorts (cohorts F, G & H) additional tests may include HBV DNA (if needed), HCV RNA (if needed) and Hepatitis D (anti-HDV qualitative).

In case an administration is delayed due to an AE, the patient should visit the site at least once a week for assessment of safety laboratory and AEs. More frequent visits may be appropriate as assessed by the Investigator.

In case the criteria for potential hepatic injury are fulfilled, a number of additional measures will be performed (please see Section 5.2.6.1 and the DILI Checklist provided in the ISF eDC system. The amount of blood taken from the patient concerned will be increased due to this additional sampling.

5.2.4 Electrocardiogram

12-lead ECGs will be performed in all patients at various time points according to Study Flow chart:

- At Screening, visits between administration and at EoT: only one time point will be evaluated.
- At days of administration two time points will be evaluated:
  For Part 1:
  1. pre-dose (-60 min. to -5 min.)
  2. shortly before the end of the infusion of trial medication
  For Part 2:
  1. Cycle 1 to 4 pre and post treatment (within 60 min after completion of administration of BI 836880) and thereafter ECG at pre- and post treatment of BI 836880 performed every second cycle (cycle 6, 8, 10, … etc.)

In case of drug-related ECG changes and whenever the investigator deems necessary, additional ECG monitoring will be performed in the respective and later cycles of treatment. Cardiac monitoring for patients presenting a QTc interval prolongation CTCAE grade ≥ 3 (i.e., average QTc >= 501 ms, or >60 ms change from baseline; or Torsade de pointes, polymorphic ventricular tachycardia, or signs/symptoms of serious arrhythmia) shall be followed as follows:

- Continuous ECG monitoring until the QTc interval ≤ 480 ms
- Cardiologist opinion for potential treatment of this event as soon as the QTc interval prolongation is observed.
- Cardiologist recommendation after QTc interval decreases to Grade 1 (≤ 480 ms) and potential follow-up.

In order not to confuse ECG recording, PK samples should be taken after performing the ECG. Decision on patient's eligibility will be taken based on Investigator medical opinion. Pathological ECG results will be recorded as AEs by the investigator.

5.2.5 Echocardiography

Echocardiography have to be conducted at screening (not older than 21 days before treatment start) and at EoT-visit. During treatment phase it has only to be done when clinically indicated.

5.2.6 Other safety parameters

5.2.6.1 Dose limiting toxicities (DLTs)

The occurrence of any of the toxicities presented in Table 5.2.6.1: 1 will be considered a DLT, if assessed by the investigator to be related to the administration of either of the study drugs. All DLTs occurring during Part 1 of the study will be considered an AESI and reported on the SAE form. Once the dose escalation part of the study has been completed (Part 1), DLTs no longer need to be reported (i.e. Part 2).

Incidence and severity of adverse events will be graded according to the common terminology criteria for adverse events (CTCAE, version 5.0).

Table 5.2.6.1: 1 Dose Limiting Toxicities (according to CTCAE V5.0)

Drug related toxicity category	Criteria defining a DLT*
Hematologic	• Grade 4 neutropenia (<500/mm3) lasting ≥5 days or complicated by infection • Grade ≥ 3 documented infection with neutropenia. • Grade ≥ 3 febrile neutropenia (ANC<1000/mm3 complicated by fever ≥38.3 °C or 101°F° C or a sustained temperature of ≥38.0C (100.4 ° F) for more than 1 hour. • Grade 3 thrombocytopenia (>= 25,000/mm3 and <50,000/mm3) associated with bleeding or requiring platelet transfusion. • Grade 4 thrombocytopenia (<25,000/mm3). • Grade 4 anaemia (i.e., life-threatening consequences or urgent intervention indicated).

Table 5.2.6.1: 1 Dose Limiting Toxicities (according to CTCAE V5.0) (cont'd)

Drug related toxicity category	Criteria defining a DLT*
Non-hematologic	Non-laboratory toxicity • Any Grade 4 or 5 AE other than disease progression. • Any Grade 2 drug-related uveitis or eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within 2 weeks or requires systemic treatment. • Any treatment-related Grade ≥ 2 toxicity that occurred during Cycle 1 that persists and results in an inability to administer ezabenlimab or BI 836880 on Cycle 2 Day 1. • Grade ≥ 2 pneumonitis of any duration • Any toxicity Grade ≥ 3 toxicity except: o Grade 3 immune-related AE that resolves to ≤ Grade 1 or to baseline with immunosuppressive therapy within 2 weeks o Grade 3 asymptomatic endocrine disorders (thyroid, pituitary, and/or adrenal insufficiency) that are managed with or without systemic corticosteroid therapy and/or hormone replacement therapy. o Grade 3 or 4 elevation in serum amylase and/or lipase that is not associated with clinical or radiographic evidence of pancreatitis o Grade 3 nausea or Grade 3 vomiting will be defined as DLT when it persists at Grade 3 longer than 48 hours despite adequate medical intervention. o Alopecia o Grade 3 fatigue that persists less than 7 days o Grade 3 infusion related reaction which can be controlled by appropriate medication according to investigator's decision, and the subsequent infusion will not be delayed for more than two weeks. o Grade 3 rash that resolves to ≤ Grade 1 within 2 weeks o Grade 3 endocrine disorders (thyroid, pituitary, and/or adrenal insufficiency) that are managed with or without systemic corticosteroid therapy and/or hormone replacement therapy, and the patient is asymptomatic. o Grade 3 tumour flare.
	Laboratory toxicity • Hypertension: systolic blood pressure >=160 mm Hg or diastolic blood pressure >=100 mm Hg, confirmed by second measurement of an additional set of 3 BP measurements, or 3 sequential ambulatory blood pressure measurements when indicated (e.g. white coat effect), and which cannot be controlled by hypertensive medication and which requires a dose reduction / discontinuation of trial medication(s) • Grade3 proteinuria (urinary protein >=3.5 g/24 hrs; 4+ proteinuria) • AST or ALT >3 times ULN and concurrent total bilirubin >2 times ULN without initial findings of cholestasis. • ≥ Grade 4 AST or ALT of any duration NOTE: Any laboratory abnormality which is considered not clinically relevant by the investigator or resolves spontaneously, or resolves with appropriate treatment is not a DLT. Clinically relevant abnormalities must be documented as AEs.
Re-Treatment Delay	All related AE leading to an interruption of BI 836880 or ezabenlimab for more than 14 days until recovery to baseline.

*It is the responsibility of the investigator to follow-up on the toxicities in a timely manner.

Late immune-related DLTs are irAEs that meet the same grading criteria as DLT criteria, but occur after Cycle 1 administration during Part 1. These, as well as all toxicities will be monitored throughout the trial. If any late immune-related DLT is reported during dose-escalation, the BLRM will be rerun including the late immune-related DLT, and updated

results will be reviewed in the SMC meeting to recommend the next dose level and cohort size.

5.2.6.2 Definition of evaluable patient

For decisions on dose escalation, an evaluable patient is defined as a patient who has received first cycle of combination treatment of BI 836880 and ezabenlimab and has been observed 3 weeks for first cycle except patients discontinue in the first cycle due to DLT. Patients who discontinue during the first treatment cycle for reasons other than a DLT will be non-evaluable for the determination of the MTD.

5.2.6.3 Maximum Tolerated Dose (MTD) and Recommended Phase II dose (RP2D)

The MTD may be considered reached if the probability that the true DLT rate is in target interval (16% - 33%) is sufficiently large. For detailed definition see statistical part (Section 7.1). The SMC may recommend stopping the dose finding phase after the criterion for MTD is fulfilled. Further patients may be included to confirm the MTD. If next dose level is recommended by the statistical model; however, the efficacy is considered sufficient at current dose level, the SMC may decide to include additional number of patients at this dose level, declare this dose as RP2D and no further dose escalation will happen.

Decision on next steps (dose escalation, de-escalation or cohort expansion) will be made by a SMC based on all available safety data, including DLT information from last cohort as described above but also findings from subsequent cycles as well as other data (e.g. PK/PD data) when available.

All SMC decisions of dose escalation, and to open a new cohort for recruitment will be communicated to the Investigators. Once MTD and RP2D are defined this information will be sent to authorities according to local regulations.

5.2.7 Assessment of adverse events

5.2.7.1 Definitions of AEs

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

An AE can therefore be any unfavorable 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.

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 hospitalization or
- requires prolongation of existing hospitalization,
- 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 jeopardize 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 hospitalization or development of dependency or abuse.

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

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 5.2.7.2, subsections **AE Collection** and **AE reporting to sponsor and timelines**”.

In accordance with the European Medicines Agency initiative on Important Medical Events, Boehringer Ingelheim has set up a list of further AEs, which by their nature, can always be considered to be “serious” even though they may not have met the criteria of an SAE as defined above.

The latest list of “Always Serious AEs” can be found in the eDC system. These events should always be reported as SAEs as described above.

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:

Dose Limiting Toxicities
All DLTs are considered to be AESIs, and must be reported as such. The definition of DLT is presented in Section 5.2.6.1. DLTs are no longer applicable in Part 2 of the study, therefore are no longer AESIs in Part 2.

Persistent hypertension despite treatment
A hypertensive episode will be considered an AESI if:

- SBP >= 140 mmHg or DBP >= 90 mmHg which persists longer than 2 days despite either he initiation of antihypertensive agent(s) in a patient without prior history of hypertension, or the intensification / addition of new antihypertensive agents in a patient with prior history of hypertension.

Immune-related adverse events (irAE)
Although all irAEs are to be reported as AEs, only clinically important irAEs need to be reported as AESIs as defined by the sponsor in Appendix 10.3. Non-clinically important irAEs, such as mild to moderate rash and hypothyroidism, for example, do not need to be reported as AESIs. If an Investigator determines that a severe irAE or other clinically significant irAE that is not included in Appendix 10.3 is medically significant, the investigator may also report this irAE as an AESI.

Recommendations for the management of irAEs are presented in Appendix 10.4.

Infusion-related reactions
All infusion-related reactions need to be reported as AESIs.

In the event of an infusion-related reaction ⩽ Grade 2, the infusion rate of BI 836880 or ezabenlimab may be decreased by 50% or interrupted until resolution of the event and re-initiated at 50% of the initial rate until completion of the infusion. In patients experiencing infusion related reactions ⩽ Grade 2, subsequent infusions may be administered at 50% of the initial rate.

If a patient experiences an infusion-related reaction, acetaminophen and/or an antihistamine (e.g., diphenhydramine) and/or corticosteroid or equivalent medication per institutional standard may be administered prior to subsequent infusions at the discretion of the Investigator for secondary prophylaxis of infusion-related reactions. If an infusion-related reaction is Grade 3 or higher in severity at any point during the study, treatment with BI 836880 or ezabenlimab will be permanently discontinued.

As with any mAb, allergic reactions to BI 836880 and ezabenlimab administration are possible. Appropriate drugs and medical equipment to treat acute anaphylactic reactions must be immediately available, and trial personnel must be trained to recognize and treat anaphylaxis. The trial site must have immediate access to emergency resuscitation teams and equipment in addition to the ability to admit patients to an intensive care unit if necessary.

The following events 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 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 must report that event as an AESI.

Potential DILI
A potential DILI is defined by the following alterations of hepatic laboratory

- Parameters:
  - **For patients with normal aminotransferase levels at baseline**: 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 without evidence of cholestasis, OR aminotransferase elevations ⩾10 fold ULN

  - **For patients with abnormal aminotransaminase levels at baseline >1 and <2.5 x ULN at baseline:** An elevation of AST and/or ALT ⩾3 fold the baseline value combined with an elevation of bilirubin ⩾2 fold ULN and the baseline value in the same blood sample; OR Aminotransferase elevations ⩾5 fold the baseline value.

  - **For patients with abnormal aminotransaminase levels at baseline >=2.5 and <=5 x ULN at baseline** (patients with liver metastases only)**:** An elevation of AST and/or ALT ⩾2 fold the baseline value combined with an elevation of bilirubin ⩾2 fold ULN and the baseline value in the same blood sample; OR Aminotransferase elevations ⩾3 fold the baseline value.

These lab findings constitute a potential DILI alert and the patients experiencing these lab abnormalities need to be followed up according to the "DILI checklist" provided in the ISF, unless an underlying other than study drug(s) cause has been determined.

In case of clinical symptoms of potential DILI (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 analyzed, if necessary in an unscheduled blood test. Should the results meet the criteria of a potential DILI alert, the procedures described in the DILI checklist should be followed.

Severity of AEs
The severity of adverse events should be classified and recorded in the CRF according to the Common Terminology Criteria for Adverse Events (CTCAE).

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

5.2.7.2 Adverse event collection and reporting

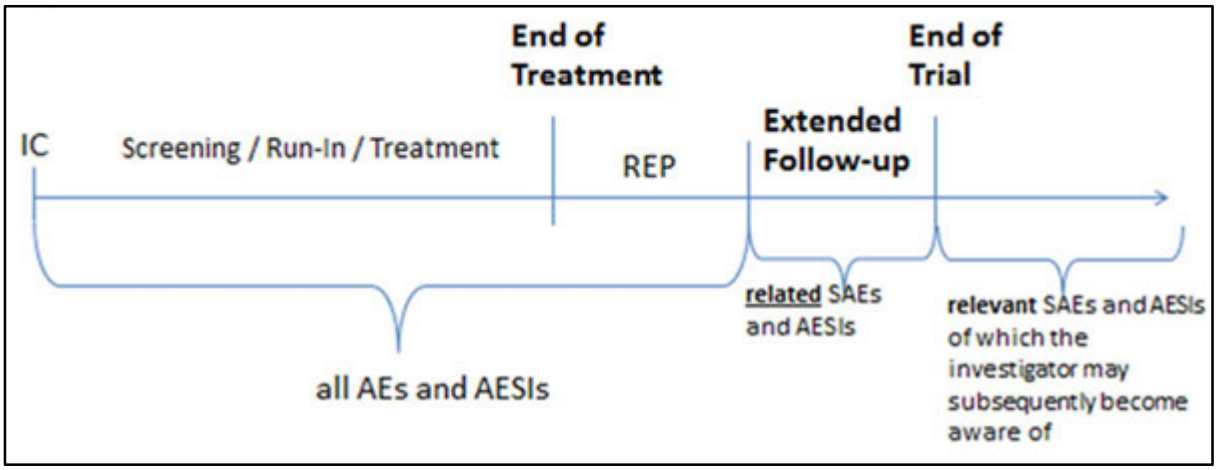
AE Collection
The following must be collected and documented on the appropriate eCRF(s) by the Investigator (Figure 5.2.7.2: 1):

- From signing the informed consent onwards until the end of the REP: all AEs (non-serious and serious), and AESIs.
- After the end of the REP (Safety Follow up visit) until individual patient's end of trial: any new occurrence of cancer of new histology, all related SAEs and all related AESIs.

- After the individual patient's end of trial: the investigator does not need to actively monitor the patient for new AEs but should report any new occurrence of cancer of new histology and 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 eCRF.

The rules for Adverse Event Reporting exemptions still apply, please see chapter "Exemptions to SAE reporting".

Figure: 5.2.7.2:1 Adverse Events collection and reporting (Cancers of new histology to be reported as described above the figure, also during the extended follow up period and after individual patient's end of trial. The term "relevant" in this figure means "related".)



The **Residual Effect Period** (REP) is defined as 42 days after the last trial medication administration. All AEs which occurred through the treatment phase and throughout the REP will be considered as on treatment (Section 7.3.4). Events which occurred after the REP will be considered as post treatment events.

Patients who discontinue trial medication prematurely and agree to be contacted further, should be followed up as described in Section 3.3.4.1, withdrawal from trial treatment.
If for a patient only vital status is collected after premature discontinuation of trial medication, from that time on until individual patient's end of trial the investigator must report, if becoming aware of, all deaths/fatal AEs regardless of causal relationship, related SAEs, related AESIs and any new occurrence of cancer of new histology. After individual patient's end of trial the same procedure applies as for patients without premature discontinuation of trial medication.

At any time the rules for Adverse Event Reporting exemptions still apply, please see chapter "Exemptions to SAE reporting".

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

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

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

- Worsening of pre-existing conditions (for underlying disease refer to chapter "Exemptions to SAE reporting")
- Changes in vital signs, ECG, echocardiography, physical examination and laboratory test results, if they are judged clinically relevant by the Investigator.

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

All (S)AEs, including those persisting after trial completion must be followed up until they have resolved, have been sufficiently characterized, or no further information can be obtained.

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.
Similarly, potential drug exposure during pregnancy must be reported if a partner of a male trial participant becomes pregnant. This requires a written consent of the pregnant partner.

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.

Exemptions to SAE reporting
Protocol specified exempted events should be collected on the appropriate CRF page only.

Disease Progression is a study endpoint for analysis of efficacy, and as such is exempted from reporting as an SAE. Progression of the patient's underlying malignancy will be recorded in the appropriate pages of the eCRF as part of efficacy data collection and will not be reported on the SAE form. Death due to disease progression is also to be recorded on the appropriate eCRF page and not on the SAE form. Disease progression and death due to disease progression will therefore not be entered in the safety database and hence not get expeditiously reported.

However, if there is evidence suggesting a causal relationship between the study drugs and the progression of the underlying malignancy, the event must be reported as SAE on the eCRF, as well as on the SAE form (in such a situation no exemption applies).

Examples of exempted events of disease progression are:

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

Disease progression is monitored at appropriate intervals by SMC and during Medical and Quality Review Meetings (MQRMs).

5.3 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

5.3.1 Assessment of pharmacokinetics

Pharmacokinetic profiles of BI 836880 and ezabenlimab in plasma will be investigated within this trial. Standard plasma PK parameters as specified in Section 2.1.3 will be calculated.

Pharmacokinetic data may additionally be analyzed using population pharmacokinetic approaches. For this purpose data may also be combined with data from other trials. Modelling activities will be planned and documented separately according to internal and external guidelines and SOP.
Exploratory pharmacokinetic and ADA analyses can be performed as necessary for safety review, for dose selection in part 2 of the trial as well as further project planning, but require sufficient lead time to collect samples, measure plasma concentrations, analyze data and prepare meaningful outputs. Exploratory data may also be used for modelling activities.

For the purpose of these exploratory analyses, PK plasma samples obtained up to at least 336 hours after drug administration will be used. A scientifically sound subset of the PK parameters specified in Section 2.1.3 will be calculated which may include Cmax, AUC and $t_{1/2}$, if these parameters can be reliably determined from the available samples and plasma

concentration time profiles. In contrast to the final PK analysis, the exploratory analyses will be based on planned sampling times rather than on actual times; the outputs will not be validated. Minor discrepancies between interim and final results may therefore occur.

As of the decision of Boehringer Ingelheim in December 2021 no additional blood samples for pharmacokinetics will be collected.

5.3.2 Methods of sample collection

For quantification of analyte plasma concentrations, samples will be drawn at the time points listed in the Flow Chart under PK sampling and specified in PK time schedules in Appendix 10.5. The provided sampling timepoints are depicted as planned timepoints, however according to Section 4.1.4, the infusion time may be adapted. In this case, the PK sampling referring to the "end" time of the infusion should be performed shortly after the end of infusion including flushing of the tubes, no matter the duration of the infusion.

The subsequently requested PK sampling should be drawn as planned. Do not adapt the time because of the variation of the duration of the infusion schema.

Plasma will be divided into duplicate aliquots for each analyte (in total 4 aliquots) and stored frozen at about -70°C at the participating sites or logistics CRO until shipment on dry ice to the bioanalytical laboratory of Boehringer Ingelheim or a Boehringer Ingelheim selected and authorized CRO.

Details about sample collection, plasma preparation, required tubes, labelling of tubes, storage and shipment (frequency and addresses) will be provided in a separate laboratory manual.

After completion of the study, the plasma samples may be used for further methodological investigations, e.g., for stability testing. However, only data related to the analyte will be generated by these additional investigations, and such data will be reported separately. The study samples will be discarded no later than 3 years after the final study report has been generated.

[redacted]

[redacted]

[redacted]

[redacted]

5.4.1 Methods of sample collection

The following tumour biopsies will be mandatory for **all patients in Part 1** (if possible from the same lesion):

- the equivalent of two 14-16G needle biopsies freshly taken during screening after IC signed and before first trial medication administration.

- the equivalent of two 14-16G needle biopsies on treatment before start of Cycle 3 (6 weeks after treatment start).

The following tumour biopsies **in Part 2,** will be:

- **Mandatory**: The equivalent of two 16G (or 4 18 G) needle biopsies should be freshly taken during screening after IC signed and before first trial medication administration. In case a fresh baseline biopsy cannot be obtained (e.g. inaccessible lesions or patient safety concern), the equivalent of 2 archival 14-16G needle biopsies, or 20 archival 4 µm sections from an archival block, if taken within 6 months of trial start with no intermediate therapy, have to be provided (except for cohort D). For cohorts E, F, G and H, a fresh on-treatment biopsy is mandatory at C3D1 (window of +/- 7 days), if possible from the same lesion as the pre-treatment biopsy.

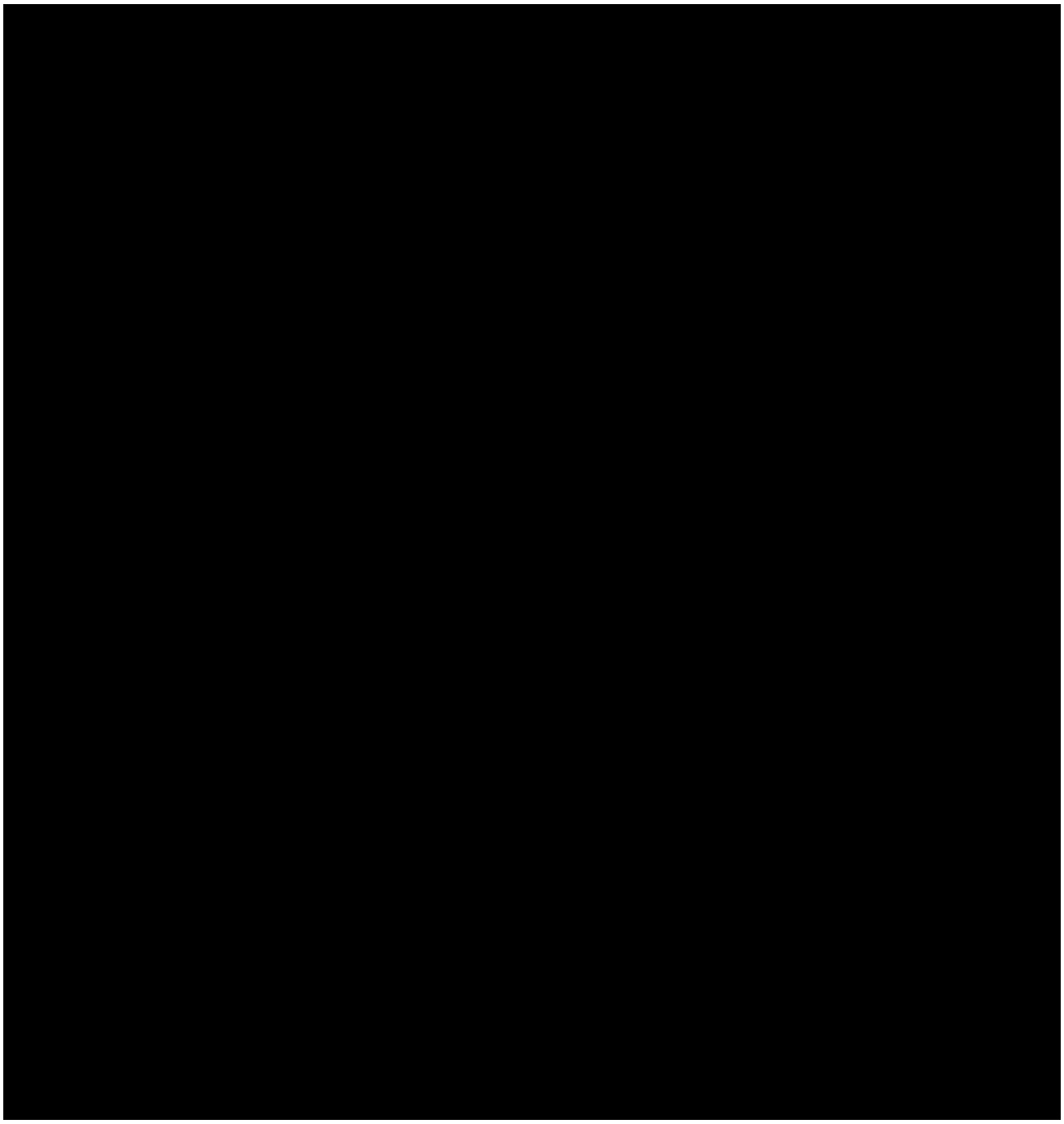
- **Optional**: The equivalent of four 18 G needle biopsies on treatment before start of Cycle 3 for cohorts A-C.

- Note for on treatment biopsies: Biopsy to be performed on a lesion different than target lesion and if there is only one lesion than biopsy may be skipped in that patient.

All samples must be adequately labelled by the trial site personnel. Details about tumor tissue and blood sample collection, plasma/serum preparation, required tubes, labelling of tubes, storage and shipment (frequency and addresses) will be provided in the laboratory manual and the ISF. Measures to be taken to ensure that patient is stable and bleeding has completely stopped prior to initiating the treatment.

As of the decision of Boehringer Ingelheim in December 2021 no additional biopsies will be collected.

[redacted]



5.4.3 Biobanking

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

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

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

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

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

[redacted]

[redacted]

5.6 APPROPRIATENESS OF MEASUREMENTS

All measurements performed during this trial are standard measurements and will be performed in order to monitor subjects' safety and to determine pharmacokinetic and pharmacodynamic parameters in an appropriate way. The scheduled measurements will allow monitoring of changes in vital signs, standard laboratory values, and ECG parameters that might occur as a result of administration of trial medication. The safety assessments are standard, are accepted for evaluation of safety and tolerability of an intravenously administered drug, and are widely used in clinical trials. The pharmacokinetic parameters and measurements outlined in Section 5.3 are generally used assessments of drug exposure. The biomarkers and pharmacodynamic parameters and measurements outlined in Section 5.4 are of exploratory nature only. The determination of the immunogenic response before or during treatment with NBEs is generally applied to monitor immunogenicity risks.

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

Patients must comply with all inclusion and exclusion criteria prior to the patient participation in the study (see Section 3.3).

All patients should adhere to the visit schedule as specified in the Flow Chart. In case a patient misses a visit within one treatment cycle and the patient belatedly reports to the investigator between the missed and the next scheduled visit, the delayed visit should be scheduled as soon as possible and documented with the actual date and the reason for the delayed visit. The next visit, should still take place at the time it was originally scheduled in this treatment cycle. Some flexibility is allowed in scheduling the visits according to the time window specified in the Flow Chart.

However, in case the day of treatment administration (visit 1 day 1 of a cycle) is delayed, all subsequent visits of a cycle will be recalculated based on the actual date of treatment of the delayed cycle.

During the treatment phase, after administration of BI 836880 and ezabenlimab, patients are required to be hospitalized (refers only to Part 1, see Section 1.4) under close surveillance with access to intensive care for at least 48 hours after administration of trial medication to allow close monitoring for infusion-related reactions or other adverse events and availability of patients for PK visits. After good tolerability of the first two cycles of trail medication the investigator may evaluate the risk for an infusion-related reaction and other adverse events in view of relevant comorbidities or disease related symptoms, and as a result, shorten the duration of surveillance to 8 hours for cycles 3 and 4 (PK samples included) and at investigator's discretion for further cycles.

During the treatment phase of Part 2, hospitalization is not required, and the period of surveillance is left at the discretion of the investigator. Investigators should consider that although infusion reactions to any monoclonal antibody typically develops within 30 minutes to two hours after the initiation of drug infusion, symptoms may be delayed for up to 24 hours. Some patients may also develop severe hypertensive episodes, and treatment should be considered accordingly. Please see Section 4.1.4 for the required criteria to administer study drugs after the first cycle. Please see Section 5.2.7.1 for guidelines on how to report and manage infusions related reactions, and Appendix 10.2.1 for BP management and study administration guidelines.

If pathological laboratory values or other issues require an additional unscheduled visit, a new eCRF page will be created for the unscheduled visit. At the unscheduled visit, it is sufficient to record only the clinical relevant labs/examinations performed.

In the event of force majeure or other disruptive circumstances (e.g. pandemic, war) the investigational plan as per this clinical trial protocol may not be feasible at a site. With the consent of the patient, sponsor and investigator may agree on alternative, back-up or rescue methodology. The implementation of these measures will depend on patient's consent,

operational feasibility, local law and regulations. If alternative methodology is implemented, the deviations from the original plan will be precisely documented.

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

The investigations as outlined in the Flow Chart will be performed at the respective visits. Specific details to conduct of physical examination, collection of vital signs (including blood pressure measurement), laboratory investigations, assessment of ECG and echocardiography can be found in Sections 5.2.2, 5.2.3 and 5.2.4.

Procedure for collection of blood samples for PK, ADA and circulating biomarkers are given in Section 5.3 and 5.4.

A more detailed overview of collection of blood samples for PK, ADA and circulating biomarkers is given in Appendix 10.5.

DCE-MRI will only be performed as described in Section 5.4.2.4.

6.2.1 Screening and run-in period(s)

The examinations required for the screening visit may be conducted within a time interval of 21 days prior to the first study drug administration. Prior to any other study related procedure, written informed consent must be obtained from the patient.

ECOG and Physical examination can be performed the day prior to the start of treatment cycle.

CT/MRI images obtained prior to study participation can be used within the study as long as they are not older than 28 days at day of first treatment.

For Glioblastoma patients only, MRI 14 days before treatment start is required.

Echocardiography must be obtained within 21 days before start of treatment.

It is possible to take blood sample a valuable time ahead (usually the day before treatment but possible up to 72 hours before).

For cohort D (Glioblastoma) patients, the baseline status on IDH and MGMT methylation need to be captured in the eCRF if available.

If for administrative or medical reasons, the patient is not entered within the defined screening period, re-assess of eligibility parameter could be allowed after discussion with Clinical Monitor. This should be considered as an exceptional situation and not a general rule.

If the patient has been determined eligible by the investigator to enter the trial (refer to Section 3.3), the investigator will assign one or more medication number(s) to the patient

through the IRT system at Visit 1 (Section 4.1.3). First dose of BI 836880 + ezabenlimab will be administered at the beginning of Visit 1 at the trial site (Day 1, cycle 1).

6.2.2 Treatment period(s)

A treatment cycle is defined as 3 weeks of duration. If initiation of a subsequent cycle is delayed due to medical reasons, additional visits beyond Day 21 may be necessary and may be performed at investigator's discretion, and should be recorded in the eCRF.

During cycle 1 (for Part 1 and 2) and 4 (only for Part 1), intensive PK-sampling will be conducted and patients have to be observed closely for any adverse events. Therefore, patients have to come to the clinic during the first four cycles every week to the clinic. In Part 1 additional visits are needed at day 2 for cycles 1, 2 and 4 and at day 3 for cycle 1. In cycles 5 and 6 the patient is requested to come to the clinic on day 8 after administration of study drug. From cycle 7 onwards no additional visits, beside day 1 including drug administration, are requested by protocol. In Part 2 from cycle 2 onwards, no additional visits, beside day 1 including drug administration, are requested by protocol.

For Part 1 and Part 2 disease response assessment by CT/MRI will be performed according to institutional practices and SOC.

6.2.3 End of treatment visit (EOT)

The EOT visit will be performed after permanent discontinuation of trial medication for any reason as soon as possible but no later than 3 weeks after permanent discontinuation of the trial medication or when the investigator decided with the patient to permanently discontinue the trial medication or became aware that the trial medication had been terminated.

6.2.4 Residual effect period (REP)

The REP is defined in Section 5.2.7.2. The End of REP the Safety Follow-up visit should not be performed earlier than 42 days after permanent discontinuation of the trial medication (last day medication was administered). In case the patient discontinued due to PD by RECIST 1.1/RANO, one additional tumor assessment should be done at the Safety Follow-up visit or time close according to the applicable interval for images. The information collected at this visit should include all new AEs that occurred after EOT and a follow-up of adverse events ongoing at EOT. Any subsequent anti-cancer therapy administered between EoT and EoR should be reported.

6.2.5 Extended follow-up period

6.2.5.1 Follow-up for progression

For patients who did not progress, additional follow-up visits after the Safety Follow-up visit will be performed every 6 weeks plus/minus 3 days.

The follow-up for progression period will end at the earliest of the following events:

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

At the end of the follow-up period, the EoFU (End of Follow-Up) visit has to be performed. The following will be obtained and / or performed during the follow-up visits and the EoFU visit.

- Record all related SAEs and all related AESI and a follow-up of adverse events ongoing since End of REP to EoFU as entered in source data
- Concomitant medications for treatment of an adverse event reported in the (e)CRF including trade name, indication and dates of administration
- Perform tumour assessment and imaging if applicable
- Treatment and date with any other anti-cancer drug including the name and type of the anti-cancer drug and/or best supportive care
- Outcome (date of and reason for death, in case the patient had PD the actual date of PD shall be recorded)
-

6.2.5.2 Follow-up for Overall Survival

Sponsor has decided that as of this protocol amendment acknowledgement no further survival status follow-up will be collected.

6.2.5.3 Trial completion for an individual patient

A patient is considered to have completed the trial in case any of the following applies:

- Completion of planned follow-up period
- Lost to follow-up
- Withdrawal to be followed-up
- Death

At the earliest of the above criteria, the Patient Completion (PC) information should be entered in the CRF.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN - MODEL

This is a Phase I, open-label, dose-escalating trial to determine the Recommended Phase 2 Dose (RP2D) of BI 836880 in combination with ezabenlimab in patients with locally advanced or metastatic non-squamous NSCLC during or after first line platinum-based chemotherapy or CPI monotherapy treatment or the combination of CPI and chemotherapy. In addition, the safety and efficacy of BI 836880 in combination with ezabenlimab will be assessed.

7.1.1 Statistical design - Part 1 (dose escalation)

7.1.1.1 Combination BLRM

The objective of Part 1 of the trial is to determine RP2D of BI 836880 in combination with ezabenlimab based on MTD, patients are entered sequentially into escalating dose cohorts. The Part 1 dose finding will be guided by a Bayesian 5-parameter logistic regression model with overdose control (R13-4803, R15-4233).

The logistic regression model is defined as follows. Let $\pi_{1,d1}$ be the probability of having a DLT when giving dose d_1 of BI 836880 as monotherapy, and $\pi_{2,d2}$ be the probability of having a DLT when giving dose d_2 of the combination partner ezabenlimab as monotherapy, respectively.

A logistic regression model is used to model the dose-toxicity relationship for each component individually:

BI 836880 part:

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

Ezabenlimab part:

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

where $\text{logit}(\pi) = \log(\pi/(1-\pi))$, the reference doses $d_1^* = 720$ mg and $d_2^* = 240$ mg are set for BI 836880 and ezabenlimab, respectively.

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

$$\pi^0_{12,d1,d2} = \pi_{1,d1} + \pi_{2,d2} - \pi_{1,d1}\pi_{2,d2}$$

with corresponding odds

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

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

between BI 836880 and ezabenlimab, a dose-dependent interaction term $-\infty<\eta<\infty$ is introduced to the model by the following definition:

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

$$r_{d1,d2} \sim \text{Binomial}(n_{d1,d2}, \pi_{12,d1,d2})$$

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

Since a Bayesian approach is applied, prior distributions f for each of the parameter vectors $\theta_1=(\log(\alpha_1),\log(\beta_1))$, $\theta_2=(\log(\alpha_2),\log(\beta_2))$ and for the interaction term η need to be specified. The prior distributions for θ_1 and θ_2 will be specified as mixtures of two multivariate normal distributions, i.e.

$$a(\theta_k) = a_{1,k}\, f_1(\theta_k) + a_{2,k}\, f_2(\theta_k)$$

with
$a_{1,k}$, $a_{2,k}$ the prior mixture weights, k=1,2 and

$$f_i(\theta_k) = \text{MVN}(\mu_{ik}, \Sigma_{ik}) \ (k=1,2),$$

the multivariate normal distribution of the i-th component with mean vector μ_{ik} and covariance matrix Σ_{ik}, where

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

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

A weakly informative normal prior distribution will be used for η.

The estimated probability $\pi_{12,d1,d2}$ of a DLT at each dose combination d_1, d_2 from the model will be summarized using the following intervals:

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

The BLRM-recommended dose combination for the next cohort is the level with the highest posterior probability of the DLT rate falling in the target interval [0.16, 0.33) among the dose combinations fulfilling the EWOC principle. Per EWOC it should be unlikely (i.e., <25% posterior probability) that the DLT rate at the dose combination will exceed 0.33. However, the maximum allowable dose increment for the subsequent cohort will be no more than 100% for each compound.

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

1. The posterior probability of the true DLT rate in the target interval [0.16, 0.33) of the MTD is above 50%, OR
2. At least 8 patients have been treated in the study, of which at least 6 at the MTD.

Prior derivation:
By the time BLRM is analyzed, safety data for ezabenlimab are expected to be available from BI Study 1381.1and preliminary safety data for BI 836880 will be available from the study 1336.1. The information can be incorporated into the prior derivation meta-analytic predictive (MAP) approach. Exact details on the evaluations of the model using hypothetical data scenarios and operating characteristics are provided in the statistical appendix.

For illustrative purposes only, we assume the following hypothetical data on BI 836880 (Table 7.1.1.1: 1) and ezabenlimab (Table 7.1.1.1: 2) are available and describe how prior distribution is derived using the MAP approach. However, at the time when BLRM is performed for 1336.11, actual data available will be used instead.

Table 7.1.1.1: 1 Hypothetical data for BI 836880

Dose BI 836880 (mg)	N of patients treated	N of patients with DLTs during MTD evaluation period	N of patients with CTCAE Grade ≥ 3 hypertension and require medical intervention within all cycles or DLTs during MTD evaluation period
40	2	0	0
120	2	0	1
360	2	0	1
720	7	0	2
1000	5	1	3

Table 7.1.1.1: 2 Hypothetical data for ezabenlimab

Dose ezabenlimab (mg)	N of patients treated	N of patients with DLTs during MTD evaluation period
80	3	0
240	6	0
400	3	0

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

For θ_1:

1. The meta-analytic-predictive prior was derived using the DLTs information of BI 836880 from BI Study 1336.1. Small between study heterogeneity is assumed. This mixture component was assigned 80% weight.
2. A second meta-analytic-predictive prior was derived using the number of patients with CTCAE Grade ≥ 3 hypertension and require medical intervention within all cycles or DLTs during MTD evaluation period from Study 1336.1. Small between study heterogeneity is assumed. This component was added with 20% weight.

For θ_2:

1. The meta-analytic-predictive prior was derived using the DLTs information of ezabenlimab from BI study 1381.1. Small between study heterogeneity is assumed. This mixture component was assigned 90% weight.
2. A high-toxicity weakly-informative component was added with 10% weight based on the a priori assumption that the median DLT rate at the starting dose of 80 mg would equal 3% and the median DLT rate at 240 mg would equal 50%. This yields $\mu_{22} = 0$, 1.151). The standard deviations were set such that large uncertainty about the parameter means is reflected, and the correlation was set to 0, thus yielding $\sigma_{22,11} = 2$, $\sigma_{22,22} = 1$ and $\rho_{22} = 0$, respectively.

The prior distribution for η will be based on the a priori assumption of positive interaction between the two compounds, a normal distribution with mean 0 and standard deviation 0.707 was chosen. At the starting dose combination, the corresponding 95% prior interval covers an approximately 4-fold increase (or decrease) in the odds of a DLT over no interaction.

A summary of the prior distribution is provided in Table 7.1.1.1: 3. Additionally, the prior probabilities of DLT at different doses, as well as the corresponding probability of under-, targeted and overdosing, are shown in Table 7.1.1.1: 4.

Table 7.1.1.1: 3 Parameters for prior distributions

Parameter	Means, standard deviations, correlation	Mixture weight
log(α_1), log(β_1): component 1	-1.936, 0.078, 0.644, 0.863, -0.072	0.80
log(α_1), log(β_1): component 2	-0.338, -0.592, 0.496, 0.680, 0.135	0.20
log(α_2), log(β_2): component 1	-3.007, -2.291, 0.802, 1.002, 0.003	0.90
log(α_2), log(β_2): component 2	-0, 1.15, 2, 1, 0	0.10
H	0, 0.707, n/a	n/a

Table 7.1.1.1: 4 Prior probabilities of DLTs

Dose (mg)	Dose (mg)	Probability of true DLT rate in			Descriptive Statistics		Quantiles		
BI 836880	Ezabenlimab	**[0,0.16)**	**[0.16,0.33)**	**[0.33,1]**	**Mean**	**StD**	**2.5%**	**50%**	**97.5%**
360	80	0.612	0.250	0.138	0.174	0.141	0.024	0.128	0.533
360	240	0.535	0.272	0.193	0.214	0.192	0.028	0.149	0.813
500	80	0.527	0.299	0.174	0.200	0.147	0.037	0.153	0.573
500	240	0.452	0.308	0.239	0.242	0.199	0.035	0.177	0.829
720	80	0.354	0.409	0.237	0.247	0.154	0.063	0.201	0.634
720	240	0.338	0.328	0.334	0.292	0.214	0.041	0.231	0.857
1000	80	0.204	0.408	0.388	0.316	0.180	0.078	0.274	0.741
1000	240	0.261	0.269	0.470	0.363	0.249	0.038	0.309	0.917

7.1.1.2 Statistical model assessment

The model was assessed using 2 different metrics:

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

In summary, the model showed very good behavior as assessed by these metrics. More details can be found in Appendix 10.5. The simulations were conducted using R Version 3.3.2 in conjunction with WinBUGS Version 1.4.

7.1.2 Statistical design - Part 2 (dose expansion cohorts)

To effectively use the information from these patients' cohorts in the assessment of the efficacy, a Bayesian hierarchical model (BHM) approach (R13-4803), which assumes full exchangeability of model parameters and allows borrowing information across patients' cohorts, will be used to analyze the response rate endpoints.

The BHM has 2 main components: a data model and a parameter model, as well as priors for the parameter model. The data model is a binomial sampling model

$$r_j | n_j \sim \text{Binomial}\left(n_j, p_j\right), j = 1, 2, 3, \ldots$$

where n_j and r_j are the number of patients and the corresponding number of patients with response in each patient cohort. The parameter model for the log-odds parameters, including an adjustment for the target rates

$$\theta_j = log\left(\frac{p_j}{1-p_j}\right) - log\left(\frac{\tilde{p}_j}{1-\tilde{p}_j}\right)$$

is specified as

$$\theta_j | \mu, \tau \sim N(\mu, \tau^2), j = 1, 2, 3, \ldots$$

where $\tilde{p}_j$ is the target response rate, μ denotes the "overall" mean of θ_j and τ determines the inter-cohort heterogeneity.

Prior distribution

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

Additional analysis of cohort F

Patients in cohort F starting treatment after 15-Jul-2021 (in accordance with protocol version7) will be considered as stage II patients whereas patients with treatment start date before 15-Jul-2021 are considered as stage I patients.

For cohort F, the first 30 patients treated in stage I were included in the aforementioned BHM model and the decision was made to expand this cohort. Patients to be treated in stage II will not be included in the BHM analysis A separate Bayesian model will be used to analyze the stage II patients' data, while incorporating the stage I patients' data in a robust meta-analytic predictive (MAP) prior as specified below.

The R package "RBesT" and functions gMAP(), automixfit() and robustify() are used to derive the robust MAP prior. At the first step, a MAP prior is derived with information from stage I (12/30 responders) together with a specification of weakly informative prior *N* (0,2) for the intercept parameter and *HN* (0.125) for variance for moderate heterogeneity between stage I and stage II. At the second step, a weakly-informative component of Beta (0.6, 1.4) is added with 10% weight to make the MAP prior more robust by implementing the two-component mixture structure (see Table 7.1.2: 1). The effective sample size of this robust MAP prior is estimated to be 14.

Table 7.1.2: 1 Robustified MAP prior

Parameter*	Beta parameters (a,b)	Mixture weight
Component 1	10.66, 15.82	0.90
Component 2	0.60, 1.40	0.10
*seed = 1209		

After all of the approximately 30 patients are treated in stage II and sufficiently evaluable for efficacy, the posterior distribution will be derived including the stage I data in a beta-binomial conjugate model with the above robust MAP prior. The Bayesian decision criterion,

to analyze the objective response rate (ORR) of the 30 additional patients in stage II is specified as:

$$posterior\ probability\ (p_{ORR} > 0.25 | Data\ from\ stage\ II) > 0.85$$

The threshold of 0.25 for the objective response is selected based on the historical data of 18% and 32.2% response rates reported for pembrolizumab (R21-2759)and for combination treatment of nivolumab and ipilumab (R21-2758) in sorafenib pre-treated patients.

A minimum observed response rate of 27% (naïve estimate) among 30 patients at stage I is required to pass this criterion. A further expansion of this cohort may be considered through a protocol amendment if this Bayesian decision criterion is passed.

7.2 NULL AND ALTERNATIVE HYPOTHESES

No formal hypothesis testing is planned in this trial. All analyses in this trial are descriptive and exploratory.

In cohort F, statistical criteria are defined and will be evaluated at the end of stage II. Please refer to Section 7.1.2 for more details on the final criterion and analysis.

7.3 PLANNED ANALYSES

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

For the determination of the MTD, only MTD-evaluable patients will be considered. For the analysis of secondary and [redacted] in Part 1, all patients in the treated set (i.e., patients treated with at least one dose of trial medication) will be included in the analysis. All analyses planned in Part 2 will be based on the treated set.

7.3.1 Primary endpoint analyses

7.3.1.1 Primary endpoint analyses for Part 1

In order to identify the MTD(s) and the recommended dose(s) for Part 2 of the trial, the number of patients with DLTs at each dose combination during the Part 1 MTD evaluation period (the first cycle of the BI 836880 plus ezabenlimab combination) must be presented by descriptive statistics. Patients who discontinue during the first treatment cycle for reasons other than a DLT will be excluded from the determination of the MTD. In addition, the number of patients with DLTs that occurred during the entire treatment period will be summarized at each dose level. The BLRM will be rerun to re-evaluate the MTD and RP2D together with all relevant data collected during Part 2.

7.3.1.2 Primary endpoint analyses for Part 2

The primary endpoint for Part 2 of the trial is OR defined by confirmed CR or PR according to RECIST 1.1 for all cohorts except GBM as assessed by the Investigator. OR in GBM cohort will be evaluated using RANO criteria. Overall response will be analyzed in terms of the shrinkage estimator of the OR rate (ORR) based on BHM.

Note on primary endpoint analysis in cohort F:

In addition, OR from stage I and stage II will be analyzed separately using a Bayesian approach with meta-analytic predictive (MAP) prior after completion of stage II. Please refer to Section 7.1.2 for more details on the derivation of the MAP prior and the final decision criterion. A naïve estimate (observed objective response rate) along with 95% CI (Clopper-Pearson) will also be provided.

7.3.2 Secondary endpoint

7.3.2.1 Secondary endpoint analyses for Part 1

All Adverse Events (AEs), drug related AEs and drug related AEs leading to dose reduction or discontinuation during treatment period will be summarized descriptively.

Details on statistical inference for PK parameters, e.g., Cmax , tmax, AUC0-504h, and accumulation ratios RA after the first (Part 1 and 2) and fourth (Part 1) infusion cycle are described in Section 7.3.5.

7.3.2.2 Secondary endpoint analyses for Part 2

Disease control (DC) will be analyzed in terms of DC rate (DCR), defined as the proportion of patients with best overall response of CR, PR, or SD according to RANO for GBM & RECIST1.1 for all other cohorts. Proportions will be presented with 95% two-sided confidence interval using the exact Clopper-Pearson method.

Duration of objective response (DoR) - for all patients with an OR, the duration of OR is defined as time from first documented CR or PR to the earliest of disease progression or death among patients with OR. If a patient did not die or progress until the last visit in the study, this patient will be censored at the last time point known to be alive and progression-free. The outcome will be assessed according to RANO for GBM & RECIST 1.1 for all other cohorts.

Progression-free survival (PFS) is defined as time from first treatment infusion until disease progression or death from any cause, whichever occurs earlier. If a patient did not die or progress until the last visit in the study, this patient will be censored at the last time point known to be alive and progression-free.

[redacted]

Kaplan-Meier estimates will be used to analyze duration of OR and PFS.

Tumor shrinkage, the difference between the minimum post-baseline sum of lesion of target lesions and baseline sum of the same target lesions, will be summarized descriptively.

PK parameters analyses for Cmax, tmax, AUC0-tz, CL, t1/2, and Vss after the first and fourth infusion cycle will be detailed in the TSAP.

[redacted]

7.3.4 Safety analyses

Adverse events will be coded using the Medical Dictionary for Drug Regulatory Activities (MedDRA). Standard BI summary tables and listings will be produced. All adverse events with an onset between start of treatment and end of the residual effect period (REP), a period of 42 days after the last dose of trial medication and adverse event that start before first dose of trial medication but deteriorate during treatment, will be considered “treatment-emergent” and be assigned to the on-treatment period for evaluation.

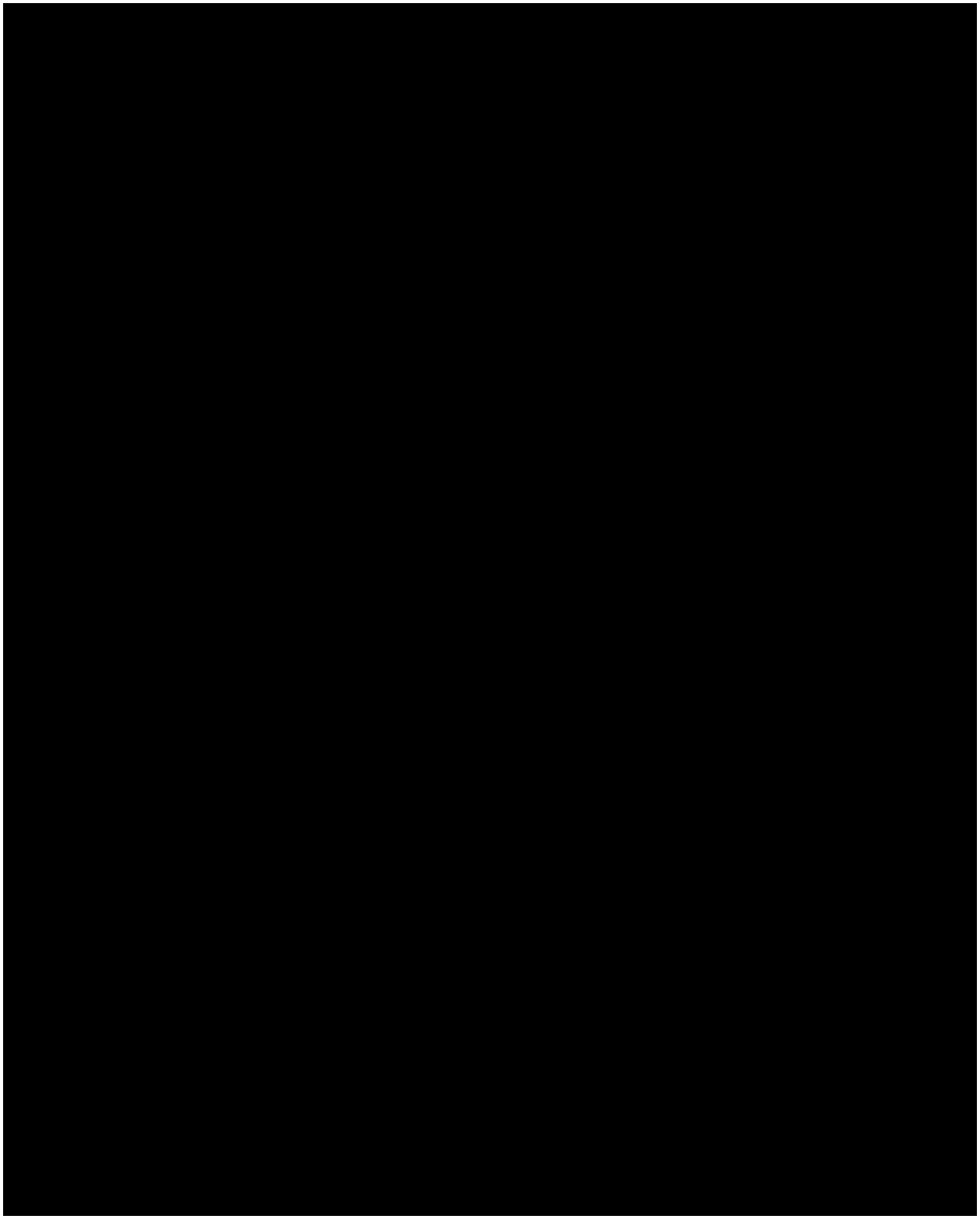
All treated patients will be included in the safety analysis. In general, safety analyses will be descriptive in nature and will be based on BI standards. No hypothesis testing is planned.

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’.

Frequency, severity, and causal relationship of adverse events will be tabulated by system organ class and preferred term after coding according to the current version of the Medical Dictionary for Drug Regulatory Activities (MedDRA).

Laboratory data will be analyzed 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.



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7.4 INTERIM ANALYSES

Part 1:

Interim safety evaluations will be performed as considered necessary. The dose-escalation design dictates that the sponsor and the SMC perform regular safety evaluations. Safety evaluations will be performed after each dose cohort by the SMC. The SMC will recommend the next dose level as well as the corresponding cohort size. SMC will recommend the RP2D that will be used in Part 2. SMC meeting minutes and outputs provided for these SMC meetings will be documented and archived.

Exploratory analyses of PK/PD may be performed at the end of Part 1 and additionally if considered informative for the study.

Part 2:

In Part 2, 290 patients are planned to be treated. 40 patients each are planned for cohorts A and B, and 30 patients each are planned for cohorts C, D, E, G, and H. In addition, as of protocol version 7, 30 more patients will be enrolled in addition to previously enrolled 30 patients in cohort F. The Sponsor may pause enrollment in any cohort at any time to carefully evaluate the safety and efficacy data of patients already enrolled in a given cohort.

An interim futility analysis will be performed for cohorts C, D, E, F, G, and H in Part 2. The interim analyses for each cohort are planned to be conducted after 15 patients in that cohort have completed their two on-treatment imaging assessments (i.e., end of cycle 4 or later depending on the cohort). For each cohort, timing of the interim analysis may be adjusted according to actual recruitment rate to facilitate or avoid delay of the trial conduct. The Sponsor may pause enrollment in a cohort before making any decisions from the interim futility analysis. The two-stage design is planned to stop further recruitment of patients if the defined efficacy boundary (see Table 7.7.2: 1) is not met at the first stage.

Exploratory analyses of PK/PD may be additionally performed during Part 2 and if considered informative for the study.

7.5 HANDLING OF MISSING DATA

[redacted]

information on all AEs, with particular emphasis on potential DLTs. For partial or missing AE onset and/or end dates, BI internal rules will be followed (see Reference Document 001-MCG-156_RD01 "Handling of missing and incomplete AE dates").

7.6 RANDOMIZATION

No randomization will be performed. In Part 1, patients will be assigned to escalating dose groups by order of admission into the trial.

7.7 DETERMINATION OF SAMPLE SIZE

7.7.1 Determination of sample size for Part 1

For Part 1, no formal statistical power calculations of sample size were performed. Approximately 12-18 patients will be expected for the dose finding part and confirmation of RP2D. Fewer patients might be needed based on the recommendation of the SMC and the actual number of cohorts tested.

7.7.2 Determination of sample size for Part 2

For Part 2, below cohorts assume:

- Cohort A:
  - patients with locally advanced or metastatic non-squamous Non-Small Cell Lung Cancer with CPI monotherapy.
- Cohort B:
  - patients with locally advanced or metastatic non-squamous Non-Small Cell Lung Cancer pre-treated with a combination of platinum-based chemotherapy and checkpoint inhibitor.
- Cohort C:
  - patients with locally advanced or metastatic Small Cell Lung Cancer, with no more than one line of chemotherapy, except platinum sensitive patients.
- Cohort D:
  - patients with histologically confirmed recurrent glioblastoma (primary), **No more than two lines of prior chemotherapy** (concurrent and adjuvant temozolomide based chemotherapy including in combination with another investigational agent is considered one line of chemotherapy).
- Cohort E:
  - patients with histologically confirmed, unresectable, Stage IV metastatic melanoma, with least one line of any kind of immune therapy.
- Cohort F (2nd line HCC):
  - patients with locally advanced or metastatic and/or unresectable Hepatocellular Carcinoma who were intolerant or progressed during 1st line sorafenib or lenvatinib treatment.

- Cohort G (1st line HCC):
  - patients with locally advanced or metastatic and/or unresectable HCC with no prior systemic treatment.
- Cohort H (2nd line HCC – atezolizumab+bevacizumab failure only):
  patients with locally advanced or metastatic and/or unresectable HCC who were intolerant or progressed during 1st line atezolizumab+bevacizumab treatment.

A total of approximately 290 patients will be treated for these 8 cohorts. 40 patients each are planned for cohorts A and B, and 30 patients are planned for cohorts C, D, E, G, H and 60 patients for cohorts F.

For cohorts A, B, E, and H, there is no literature available for the target patients. As there are no treatments of proven efficacy for this population, it is assumed around 5% ORR with background therapy. The futility boundary for cohort E and cohort H is set as 7% at planned interim futility analysis timing. The early stopping probabilities are shown in Table 7.7.2: 1.

For cohort C (SCLC), around 20% ORR with anti-PD-1 antibody monotherapy is assumed. In Checkmate-032 (R19-1713) which is an open label phase I/II trial of Nivolumab in patients with SCLC who experienced disease progression after platinum-based chemotherapy, the ORR was 12% [95% CI, 6.5-19.5] (N=109). In KEYNOTE-158 (R19-1713), which is a phase II basket study of Pembrolizumab, patients with advanced SCLC had an ORR of 18.7% [95% CI, 11.8-27.4] (N=107). In KEYNOTE-028 (R19-1713), which is a phase Ib basket trial, patients with extensive-stage SCLC showed an ORR of 33% [95% CI, 16-55] (N=24). Based on above result, the futility boundary for cohort C is set as 20% at planned interim futility analysis timing.

For cohort D (GBM), around 20% ORR with Bevacizumab is assumed. In a recent phase II study (R22-0513) comparing standard dose bevacizumab versus low dose bevacizumab plus lomustine, in patients with recurrent glioblastoma following standard radiation and temozologmide, the ORR was 19% [95% CI, 8-36] (N = 36) based on RANO criteria for the standard dose bevacizumab arm. Based on above results, the futility boundary for cohort D is set as 20% at planned interim futility analysis timing.

For cohort F (2nd line HCC with sorafenib or lenvatinib failure with treatment start date before 15-Jul-2021 (stage I)), around 15% ORR with anti-PD-1 antibody monotherapy is assumed. In Checkmate-040 (R17-3829) which is an open label phase I/II trial of Nivolumab in patients with advanced hepatocellular carcinoma, the ORR was 20% [95% CI, 15-26] (N=50) in dose expansion phase and 15% [95% CI, 6-28] (N=10) in the dose escalation phase. In KEYNOTE-224 (R19-0168) which is a phase 2 study of Pembrolizumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib, the ORR was 17% [95% CI, 11-26] (N=104). Based on above result, the futility boundary for cohort F is set as 15% at planned interim futility analysis timing.

Note: Stage II patients (treatment start date after 15-Jul-2021 according to protocol version 7) were not considered in the above sample size justification. Please refer to Section 7.7.3 below for the sample size justification of the stage II patients.

For cohort G (1st line HCC), around 20% ORR with target monotherapies is assumed. In REFLECT (R20-3051), which is a Phase 3 study comparing Lenvatinib vs. Sorafenib, the ORR was 19% [95%, CI 17-21] (N = 478) for Lenvatinib and 7% [95%, CI 6-8] (N = 476) for Sorafenib. In IMbrave150 (R22-0533), which is a Phase III trial comparing Atezolizumab plus Bevacizumab vs. Sorafenib, the ORR for Sorafenib arm observed was 12% [95% CI, 7-17] (N = 165). In Checkmate-459 (R22-0532), which is a phase III study comparing Nivolumab vs. Sorafenib, the observed ORR was 7% [95% CI, 4-10] (N = 372). Based on above result, the futility boundary for cohort G is set as 20% at planned interim futility analysis timing.

Proposed sample size will provide accumulative safety and tolerability data for the investigational combination across different tumor types. Different homogeneous scenarios and heterogeneous scenarios as well as different sample sizes are considered in the simulations to assess the operating characteristics of the BHM approach. The simulation results as shown in Table 7.7.2: 2 below show that, with the proposed cohort size and interim futility analysis in SCLC, MLN, GBM and HCC cohorts, the BHM approach has reasonable probability of reaching the pre-specified response rate under a wide range of scenarios. The probability of observing a ≥ 15% increase in the shrinkage estimator of the ORR under negative scenario is well controlled on cohort level (< 1%). Desirable true positive probabilities (~> 60%) and false negative probabilities (<2%) are also demonstrated under nugget scenarios for each cohort on proposed sample size.

Table 7.7.2: 1 Early stopping probabilities at interim for cohorts C-H based on observed ORR under different scenarios

Scenario ***ORR (%) in cohort (C,D,E,F,G,H)***	**Early stopping criterion** ***Observed ORR***	**Early stopping probability** ***In cohort C/D/E/F/G/H***
Positive: (40,40,25,35,40,25)	Cohort C: <20% (<3 out of 15) Cohort D: <20% (<3 out of 15) Cohort E: <7% (<2 out of 15) Cohort F: <15% (<3 out of 15) Cohort G: <20% (<3 out of 15) Cohort H: <7% (<2 out of 15)	3%/3%/8%/6%/3%/8%
Negative: (20,20,5,15,20,5)		40%/40%/83%/60%/40%/83%
Intermediate: (30,30,15,25,30,15)		13%/13%/32%/24%/13%/32%
Nugget 1: (20,20,5,15,20,5)		40%/40%/83%/60%/40%/83%
Nugget 2: (20,20,25,15,20,5)		40%/40%/8%/60%/40%/83%
Nugget 3: (40,40,25,35,40,25)		3%/3%/8%/6%/3%/8%

Table 7.7.2: 2 Operating characteristics of the Bayesian Hierarchical Modelling approach for final analysis under different scenarios with futility evaluation at the interim

Sample size	**Scenario (ORR (%) in each patient cohort)**	**Probability of shrinkage estimator of the ORR ≥ (20%,20%, 35%,35%, 20%,30%, 35%,20%) in at least one cohort at final**	**Probability of shrinkage estimator of the ORR ≥ (20%,20%, 35%,35%, 20%,30%, 35%,20%) in each cohort at final**	**Probability of shrinkage estimator of the ORR ≥ (25%,25%, 40%,40%, 25%,35%, 40%,25%) in at least one cohort at final**	**Probability of shrinkage estimator of the ORR ≥ (25%,25%, 40%,40%, 25%,35%, 40%,25%) in each cohort at final**
(40,40, 30,30, 30,30, 30,30)	Positive: (25,25,40,40,25,35,40,25)	99%	91%/91%/82%/82%/ 86%/82%/81%/85%	84%	49%/47%/47%/46%/ 46%/47%/46%/46%
	Negative: (5,5,20,20,5,15,20,5)	1.2%	0.0%/0.0%/0.2%/0.4%/ 0.0%/0.0%/0.6%/0.0%	0.3%	0.0%/0.0%/0.0%/0.1%/ 0.0%/0.0%/0.2%/0.0%
	Intermediate: (15,15,30,30,15,25,30,15)	30%	10%/8%/5%/6%/ 9%/6%/8%/7%	8%	1%/0.9%/1%/1%/ 0.8%/0.7%/2%/1%
	Nugget 1: (25,25,20,20,5,15,20,5)	77%	56%/58%/1%/0.7%/ 0.0%/0.6%/0.8/0.0%	49%	32%/28%/0.4%/0.1%/ 0.0%/0.1%/0.0%/0.0%
	Nugget 2: (25,25,20,20,25,15,20,5)	89%	63%/61%/1%/1%/ 58%/0.5%/1%/0.0%	65%	35%/34%/0.2%/0.3%/ 31%/0.0%/0.1%/0.0%
	Nugget 3: (5,5,40,40,25,35,40,25)	96%	0.0%/0.2%/59%/59%/ 61%/62%/60%/61%	80%	0.0%/0.0%/32%/32%/ 31%/32%/33%/31%
(30,30, 25,25, 25,25, 25,25)	Positive: (25,25,40,40,25,35,40,25)	99%	89%/89%/79%/79%/ 88%/81%/77%/87%	81%	49%/47%/46%/45%/ 47%/46%/46%/46%
	Negative: (5,5,20,20,5,15,20,5)	2%	0.0%/0.0%/0.5%/0.7%/ 0.0%/0.0%/1%/0.0%	0.3%	0.0%/0.0%/0.1%/0.1%/ 0.0%/0.0%/0.1%/0.0%
	Intermediate: (15,15,30,30,15,25,30,15)	34%	12%/9%/6%/7%/ 10%/7%/9%/9%	10%	2%/1%/1%/2%/ 1%/0.8%/2%/2%
	Nugget 1: (25,25,20,20,5,15,20,5)	69%	50%/50%/2%/1%/ 0.0%/0.9%/0.9%/0.0%	45%	29%/27%/0.3%/0.3%/ 0.0%/0.1%/0.1%/0.0%
	Nugget 2: (25,25,20,20,25,15,20,5)	84%	57%/55%/1%/1%/ 53%/1%/1%/0.0%	63%	32%/30%/0.3%/0.3%/ 29%/0.0%/0.4%/0.0%
	Nugget 3: (5,5,40,40,25,35,40,25)	93%	1%/1%/54%/54%/ 61%/59%/56%/62%	75%	0.0%/0.0%/31%/31%/ 30%/30%/31%/30%

7.7.3 Determination of additional sample size for stage II in cohort F

With an additional sample size of approximately 30 in stage II, the probability to pass the defined Bayesian decision criterion (in Section 7.1.2) is 96% when the true underlying ORR is 40%. When true underlying ORR is 20%, the probability to pass the defined Bayesian decision criterion is 24% (Table 7.7.3: 1).

Table 7.7.3: 1 Probability of satisfying statistical criterion after stage II

True ORR	Probability of satisfying statistical criterion after stage II
0.20	0.24
0.25	0.49
0.30	0.72
0.35	0.88
0.40	0.96
0.45	0.98

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

The trial will be carried out in accordance with the Medical Devices Directive (93/42/EEC) and the harmonised standards for Medical Devices (ISO 14155, current version).
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 Standard Operating Procedures (SOPs), the EU regulation 536/2014 the Japanese GCP regulations (Ministry of Health and Welfare Ordinance No. 28, March 27, 1997) and other relevant regulations.

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

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

The Boehringer Ingelheim transparency and publication policy can be found on the following web page: trials.boehringer-ingelheim.com. The rights of the investigator and of the sponsor with regards 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. The certificate of insurance cover is made available to the investigator and the patients, and is stored in the ISF.

8.1 TRIAL APPROVAL, PATIENT INFORMATION, INFORMED CONSENT

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

Prior to patient participation in the trial, written informed consent must be obtained from each patient (or the patient's legally accepted representative) according to ICH / GCP and to the regulatory and legal requirements of the participating country. Each signature must be personally dated by each signatory and the informed consent and any additional patient-information form retained by the investigator as part of the trial records. A signed copy of the informed consent and any additional patient information must be given to each patient or the patient's legally accepted representative."

The investigator must give a full explanation to trial patients based on the patient information form. A language understandable to the patient should be chosen, technical terms and expressions avoided, if possible.

The patient must be given sufficient time to consider participation in the trial. The investigator obtains written consent of the patient's own free will with the informed consent form after confirming that the patient understands the contents. The investigator must sign (or place a seal on) and date the informed consent form. If a trial collaborator has given a supplementary explanation, the trial collaborator also signs (or places a seal on) and dates the informed consent.

Re-consenting may become necessary when new relevant information becomes available and should be conducted according to the sponsor's instructions.

The consent and re-consenting process should be properly documented in the source documentation.

8.2 DATA QUALITY ASSURANCE

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

8.3 RECORDS

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

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 good documentation practices and be attributable, legible, contemporaneous, original and accurate. Changes to the data should be traceable (audit trail). Data reported on the CRF must be consistent with the source data or the discrepancies must be explained.

The current medical history of the patient may not be sufficient to confirm eligibility for the trial and the investigator may need to request previous medical histories and evidence of any diagnostic tests. In this case the investigator must make 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.

During the site visit the sponsor's CRA or auditor must be granted access to the original patient file (please see Section 8.3.2).

The investigator must ensure that all patient identifiers (e.g. patient's name, initials, address, phone number, social security number) have properly been removed or redacted from any copy of the patients' source documents before sending them to the sponsor.

If the patient is not compliant with the protocol, any corrective action e.g. re-training must be documented in the patient file.

For the CRF, data must be derived from source documents, for example:

- Patient identification: gender, 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.

8.3.2 Direct access to source data and documents

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

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

8.3.3 Storage period of records

Trial 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 5.2.7.2, 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 below. Patient privacy will be ensured by using patient identification code numbers.

Data protection and data security measures are implemented for the collection, storage and processing of patient data in accordance with the principles 6 and 12 of the WHO GCP handbook.

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

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

Measures are in place to comply with the applicable rules for the collection, storage and future use of biological samples from clinical trial participants and the corresponding data, in particular

- A Quality Management System has been implemented to ensure the adherence with the Principles of Good Clinical Practice as outlined in 'Note For Guidance On Good Clinical Practice' (CPMP/ICH/13 5/95)

- The BI-internal facilities storing and analyzing biological samples and data from clinical trial participants as well as the laboratories' activities for clinical trials sponsored by Boehringer Ingelheim are regularly audited. The analytical groups and the banking facility are therefore assessed to be qualified for the storage and use of biological samples and data collected in clinical trials.

- Samples and data are used only if an appropriate informed consent is available.

8.6 TRIAL MILESTONES

The **start of the trial** is defined as the date when the first patient in the whole trial signs informed consent.

The end of the trial is defined as the date of the last visit of the last patient in the whole trial ("Last Patient Out"), or when all patients have been discontinued from study treatment and followed until the end of REP.

The "**Last Patient Drug Discontinuation"** (LPDD) date is defined as the date on which the last patient at an individual trial site ends trial medication (as scheduled per protocol or prematurely). Individual investigators will be notified of SUSARs occurring with the trial medication until 30 days after LPDD at their site.

Early termination of the trial is defined as the premature termination of the trial due to any reason before the end of the trial as specified in this protocol.

Temporary halt of the trial is defined as any unplanned interruption of the trial by the sponsor with the intention to resume it.

Suspension of the trial is defined as an interruption of the trial based on a Health Authority request.

The IEC / competent authority in each participating EU member state will be notified about the trial milestones according to the respective laws.

A final report of the clinical trial data will be written only after all patients have completed the trial in all countries (EU or non-EU) 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 as a whole, regardless of the country of the last patient (EU or non-EU).

8.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL

The trial is sponsored by Boehringer Ingelheim (BI).

A Coordinating Investigator is responsible to coordinate investigators at the different sites participating in this trial. Tasks and responsibilities are defined in a contract.

A Study Monitoring Committee (SMC) composed of participating investigators and members of the BI trial team will be established to review individual and aggregated safety and efficacy data at regular intervals to determine the safety profile and risk/benefit ratio and

recommend next dose level/does appropriateness of further enrolment. Details of the SMC responsibilities and procedures are described in the SMC charter.

Relevant documentation on the participating (Principal) Investigators (e.g. their curricula vitae) will be filed in the (Investigator Site File) 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, responsible for coordinating all required activities, in order to

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

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

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

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

A central laboratory service and an IRT vendor will be used in this trial. Details will be provided in the IRT Manual and Central Laboratory Manual, available in the ISF.

9. REFERENCES

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10. APPENDICES

10.1 INSTRUCTIONS FOR USE

Instructions for Pharmacist: available in the ISF.

10.2 BLOOD PRESSURE MEASUREMENT PROCEDURE

Blood pressure measurements should be performed on the same arm and, if possible, by the same person. The machines or devices to be used for blood pressure measurement should be certified. The same method and device must be used throughout the trial for a patient i.e. if a patient receives the first blood pressure measurement for example with an electronic device, the same method and device should be used throughout the study for this patient (without switching to manual blood pressure measurement). On the other hand, inter-patient variability is acceptable, i.e. a study site is allowed to consistently use an electronic device to measure the blood pressure in a given patient throughout the study and a manual technique in another patient. The blood pressure measurement should be taken after the patient has rested quietly in a seated position for at least five minutes.

In Part 1, three blood pressure measurements will be taken two minutes apart and all three results have to be entered in the eCRF.

In Part 2, only a single blood pressure measurement is required per scheduled time point, i.e. one measurement before the study drugs have been administered, and one measurement after the study drugs are administered. Please see Section 5.2.2 for further details, and Appendix 10.2.1 for management guidelines.

10.2.1 Blood Pressure Management and Study Drug Administration Guidelines

Table 10.2.1: 1 BP management and study drug administration guidelines following completion of cycle 1, based on pre-infusion SBP and DBP measured on study drug administration visits.

Pre-infusion clinic BP (mmHg) on pre-planned infusion visits	SBP <160 and DBP <100	SBP 160-179 or DBP 100-109	SBP≥180 or DBP≥110	Hypertensive crisis**
Action to be taken with BI 836880 and ezabenlimab	Proceed with study drug administration as scheduled / re-start.	Temporarily delay administration of both study drugs until BP < 160/100.	Delay administration of both study drugs until next pre-scheduled study drug administration.	Discontinue both study drugs.
Antihypertensive treatment	As deemed necessary by the investigator.*	Wait 10-15 minutes and ensure patient is relaxed, and re-measure BP: – If BP <160/100 on re-assessment, administer both study drugs; – If SBP remains 160-179 or DBP 100-109, initiate / modify antihypertensive regimens, delay administration of both study drugs, and re-assess within 12-48 hours of antihypertensive agent initiation/modification. After 12-48 hours: – If BP <160/100, administer both study drugs. – If BP remains ≥160/100, repeat after 10-15 minutes; if BP remains ≥160/100 hold study drug administration until next pre-planned infusion visit, and initiate / modify antihypertensive regimens.	Initiate / modify antihypertensive regimens, and re-assess at the next scheduled infusion visit.	Emergency admission for in-patient care

* Investigators should consider initiating / modifying antihypertensive regimens if SBP < 160 mmHg or DBP > 100 mmHg if their medical assessment is that lowering BP further is clinically indicated (for example, patient has cardiovascular risk factors), and discontinuing or modifying antihypertensive agents if there are symptoms /signs of hypotension.

** Hypertensive crisis defined as patients with significantly elevated blood pressure with signs or symptoms of acute, ongoing target-organ damage.

10.3 IMMUNE-RELATED ADVERSE EVENTS AS ADVERSE EVENTS OF SPECIAL INTEREST

Please see below in the Table 10.3: 1 regarding irAEs which must be reported as AESIs.

Table 10.3: 1 irAEs which must be reported as AESIs.

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

Table 10.3: 1 irAEs which must be reported as AESIs.(cont'd)

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

Table 10.3: 1 irAEs which must be reported as AESIs.(cont'd)

Immune-related adverse events of special interest
Renal (reported as an AESI if ≥ Grade 2)
• Nephritis • Nephritis autoimmune • Renal failure • Renal failure acute • Creatinine elevations (report as an irAE if ≥Grade 3 or any grade resulting in dose modification or use of systemic steroids to treat the AE)
Skin (reported as an AESI)
• Dermatitis exfoliative • Erythema multiforme • Stevens-Johnson syndrome • Toxic epidermal necrolysis
Skin (reported as an AESI if ≥ Grade 3)
• Pruritus • Rash • Rash generalized • Rash maculopapular • Any rash considered clinically significant in the physician's judgment
Other (reported as an AESI)
• Myocarditis • Pancreatitis • Pericarditis • Any other Grade 3 event that is considered immune-related by the physician

10.4 MANAGEMENT OF IMMUNE-RELATED ADVERSE EVENTS

Regarding diagnosis, grading and therapeutic management of immune-related adverse events, grading and treatment, up-to-date published guidelines should be considered (e.g. P19-00269). Only limited guidance on management of specific irAEs can be given here.

Please refer to published guidelines (e.g. ASCO guideline, Brahmer (P19-00269)) for details.

In general,

- For irAEs listed below, it is not considered applicable stating that only if a causal relationship to one trial drug can be unequivocally established, the other trial drug may be continued. On combination treatment both drugs (BI 836880 and

ezabenlimab) will be stopped, paused, or re-exposed together. Any exceptions to this have to be agreed with the sponsor.

- BI ezabenlimab and BI 836880 should be continued with close monitoring in case of grade 1 irAEs, with the exception of irAEs that may rapidly evolve into severe or fatal conditions (encephalitis of any grade, myocarditis of any grade, pneumonitis that is grade 1 but shows radiographic evidence of worsening – see detailed guidance below). A dose reduction of BI 836880 may be considered, but is not required for the first occurrence of an irAE grade 1.

- For most Grade 2 irAEs, ezabenlimab and BI 836880 should be withheld and treatment with corticosteroids is commonly warranted, usually with an initial dose of 0.5 to 1 mg/kg daily. Restart of therapy is commonly possible once symptoms and/or laboratory values have resolved to grade 1 or less, and on corticosteroid ≤ 10 mg per day prednisone / prednisone equivalent per day. A dose reduction of BI 836880 should be considered, but is not required for the first occurrence of an irAE, but is mandatory if the same irAE recurs upon rechallenge with BI 836880.

- For Grade 3 irAEs, ezabenlimab and BI 836880 has to be withheld, and treatment with high-dose corticosteroids (1-2mg/kg/d) is usually warranted. Upon improvement, steroids should be tapered over 4-6 weeks. Non-steroidal immunosuppressives (e.g. infliximab, mycophonlate mofetil) should be considered if no improvement or worsening occurs within the initial 48 to 72 hours. Upon recovery to grade 1 or less, and on corticosteroid ≤ 10 mg per day, restarting of ezabenlimab and BI 836880 may be considered for selected irAEs, but caution is advised, in particular in patients with early-onset irAEs. Expert consultancy is recommended prior to restart of therapy.

- Most Grade 4 irAEs warrant permanent discontinuation of ezabenlimab and BI 836880.

- Restart of therapy is commonly possible for endocrine irAEs regardless of grade once stable hormone replacement has been instituted and symptoms have recovered. In case of multiple hormone deficiencies, corticosteroid replacement has to precede thyroid hormone replacement therapy by several days in order to avoid adrenal crisis.

- A dose reduction of BI 836880 may be considered, but is not required for the first occurrence of an endocrine irAE.

In case of prolonged steroid therapy or treatment with immunosuppressive consider the possibility of opportunistic infections and tuberculosis reactivation, administer prophylactic antibiotics where appropriate.

Commonly, referral to experts in the management of organ-specific conditions is highly recommended, especially for irAEs grade 3 or grade 4, or irAEs where management is complex.

Ezabenlimab and BI 836880 should be permanently discontinued for immune related:

- encephalitis, aseptic meningitis, transverse myelitis, or Guillain-Barre syndrome of any grade
- acquired thrombotic thrombocytopenic purpura of any grade
- myocarditis of any grade
- myasthenia gravis, peripheral neuropathy or autonomic neuropathy of grade ≥3
- myositis grade 2 with objective findings (see below), any myositis grade ≥3
- hepatitis grade ≥3 (transaminase >5 times ULN [or >10x ULN if baseline was >2.5-5x ULN] or total bilirubin >3x ULN [or >5x ULN if baseline was >1.5-3x ULN], recurrent hepatitis grade ≥2
- nephritis grade ≥3, persisting grade 2 nephritis unresponsive to initial steroid therapy
- or worsening, and recurrent nephritis grade ≥2
- pneumonitis grade ≥3,
- rash, bullous dermatoses, severe cutaneous adverse reaction, Stevens Johnson Syndrome, toxic epidermal necrolysis of grade 4, and recurrent rash grade ≥3
- colitis grade 4, and recurrent colitis of any grade
- uveitis, iritis, episcleritis of grade ≥3
- autoimmune-hemolytic anemia grade ≥2
- haemolytic uremic syndrome grade ≥3
- immune thrombocytopenia grade 4
- any recurrent irAE grade ≥3,
- 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.

For BI 836880, up to 1 dose reductions are allowed if the treatment pause due to an AE. Dose adjustment of ezabenlimab besides interrupting of both compounds or permanently discontinuing ezabenlimab are not allowed (see Section 4.1.4).

Pneumonitis:

- For Grade 1 pneumonitis with radiographic evidence of worsening, withhold ezabenlimab and BI 836880 until improvement or resolution; ezabenlimab and BI 836880 may be reintroduced upon radiographic improvement. In the absence of radiographic improvement within 3-4 weeks, follow guidance as for grade 2 event.
- For Grade 2 pneumonitis, hold ezabenlimab and BI 836880 until resolution to at least grade 1. If not already started, initiate therapy for the event as per available guidelines. Follow guidance as for grade 3 pneumonitis if no clinical improvement after 48 -72 hr of starting therapy.
- For Grade 3-4 pneumonitis, permanently discontinue ezabenlimab and BI 836880 and immediately initiate treatment according to available guidelines.

Diarrhoea/Colitis:

- For Grade 1 diarrhoea/colitis, consider interruption of ezabenlimab and BI 836880 therapy.

- For Grade 2 diarrhea/colitis, withhold ezabenlimab and BI 836880 until patient´s symptoms recovered to grade 1 or less. Consider initiating treatment with steroids.
- For Grade 3 diarrhoea/colitis, withhold ezabenlimab and BI 836880 and immediately start treatment (steroids, non-steroidal immunosuppressants) as per available guidelines.
- For Grade 4 diarrhoea/colitis, permanently discontinue ezabenlimab and BI 836880 and immediately commence adequate therapy (e.g. i.v. corticosteroids).
- For Grade 1-3 colitis, restart of ezabenlimab and BI 836880 may be considered once symptoms improve to Grade 1 or less without need for continued steroids. After careful benefit risk assessment, ezabenlimab and BI 836880 may also be restarted after recovery to grade 1 or less, and on corticosteroid ≤ 10 mg per day
- Ezabenlima and BI 836880 should be permanently discontinued for recurrent diarrhoea/colitis of any grade.

Diabetes

- Consider withholding ezabenlimab and BI 836880 in case of grade 2 hyperglycemia.
- Check for ketonuria. In case of new onset of diabetes or unexpected worsening of preexisting diabetes, check for new manifestation of type 1 diabetes.
- For new onset Type 1 diabetes mellitus, or Grade 3-4 hyperglycaemia associated with ketosis (ketonuria or metabolic acidosis)
    - Initiate insulin therapy
    - Evaluate subjects as appropriate per available guidelines regarding presence of type 1 diabetes
    - Ezabenlimab and BI 836880 should be withheld until glucose level is controlled with insulin with no sign of ketoacidosis.
- Ezabenlimab and BI 836880 may be restarted once insulin therapy has established stable glycemic control.

Thyroid disorders:

Thyroid disorders can occur at any time during treatment. Monitor subjects for changes in thyroid function (at screening and in regular intervals during treatment as indicated in Flow Chart (safety lab) and Section 5.2.3, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders. For diagnosed thyroid disorders, thyroid hormone supplementation and monitoring should occur as per available guidelines.

- Primary hypothyroidism:
    - For Grade 1 hypothyroidism, ezabenlimab and BI 836880 may be continued, with regular monitoring of thyroid values.
    - For Grade 2 hypothyroidism, consider withholding ezabenlimab and BI 836880
    - For Grade 3-4 hypothyroidism, withhold ezabenlimab and BI 836880, consider admission and IV therapy, especially in case of myxedema
    - Ezabenlimab and BI 836880 may be restarted once symptoms resolve to baseline with appropriate thyroid hormone supplementation

- Primary hyperthyroidism:
  - For Grade 1 hyperthyroidism, ezabenlimab and BI 836880 may be continued, with regular monitoring of thyroid values.
  - For Grade 2 hyperthyroidism, consider withholding ezabenlimab and BI 836880, initiate therapy as per available guidelines.
  - For Grade 3-4 hyperthyroidism, withhold ezabenlimab and BI 836880. Consider hospitalization, especially in case of Thyrotoxicosis.
  - Ezabenlimab and BI 836880 may be restarted once symptoms resolve to baseline.
    Note: in case of concomitant adrenal dysfunction, this must be corrected first, prior to thyroid hormone replacement (reduced stress tolerance)

Adrenal insufficiency

- Interruption of ezabenlimab and BI 836880 therapy should be considered for adrenal insufficiency grade 1 or 2, and is warranted for grade 3 and grade 4 adrenal insufficiency, until patient is stabilized on hormone replacement therapy.
- Therapy with ezabenlimab and BI 836880 may be restarted once stable replacement
- therapy has been achieved.
- Note: in case of concomitant hypothyroidism, steroid replacement therapy should precede thyroid hormone substitution to avoid adrenal crisis.

Hypophysitis

- Diagnostic workup for hypophysitis should be considered e.g. for patients with multiple endocrinopathies, unexplained fatigue, new severe headaches or vision changes.
- Patients should be appropriately advised regarding potentially reduced stress tolerance and increased substitution demands e.g. in case of infections, and to wear a medical alert bracelet to inform medical personnel about potentially increased hormone demands in situations of stress, in case of emergencies.
- Interruption of ezabenlimab and BI 836880 therapy should be considered for Grade 1 or 2 hypophysitis, and is warranted for Grade 3 and higher hypophysitis, until patient is stabilized on hormone replacement therapy.

Hepatitis

- Work-up for other causes of elevated liver enzymes, see also section on potential DILI (Section 5.2.7).
- For Grade 1 hepatitis (elevated AST/ALT < 3x ULN and/or total bilirubin <1.5x ULN), ezabenlimab and BI 836880 may be continued, close monitoring of liver values is warranted.
- For Grade 2 hepatitis (AST/ALT 3–5x ULN and/or total bilirubin >1.5 to ≤ 3x ULN), ezabenlimab and BI 836880 should be suspended. Monitoring of liver values every 3 days is recommended. Initiate treatment according to available guidelines. Restarting of ezabenlimab and 836880 may be considered upon recovery to grade 1 or less, and on corticosteroid ≤ 10 mg per day.
- For Grade 3 or higher hepatitis, ezabenlimab and BI 836880 has to be permanently discontinued. Immediately initiate treatment as per guidelines.

For eligible patients with elevated screening/baseline AST/ALT (>2.5-5x ULN or bilirubin >1.5-3x ULN):

- Carefully monitor patients for signs of autoimmune hepatitis.
- In case of increased levels of AST/ALT >2x baseline to ≤10x ULN and/or bilirubin >2x baseline to ≤5x ULN, ezabenlimab and BI 836880 should be suspended. Monitoring of liver values every 3 days or more frequently, if clinically indicated, is recommended. Restarting of ezabenlimab and BI 836880 may be considered upon recovery to baseline or less, and on corticosteroid ≤ 10 mg per day.
- In case of increased AST/ALT >10x ULN and/or bilirubin >5x ULN, ezabenlimab and BI 836880 have to be permanently discontinued. Initiate treatment as per guidelines.

Nephritis

- For Grade 1 nephritis, consider temporarily withholding ezabenlimab and BI 836880.
- For Grade 2 nephritis, withhold ezabenlimab and BI 836880. Consult nephrology. Initiate treatment according to guidelines. In case of no improvement or worsening, permanently discontinue ezabenlimab and BI 836880. Ezabenlimab and BI 836880 may only be re-started upon recovery to grade 1 or less, and on corticosteroid ≤ 10 mg per day.
- For Grade 3 or higher nephritis, permanently discontinue ezabenlimab and BI 836880. Consult nephrology. Treat with steroids 1-2 mg/kg prednisone or equivalent. If improved to grade 1 or less, taper corticosteroids over no less than 4-6 weeks.
- Ezabenlimab and BI 836880 should also be permanently discontinued for recurrent nephritis grade 2 or higher.

Rash

- For Grade 1 rash, continue ezabenlimab and BI 836880. Initiate topical treatment.
- For Grade 2 rash, ezabenlimab and BI 836880 may be continued, in case of no improvement upon weekly monitoring, consider interruption of ezabenlimab and BI 836880 therapy. Treat topically, add systemic therapies as clinically appropriate.
- For Grade 3 rash, withhold ezabenlimab and BI 836880. Initiate topical and systemic therapy as per available guidelines. Upon improvement of event to grade 1 or less, and on corticosteroid ≤ 10 mg per day, consult with dermatology whether therapy with ezabenlimab and BI 836880 might be restarted, especially in case no alternative anti-neoplastic therapy is available.
- For Grade 4 rash, ezabenlimab and BI 836880 should be permanently discontinued.
- Ezabenlimab and BI 836880 should also be discontinued for recurrent rash grade 3 or higher.

Bullous dermatosis

- For Grade 1 bullous dermatosis, use local wound care and observation. Ezabenlimab and BI 836880 can be continued.
- For Grade 2 bullous dermatosis, withhold ezabenlimab and BI 836880. Administer topical therapy, add systemic therapy as clinically adequate.

- For Grade 3 bullous dermatosis, withhold ezabenlimab and BI 836880, initiate topical and systemic therapy as per available guidelines. Restarting of ezabenlimab and BI 836880 may be considered after dermatology consultation.
- For Grade 4 bullous dermatosis, permanently discontinue ezabenlimab and BI 836880.

Severe cutaneous adverse reaction (SCAR), Stevens Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN)

- For Grade 2 events, withhold ezabenlimab and BI 836880, initiate treatment as per available guidelines. Closely monitor for improvement or worsening.
- For Grade 3 events, withhold ezabelimab and BI 836880. Initiate treatment as per available guidelines. In case mucous membranes are affected, involve appropriate disciplines in management to prevent sequelae from scarring (e.g. ophthalmology).
- For Grade 4 events, permanently discontinue ezabenlimab and BI 836880, immediately administer adequate therapy. Immediate admission to burn center or intensive care with dermatology and wound care is recommended, involve appropriate other disciplines as needed in management of mucosal involvement.

In case of Grade 2 or Grade 3 events, ezabenlimab and BI 836880 may only be re-started upon event recovered to Grade 1 or less, on corticosteroid ≤ 10 mg per day, and after consultation with dermatology.

Encephalitis/Aseptic meningitis

- Ezabenlimab and BI 836880 should be permanently discontinued for any grade.

Myasthenia gravis

- For Grade 2 myasthenia gravis, withhold ezabenlimab and BI 836880.
- For Grade 3 or 4 myasthenia gravis, permanently discontinue ezabenzimab and BI 836880

Guillain Barré Syndrome (GBS)

- Discontinue ezabenlimab and BI 836880 permanently for any grade GBS.

Transverse Myelitis

- Discontinue ezabenlimab and BI 836880 permanently for any grade transverse myelitis.

Peripheral neuropathy, autonomic neuropathy

- For Grade 1 events, may continue ezabenlimab and BI 836880, but with low threshold to discontinue while monitoring closely for worsening.
- For Grade 2 events, withhold ezabenlimab and BI 836880 until resolution to grade 1 or less, and on corticosteroid ≤ 10 mg per day. Initiate therapy as appropriate per available guidelines.
- For Grade 3 or grade 4 events, permanently discontinue ezabenlimab and BI 836880.

Inflammatory Arthritis

- For Grade 1 arthritis, ezabenlimab and BI 836880 can be continued. Administer analgetic treatment (acetaminophen, NSAID).
- For Grade 2-4 arthritis, withhold ezabenlimab and BI 836880. Initiate treatment as per available guidelines, care regarding reactivation of tuberculosis/opportunistic infections in case of prolonged immunosuppressive/disease modifying anti-rheumatic drugs DMARD therapy.

Ezabenlimab and BI 836880 may be restarted after consultancy with rheumatology once recovery to grade 1 or less, and on corticosteroid ≤ 10 mg per day.

Myositis

Diagnostic workup should consider the need to also evaluate myocardial involvement.

- For Grade 1 myositis, ezabenlimab and BI 836880 may be continued. Initiate adequate therapy as clinically warranted. In case of elevated CK or muscle weakness, treat as grade 2.
- For Grade 2 myositis, withhold ezabenlimab and BI 836880, discontinue permanently in patients with objective findings (elevated enzymes, abnormal EMG, abnormal muscle MRI or biopsy). Initiate therapy as per available guidelines. Resuming ezabenlimab and BI 836880 may be considered in patients without objective findings, symptoms have resolved to grade 1 or less without any immunosuppressive therapy, and after consultation with rheumatology/neurology.
- For Grade 3 or 4 myositis, permanently discontinue ezabenlimab and BI 836880.
- Ezabenlimab and BI 836880 should be permanently discontinued if there is any evidence of myocardial involvement.

Polymyalgia-like syndrome

- For Grade 1 event, ezabenlimab and BI 836880 can be continued.
- For Grade 2 event, withhold ezabenlimab and BI 836880 and promptly initiate adequate therapy. If no improvement, treat as grade 3.
- For Grade 3 or Grade 4 event, withhold ezabenlimab and BI 836880, promptly initiate adequate therapy. Rheumatology consultancy is highly recommended.

Ezabenlimaband BI 836880 may be resumed after careful assessment of risks and benefits, rheumatology consultancy highly recommended prior to reinitiation. Ezabenlimab and BI 836880 may only be re-started upon recovery to grade 1 or less and on corticosteroid ≤ 10 mg per day.

Myocarditis

- Discontinue ezabenlimab and BI 836880 permanently for any grade of myocarditis.

Uveitis/Iritis, Episcleritis

- For Grade 1 events, treatment with ezabenlimab and BI 836880 can continue. Treat topically as needed.
- For Grade 2 events, withhold therapy with ezabenlimab and BI 836880, urgent ophthalmology referral is recommended. Initiate topical treatment, consider systemic therapy if needed. Restart of ezabenlimab and BI 836880 is permitted once resolved to grade 1 or less, and off systemic steroids (for the ocular condition, if steroids needed for other irAEs, up to 10 mg prednisone or equivalent are permitted). Continuation of

topical/ocular steroids is permitted and does not prohibit resuming ezabenlimab and BI 836880 therapy.
- For Grade 3 or 4 events, permanently discontinue ezabenlimab and BI 836880 therapy. Seek emergent ophthalmology consultation. Initiate adequate local and systemic treatment.

Autoimmune-hemolytic anemia (AIHA)
- For Grade 1 AIHA, continue treatment with ezabenlimab and BI 836880. Close follow-up of anemia and other lab values.
- For Grade 2-4 AIHA, discontinue ezabenlimab and BI 836880 permanently. Initiate systemic therapy as per guideline. Consult Hematology.

Acquired thrombotic thrombocytopenic purpura (TTP), haemolytic uremic syndrome.
Timely recognition upon suggestive findings is essential, timely/immediate involvement of hematology consultancy may be beneficial.
- For any grade TTP, permanently discontinue ezabenlimab and BI 836880.
- For HUS (TTP excluded), withhold ezabenlimab and BI 836880 for grade 1 and grade 2, provide supportive care. Upon full recovery, ezabenlimab and BI 836880 may be restarted after carefully weighing of risks and benefits.
- For Grade 3 or Grade 4 HUS, discontinue ezabenlimab and BI 836880 permanently.

Immune thrombocytopenia (ITP)
- In case of Grade 1 ITP, ezabenlimab and BI 836880 can be continued.
- For Grade 2 or Grade 3 ITP, withhold ezabenlimab and BI 836880 and initiate systemic therapy. ezabenlimab and BI 836880 may be restarted upon resolution to at least grade 1.
- For Grade 4 ITP, permanently discontinue ezabenlimab and BI 836880.

Infusion related reactions (IRRs):
- Signs and symptoms of IRRs usually develop during or shortly after ezabenlimab infusion and generally resolve completely within 24 hours of completion of infusion. If symptoms develop during infusion, they may be managed with slowing or transient interruption of infusion.

Please refer to Section 5.2.7 for more details about infusion related reactions.

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

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

10.6 STATISTICAL APPENDIX INCLUDING MODEL PERFORMANCE AND DATA SCENARIOS

The combination BLRMs with overdose control is introduced in Section 7.1 with the prior distributions for the model parameters fully specified. It will be used to guide dose escalation in this study for the BI 836880 plus ezabenlimab combination in the dose-escalation part of this study. Once patients in each cohort have completed the combination MTD evaluation period, the prior distribution will be updated through Gibbs sampling procedures with the accumulated DLT data from the MTD evaluation period. Posterior probabilities for the rate of DLTs will be summarized from BLRM. Selection of the next dose will be based on these probabilities as well as on other safety and laboratory data.

The purpose of this statistical appendix is to evaluate the model behavior and model performance. To evaluate the model behavior, Section 10.5.1 illustrates a series of different scenarios that mimic the once which might arise during the actual study conduct. On-study recommendations for the next dose combinations by the BLRM with overdose control principle are also provided under various hypothetical outcome scenarios in early cohorts to show how EWOC facilitates on-trial dose-escalation decisions.

10.6.1 Hypothetical data scenarios

These scenarios reflect potential on-study data constellations and related escalation as allowed by the model. It is assumed that each cohort has 3 patients who are all evaluable. At the 1st occurrence of a DLT, additional 3 patients will be added to the current cohort. For each scenario, the probability of overdose for the current dose, as well as the next potential dose and related probabilities of under-dosing, target dosing, and over-dosing are shown (see Table 10.6.1: 1).

For example, Scenario 1A represents the case that no DLT is observed in the first 2 patients at the starting dose combination of BI 836880 360 mg plus ezabenlimab 240 mg (denoted by 360 mg/240 mg for easier reference). In this case, there are 2 next allowed dose combinations from the model, i.e., 500 mg/240 mg, and 720 mg/240 mg, among which, 720 mg/240 mg has the highest probability of being in the target region. Scenario 1B shows 1 DLT observed in 3 patients at 360mg/240mg, the dose recommended will remain at this level. But if 3 more patients is added to this cohort and number of DLT remains at 1, the next dose allowed will be 500mg/240mg (Scenario 1C).

Scenario 2D: after no DLT observed in 2 patients of 360mg/240mg dose combination, if 2 DLT observed in 6 patients of 500mg/240mg cohort, the dose cannot be escalated further.

Scenario 3A: no DLT in first 3 cohort, the next recommended dose combination will be 1000mg/240mg. If there is 1 DLT out of 3 or 6 patients in 720mg/240mg cohort, the dose recommended will remain at 720mg/240mg as shown in Scenario 3B-3E.

Table 10.6.1: 1 Hypothetical data scenarios

Scenario	Dose comb. BI 836880/ ezabenlimab (mg/mg)	# DLT	# Pat	Current Dose: P(OD)	Next allowed dose comb. (mg/mg)*	Summary of toxicity of next Combination dose		
						P(under dose)	P(target dose)	P(over dose)
1A	360/240	0	2	0.075	500/240 720/240	0.578 0.427	0.312 0.363	0.110 0.210
1B	360/240	1	3	0.226	360/240	0.391	0.384	0.226
1C	360/240	1	6	0.080	500/240	0.461	0.406	0.133
2A	360/240 500/240	0 0	2 3	0.034	720/240	0.551	0.347	0.102
2B	360/240 500/240	0 1	2 3	0.151	500/240	0.434	0.415	0.151
2C	360/240 500/240	0 1	2 6	0.055	720/240	0.392	0.449	0.160
2D	360/240 500/240	0 2	2 6	0.188	500/240	0.313	0.499	0.188
3A	360/240 500/240 720/240	0 0 1	2 3 3	0.139	720/240	0.395	0.466	0.139
3B	360/240 500/240 720/240	0 0 1	2 3 6	0.053	720/240	0.539	0.408	0.053
3C	360/240 500/240 720/240	0 0 2	2 3 6	0.168	720/240	0.289	0.543	0.168
3D	360/240 500/240 720/240	0 1 2	2 6 6	0.222	720/240	0.201	0.577	0.222

The simulations for scenarios and operating characteristics were conducted using R Studio Version 3.2.2 in conjunction with WinBUGS 1.4.3.

10.6.2 Operating characteristics of combination BLRM

Operating characteristics are a way to assess the long-run behavior of a model by illustrating the precision of design in estimating the MTD. Under an assumed true dose-toxicity curve, metrics such as the probability of recommending a dose with true DLT rate in the target interval can be approximated via simulation.

Table 10.6.2: 1 describes 3 assumed true dose-toxicity scenarios which were used to assess the operating characteristics of the combination model. These scenarios reflect a wide range of possible cases as follows:

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

Table 10.6.2: 1 Assumed True Dose-Toxicity Scenarios

Scenario C1, P(DLT)	Dose ezabenlimab (mg)	
Dose BI 836880 (mg)	80	240
360	0.138	0.193
500	0.174	0.239
720	0.237	0.334
1000	0.388	0.470
Scenario C2, P(DLT)	Dose ezabenlimab (mg)	
Dose BI 836880 (mg)	80	240
360	0.07	0.10
500	0.08	0.15
720	0.10	0.20
1000	0.20	0.30
Scenario C3, P(DLT)	Dose ezabenlimab (mg)	
Dose BI 836880 (mg)	80	240
360	0.20	0.30
500	0.25	0.35
720	0.30	0.45
1000	0.45	0.65

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

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

- Escalate to the maximal dose combination possible and satisfies the overdose criterion if it is ≤300% increase from the current dose.
- If the recommended dose combination satisfying the overdose criterion is > 300% increase in dose for each compound, then escalate to the highest dose combination which is ≤ 300% increase from the current dose for each compound.
- If any DLT occurs, extra 3 patients will be tested at the current dose combination.

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

- The next recommended dose is the same as the current dose;
- At least 1 DLT is observed;
- At least 6 patients have been treated at the MTD dose combination declared by the model;
- At least 9 patients have been evaluated OR the posterior probability of targeted toxicity reaches 50%.

It was then assessed how often a dose was declared as MTD with true DLT rate in the underdose, targeted-, or over-dose range. Furthermore, the average, minimum and maximum number of patients per trial and the average number of DLTs per trial are reported. Results are shown in Table 10.6.2: 2.

Table 10.6.2: 2 Simulated Operating Characteristics

Scenario	% of Trials Declaring an MTD with True DLT Rate in				# Patients	# DLT
	Underdose	Target dose	Overdose	Stopped	Mean (Min-Max)	Mean (Min-Max)
C1: Aligned with prior	33.6	51.9	14.3	0.2	12.75 (6-30)	3.28 (1-12)
C2: Low Tox	50.4	49.6	0	0	15.13 (6-33)	2.209 (1-10)
C3: High Tox	0	91.8	8.2	0	12.74 (6-30)	3.28 (1-12)

In Scenario C1, which reflects the case that the true dose-toxicity is approximately aligned with prior means, almost all of the simulated trials identified the MTD. Approximately 52% of trials were in the target interval and none of them were in the underdose interval. There were 14.3% in the overdose interval and 0.2% of the trials were prematurely stopped either because the MTD was not identified or because the probability of overdose associated with the simulated starting dose had already exceeded the 25% threshold.

Scenario C2 (Low-toxicity scenario) shows similar results with previous Scenario 1 overall. No simulated trials declared a MTD with a true DLT rate in the overdose interval. All of the simulated trials identified the MTD with approximately 50% in the target dose interval and 50% are in the underdose interval, and no trials were prematurely stopped.

Scenario C3 (High-toxicity scenario) illustrates a case with higher-than-expected toxicity. In this case, approximately 92% of the simulated trials identified the MTD within the target interval. Approximately 8% of the simulated trials declared the MTD in the overdose interval, but no trials were prematurely stopped.

By reviewing the metrics presented in Table 10.6.2: 2 it can be seen that the model is not sensitive to different scenarios of true DLT rates. Across three scenarios, the average number of patients participated in dose-escalation ranges from 12.74 to 15.13 and the average number of DLTs observed ranged from 2.209 to 3.28. In general, this model is conservative due to the overdose control criteria. In all scenarios, the probabilities of recommending a dose combination with true P(DLT) ≥33% as MTD are much smaller than probabilities of recommending a dose combination with true P(DLT) between 16% and 33% as MTD.

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

10.7 APPENDIX - PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.

ECOG Performance Status Scale		Karnofsky Performance Scale	
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

11.1 GLOBAL AMENDMENT 1

Date of amendment		23 Apr 2018
EudraCT number **EU number**		2017-001378-41
BI Trial number		1336-0011
BI Investigational Product(s)		BI 836880 BI 754091
Title of protocol		An open label phase Ib dose finding study of BI 836880 in combination with BI 754091 to characterize safety, tolerability, pharmacokinetics, pharmacodynamics and efficacy in check point inhibitor naïve patient with locally advanced or metastatic non-squamous Non-Small Cell Lung Cancer who progressed during or after first line platinum-based treatment.
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		Coverpage
Description of change		Format changes of the coverpages. New TCM included: [redacted] Phone: [redacted] Fax: [redacted]
Rationale for change		New TCM included
Section to be changed		3.1 Overall Trial Design and Plan
Description of change		Information added: At first dose level, first patient will be treated and observed for at least 15 days before allowing the second patient to receive BI 836880 and BI 745901 infusions. A safety monitoring committee (SMC) meeting will be held to decide if the 2nd patient can be enrolled to the study. Subsequent enrollment at all

		dose levels within dose escalation, each patient in a given cohort (dose level) will be observed for a minimum of 48 hours after first BI 836880 and BI 745901 application for acute reaction monitoring before allowing treatment for subsequent patient in the same cohort. As descript at the point 6.1 of the protocol, during the treatment phase, after administration of BI 836880 and BI 754091, patients are required to be hospitalized under close surveillance with access to intensive care for at least 48 hours after administration of trial medication to allow close monitoring for infusion-related reactions or other adverse events and availability of patients for PK visits. The sponsor will contact the investigator to verify if any acute reaction was investigated before allowing treatment for subsequent patient in the same cohort.
Rationale for change		To plan a sequential administration for patients in the 1st cohort (Part I) after the first patient.
Section to be changed		3.3.2 Inclusion Criteria
Description of change		Change of the contraception days from 120 to 150 Male or female patients. Women of childbearing potential (WOCBP) and men able to father a child must be ready and able to use highly effective methods of birth control per ICH M3 (R2) that result in a low failure rate of less than 1% per year when used consistently and correctly, starting with the screening visit and through 150 days after the last dose of BI 836880 and BI 754091 treatment, respectively.
Rationale for change		In view of the preliminary pharmacokinetic data observed in humans for BI 754091 (t1/2 ~29 days), it would be appropriate to adapt the duration of contraceptive measures, according to the instructions of CTFG related to the contraception.
Section to be changed		5.2.4 Electrocardiogram
Description of change		Information added Cardiac monitoring for patients presenting a QTc interval prolongation CTCAE grade ≥ 3 ‘>500 ms) shall be followed as follows: Continuous ECG monitoring until the QTc interval < 480 ms

		- Cardiologist opinion for potential treatment of this event as soon as the QTc interval prolongation is observed. - Cardiologist recommendation after QTc interval normalisation (< 480 ms) and potential follow-up
Rationale for change		To describe the procedure for handling of CTCAE>= Grade 3 QTC interval prolongation

11.2 GLOBAL AMENDMENT 2

Date of amendment		21 Feb 2019
EudraCT number **EU number**		2017-001378-41
BI Trial number		1336-0011
BI Investigational Product(s)		BI 836880 BI 754091
Title of protocol		An open label phase Ib dose finding study of BI 836880 in combination with BI 754091 to characterize safety, tolerability, pharmacokinetics, pharmacodynamics and efficacy in check point inhibitor naïve patient with locally advanced or metastatic non-squamous Non-Small Cell Lung Cancer who progressed during or after first line platinum-based treatment.
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		Title
Description of change		Changed from: An open label phase Ib dose finding study of BI 836880 in combination with BI 754091 to characterize safety, tolerability, pharmacokinetics, pharmacodynamics and efficacy in check point inhibitor naïve patient with locally advanced or metastatic non-squamous Non-Small Cell Lung Cancer who progressed during or after first line platinum-based treatment. To: An open label phase Ib dose finding study of BI 836880 in combination with BI 754091 to characterize safety, tolerability, pharmacokinetics, pharmacodynamics and efficacy in check point inhibitor naïve and previously treated patients with locally advanced or metastatic non-squamous Non-Small Cell Lung Cancer
Rationale for change		The title was adapted to the new population
Section to be changed		Synopsis - Title
Description of change		Changed from:

		An open label phase Ib dose finding study of BI 836880 in combination with BI 754091 to characterize safety, tolerability, pharmacokinetics, pharmacodynamics and efficacy in check point inhibitor naïve patient with locally advanced or metastatic non-squamous Non-Small Cell Lung Cancer who progressed during or after first line platinum-based treatment To: An open label phase Ib dose finding study of BI 836880 in combination with BI 754091 to characterize safety, tolerability, pharmacokinetics, pharmacodynamics and efficacy in check point inhibitor naïve and previously treated patient with locally advanced or metastatic non-squamous Non-Small Cell Lung Cancer
Rationale for change		The title was adapted to the new population
Section to be changed		Synopsis – study design
Description of change		Changed from: This is a Phase Ib study, containing two parts; Part 1 (dose escalation of BI 836880 in combination with BI 754091) and Part 2 (expansion phase in two cohorts) in patients with locally advanced or metastatic non-squamous NSCLC who progressed during or after first line platinum-based therapy. **Part 1**: Dose escalation of BI 836880 in combination with BI 754091 in check point inhibitor naive patients with locally advanced or metastatic non-squamous NSCLC who progressed during or after first line platinum-based therapy. To: This is a Phase Ib study, containing two parts; Part 1 (dose escalation of BI 836880 in combination with BI 754091) and Part 2 (expansion phase in two cohorts). **Part 1**: Dose escalation of BI 836880 in combination with BI 754091 in check point inhibitor naïve or previously treated patients with locally advanced or metastatic non-squamous NSCLC who

		progressed during or after first line (in case of CPI naïve patients) platinum-based therapy and patients who progressed during or relapsed after completion of at least 2 cycles (in case of CPI relapsing patients) of platinum-based chemotherapy and a CPI treatment (monotherapy or in combination with chemotherapy).
Rationale for change		Adapted to the new population
Section to be changed		Synopsis - objectives
Description of change		Changed from: **Primary objective:** • To determine the Recommended Phase 2 Dose (RP2D) of BI 836880 in combination with BI 754091 in check point inhibitor naïve patients with locally advanced or metastatic non-squamous NSCLC who progressed during or after first line platinum-based. To: **Primary objective:** • To determine the Recommended Phase 2 Dose (RP2D) of BI 836880 in combination with BI 754091 in check point inhibitor naïve or previously treated patients with locally advanced or metastatic non-squamous NSCLC who progressed during or after first line platinum-based chemotherapy.
Rationale for change		Adapted regarding the new population and clarification
Section to be changed		Synopsis- diagnosis
Description of change		Changed from: Patients with locally advanced or metastatic non-squamous NSCLC progressing during or after first line platinum-based therapy with either low PD-L1 expression (PD-L1 expression in 1-49% of tumor cells) or high PD-L1 expression (PD-L1 expression in ≥ 50% of tumor cells) To: Naïve or previously CPI treated patients with locally advanced or metastatic non-squamous NSCLC who progressed during or after first line (in case of CPI naïve patients) platinum-based therapy and patients who progressed during or

		relapsed after completion of at least 2 cycles (in case of CPI relapsing patients) of platinum-based chemotherapy and a CPI treatment (monotherapy or in combination with chemotherapy). Patient´s with either low PD-L1 expression (PD-L1 expression in 1-49% of tumor cells) or high PD-L1 expression (PD-L1 expression in ≥ 50% of tumor cells).
Rationale for change		Adaption regarding the added population
Section to be changed		Synopsis –main in- and exclusion criteria #4
Description of change		Changed from: Documented disease progression or relapse (based on investigator's assessment) during or after completion of at least 2 courses of platinum-based chemotherapy as first line treatment. This includes patients relapsing within 6 months of completing (neo)adjuvant/curative-intent chemotherapy or chemoradiotherapy To: 1. Documented disease progression or relapse (based on investigator's assessment) during or after completion of at least 2 cycles of platinum-based chemotherapy as first line treatment of Stage IIIB/IV non- squamous NSCLC or for CPI experienced patients during or after completion of at least 2 cycles of platinum-based chemotherapy and a CPI treatment (monotherapy or in combination with chemotherapy). This includes patients relapsing within 6 months of completing (neo)adjuvant/curative-intent chemotherapy/CPI or chemoradiotherapy
Rationale for change		Adaption to the population
Section to be changed		Synopsis – test Product(s)
Description of change		Deletion of: and diluent for BI 836880 drug product
Rationale for change		Adaption to new BI 836880 formulation
		Synopsis – Safety criteria
		Info of change from CTCAE verion 4.03 to version 5.0
		CTCAE version change
Section to be changed		Flow Chart
Description of change		Change of the EoR visit window from alst admin +42 (-2 /+3)to : EoR last admin+42 (+3)

Rationale for change		Should not be shorter than 42 days
Section to be changed		Flow chart food note #8
Description of change		Change from: Tumour assessment should be done every 6 weeks starting from first trial medication infusion. To: Tumour assessment should be done every 6 weeks (in accordance to local requirements) starting from first trial medication infusion.
Rationale for change		Adding local requirements information
Section to be changed		Abbreviations
Description of change		Adding ANG2 Angiopoietin-2
Rationale for change		Adding missing information
Section to be changed		Section 2.1.1
Description of change		Change from: **PART 1:** Primary objective: • To determine the Recommended Phase 2 Dose (RP2D) of BI 836880 in combination with BI 754091 in check point inhibitor naïve patients with locally advanced or metastatic non-squamous NSCLC who progressed during or after first line platinum-based treatment, and. To: Primary objective: • To determine the Recommended Phase 2 Dose (RP2D) of BI 836880 in combination with BI 754091 in patients with locally advanced or metastatic non-squamous NSCLC who progressed during or after first line (in case of CPI naïve patients) platinum-based therapy and patients who relapsed after completion of at least 2 cycles (in case of CPI relapsing patients) of platinum-based chemotherapy and a CPI treatment (monotherapy or in combination with chemotherapy).
Rationale for change		Adaption to the new added population
Section to be changed		3.1
Description of change		Change from: The eligible patient population will be check point inhibitor naive patients with locally advanced or metastatic non - squamous NSCLC who

		progressed during or after first line platinum-based treatment. The trial will consist in 2 Parts; Part 1 and part 2: **<u>Part 1</u>**: Dose escalation of BI 836880 in combination with BI 754091 in patients with locally advanced or metastatic non-squamous NSCLC progressing during or after first line platinum-based therapy. To: The eligible patient population will be check point inhibitor naïve and experienced patients with locally advanced or metastatic non - squamous NSCLC. Patients who progressed during or after first line (in case of CPI naïve patients) platinum-based therapy and patients who progressed during or relapsed after completion of at least 2 cycles (in case of CPI relapsing patients) of platinum-based chemotherapy and a CPI treatment (monotherapy or in combination with chemotherapy).. The trial will consist in 2 Parts; Part 1 and part 2: **<u>Part 1</u>**: Dose escalation of BI 836880 in combination with BI 754091 in patients with locally advanced or metastatic non-squamous NSCLC who progressed during or after first line (in case of CPI naïve patients) platinum-based therapy or relapsed after completion of at least 2 cycles (in case of CPI relapsing patients) of platinum-based chemotherapy and a CPI treatment (monotherapy or in combination with chemotherapy).
Rationale for change		Adaption regarding the added population
Section to be changed		3.2
Description of change		Changed from: The eligible patients are patients with locally advanced or metastatic non - squamous NSCLC who progressed during or after first line platinum-based treatment. To: The eligible patients are patients with locally advanced or metastatic non - squamous NSCLC who progressed during or after first line (in case of naïve patients) of platinum-based therapy. Additional we include patients who relapsed after completion of at least 2 cycles (in case of relapsed

		patients) of platinum-based chemotherapy and a CPI treatment (monotherapy or in combination with chemotherapy).
Rationale for change		Adaption regarding the added population
Section to be changed		3.3
Description of change		Changed from: Eligible patients are patients with locally advanced or metastatic non-squamous NSCLC which progressed during or after first line platinum-based treatment and who are check point inhibitor naïve. To: Eligible patients are patients with locally advanced or metastatic non-squamous NSCLC which progressed during or after first line (in case of naïve patients) of platinum-based therapy and patients who relapsed after completion of at least 2 cycles (in case of relapsed patients) of platinum-based chemotherapy and a CPI treatment (monotherapy or in combination with chemotherapy).
Rationale for change		Adaption regarding the added population
Section to be changed		3.3.1
Description of change		Changed from: Patients with advanced/metastatic non squamous NSCLC who have progressed during or after first line platinum- based therapy. Patients should be check point inhibitors naïve. To: Patients with advanced/metastatic non squamous NSCLC who have progressed during or after first line (in case of naïve patients) of platinum-based therapy and patients who relapsed after completion of at least 2 cycles (in case of relapsed patients) of platinum-based chemotherapy and a CPI treatment (monotherapy or in combination with chemotherapy).
Rationale for change		
Section to be changed		3.3.2 Inclusion Criteria
Description of change		Inclusion criteria #3 and #4 were changed from: 1. No previous treatment with check-point inhibitor.

		2. Documented disease progression or relapse (based on investigator's assessment) during or after completion of at least 2 cycles of platinum-based chemotherapy as first line treatment of Stage IIIB/IV NSCLC. This includes patients relapsing within 6 months of completing (neo)adjuvant/curative-intent chemotherapy or chemoradiotherapy To: 1. No previous treatment with check-point inhibitor. Or patients with CPI based treatment as last therapy before entering the trial. 2. Documented disease progression or relapse (based on investigator's assessment) during or after completion of at least 2 cycles of platinum-based chemotherapy as first line treatment of Stage IIIB/IV non- squamous NSCLC or for CPI experienced patients during or after completion of at least 2 cycles of platinum-based chemotherapy and a CPI treatment (monotherapy or in combination with chemotherapy). This includes patients relapsing within 6 months of completing (neo)adjuvant/curative-intent chemotherapy/CPI or chemoradiotherapy
Section to be changed		3.3.3 Exclusion Criteria
Description of change		8. Patients with personal or family history of QT prolongation and/or long QT syndrome, or prolonged QTcF at baseline (> 470 ms). Changed to: 1. Patients with personal or family history of QT prolongation and/or long QT syndrome, or prolonged QTcF at baseline (> 480 ms).
Rationale for change		Clarification of the QTcF
Rationale for change		Adaption regarding the new population
Section to be changed		3.3.4.1 Withdrawal from trial treatment
Description of change		Added information: • The patient can no longer be treated with trial drug after a drug related Adverse Event CTCAE Grade 4.

		• The patient can no longer be treated with trial drug after a DLT, which did not recover to CTCAE Grade 1 or pre-treatment values within 2 weeks.
Rationale for change		Request by the German EC
Section to be changed		4.1.1 Identity of the Investigational Medicinal Products
Description of change		In this trial the IMP BI 836880 will be switched to a new pharmaceutical formulation which is diluted in a standard 5% Glucose/Dextrose solution. The new formulation will be made available in this trial at the latest before expiry of the old formulation prepared with a drug specific Diluent. Details of the trial medications, BI 836880, BI 754091, and respective diluents, are presented in Tables 4.1.1: 1 and 4.1.1:2, in the IB's for BI 836880 and BI 754091 as well as in the Instruction for the Pharmacist (IfP). Deletion of Table 4.1.1: 2
Rationale for change		Change of the IMP formulation BI 836880. Diluent will not be used anymore with the new formulation.
Section to be changed		4.1.4 Re-treatment criteria
Description of change		Adding of information: In case of a DLT (drug related AEs CTCAE Grade 3, 4 according to Table 5.2.6.1: 1) the patient will discontinue treatment. Once a DLT has recovered to CTCAE grade 1 or pre-treatment values, the study drugs may be re-started at a lower dose level in case the patients benefits from the study drug after discussion between investigator and Clinical Monitor at Boehringer Ingelheim And change of • QTcF <=470 ms (according to Exclusion-Criterion #8) To: • QTcF <=480 ms (according to Exclusion-Criterion #8)
Rationale for change		Request by German EC, clarification on the QTcF
Section to be changed		4.1.7 Storage condition
Description of change		Change from:

		BI 836880 vials and Diluent Buffer vials and BI754091 vials must be stored in their original packaging. To: BI 836880 vials (old and new formulation) and BI754091 vials must be stored in their original packaging.
Rationale for change		Adaption regarding new IMP formulation
Section to be changed		5.2.2 Body temperature
Description of change		Change from: Not acceptable/preferred methods include: IR-measurement in ear, forehead or temple. To: Not preferred methods but accepted include: IR-measurement in ear, forehead or temple.
Rationale for change		Clarification
Section to be changed		5.2.3 Safety laboratory parameter
Description of change		Change from: In case the criteria for hepatic injury are fulfilled, a number of additional measures will be performed (please see Section 5.2.6.1 and the DILI Checklist provided in the ISF eDC system. The amount of blood taken from the patient concerned will be increased due to this additional sampling. To: In case the criteria for potential hepatic injury are fulfilled, a number of additional measures will be performed (please see Section 5.2.6.1 and the DILI Checklist provided in the ISF eDC system. The amount of blood taken from the patient concerned will be increased due to this additional sampling.
Rationale for change		Clarification by adding the word “potential”
Section to be changed		5.2.4 Electrocardiogram
Description of change		Change from: Cardiac monitoring for patients presenting a QTc interval prolongation CTCAE grade ≥ 3 ‘>500 ms) shall be followed as follows: - Continuous ECG monitoring until the QTc interval < 480 ms

		- Cardiologist opinion for potential treatment of this event as soon as the QTc interval prolongation is observed. - Cardiologist recommendation after QTc interval normalisation (< 480 ms) and potential follow-up. To: Cardiac monitoring for patients presenting a QTc interval prolongation CTCAE grade ≥ 3 (i.e., average QTc >= 501 ms, or >60 ms change from baseline; or Torsade de pointes, polymorphic ventricular tachycardia, or signs/symptoms of serious arrhythmia) shall be followed as follows: - Continuous ECG monitoring until the QTc interval ≤ 480 ms - Cardiologist opinion for potential treatment of this event as soon as the QTc interval prolongation is observed. - Cardiologist recommendation after QTc interval decreases to Grade 1 (≤ 480 ms) and potential follow-up.
Rationale for change		Needed clarification regarding cardiac monitoring.
Section to be changed		5.2.6.1 Dose limiting toxicities (DLTs
Description of change		Changed from: The occurrence of any of the toxicities presented in Table 5.2.6.1: 1 will be considered a DLT, if assessed by the investigator to be related to the administration of either study drug. A DLT occurring during Part 1 of the study will be considered an AESI and reported on the SAE form. Incidence and severity of adverse events will be graded according to the common terminology criteria for adverse events (CTCAE, version 4.03), Previous anti-PD-l mAbs have been associated in the clinical setting with inflammatory adverse reactions resulting from increased or excessive immune activity (irAEs), likely to be related to the mechanism of action. These adverse reactions, which can be severe, may involve the gastrointestinal, skin, liver, endocrine, respiratory, renal, or other organ systems.

Table 5.2.6.1: 1 Dose Limiting Toxicities (according to CTCAE V4.03)

Drug related toxicity category	Criteria defining a DLT*
Hematologic	• Grade 4 neutropenia lasting ≥5 days or complicated by infection • Grade ≥ 3 documented infection with neutropenia. • Grade ≥ 3 febrile neutropenia (ANC<1000/mm3 complicated by fever ≥38.5° C or a sustained temperature of ≥38.0° C for more than 1 hour. • Grade 3 thrombocytopenia associated with bleeding or requiring platelet transfusion. • Grade 4 thrombocytopenia (<25,000/m3). • Grade 4 anaemia.

Table 5.2.6.1: 1 Dose Limiting Toxicities (according to CTCAE V4.03) (cont'd)

Drug related toxicity category	Criteria defining a DLT*
Non-hematologic	Non-laboratory toxicity • Any Grade 4 or 5 AE other than disease progression. • Any Grade 2 drug-related uveitis or eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within 2 weeks or requires systemic treatment. • Any treatment-related ≥ Grade 2 toxicity that persists and results in an inability to administer BI 754091 or BI 836880 on Cycle 2 Day 1. • any grade ≥ 2 pneumonitis of any duration • Any toxicity Grade ≥ 3 toxicity except: o Grade 3 immune-related AE that resolves to ≤ Grade 1 or to baseline with immunosuppressive therapy within 2 weeks o Grade 3 asymptomatic endocrine disorders (thyroid, pituitary, and/or adrenal insufficiency) that are managed with or without systemic

				corticosteroid therapy and/or hormone replacement therapy. o Grade 3 or 4 elevation in serum amylase and/or lipase that is not associated with clinical or radiographic evidence of pancreatitis o Grade 3 nausea or vomiting that lasts <48 hours, and resolves to ≤Grade 1 either spontaneously or with conventional medical intervention o Alopecia o Grade 3 fatigue that persists less than 7 days o Grade 3 infusion related reaction which can be controlled by appropriate medication according to investigator's decision, and the subsequent infusion will not be delayed for more than two weeks. o Grade 3 rash that resolves to ≤ Grade 1 within 2 weeks o Grade 3 or 4 elevation in serum amylase and/or lipase that is not associated with clinical or radiographic evidence of pancreatitis o Grade 3 endocrine disorders (thyroid, pituitary, and/or adrenal insufficiency) that are managed with or without systemic corticosteroid therapy and/or hormone replacement therapy, and the patient is asymptomatic. o Grade 3 tumour flare. Laboratory toxicity • Hypertension: systolic blood pressure >=160 mm Hg or diastolic blood pressure >=100 mm Hg, confirmed by second measurement of an additional set of 3 BP measurements, or 3 sequential ambulatory blood pressure measurements when indicated (e.g. white coat effect), and which cannot be controlled by hypertensive medication and which requires a dose reduction / discontinuation of trial medication(s) • Grade>=3 proteinuria (urinary protein >= 3.5 g/day)

To:
The occurrence of any of the toxicities presented in Table 5.2.6.1: 1 will be considered a DLT, if assessed by the investigator to be related to the administration of either of the study drugs. All DLTs occurring during Part 1 of the study will be considered an AESI and reported on the SAE form.
Incidence and severity of adverse events will be graded according to the common terminology criteria for adverse events (CTCAE, version 5.0),

Table 5.2.6.1: 1 Dose Limiting Toxicities (according to CTCAE V5.0

Drug related toxicity category	Criteria defining a DLT*
Hematologic	• Grade 4 neutropenia (<500/mm3) lasting ≥5 days or complicated by infection • Grade ≥ 3 documented infection with neutropenia. • Grade ≥ 3 febrile neutropenia (ANC<1000/mm3 complicated by fever ≥38.3 °C or 101°F° C or a sustained temperature of ≥38.0C (100.4 ° F) for more than 1 hour. • Grade 3 thrombocytopenia (>= 25,000/mm3 and <50,000/mm3) associated with bleeding or requiring platelet transfusion. • Grade 4 thrombocytopenia (<25,000/mm3). Grade 4 anaemia (i.e., life-threatening consequences or urgent intervention indicated) • .

Table 5.2.6.1: 1 Dose Limiting Toxicities (according to CTCAE V5.0) (cont'd)

Drug related toxicity category	Criteria defining a DLT*
Non-hematologic	Non-laboratory toxicity • Any Grade 4 or 5 AE other than disease progression. • Any Grade 2 drug-related uveitis or eye pain or blurred vision that does not respond to topical therapy and

				does not improve to Grade 1 severity within 2 weeks or requires systemic treatment. • Any treatment-related Grade ≥ 2 toxicity that occurred during Cycle 1 that persists and results in an inability to administer BI 754091 or BI 836880 on Cycle 2 Day 1. • any grade ≥ 2 pneumonitis of any duration • Any toxicity Grade ≥ 3 toxicity except: o Grade 3 immune-related AE that resolves to ≤ Grade 1 or to baseline with immunosuppressive therapy within 2 weeks o Grade 3 asymptomatic endocrine disorders (thyroid, pituitary, and/or adrenal insufficiency) that are managed with or without systemic corticosteroid therapy and/or hormone replacement therapy. o Grade 3 or 4 elevation in serum amylase and/or lipase that is not associated with clinical or radiographic evidence of pancreatitis o Grade 3 nausea or vomiting that lasts <48 hours, and resolves to ≤Grade 1 either spontaneously or with conventional medical intervention o Alopecia o Grade 3 fatigue that persists less than 7 days o Grade 3 infusion related reaction which can be controlled by appropriate medication according to investigator's decision, and the subsequent infusion will not be delayed for more than two weeks. o Grade 3 rash that resolves to ≤ Grade 1 within 2 weeks o Grade 3 endocrine disorders (thyroid, pituitary, and/or adrenal insufficiency) that are managed with or without systemic corticosteroid therapy and/or hormone replacement therapy, and the patient is asymptomatic. o Grade 3 tumour flare. Laboratory toxicity

		• Hypertension: systolic blood pressure >=160 mm Hg or diastolic blood pressure >=100 mm Hg, confirmed by second measurement of an additional set of 3 BP measurements, or 3 sequential ambulatory blood pressure measurements when indicated (e.g. white coat effect), and which cannot be controlled by hypertensive medication and which requires a dose reduction / discontinuation of trial medication(s) • Grade3 proteinuria (urinary protein >=3.5 g/24 hrs; 4+ proteinuria)
Rationale for change		Clarification and adaptions to CTCAE V5.0
Section to be changed		10.2 BLOOD PRESSURE MEASUREMENT PROCEDURE
Description of change		Change from: The preferred method of blood pressure measurement is by a standard mercury sphygmomanometer. If a standard mercury sphygmomanometer is not available, alternative devices according to website dableducational.org may be used. At screening, blood pressure should be taken in both arms. If the pressures differ by more than 10 mmHg (as in the presence of a subclavian steal syndrome), the arm with the higher pressure (either systolic or - if needed to decide - diastolic) should be used for subsequent measurements. Blood pressure measurements should be performed on the same arm and, if possible, by the same person. The same method and device must be used throughout the trial for a patient i.e. if a patient receives the first blood pressure measurement for example with an electronic device, the same method and device should be used throughout the study for this patient (without switching to manual blood pressure measurement). On the other hand, inter-patient variability is acceptable, i.e. a study site is allowed to consistently use an electronic device to measure the blood pressure in a given patient throughout the study and a manual technique in another patient. After patients have rested quietly, in the seated position for five minutes, three blood pressure measurements will be taken two minutes apart and all three results have to be entered in the

		eCRF. The seated pulse rate will be taken during the two-minute interval between the second and third blood pressure reading. Blood pressure measurements should be recorded to the nearest 2 mmHg only when measured with a manual sphygmomanometer; when digital devices are used the value from the device should be rounded to the nearest 1 mmHg. For calculation of mean values, decimal places should be rounded to integers (e.g. a DBP of 94.5 would be rounded to 95 mmHg and a DBP of 109.4 would be rounded to 109 mmHg). The above mentioned procedure is considered as standardized conventional blood pressure measurement (CBPM). In case of a suspected "white coat effect" it is recommended to repeat the measurement in a pleasant condition after sufficient rest. Ambulatory blood pressure measurement (ABPM) can be an option in specific cases to observe BP profiles over a longer period (e.g. during infusion and thereafter) and even outside the hospital in private surrounding. However treatment decisions should be based whenever possible on CBPM as described above and ABPM should be used for observation only. In case BP values from ABPM should be used for treatment related decisions, this has to be taken from appropriate timepoints and validated ABPM devices according to website dableducational.org should be used. Values from self-blood pressure measurement (SBPM) communicated from patient to investigator is not considered valuable for study related decisions. Blood pressure measurements should be performed on the same arm and, if possible, by the same person. The machines or devices to be used for blood pressure measurement should be certified. The same method and device must be used throughout the trial for a patient i.e. if a patient receives the first blood pressure measurement for example with an electronic device, the same method and device should be used throughout the study for this patient (without switching to manual blood pressure measurement). On the other hand, inter-patient variability is acceptable, i.e. a study site is allowed

		to consistently use an electronic device to measure the blood pressure in a given patient throughout the study and a manual technique in another patient. After patients have rested quietly, in seated position for minutes, three blood pressure measurements will be taken two minutes apart and all three results have to be entered in the eCRF. In case of a suspected “white coat effect” it is recommended to repeat the measurement in a pleasant condition after sufficient rest. Values from self-blood pressure measurements (SBPM) communicated from patient to investigator are not considered valuable for study related decisions.
Rationale for change		Adaption of regarding clinical standard methods
Section to be changed		Table 10.6.1: 1
Description of change		PK VEGF/ANG2 sample V4D3 was deleted wording adapted to: According to Section 4.1.4 of the protocol, the infusion time may be adapted. In this case, the PK sampling referring to the” start” and “end” time of the infusion should be performed shortly after the end of infusion, no matter the duration of the infusion. The subsequently requested PK sampling should be drawn as planned. Do not adapt the time because of the variation of the duration of the infusion schema.
Rationale for change		Typo in the tracker and clarification

11.3 GLOBAL AMENDMENT 3

Date of amendment		12 Jul 2019
EudraCT number **EU number**		2017-001378-41
BI Trial number		1336-0011
BI Investigational Product(s)		BI 836880 BI 754091
Title of protocol		An open label phase Ib dose finding study of BI 836880 in combination with BI 754091 to characterize safety, tolerability, pharmacokinetics, pharmacodynamics and efficacy in check point inhibitor naïve and previously treated patients with locally advanced or metastatic non-squamous Non-Small Cell Lung Cancer
Global Amendment due to urgent safety reasons		☐
Global Amendment		☒
Section to be changed		Title
Description of change		Changed from: An open label phase Ib dose finding study of BI 836880 in combination with BI 754091 to characterize safety, tolerability, pharmacokinetics, pharmacodynamics and efficacy in check point inhibitor naïve and previously treated patients with locally advanced or metastatic non-squamous Non-Small Cell Lung Cancer To: An open label phase Ib dose finding study of BI 836880 in combination with BI 754091 to characterize safety, tolerability, pharmacokinetics, pharmacodynamics and efficacy in patients with locally advanced or metastatic non-squamous Non-Small Cell Lung and in other solid tumors
Rationale for change		The title was adapted to the new populations
Section to be changed		Lay Title
Description of change		Changed from: This study aims to find the best doses of BI 836880 combined with BI 754091 in patients with a certain type of advanced lung cancer (NSCLC).

		To: A study to test different doses of BI 836880 combined with BI 754091 in patients with advanced non-small cell lung cancer followed by other types of advanced solid tumours
Rationale for change		The title was adapted to the new populations
Section to be changed		Synopsyis Title
Description of change		Changed from: An open label phase Ib dose finding study of BI 836880 in combination with BI 754091 to characterize safety, tolerability, pharmacokinetics, pharmacodynamics and efficacy in check point inhibitor naïve and previously treated patients with locally advanced or metastatic non-squamous Non-Small Cell Lung Cancer To: An open label phase Ib dose finding study of BI 836880 in combination with BI 754091 to characterize safety, tolerability, pharmacokinetics, pharmacodynamics and efficacy in ~~previously treated~~ patients with locally advanced or metastatic non-squamous Non-Small Cell Lung and in other solid tumors
Rationale for change		The title was adapted to the new populations
Section to be changed		Synopsis study design
Description of change		Changed from: This is a Phase Ib study, containing two parts; Part 1 (dose escalation of BI 836880 in combination with BI 754091) and Part 2 (expansion phase in two cohorts). To: This is a Phase Ib study, containing two parts; Part 1 (dose escalation of BI 836880 in combination with BI 754091) and Part 2 (expansion phase in 6 cohorts).
Rationale for change		The title was adapted to the new populations
Section to be changed		Synopsis study design

Description of change		Changed from: **Part 2**: Open label, non-randomized expansion phase to assess efficacy and safety of BI 836880 in combination with BI 754091 in check point inhibitor naïve patients with locally advanced or metastatic non-squamous NSCL, PD-L1 high and PD-L1 low, **Cohort A**: Patients with locally advanced or metastatic non-squamous NSCLC with low PD-L1 expression (PD-L1 expression in 1-49% of tumor cells) **Cohort B**: Patients with locally advanced or metastatic non-squamous NSCLC with high PD-L1 expression (PD-L1 expression in ≥ 50% of tumor cells) To: **Part 2**: Open label, non-randomized expansion phase to assess efficacy and safety of BI 836880 in combination with BI 754091: **Cohort A (NSCLC):** Patient with pathologically confirmed locally advanced or metastatic non-squamous NSCLC who progressed during or after check-point inhibitor monotherapy treatment as the most recent anticancer treatment. **Cohort B (NSCLC):** Patient with pathologically confirmed locally advanced or metastatic non-squamous NSCLC who progressed during or after **platinum-based chemotherapy and a check-point inhibitor combination treatment as the** most recent anticancer treatment. **Cohort C (SCLC):** Patient with pathologically confirmed locally advanced or metastatic Small Cell Lung Cancer (SCLC) **who progressed during or after first line** standard chemotherapy regimen. **Cohort D (Glioblastoma):** Patient with histologically confirmed recurrent glioblastoma with **no more than one previous line of chemotherapy** (concurrent and adjuvant temozolomide based chemotherapy including in combination with another investigational agent is considered one line of chemotherapy). **Cohort E (Melanoma):** Patient with histologically confirmed, unresectable, Stage IV metastatic melanoma who progressed during or after CPI based regimen.

		Cohort F (Hepatocellular Carcinoma): Patient with locally advanced or metastatic and/or unresectable Hepatocellular Carcinoma (HCC) who were intolerant or progressed during 1st line sorafenib or lenvatinib treatment; subsequent CPI therapy is allowed as the most recent anticancer treatment
Rationale for change		Adapted regarding the new populations
Section to be changed		Synopsis -Objectives
Description of change		Changed from: **PART 2:** **Primary objective:** • To assess anti-tumour activity of BI 836880 in combination with BI 754091 in check point inhibitor naïve patients with locally advanced or metastatic non-squamous NSCLC who progressed during or after first line platinum-based treatment. o **Cohort A**: Patients with locally advanced or metastatic non-squamous NSCLC with low PD-L1 expression (PD-L1 expression in 1-49% of tumor cells) o **Cohort B**: Patients with locally advanced or metastatic non-squamous NSCLC with high PD-L1 expression (PD-L1 expression in ≥ 50% of tumor cells) **Secondary objective**: • To provide safety data and further investigate clinical efficacy including disease control (DC), duration of objective response (DoR), progression free survival (PFS), and tumour shrinkage • To evaluate the basic pharmacokinetics of BI 836880 and BI 754091 during combination therapy after the first and fourth infusion cycle. [redacted]

		To: **PART 2:** **Primary objective:** • To assess anti-tumour activity of BI 836880 in combination with BI 754091 in patients with locally advanced or metastatic non-squamous NSCLC and other solid tumors. **Secondary objective**: • To provide safety data and further investigate clinical efficacy including disease control (DC), duration of objective response (DoR), progression free survival (PFS), and tumour shrinkage. • To evaluate the basic pharmacokinetics of BI 836880 and BI 754091 during combination therapy after the first infusion cycle. [redacted]
Rationale for change		Adaption regarding the new populations
Section to be changed		Synopsis - Endpoints
Description of change		Changed from: **PART 2:** The primary endpoint is Objective Response (OR), defined as best overall response (RECIST1.1) of complete response (CR) or partial response (PR) from first treatment infusion until the earliest of disease progression, death or last evaluable tumour assessment before start of subsequent anti-cancer therapy, lost to follow-up, withdrawal of consent. To: **PART 2:** The primary endpoint is the shrinkage estimator of objective response (OR) based on BHM. OR is defined as best overall response (RECIST1.1) of complete response (CR) or partial response (PR) from first treatment infusion until the earliest of disease progression, death or last evaluable

		tumour assessment before start of subsequent anti-cancer therapy, lost to follow-up or withdrawal of consent.
Rationale for change		Synopsis Endpoints – Secondary endpoints/part 2
Section to be changed		Changed from: • Pharmacokientic parameters C_{max}, t_{max}, AUC_{0-504h} after the first and fourth infusion cycle. To: • Pharmacokinetic parameters C_{max}, t_{max}, AUC_{0-504h} after the first infusion cycle.
Description of change		Adaption to new requirements
Rationale for change		Adaption regarding the new populations
Section to be changed		Synopsis_ **Number of patients entered:**
Description of change		Changed from: A total of 80 patients approximately will be entered (Part 1 and Part 2) To: A total of 255 patients (28 part 1 plus 227 part 2) approximately will be entered (Part 1 and Part 2)
Rationale for change		Adaption to the additional needed patients
Section to be changed		Synopsis- **Number of patients on each treatment:**
Description of change		Changed from: Part 1: 20 to 25 evaluable patients Part 2 : 60 evaluable patients (30 patients per cohort) To: Part 1: 12 to18 evaluable patients Part 2: 80 evaluable locally advanced or metastatic non-squamous NSCLC patients (Cohort A and B; 40 patients per cohort) and 30 evaluable patients in each of the other 4 cohorts. In total 200 patients.
Rationale for change		Adaption to the additional needed patients
Section to be changed		Synopsis- Diagnosis
Description of change		Changed from: Naïve or previously checkpoint inhibitor treated patients with locally advanced or metastatic non-squamous NSCLC who progressed during or after first line (in case of checkpoint inhibitor naïve patients) platinum-based therapy and patients who progressed during or relapsed after completion of at least 2 cycles (in case of checkpoint inhibitor relapsing

		patients) of platinum-based chemotherapy and a checkpoint inhibitor treatment (monotherapy or in combination with chemotherapy). Patients with either low PD-L1 expression (PD-L1 expression in 1-49% of tumor cells) or high PD-L1 expression (PD-L1 expression in ≥ 50% of tumor cells). To: Part 1: Naïve or previously checkpoint inhibitor CPI treated patients with locally advanced or metastatic non-squamous NSCLC who progressed during or after first line (in case of checkpoint inhibitorCPI naïve patients) platinum-based therapy and patients who progressed during or relapsed after completion of at least 2 cycles (in case of checkpoint inhibitorCPI relapsing patients) of platinum-based chemotherapy and a checkpoint inhibitor CPI treatment (monotherapy or in combination with chemotherapy). Part 2: Cohort A and B: Patients with locally advanced or metastatic non-squamous NSCLC who progressed or relapsed during or after a CPI based treatment as monotherapy or in combination with platinum-based chemotherapy. Cohort C: Patient with metastatic SCLC Cohort D: Patients with recurrent glioblastoma Cohort E: Patients with metastatic melanoma Cohort F: Patients with hepatocellular carcinoma
Rationale for change		Adaptions regarding the new cohorts in part 2
Section to be changed		Synopsis- **Main in- and exclusion criteria**
Description of change		Changed from: 1. Age ≥ 18 years 2. Pathologically confirmed diagnosis of non-squamous NSCLC 3. Locally advanced (stage IIIb) or metastatic (stage IV) NSCLC 4. Documented disease progression or relapse (based on investigator's assessment) during or after completion of at least 2 cycles of platinum-based chemotherapy as first line treatment of Stage IIIB/IV non- squamous NSCLC or for checkpoint inhibitor experienced patients during or after completion of at least 2 cycles of platinum-based chemotherapy and a checkpoint inhibitor treatment (monotherapy or in combination with chemotherapy).

		This includes patients relapsing within 6 months of completing (neo)adjuvant/curative-intent chemotherapy/CPI or chemoradiotherapy 5. At least one target lesion (outside the brain), that can be accurately measured per RECIST v 1.1 6. Availability and willingness to provide a fresh tumour tissue sample obtained after relapse or progression on or after prior therapy. For Part 2, In case a fresh biopsy cannot be obtained (e.g. inaccessible lesions or patient safety concern), an archived specimen obtained up to 6 months prior to cycle 1, visit 1 (C1V1) may be submitted in case no systemic antineoplastic therapy has been administered between the biopsy and C1V1 7. ECOG performance status of 0 or 1 8. Adequate hepatic, renal and bone marrow functions 9. No prior therapy with any immune checkpoint inhibitor To: Inclusion Criteria: <u>For part 1:</u> • Age ≥ 18 years • Pathologically confirmed diagnosis of non-squamous NSCLC • Locally advanced (stage IIIb) or metastatic (stage IV) NSCLC • Documented disease progression or relapse (based on investigator's assessment) during or after completion of at least 2 cycles of platinum-based chemotherapy as first line treatment of Stage IIIB/IV non- squamous NSCLC or for checkpoint inhibitor experienced patients during or after completion of at least 2 cycles of platinum-based chemotherapy and a checkpoint inhibitor treatment (monotherapy or in combination with chemotherapy). This includes patients relapsing within 6 months of completing (neo)adjuvant/curative-intent chemotherapy/CPI or chemoradiotherapy. • At least one target lesion (outside the brain), that can be accurately measured per RECIST v 1.1 • Availability and willingness to provide a fresh tumour tissue sample obtained after relapse or progression on or after prior therapy. • ECOG performance status of 0 or 1 • Adequate hepatic, renal and bone marrow functions For part 2: 1 Of full age (according to local legislation, usually ≥ 18 years) at screening 2 At least one target lesion outside the brain (excluding the glioblastoma patients), that can be accurately measured per RECIST v 1.1 3 ECOG performance status ≤ 1

Inclusion for:

Cohort A (NSCLC):

- Pathologically confirmed locally advanced or metastatic non-squamous NSCLC
- **Prior Check-point inhibitor monotherapy either as 1st or 2nd line** as the last therapy before entering trial**. No more than one regimen of prior chemotherapy.**
- Approximately 10 patients will be recruited who have primary resistance to CPI based therapy which is defined as those advanced or metastatic IIIB/IV non-squamous NSCLC patients who previously received at least 2 cycles of CPI treatment without achieving benefit (SD <6 months or progressive disease in <6 months).
- Approximately 30 patients will be recruited who have secondary resistance to CPI based therapy which is defined as those advanced or metastatic IIIB/IV non-squamous NSCLC patients who had a documented minimum duration of benefit of 6 months and minimum treatment duration of 2 months on the previous CPI treatment without experiencing disease progression during that period.
- Patients with NSCLC known to harbor an ALK rearrangement, or EGFR mutation are only eligible after experiencing disease progression (during or after treatment) or intolerance to EGFR TKI or ALK TKI therapy.

Cohort B (NSCLC):

- Pathologically confirmed locally advanced or metastatic non-squamous NSCLC
- **1st line Platinum-based chemotherapy and a check-point inhibitor combination treatment** as the most recent therapy before entering trial
- Approximately 10 patients will be recruited who have primary resistance to the combination therapy which is defined as those advanced or metastatic IIIB/IV non-squamous NSCLC patients who previously received at least 2 cycles of platinum-based chemotherapy and CPI treatment without achieving benefit (SD < 8 months or progressive disease in < 8 months).
- Approximately 30 patients will be recruited who have secondary resistance to CPI based therapy which is defined as those advanced or metastatic IIIB/IV non-squamous NSCLC patients who had a documented minimum duration

			of benefit (minimum of stable disease) of 8 months who received CPI and platinum-based chemotherapy in a first line setting. - Patients with NSCLC known to harbor an ALK rearrangement, or EGFR mutation are only eligible after experiencing disease progression (during or after treatment) or intolerance to EGFR TKI or ALK TKI therapy.
			Cohort C (SCLC): - Pathologically confirmed locally advanced or metastatic SCLC - **No more than one line of chemotherapy** with or without in combination with CPI Documented disease progression during or after first line standard chemotherapy regimen with or without in combination with CPIs
			Cohort D (recurrent glioblastoma): - Histologically confirmed denovo glioblastoma (primary) - **No more than one line of chemotherapy** (concurrent and adjuvant temozolomide based chemotherapy including in combination with another investigational agent is considered one line of chemotherapy). - Documented first progression after radiotherapy (RT) and concurrent/adjuvant chemotherapy - An interval of at least 12 weeks from the completion of radiation therapy to start of study drug unless there is a new area of enhancement consistent with recurrent tumor outside the radiation field or there is unequivocal histologic confirmation of tumor progression - Patient may have been operated for recurrence. If operated: residual and measurable disease after surgery is required; surgical site must be adequately healed free of drainage or cellulitis, and the underlying cranioplasty must appear intact at the time of randomization
			Cohort E (Melanoma): - Histologically confirmed, unresectable, Stage IV metastatic melanoma - **At least one line of any kind of CPI based regimen as last treatment before entering the study** - Documented progression during or after CPI therapy based regimen

Cohort F (Hepatocellular Carcinoma):

- Patients must have diagnosis of locally advanced or metastatic and/or unresectable histologically confirmed advanced hepatocellular carcinoma, not eligible for surgical and/or locoregional therapies
- Patients should have progressed or discontinued first line treatment with sorafenib or lenvatinib, due to lack of tolerability. Patients who received 2nd line treatment with anti-PD1 therapy (but not other therapy) after failure of sorafenib are also eligible.
- Documented virology status of hepatitis, as confirmed by screening hepatitis B surface antigen (HBsAg), antibody to hepatitis B core antigen (anti-HBc), and/or anti-hepatitis C virus (anti-HCV)
- Child-Pugh score class A
- Anti-viral therapy per local standard-of-care if active hepatitis B virus (HBV) (but not other therapy) after failure of sorafenib are also eligible.

4 Adequate hepatic, renal and bone marrow functions

5 Availability and willingness to provide a fresh tumor tissue sample obtained after relapse or progression on or after prior therapy. In case a fresh biopsy cannot be obtained (e.g. inaccessible lesions or patient safety concern), an archived specimen obtained up to 6 months prior to cycle 1, visit 1 (C1V1) may be submitted in case no systemic antineoplastic therapy has been administered between the biopsy and C1V1 (except for cohort D). For cohorts E and, F, a fresh on-treatment biopsy is mandatory at C3D1, if possible from the same lesion as the pre-treatment biopsy.

6 Life expectancy ≥ 3 months after start of the treatment in the opinion of the investigator

Exclusion Criteria:

Part 2:

1 Not more than one CPI based treatment regimen prior to entering study (eg. anti-Programmed Death receptor-1 (PD-1), anti-Programmed Death-1 ligand-1 (PD-L1), anti-PD-L2, or anti-cytotoxic T lymphocyte associated antigen-4 (anti-CTLA-4) antibody); Exception is for Melanoma cohort (Cohort E)

		2 Active hepatitis B virus (HBV) or hepatitis C virus (HCV) infection (exception for patients in HCC cohort Cohort F). 3 Prior treatment with any antiangiogenic treatment (e.g. bevacizumab, cediranib, aflibercept, vandetanib, XL-184, sunitinib, etc) except for sorafenib and lenvatinib in HCC cohort (Cohort F) 4 Patients with known active second malignancy other than non-melanoma skin cancers, non-metastatic prostate cancer, in situ cervical cancer, and ductal or lobular carcinoma in situ of the breast. Patients are not considered to have a currently active malignancy if they have completed anticancer therapy and have been disease free for greater than 2 years prior to screening Further exclusion criteria: Exclusion criteria for Glioblastoma: 5 Tumor primarily localized to the brainstem or spinal cord. 6 Presence of diffuse leptomeningeal disease or extracranial disease. Exclusion criteria for Melanoma cohort: 7 Uveal or ocular melanoma Exclusion criteria for HCC cohort: 8 Co-infection with HBV and HCV or HBV and hepatitis D virus (HDV) 9 Known fibrolamellar HCC, sarcomatoid HCC, or mixed cholangiocarcinoma and HCC 10 History of hepatic encephalopathy 11 Untreated or incompletely treated varices with bleeding or high-risk for bleeding 12 Untreated active Hepatitis B virus (HBV) 13 Treatment with any HCV anti-viral therapy within 4 weeks prior to Cycle 1 Day 1
Rationale for change		Adaption to the new patient population
Section to be changed		Synopsis - **Statistical methods**
Description of change		Changed from: **Part 2**: Efficacy response endpoints and safety related data will be summarized descriptively. For PFS and duration of response, the median and 95% two-sided confidence interval will be presented using the Kaplan-Meier method. No hypothesis testing is planned in this trial

		To: **Part 2**: Objective response rate as primary endpoints will be estimated by Bayesian hierarchical model (BHM) approach, which assumes full exchangeability of model parameters and allows borrowing information across patients' cohorts. Other efficacy endpoints and endpoints and safety related data will be summarized descriptively. For PFS and duration of response, the median and 95% two-sided confidence interval will be presented using the Kaplan-Meier method. No hypothesis testing is planned in this trial
Rationale for change		Adaption to the additional cohorts
Section to be changed		Abbreviations
Description of change		Adding of different abbreviations
Rationale for change		To address changes for CTP v 4.0
Section to be changed		Change of the Flowchart
Description of change		Changed from: Flowchart part1and part2 To: 2 different Flow charts one for part 1 and one for part 2
Rationale for change		Adaption to the different needs for the part 2
Section to be changed		1.1
Description of change		Changed from: VEGF-A induces accumulation of MDSCs, immature DC, Treg and tumour-associated macrophage. To: VEGF-A induces accumulation of Myeloid-derived suppressor cells (MDSCs), immature DC, Treg and tumour-associated macrophage.
Rationale for change		Adaption to the different needs for the part 2
Section to be changed		1.1

Description of change		Changed from: More recently, three PD-1/anti-PD-L1 immune checkpoint inhibitor have been approved for second line NSCLC treatment. All three compounds (nivolumab, pembrolizumab and atezolizumab) are currently indicated for second line treatment of both squamous and non-squamous NSCLC. The use of pembrolizumab is currently restricted to second line patients whose tumors express PD-L1 (>1% of tumor cells being PD-L1 positive using IHC) where as nivolumab and atezolizumab's use is open to patients regardless of PD-L1 expression levels. Furthermore, and based on positive Phase III trial in advanced/metastatic NSCLC on (KEYNOTE 024 trial) showing PFS and OS improvement in pembrolizumab monotherapy arm (versus standard chemotherapy) (R16-4783), Pembrolizumab has been approved for 1st line treatment in patients with tumors expressing PD-L1 in ≥ 50% of tumor cells. To: More recently, three PD-1/anti-PD-L1 immune CPI have been approved for second line NSCLC treatment. All three compounds (nivolumab, pembrolizumab and atezolizumab) are currently approved for second line treatment of both squamous and non-squamous NSCLC. The use of pembrolizumab is currently restricted to patients whose tumors express PD-L1 (>1% of tumor cells being PD-L1 positive using IHC) where as nivolumab and atezolizumab's use is open to patients regardless of PD-L1 expression levels. Previously, based on positive Phase III trial in advanced/metastatic NSCLC on (KEYNOTE 024 trial) showing PFS and OS improvement in pembrolizumab monotherapy arm (versus standard chemotherapy) (R16-4783), Pembrolizumab has been approved for 1st line treatment in patients with tumors expressing PD-L1 in ≥ 50% of tumor cells. FDA based on KEYNOTE-042 (NCT02220894) trial approved pembrolizumab monotherapy for the first-line treatment of patients with stage III NSCLC who are not candidates for surgical resection or definitive chemoradiation or metastatic NSCLC. Patients' tumors must have no EGFR or ALK genomic aberrations and express PD-L1 (Tumor Proportion Score [TPS] ≥1%) determined by an FDA-approved test. Atezolizumab in combination with bevacizumab, paclitaxel, and carboplatin, is also indicated for the first-line treatment of patients with metastatic NSCLC with no EGFR or ALK genomic tumor aberrations. Small cell lung cancer (SCLC) is a neuroendocrine tumor that represents about 15 percent of all lung cancers. SCLC occurs predominantly in smokers and is distinguished clinically from most types of non-small cell lung cancer (NSCLC) by its rapid doubling time, high growth fraction, and the early development of metastases. SCLC usually presents with

		disseminated disease, and treatment strategies have focused on systemic therapy. Although SCLC is highly responsive to both chemotherapy and radiotherapy (RT), it commonly relapses within months despite treatment. SCLC is usually staged as either limited or extensive. The standard treatment in limited SCLC is chemoradiation. The chemo drugs used are usually etoposide or irinotecan plus either cisplatin or carboplatin. Atezolizumab is approved as a first line treatment for extensive SCLC. The addition of atezolizumab to chemotherapy in the first-line treatment of extensive-stage small-cell lung cancer resulted in significantly longer overall survival and progression-free survival than chemotherapy alone (IMpower 133). (R19-1714) Nivolumab is approved for metastatic small cell lung cancer with progression after platinum based chemotherapy and at least one other line of therapy. Nivolumab monotherapy provided durable responses and was well tolerated as a third- or later-line treatment for recurrent SCLC (CHECKMATE 032). (R19-1713) High-grade gliomas are malignant and often rapidly progressive brain tumors that are divided into anaplastic gliomas (anaplastic astrocytoma, anaplastic oligodendroglioma) and glioblastoma based upon their histopathologic and molecular features. Despite the survival benefit associated with adjuvant radiation and chemotherapy, the majority of patients relapse following initial therapy. The most commonly used systemic agents in recurrent or progressive high-grade gliomas are bevacizumab, nitrosoureas, and temozolomide rechallenge (since the majority of patients will have received temozolomide at part of initial therapy). In the largest randomized trial to test whether combination therapy is superior to single-agent therapy, the addition of bevacizumab to lomustine improved progression-free but not overall survival compared with lomustine alone. Early experience with CPIs such as pembrolizumab and nivolumab in unselected patients with recurrent high-grade glioma has shown only modest activity. Preliminary results of a phase III trial of nivolumab versus bevacizumab in recurrent glioblastoma found no difference in overall survival (CHECKMATE 143) Most cases of malignant melanoma diagnosed at an early stage and surgical excision can be curative. However, a few patients have metastatic disease at presentation, and some develop metastases after their initial definitive treatment. High-dose interleukin-2 (IL-2) was the first treatment to modify the natural history of patients with metastatic melanoma resulting in cure in a small fraction of patients. However, its severe toxicity has limited its application to carefully selected patients treated at centers with experience in managing the side effects of treatment. Immunotherapy is an important systemic treatment modality for metastatic melanoma. Checkpoint inhibition with an anti-programmed cell death 1 (PD-1) antibody (pembrolizumab, nivolumab) in combination with the anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4)

		antibody ipilimumab has better efficacy (response rates, progression-free survival) than single-agent anti-PD-1 therapy in patients with advanced melanoma who are candidates for systemic therapy. Survival data from phase III trials suggest that 50 percent of patients receiving nivolumab (CHECKMATE-066) and 50 to 60 percent of patients receiving the combination of nivolumab and ipilimumab (CHECKMATE-067) will remain alive at three years. In the phase III KEYNOTE-006 trial, pembrolizumab demonstrated significantly longer PFS and improved overall survival compared with ipilimumab in patients with advanced melanoma. Overall survival was significantly prolonged with pembrolizumab compared with ipilimumab (four-year overall survival rate 41.7 versus 34.1 percent; HR 0.73, 95% CI 0.61-0.89). Hepatocellular carcinoma (HCC) typically diagnosed late in its course is an aggressive tumor that often occurs in the setting of chronic liver disease and cirrhosis. Although the mainstay of therapy is surgical resection, the majority of patients are not eligible because of tumor extent or underlying liver dysfunction. There has been a resurgence of interest and enthusiasm for systemic therapy of HCC with the emergence of data showing that the molecularly targeted agents sorafenib, levatinib and regorafenib improve survival versus best supportive care alone. Both sorafenib and levatinib have been for the first-line treatment of patients with unresectable HCC. (R12-0948) Sorafenib HCC Assessment Randomized Protocol (SHARP) trial demonstrated that angiogenesis biomarkers Ang2 and VEGF were independent predictors of survival in patients with advanced HCC but not were predictive of response to sorafenib. Subsequently, a survival benefit has also been shown in the second-line setting patients for HCC who had disease progression on or after sorafenib or were intolerant to sorafenib in nivolumab (CHECKMATE-040) and pembrolizumab (KEYNOTE-224; NCT02702414) trials. Both have received approval based on these studies.
Rationale for change		New information and adaption for the changes in part 2
Section to be changed		1.2
Description of change		Changed from: There was a moderate (~ 2-fold) BI836880 is currently tested in monotherapy in 2 phase I trials. Nineteen and 10 patients received BI836880 in trial 1336.1 (every 3 weeks schedule) and in trial 1336.6 (weekly schedule), respectively. Dose levels between 40 mg and 1000 mg of BI 836880 are tested. In the every 3 weeks trial, the dose of 720 mg is currently expanded to confirm it as recommended phase 2 dose.

		To: BI836880 is currently tested in monotherapy in 2 phase I trials. As of August 2018, 47 patients had been treated with BI836880 monotherapy in 2 Phase I dose escalation clinical trials: trial (1336.1), BI 836880 given every 3 weeks and trial (1336.6) BI 836880 given every one week. Dose levels between 40 mg and 1000 mg of BI 836880 are tested. In the every 3 weeks trial, the dose of 720 mg is currently expanded to confirm it as recommended phase 2 dose.
Rationale for change		New available information
Section to be changed		1.2
Description of change		Changed from: An exploratory, preliminary PK and biomarker analysis performed in these two trials has shown that systemic VEGF levels are completely blocked already at the lowest dose of 40 mg i.v., while systemic ANG2 levels were blocked dose-dependently showing complete inhibition at dosages starting at 360 mg 3-weekly or 120 mg weekly. At these dosages both, systemic VEGF and ANG2, remain below limit of quantitation even before start of next treatment. Plasma concentrations of BI 836880 increased dose-dependently (based on C_{max} and AUC), over the dose ranges 40-1000 mg (1336.1 q3w) and 40-180 mg (1336.6 qw). A slight accumulation could be observed over treatment cycles 1, 2 and 4 based on Cmax and partial AUCs in both trials (accumulation ratios were up to 1.5) while the elimination seemed dose-independent. In 1336.1 (q3w), the gmean half-life over all dose groups was 197 hours (cycle 1, n=12), 238 hours (cycle 2, n=7), and 343 hours (cycle 4, n=4). It seems as if the required trough values of 20 mg/L (according to preclinical experiments) could be achieved at dosages starting from **720 mg q3w**. For a more detailed description of the drug profile refer to the current Investigator's Brochures (IB). BI 754091 is a humanized IgG4 pro-monocolonal antibody showing potent and selective binding to human PD-1. BI 754091 has highly human frameworks and a low predicted immunogenicity score. The BI 754091 molecule has a molecular weight approximately 148 kilodaltons. To: PK and biomarker analysis performed in 1336.1 has shown that systemic VEGF levels are completely blocked already at the lowest dose of 40 mg i.v., while systemic ANG2 levels were blocked dose-dependently showing

		complete inhibition at dosages starting at 360 mg 3-weekly or 120 mg weekly. At these dosages both, systemic VEGF and ANG2, remain below limit of quantitation even before start of next treatment. Plasma concentrations of BI 836880 increased dose-dependently (based on C_{max} and AUC), over the dose ranges 40-1000 mg (1336.1 q3w) and 40-180 mg (1336.6 qw). A slight accumulation could be observed over treatment cycles 1, 2 and 4 based on Cmax and partial AUCs (accumulation ratios were up to 1.5) while the elimination seemed dose-independent. In 1336.1 (q3w), the the gMean half-life over all dose groups ranged from 210 to 289 hours It seems as if the required trough values of 20 mg/L (according to preclinical experiments) could be achieved at dosages starting from **720 mg q3w** (c23621412-01). In an exploratory, preliminary PK and biomarker analysis performed the results of the 1336.6 could be confirmed. For a more detailed description of the drug profile refer to the current Investigator's Brochures (IB). BI 754091 is a humanized IgG4 pro-monocolonal antibody showing potent and selective binding to human PD-1. BI 754091 has highly human frameworks and a low predicted immunogenicity score. The BI 754091 molecule has a molecular weight approximately 148 kilo Daltons.
Rationale for change		New scientific information available
Section to be changed		1.2
Description of change		Changed from: BI 754091 is currently being tested in the 1381.1 monotherapy first in man trial and 1381.2 combination trial. In 1381.1, a total of 17 patients received BI 754091 monotherapy, 9 patients has been treated in the dose escalation part at 3 dose levels (80 mg, 240 mg and 400 mg) and 8 patients in the expansion part. In the dose escalation part, there were no DLTs or drug-related SAE reported in any cohort. The most common reported AEs are nausea, fatigue, decreased appetite, constipation and arthralgia. The dose of 240 mg of BI 754091 once every 3 weeks was chosen to be further explored in monotherapy expansion and is recommended as a starting dose in combination trials. In the expansion part, the 8 patients received BI 754091 at 240 mg. The most common reported AEs are fatigue and nausea. No patient had a Grade 4, Grade 5 AE or a DLT.

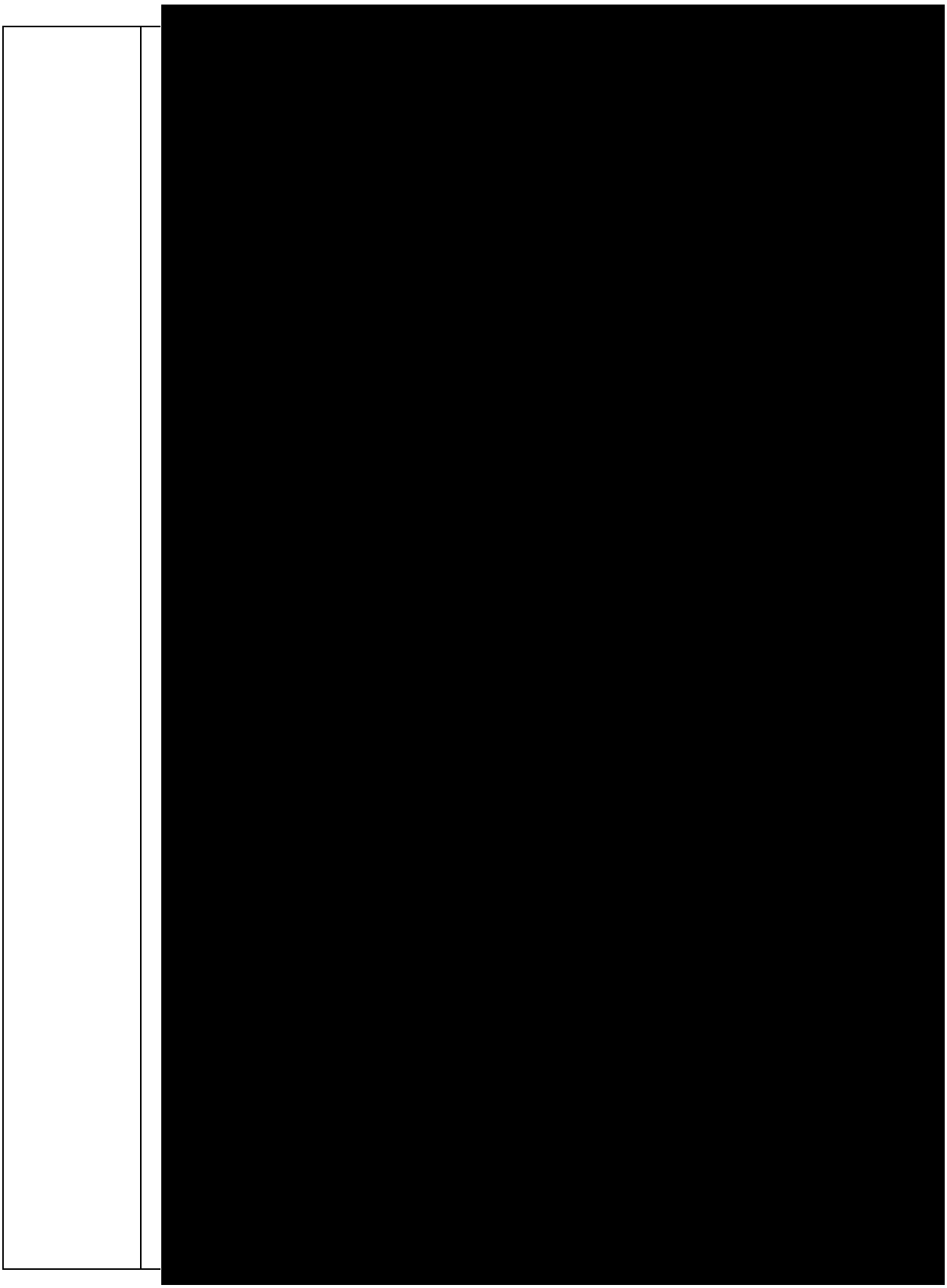
		To: A total of 139 patients have been dosed with BI 754091 in clinical trials, 56 patients with monotherapy BI 754091, and 83 patients with BI 754091 plus BI 754111 ((monoclonal IgG4pro antibody targeting the human LAG-3). At the data cut-off, there were no DLTs or Grade 5 AEs experienced by any patient on monotherapy treatment. The overall most common AEs for patients treated with monotherapy BI 754091 were fatigue, nausea, and decreased appetite. Thirteen of the 56 patients on monotherapy BI 754091 experienced irAEs of rash, maculo-papular rash, colitis, diarrhoea, hypothyroidism, increased ALT, increased AST, arthralgia, pneumonitis, and pruritus. There were one ≥ Grade 3 irAE (Grade 3 increased AST) experienced by patients in the monotherapy population.
Rationale for change		New available information
Section to be changed		*1.3*
Description of change		Changed from: Either check point (PD-1 and PD-L1) inhibition or angiogenesis inhibition (VEGF, Ang-2) inhibition demonstrate antitumor activity with a clinical benefit in NSCLC patients outcome. Despite this effect, an important number of patients will not respond to such therapy and most of patients who benefit from treatment will relapse and die from their disease. Defining novel therapeutic strategy is needed to improve NSCLC patient outcome. …. This trial will evaluate the tolerability of the combination of BI836880 and BI 754091 and the effect of the triple inhibition in 2 populations of patients with NSCLC, according to the PD-L1 status. This will allow a decision on further development of this combination in NSCLC patients and the start of a dedicated Phase II program. To: Check point (PD-1 and PD-L1) inhibition and angiogenesis inhibition (VEGF, Ang-2) demonstrated antitumor activity with a clinical benefit in several tumor types. Despite this effect, an important number of patients will not respond to such therapy and most of patients who benefit from treatment will relapse and die from their disease. Defining novel therapeutic strategy is needed to improve survival in patients with NSCLC patient and other solid tumors. …. This trial will evaluate the tolerability of the combination of BI836880 and BI 754091 and the effect of the triple inhibition in 2 populations of patients with NSCLC, according to previous PD-1 / PD-L1 inhibitor treatment. This combination will also be tested in other unmet need

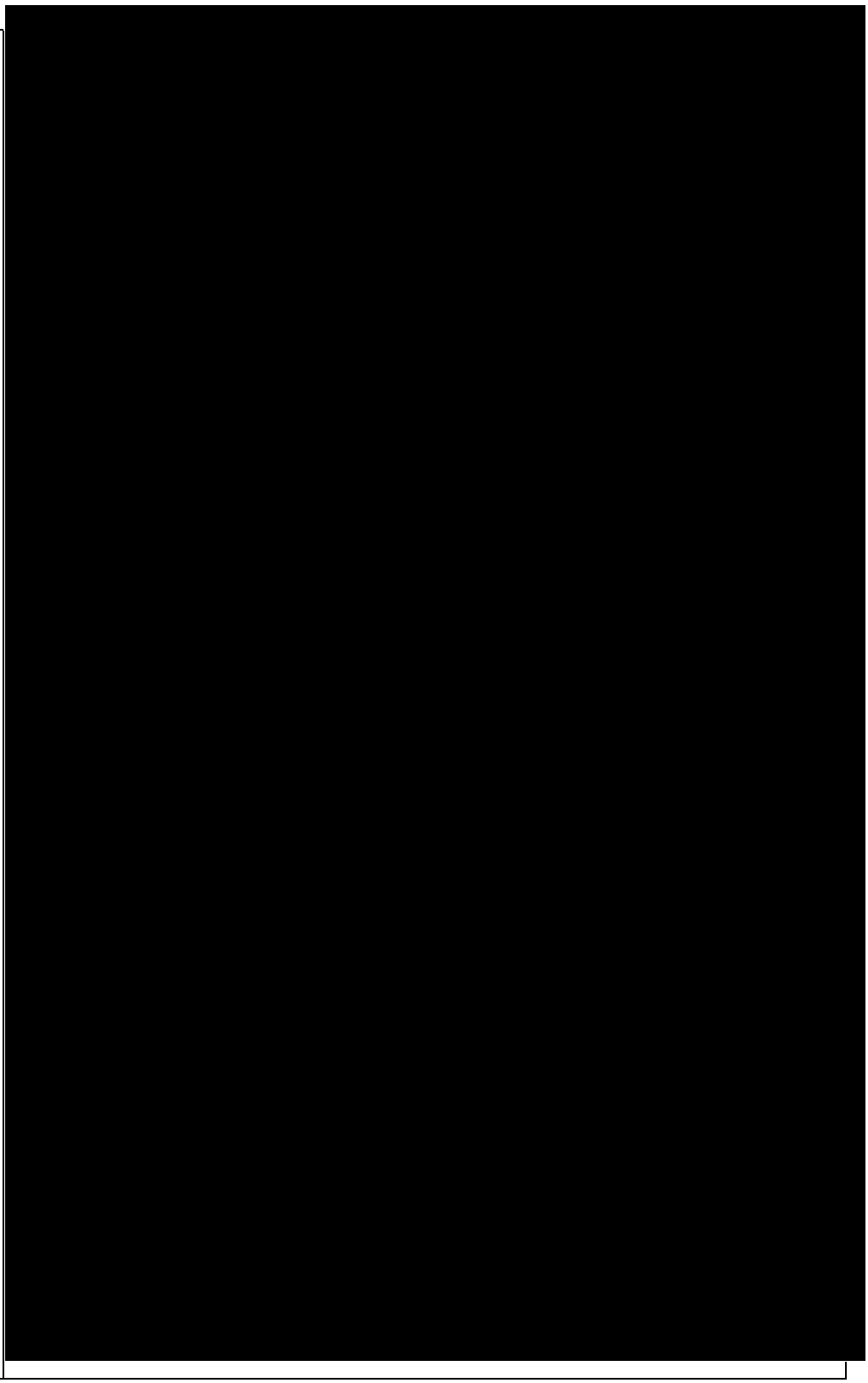
		indications as exploratory expansion cohorts in which either a high baseline Ang-2 or increase of Ang-2 at recurrence has been reported. Ang2 and VEGF have been reported as independent predictors of survival in patients with advanced HCC. Similarly, Ang2 and VEGF have also been reported as predictors of outcome for some CPI therapy in metastaic melanoma and supporting a rational combinatorial approach to improve the efficacy of immune therapy. (R19-1712) This will allow a decision on further development of this combination in patients and the start of a dedicated Phase II/III program
Rationale for change		Adaption to the new part 2
Section to be changed		1.4
Description of change		Changed from: Most of these reported AEs were grade 1-2 (CTCAE version 4.03) (See BI 836880 IB section 6.3). In total, 3 dose limiting toxicities were reported and consisted in pulmonary embolism in 1 patient (trial 1336.1) proteinuria in 1 patient (1336.6) and proteinuria and hypertension in 1 patient (1336.6). To: Most of these reported AEs were grade 1-2 (CTCAE version 4.03). In total, 5 dose limiting toxicities were reported. In trial 1336.1 one patient treated on the highest dose level (1000mg) experienced a pulmonary embolism. In trial1336.6 4 patients were reported with DLTs (proteinuria, proteinuria and hypertension, hypertention and respiratory distress one patient each). (See BI 836880 IB section 6.3).
Rationale for change		New available information
Section to be changed		1.4
Description of change		Changed from: The combination of an immune checkpoint inhibitor with a VEGF blocker has previously been tested in a phase I trial combining atezolizumab with bevacizumab in patients with renal cell carcinoma…. Despite the good safety profile reported for both drugs, patients should be advised of the potential risk of side effects from these investigational drugs. Due to observed hypertension and potential infusion reactions, a 48 hours hospitalization is required after first administration of trial medications for closer observation with access to intensive care for ensuring patient safety.

		To: The combination of an immune CPI with a VEGF blocker has previously been tested in multiple phase I, phase II and phase III trial combining atezolizumab with bevacizumab in patients with advanced solid tumors. The safety of TECENTRIQ with bevacizumab, paclitaxel and carboplatin was evaluated in IMpower150 in metastatic NSCLC. … Despite the good safety profile reported for both drugs, patients should be advised of the potential risk of side effects from these investigational drugs. In Part 1, due to observed hypertension and potential infusion reactions, a 48 hours hospitalization is required after first administration of trial medications for closer observation with access to intensive care for ensuring patient safety. In Part 2, hospitalization is optional. Furthermore, Patients with uncontrolled hypertension, with history of severe haemorrhage or thromboembolism are not allowed to participate to this study. Other side effects 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.
Rationale for change		New available information
Section to be changed		1.4
Description of change		Changed from: In summary, considering the unmet medical need for new treatment armamentarium in patients with advanced or metastatic NSCLC who are progressing during or after prior therapy with platinum-based chemotherapy, the anti-tumour activity of VEGF blockade or PD-1 inhibition and the good safety profiles of BI836880 and BI 754091 monotherapy and the existing data suggesting that a combination of PD-1 blockade with VEGF blockade is a promising therapeutic strategy, the benefit risk assessment for patients included into this trial is considered to be favourable. To: In summary, considering the unmet medical need for new treatment armamentarium in patients with advanced or metastatic NSCLC who are progressing during or after prior PD-1 /PD-L1 based therapy and other solid tumours, the anti-tumour activity of VEGF blockade or PD-1 inhibition and the good safety profiles of BI836880 and BI 754091 monotherapy and the existing data suggesting that a combination of PD-1 blockade with VEGF blockade is a promising therapeutic strategy, the benefit risk assessment for patients included into this trial is considered to be favourable.

Rationale for change		New available information
Section to be changed		2.1.1 Main Objectives –Part 2
Description of change		Changed from: **PART 2:** Primary objective: • To assess anti-tumour activity of BI 836880 in combination with BI 754091 in check point inhibitor naïve patients with locally advanced or metastatic non-squamous NSCLC who progressed during or after first line platinum-based treatment. o **Cohort A**: Patients with locally advanced or metastatic non-squamous NSCLC with low PD-L1 expression (PD-L1 expression in 1-49% of tumor cells) o **Cohort B**: Patients with locally advanced or metastatic non-squamous NSCLC with high PD-L1 expression (PD-L1 expression in ≥ 50% of tumor cells) To: **PART 2:** Primary objective: • To assess anti-tumour activity of BI 836880 in combination with BI 754091 in patients with locally advanced or metastatic non-squamous NSCLC and other solid tumors Secondary objective: • To provide safety data and further investigate clinical efficacy including disease control (DC), duration of objective response (DoR), progression free survival (PFS), and tumour shrinkage • To evaluate the basic pharmacokinetics of BI 836880 and BI 754091 during combination therapy after the first infusion cycle.
Section to be changed		2.1.2 Primary endpoints
Description of change		Change from: **PART 2:** The primary endpoint is Objective Response (OR), defined as best overall response of complete response (CR) or partial response (PR) from first treatment infusion until the earliest of disease progression, death or last evaluable tumour assessment before start of subsequent anti-cancer therapy, lost to follow-up, withdrawal of consent.

		To: **PART 2:** The primary endpoint is the shrinkage estimator of Objective Response (OR) based on BHM, defined as best overall response of complete response (CR) or partial response (PR) from first treatment infusion until the earliest of disease progression, death or last evaluable tumour assessment before start of subsequent anti-cancer therapy, lost to follow-up, withdrawal of consent.
Rationale for change		Re-worded for better clarity
Rationale for change		Adaption to the new requirements
Section to be changed		[redacted]
Description of change		





		[redacted]
Rationale for change		
Section to be changed		3.1
Description of change		Changed from: This is a Phase I, non-randomized, uncontrolled, open-label, dose escalating study of BI 836880 administered in combination with BI 754091 intravenously every 3 weeks. The eligible patient population will be check point inhibitor naïve and experienced patients with locally advanced or metastatic non - squamous NSCLC. Patients who progressed during or after first line (in case of checkpoint inhibitor naïve patients) platinum-based therapy and patients who progressed during or relapsed after completion of at least 2 cycles (in case of checkpoint inhibitor relapsing patients) of platinum-based chemotherapy and a checkpoint inhibitor treatment (monotherapy or in combination with chemotherapy). The trial will consist in 2 Parts; Part 1 and part 2:

		To: This is a Phase I, non-randomized, uncontrolled, open-label, dose escalating study of BI 836880 administered in combination with BI 754091 intravenously every 3 weeks. The eligible patient population will be CPI naïve and experienced patients with locally advanced or metastatic non - squamous NSCLC who progressed during or after first line platinum-based chemotherapy or CPI monotherapy treatment or the combination of CPI and chemotherapy. The trial will consist in 2 Parts; Part 1 and part 2:
Rationale for change		Adaption to the new requirements
Section to be changed		3.1 Part 2
Description of change		Changed from: Open label, non-randomized expansion phase to assess efficacy and safety of BI 836880 in combination with BI 754091 in check point inhibitor naive patients with locally advanced or metastatic non-squamous PD-L1 high and PD-L1 low, NSCLC It is fore seen to enroll up to 60 patients in part 2. Eligible patients will be entered in 2 Cohorts, 30 patients per cohort according to their PD-L1 expression level: ▪ **Cohort A**: Patients with locally advanced or metastatic non-squamous NSCLC with low PD-L1 expression (PD-L1 expression in 1-49% of tumor cells) ▪ **Cohort B**: Patients with locally advanced or metastatic non-squamous NSCLC with high PD-L1 expression (PD-L1 expression in ≥ 50% of tumor cells) To: It is foreseen to enroll up to 200 patients full of age (according to local legislation, usually ≥ 18 years) at screening in 5 different indications: Patients with locally advanced or metastatic 2nd line CPI resistant non-squamous Non-Small Cell Lung Cancer (NSCLC) and ≥2nd line Small Cell Lung Cancer (SCLC) and recurrent glioblastoma and IO failure metastatic melanoma and HCC patients who were intolerant or progressed during or after standard first line treatment with sorafenib or lenvatinib. Patients who received 2nd line treatment with anti-PD1 therapy (but not other therapy) after failure of sorafenib or lenvatinib are also eligible (see image below – **please note the cohorts will run in parallel, not consequential**). Figure added

Rationale for change		Adaption to the new requirements
Section to be changed		3.1
Description of change		Figure 3.1:1 changed
Rationale for change		Adaption to the new requirements
Section to be changed		3.2
Description of change		Changed from: This is a Phase I, non-randomized, uncontrolled, open-label, dose escalating study of BI 836880 administered in combination with BI 754091 intravenously. The eligible patients are patients with locally advanced or metastatic non - squamous NSCLC who progressed during or after first line (in case of naïve patients) of platinum-based therapy. Additional we include patients who relapsed after completion of at least 2 cycles (in case of relapsed patients) of platinum-based chemotherapy and a checkpoint inhibitor treatment (monotherapy or in combination with chemotherapy). Dose escalation will be guided by a Bayesian logistic regression model (*details refer to Section 7.1*). Once RP2D is determined in Part 1, it is planned to enroll 60 patients (30 per arm) as described in Section 3.1. To: In the part 1, this is a Phase I, non-randomized, uncontrolled, open-label, dose escalating study of BI 836880 administered in combination with BI 754091 intravenously. The eligible patients are patients with locally advanced or metastatic non - squamous NSCLC who progressed during or after first line (in case of naïve patients) of platinum-based therapy. Additional we include patients who relapsed after completion of at least 2 cycles (in case of relapsed patients) of platinum-based chemotherapy and a checkpoint inhibitor treatment (monotherapy or in combination with chemotherapy). Dose escalation will be guided by a Bayesian logistic regression model (*details refer to Section 7.1*). Part 2 is an open-label expansion phase to assess efficacy and safety of BI 836880 in combination with BI 754091 in pretreated or naïve check point inhibitor patients with locally advanced or metastatic non-squamous NSCLC, small cell lung cancer, recurrent glioblastoma, malignant melanoma and hepatocellular carcinoma. Once RP2D is determined in Part 1, it is planned to enroll up to 200 patients as described in Section 3.1.

Rationale for change		Adaption to the new requirements
Section to be changed		3.3
Description of change		Changed from: Eligible patients are patients with locally advanced or metastatic non-squamous NSCLC which progressed during or after first line (in case of naïve patients) of platinum-based therapy and patients who relapsed after completion of at least 2 cycles (in case of relapsed patients) of platinum-based chemotherapy and a checkpoint inhibitor treatment (monotherapy or in combination with chemotherapy). In trial Part 2, patients should have either low PD-L1 expression (PD-L1 expression in 1-49% of tumor cells) or high PD-L1 expression (PD-L1 expression in ≥ 50% of tumor cells). This study is planned to be conducted in approximately 4 sites per country in Germany, France, Spain, Taiwan, Korea, US and other EU countries. Approximately 80 patients will be enrolled. To: Eligible patients for Part 1 are patients with locally advanced or metastatic non-squamous NSCLC which progressed during or after first line (in case of naïve patients) of platinum-based therapy and patients who relapsed after completion of at least 2 cycles (in case of relapsed patients) of platinum-based chemotherapy and a checkpoint inhibitor treatment (monotherapy or in combination with chemotherapy). In Part 2, CPI pretreated or naïve patients with locally advanced or metastatic non-squamous NSCLC, small cell lung cancer, recurrent glioblastoma, malignant melanoma and hepatocellular carcinoma will be enrolled. This study is planned to be conducted in approximately 50 sites. These sites will be located in in Australia, Asia (incl. China, South Korea), North America (incl. US) EU (incl. Germany, France, Spain, UK, Russia, Poland, Ukraine). Approximately 80 patients will be enrolled in the NSCLC cohort and 30 patients each in the SCLC, metastatic melanoma, recurrent glioblastoma and HCC cohorts.
Rationale for change		Adaption to new settings
Section to be changed		3.3.1
Description of change		Changed from: Patients with advanced/metastatic non squamous NSCLC who have progressed during or after first line (in case of naïve patients) of platinum-based therapy and patients who relapsed after completion of at least 2 cycles (in case of relapsed patients) of platinum-based chemotherapy and a checkpoint inhibitor treatment (monotherapy or in combination with chemotherapy). Patients included in Part1 are not eligible to participate in Part 2.

		Please refer to Section 8.3.1 (Source Documents) for the documentation requirements pertaining to the in- and exclusion criteria. To: For the part 1 we look for patients with advanced/metastatic non squamous NSCLC who have progressed during or after first line (in case of naïve patients) of platinum-based therapy and patients who relapsed after completion of at least 2 cycles (in case of relapsed patients) of a CPI treatment alone or in combination with platinum-based chemotherapy (monotherapy or in combination with chemotherapy). Patients included in Part1 are not eligible to participate in Part 2. For the part 2 we look for patients with locally advanced or metastatic 2nd line CPI resistant NSCLC and 2nd line SCLC, recurrent glioblastoma, IO failure metastatic melanoma and HCC pts who are intolerant or failed the first line treatment with sorafenib or lenvatinib. Patients who received 2nd line treatment with anti-PD1 therapy (but not other therapy) after failure of sorafenib or lenvatinib are also eligible.
Rationale for change		Adaption to new settings
Section to be changed		3.3.2
Description of change		Changed from: Added: For the part 1 . #11 Availability and willingness to provide a fresh tumour tissue sample obtained at baseline, (Part 1 and Part 2) and after 2 cycles of treatment (Part 1 only). For Part 2, in case a fresh baseline biopsy cannot be obtained (e.g. inaccessible lesions or patient safety concern), an archived specimen obtained up to 6 months prior to first study treatment may be submitted in case no systemic antineoplastic therapy has been administered between the biopsy and first study treatment. To: *#11* Availability and willingness to provide a fresh tumour tissue sample obtained at baseline, and after 2 cycles of treatment Added:For the part 2: **Main Inclusion Criteria for all cohorts** *1.* Of full age (according to local legislation, usually ≥ 18 years) at screening

2. At least one measurable untreated lesion according to RECIST v1.1
3. ECOG performance status ≤ 1
4. Adequate organ function as all of the following (all screening labs should be performed at local lab within 10 days prior to treatment initiation):

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1.5 x 10^9/L.
Platelets	≥75 x 10^9/L.
Hemoglobin	≥9.0 g/dL or ≥5.6 mmol/L.
Renal	
Creatinine **OR** Measured or calculated[a] creatinine clearance (Glomerular Filtration Rate (GFR) can also be used in place of creatinine or CrCl)	≤ 1.5 x ULN **OR** ≥50 mL/min for patients with creatinine levels >1.5x ULN.
Hepatic	
Total bilirubin	≤1.5 times the upper limit of normal (ULN).
AST (SGOT) and ALT (SGPT)	≤2.5 x ULN **OR** ≤5 x ULN for patients with liver metastases.
Coagulation	
• International Normalised Ratio (INR) or Prothrombin Time (PT)	• ≤1.5xULN unless patient is receiving anticoagulant therapy as long as PT is within therapeutic range of intended use of anticoagulants.
• Activated Partial Thromboplastin Time (aPTT)	• ≤1.5xULN unless patient is receiving anticoagulant therapy as long as PTT is within therapeutic range of intended use of anticoagulants.
[a] Creatinine clearance should be calculated per institutional standard.	

		5. Availability and willingness to provide a fresh tumor tissue sample obtained after relapse or progression on or after prior therapy. For Part 2, In case a fresh biopsy cannot be obtained (e.g. inaccessible lesions or patient safety concern), an archived specimen obtained up to 6 months prior to cycle 1, visit 1 (C1V1) may be submitted in case no systemic antineoplastic therapy has been administered between the biopsy and C1V1 (except for cohort D). For cohorts E and, F, a fresh on-treatment biopsy is mandatory at C3D1, if possible from the same lesion as the pre-treatment biopsy. 6. Life expectancy ≥ 3 months after start of the treatment in the opinion of the investigator 7. Recovery from all reversible adverse events of previous anti-cancer therapies to baseline or CTCAE grade 1, except for alopecia (any grade), sensory peripheral neuropathy, must be ≤ CTCAE grade 2 or considered not clinically significant. 8. Signed and dated written informed consent in accordance with ICH-GCP and local legislation prior to admission to the trial 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 ICH M3 (R2) that result in a low failure rate of less than 1% per year when used consistently and correctly, starting with the screening visit and through 150 days after the last dose of BI 836880 and BI 754091 treatment, respectively. A list of contraception methods meeting these criteria is provided in the patient information. For further detail refer to Section 4.2.2.3. Note: Female patients of childbearing potential must have a negative urine or serum pregnancy test within 72 hours prior to taking study medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required. The serum pregnancy test must be negative for the patient to be eligible.

[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.

		Inclusion for: **Cohort A (NSCLC):** - Pathologically confirmed locally advanced or metastatic IIIB/IV non-squamous NSCLC - **Prior Check-point inhibitor monotherapy either as 1st or 2nd line** as the last therapy before entering trial**. No more than one regimen of prior chemotherapy.** - Approximately 10 patients will be recruited who have primary resistance to CPI based therapy which is defined as those advanced or metastatic IIIB/IV non-squamous NSCLC patients who previously received at least 2 cycles of CPI treatment without achieving benefit (RECIST v1.1 SD <6 months or progressive disease in <6 months). - Approximately 30 patients will be recruited who have secondary resistance to CPI based therapy which is defined as those advanced or metastatic IIIB/IV non-squamous NSCLC patients who had a documented minimum duration of benefit of (minimum of stable disease) 6 months and minimum treatment duration of 2 months on the previous CPI treatment without experiencing disease progression during that period. Patients with NSCLC known to harbor an ALK rearrangement, or EGFR mutation are only eligible after experiencing disease progression (during or after treatment) or intolerance to EGFR TKI or ALK TKI therapy.
		- **Cohort B (NSCLC):** - Pathologically confirmed locally advanced or metastatic IIIB/IV non-squamous NSCLC - **1st line Platinum-based chemotherapy and a check-point inhibitor combination treatment** as the most recent therapy before entering trial - Approximately 10 patients will be recruited who have primary resistance to the combination therapy which is defined as those advanced or metastatic IIIB/IV non-squamous NSCLC patients who previously received at least 2 cycles of platinum-based chemotherapy and CPI treatment without achieving benefit (RECIST v1.1 SD < 8 months or progressive disease in < 8 months). - Approximately 30 patients will be recruited who have secondary resistance to CPI based therapy which is defined as those advanced or metastatic IIIB/IV non-squamous NSCLC patients who had a documented minimum duration of benefit (minimum

		of stable disease) of 8 months who received CPI and platinum-based chemotherapy in a first line setting. - Patients with NSCLC known to harbor an ALK rearrangement, or EGFR mutation are only eligible after experiencing disease progression (during or after treatment) or intolerance to EGFR TKI or ALK TKI therapy.
		Cohort C (SCLC): - Pathologically confirmed locally advanced or metastatic SCLC - **No more than one line of chemotherapy** with or without combination with CPI - Documented disease progression during or after first line standard chemotherapy regimen with or without combination with anti-PD (L)1
		Cohort D (recurrent glioblastoma): - Histologically confirmed denovo glioblastoma (primary) - **No more than one line of chemotherapy** (concurrent and adjuvant temozolomide based chemotherapy including in combination with another investigational agent is considered one line of chemotherapy). - Documented first progression after radiotherapy (RT) and concurrent/adjuvant chemotherapy - An interval of at least 12 weeks from the completion of radiation therapy to start of study drug unless there is a new area of enhancement consistent with recurrent tumor outside the radiation field or there is unequivocal histologic confirmation of tumor progression - Patient may have been operated for recurrence. If operated: residual and measurable disease after surgery is required; surgical site must be adequately healed free of drainage or cellulitis, and the underlying cranioplasty must appear intact at the time of randomization
		Cohort E (Melanoma): - Histologically confirmed, unresectable, Stage IV metastatic melanoma - **At least one line of any kind of CPI based regimen as last treatment before entering the study** - Documented progression during or after CPI therapy based regimen

		Cohort F (Hepatocellular Carcinoma): - Patients must have diagnosis of locally advanced or metastatic and/or unresectable histologically confirmed advanced hepatocellular carcinoma, not eligible for surgical and/or locoregional therapies - Patients should have progressed or discontinued first line treatment with sorafenib or lenvatinib, due to lack of tolerability. Patients who received 2nd line treatment with anti-PD1 therapy (but not other therapy) after failure of sorafenib are also eligible. - Child-Pugh score class A - Documented virology status of hepatitis, as confirmed by screening hepatitis B surface antigen (HBsAg), antibody to hepatitis B core antigen (anti-HBc), and/or anti-hepatitis C virus (anti-HCV) - Anti-viral therapy per local standard-of-care if active hepatitis B virus (HBV)
Rationale for change		Adaption for the new cohorts
Section to be changed		*3.3.3* Exclusion Criteria
Description of change		Added info for Part 1 exclusion criteria And: For the part 2: 1. Known hypersensitivity to the trial drugs or their excipients or risk of allergic of anaphylactic reaction to drug product according to Investigator judgement (e.g. patient with history of anaphylactic reaction or autoimmune disease that is not controlled by nonsteroidal anti-inflammatory drugs (NSAIDs), inhaled corticosteroids, or the equivalent of </= 10 mg/day prednisone). 2. Not more than one CPI based treatment regimen prior to entering study (eg. anti-Programmed Death receptor-1 (PD-1), anti-Programmed Death-1 ligand-1 (PD-L1), anti-PD-L2, or anti-cytotoxic T lymphocyte associated antigen-4 (anti-CTLA-4) antibody); Exception is for Melanoma cohort (Cohort E) 3. Known HIV infection *4.* Active hepatitis B virus (HBV) or hepatitis C virus (HCV) infection (exception for patients in HCC cohort).

		5. History of severe hypersensitivity reactions to other mAbs. 6. Immunosuppressive corticosteroid doses (> 10 mg prednisone daily or equivalent) within 4 weeks prior to the first dose of trial medication. 7. Current or prior treatment with any systemic anti-cancer therapy either within 28 days or a minimum of 5 half-lives, whichever is longer before start of treatment. 8. Serious concomitant disease, especially those affecting compliance with trial requirements or which are considered relevant for the evaluation of the endpoints of the trial drug, such as neurologic, psychiatric, infectious disease or active ulcers (gastrointestinal tract, skin) or laboratory abnormality that may increase the risk associated with trial participation or trial drug administration, and in the judgment of the investigator would make the patient inappropriate for entry into the trial. 9. Major injuries and/or surgery or bone fracture within 4 weeks of start of treatment, or planned surgical procedures during the trial period. 10. Patients with personal or family history of QT prolongation and/or long QT syndrome, or prolonged QTcF at baseline (> 480 ms). 11. Significant cardiovascular/cerebrovascular diseases (i.e. uncontrolled hypertension, unstable angina, history of infarction within past 6 months, congestive heart failure > NYHA II). Uncontrolled hypertension defined as: Blood pressure in rested and relaxed condition >= 140 mmHg, systolic or >= 90 mmHg diastolic (with or without medication), measured according to Appendix 10.2. 12. LVEF < 50% 13. History of severe hemorrhagic or thromboembolic event in the past 12 months (excluding central venous catheter thrombosis and peripheral deep vein thrombosis). 14. Known inherited predisposition to bleeding or to thrombosis in the opinion of the investigator. 15. Patient with brain metastases that are symptomatic and/or require therapy. 16. Patients who require full-dose anticoagulation (according to local guidelines).

		17. No Vitamin K antagonist and other anticoagulation allowed; LMWH allowed only for prevention not for curative treatment. 18. History of pneumonitis within the last 5 years 19. Patients who are under judicial protection and patients who are legally institutionalized. 20. Patients unable or unwilling to comply with protocol 21. Previous enrolment in this trial. 22. Chronic alcohol or drug abuse or any condition that, in the investigator's opinion, makes them an unreliable trial patient or unlikely to complete the trial. 23. Women who are pregnant, nursing, or who plan to become pregnant in the trial 24. Symptomatic pleural effusion, pericardial effusion, or ascites 25. Prior treatment with any antiangiogenic treatment (e.g. bevacizumab, cediranib, aflibercept, vandetanib, XL-184, sunitinib, etc) except for sorafenib and lenvatinib in HCC cohort (Cohort F) 26. Has received a live vaccine within 30 days prior to the first dose of study drug 27. Patients with known active second malignancy other than non-melanoma skin cancers, non-metastatic prostate cancer, in situ cervical cancer, and ductal or lobular carcinoma in situ of the breast. Patients are not considered to have a currently active malignancy if they have completed anticancer therapy and have been disease free for greater than 2 years prior to screening Further exclusion criteria: Exclusion criteria for Glioblastoma cohort: 1. Has tumor primarily localized to the brainstem or spinal cord. 2. Has presence of diffuse leptomeningeal disease or extracranial disease. Exclusion criteria for Melanoma cohort: 1. Uveal or ocular melanoma

		Exclusion criteria for HCC cohort: 1. 1.Co-infection with HBV and HCV or HBV and hepatitis D virus (HDV) 2. Known fibrolamellar HCC, sarcomatoid HCC, or mixed cholangiocarcinoma and HCC 3. History of hepatic encephalopathy 4. Participants with untreated or incompletely treated varices with bleeding or high-risk for bleeding 5. Treatment with any HCV anti-viral therapy within 4 weeks prior to Cycle 1 Day 1
Rationale for change		Adding information for the Part 2
Section to be changed		4.1.2.1
Description of change		Changed from: BI836880 is currently tested in monotherapy in 2 phase I trials. 19 and 10 patients received BI836880 in trial 1336.1 (every 3 week schedule) and in trial 1336.6 (weekly schedule), respectively. Dose levels between 40 mg and 1000 mg of BI 836880 were tested in the every 3 week trial. Most commonly reported adverse events are hypertension, asthenia, nausea, vomiting, diarrhea and constipation. Other relevant adverse events (mode of action related) include, peripheral edema, bleeding (epistaxis), and proteinuria. At BI 836880 dose of 1000 mg, 1 DLT (pulmonary embolism) amongst the 5 treated patients was reported. BI 836880 720 mg dose level has been expanded and 9 additional patients have been treated. No Grade 4 AE or DLT was reported amongst the 16 patient treated at this dose level. Exploratory PK and PD analysis was performed. BI 836880 plasma kinetics are dose-proportional over the dose ranges 40-1000 mg (Trial 1336.1 q3w) based on Cmax and partial AUCs. The gmean half-life over all dose groups was 197 hours (cycle 1, n=12), 238 hours (cycle 2, n=7), and 343 hours (cycle 4, n=4). The required trough values of 20 mg/L (according to preclinical experiments) could be achieved at dosages starting from 720 mg every 3 weeks. Biomarker analysis has shown complete systemic VEGF levels blocked at the lowest dose of 40 mg. Systemic ANG2 levels were blocked dose-dependently showing complete inhibition at dosages starting at 360 mg every 3-weeks. At these dosages both, systemic VEGF and ANG2, remain below limit of quantitation even before start of next treatment.

		Based on safety data as well as PK and PD analysis, the dose of 720 mg is selected as recommended phase 2 dose (RP2D). This dose will be the highest dose that can be tested in combination with BI 754091. The dose below this dose tested in monotherapy trial (360 mg) is safe and showed complete inhibition of systemic targets, and will used as starting dose for the combination with BI 754091. However because of the important safety difference between 360 and 720 mg (mainly occurrence and severity of hypertension), a BI 836880 intermediate dose will be tested. The 2 highest tested dose levels will be expanded before selection of BI 836880 dose to be used for Part 2 of the trial. To: BI836880 is currently tested in monotherapy in 2 phase I trials. 29 and 24 patients received BI836880 in trial 1336.1 (every 3 week schedule) and in trial 1336.6 (weekly schedule), respectively. Dose levels between 40 mg and 1000 mg of BI 836880 were tested in the every 3 week trial. Most commonly reported adverse events are hypertension, asthenia, nausea, vomiting, diarrhea and constipation. 5 DLTs were reported among the two studies (pulmonary embolism, proteinuria, hypertension, respiratory distress). Other relevant adverse events (mode of action related) include, peripheral edema, bleeding (epistaxis), and proteinuria. Based on safety data as well as PK and PD analysis, the dose of 720 mg is selected as recommended phase 2 dose (RP2D). This dose will be the highest dose that can be tested in combination with BI 754091. The dose below this dose tested in monotherapy trial (360 mg) is safe and showed complete inhibition of systemic targets, and will used as starting dose for the combination with BI 754091. However because of the important safety difference between 360 and 720 mg (mainly occurrence and severity of hypertension), a BI 836880 intermediate dose of 500 mg will be tested. The highest tested dose levels will be expanded before selection of BI 836880 dose to be used for Part 2 of the trial.
Section to be changed		4.1.2.2 Part 2
Description of change		Change from: Once the 2 highest tested doses are completed and at least 9 patients received at least 1 cycle at each dose level, an interim safety, PK and PD analysis of all patients treated in Part 1 will be performed. Based on all this data, the SMC will select BI 836880 dose (RP2D) to be used in combination with BI 754091 for Part 2 of the trial. To: Once at least 6 patients have received at least 1 cycle at the maximum dose level, a safety evaluation of all patients treated in Part 1 will be performed. Based on all this safety data, the SMC may approve the

		selected BI 836880 dose (RP2D) to be used in combination with BI 754091 for Part 2 of the trial. This data will be supported with the PK and PD analysis of at least 3 patients in each dose cohort.
Rationale for change		Adaption because of new available data, SMC agreed
Rationale for change		New available Information
Section to be changed		4.1.4
Description of change		Changed from: … In case no relevant infusion reactions are observed, this can be shorten to about 30 minutes but should not be prolonged to more than 6 hours for BI 836880 and should not be prolonged to more than 2 hours for BI 754091, also in case of technical issues. To: In case no relevant infusion reactions are observed, this can be shorten to about 30 minutes for BI836880 only but should not be prolonged to more than 6 hours for BI 836880 and should not be prolonged to more than 2 hours for BI 754091, also in case of technical issues.
Rationale for change		Clarification
Section to be changed		4.1.4 Re-treatment criteria
Description of change		Changed from: • QTcF <=480 ms (according to Exclusion-Criterion #8) To: • In the Part 1: QTcF <=480 ms (according to Exclusion-Criterion #8)
Rationale for change		Clarification for Part 1
Section to be changed		4.1.4 Dose reduction guidelines
Description of change		Changed from: Administration of trial drugs has to be stopped temporarily in case of a DLT (see Section 5.2.6.1). Patients may continue therapy only after recovery from DLT to at least fulfil retreatment criteria. The future dose of BI 836880 must be a tested dose which is one dose level below the dose received by the patient (Table 4.1.4: 1 below) Treatment has to be discontinued in case the DLT is not reversible.

Table 4.1.4: 1 Dose reduction recommendations for BI 836880

BI 836880 received dose	BI 836880 reduced dose
720 mg	500 mg
500 mg	360 mg
360 mg	Stop BI 836880

In case of AEs (DLTs) that can be definitely characterized as BI 754091 related, dose can be reduced.

Table 4.1.4: 2 Dose reduction recommendations for BI 754091

BI 754091 received dose	BI 754091 reduced dose
240 mg	80 mg

For each drug, only one dose reduction will be allowed per patient.

To:
Part 1:
Administration of trial drugs has to be stopped temporarily in case of a DLT (see Section 5.2.6.1). Patients may continue therapy only after recovery from DLT to at least fulfil retreatment criteria. The future dose of BI 836880 must be a tested dose which is one dose level below the dose received by the patient (Table 4.1.4: 1 and 4.1.4: 2 below) Treatment has to be discontinued in case the DLT is not reversible.

Table 4.1.4: 1 Dose reduction recommendations for BI 836880 in Part 1

BI 836880 received dose	BI 836880 reduced dose
720 mg	500 mg
500 mg	360 mg
360 mg	Stop BI 836880

In case of AEs (DLTs) that can be definitely characterized as BI 754091 related, dose can be reduced.

		Table 4.1.4: 2 Dose reduction recommendations for BI 754091 in Part 1 | BI 754091 received dose | BI 754091 reduced dose | | --- | --- | | 240 mg | 80 mg | For each drug, only one dose reduction will be allowed per patient. Part 2: In the dose expansion study, dose reductions or escalations of BI 836880 or BI 754091 in any patient **is not** allowed. The dose may be delayed for up to 6 weeks because of AEs, following discussion with the sponsor. During combination therapy, if treatment is held or discontinued due to an AE(s), both BI 836880 and BI 754091 will be held or discontinued together. If treatment is to be restarted after resolution (≤ Grade 1 or baseline) of the AE, both BI 836880 and BI 754091 must be started together.
Rationale for change		Clarification regarding the Part 2 procedure
Section to be changed		4.2.2.1
Description of change		Changed from: Previous anti-cancer therapy must have been discontinued before first administration of trial drug and the patient must have recovered from all clinically relevant reversible toxicities (see Exclusion Criteria Section 3.3.3 for further details). Concomitant anti-cancer therapy is not allowed. Radiotherapy for local symptom control of non-target lesions can be allowed after consulting the investigator and sponsor. To: • Previous anti-cancer therapy must have been discontinued before first administration of trial drug and the patient must have recovered from all clinically relevant reversible toxicities (see Exclusion Criteria Section 3.3.3 for further details). • Concomitant anti-cancer therapy is not allowed. Radiotherapy for local symptom control of non-target lesions can be allowed after consulting the investigator and sponsor.

		• Immunosuppressive medications including, but not limited to systemic corticosteroids at doses exceeding 10 mg/day of prednisone or equivalent, methotrexate, azathioprine, and tumour necrosis factor-alpha blockers are prohibited. Use of immunosuppressive medications for the management of investigational product-related AEs or in patients with contrast allergies is acceptable, and does not necessarily warrant immediate treatment discontinuation. In addition, use of inhaled, topical, intranasal corticosteroids or local steroid injections (e.g., intra-articular injection) is permitted. Temporary uses of corticosteroids for concurrent illnesses (e.g., food allergies, computed tomography (CT) scan contrast hypersensitivity) are acceptable upon discussion with the Medical Monitor. • Live attenuated vaccines are prohibited during the trial through 30 days after the last dose of investigational product. Herbal preparations/medications are not allowed throughout the trial unless agreed to by the Principal Investigator. These herbal medications include, but are not limited to: St. John's wort, kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, and ginseng. If instructed by the Principal Investigator, patients should stop using these herbal medications 7 days prior to first dose of study treatment.
Rationale for change		Clarification to the restrictions
Section to be changed		4.2.2.3
Description of change		Added info: Due to the advanced stage of disease of Phase I trial patient populations and the high medical need, females of childbearing potential can be included in this trial provided that they agree to use a highly-effective contraception method. These are methods of birth control per the International Committee on Harmonisation (ICH) M3 (R2) that result in a low failure rate of less than 1% per year when used consistently and correctly. Highly-effective methods of contraception include: • Oral, injected, or implanted hormonal methods of contraception, or • Intrauterine device or intrauterine system, or • 'Double-barrier' methods of contraception: Male condom in combination with female diaphragm/cervical cap plus spermicidal foam/gel/film/cream. Details of these contraception methods are described in the patient information in the ICF.

		Women of childbearing potential must follow these methods during the trial and for at least 6 months after the end of the trial treatment. Although use of a contraceptive pill is considered a highly-effective method of birth control, women of childbearing potential taking a contraceptive pill must use an additional barrier method for the entire duration of the trial treatment intake and for 6 months after the end of the trial treatment intake. Male patients with partners of childbearing potential must agree to use condoms and ensure their partner is using an additional highly-effective method of birth control, during the trial and until at least 6 months after the end of the trial treatment.
Rationale for change		More details regarding restrictions for women of childbearing potential
Section to be changed		5.1
Description of change		Changed from: … Efficacy endpoints will be assessed every 6 weeks at time points specified in the FC. An additional evaluation at EoT is only applicable; when patient has no PD documented, will not continue with regular imaging in Follow-up period and did not have imaging within the last 4 weeks before EoT. At EoR visit, in case a patient has discontinued due to PD by RECIST 1.1, one additional tumour assessment should be done. To: Efficacy endpoints will be assessed every 2 cycles (6 weeks) as specified in the FC. An additional evaluation at EoT is only applicable; when patient has no PD documented, will not continue with regular imaging in Follow-up period and did not have imaging within the last 4 weeks before EoT. At EoR visit, in case a patient has discontinued due to PD by RECIST 1.1, one additional tumor assessment should be done in case no other cancer treatment has been initiated.
Rationale for change		Clarification of wording.
Section to be changed		5.2.2
Description of change		Changed from: **Blood pressure** Systolic and diastolic blood pressure as well as pulse rate (electronically or by palpation, count for 1 minute) will be measured after 5 minutes of rest in the seated position. The blood pressure measurement should be performed three times at each time point and the values of these measurements will be entered in the eCRF. Further details on the procedure for blood pressure measurements are given in Appendix 10.2.

		To: **Blood pressure** Systolic and diastolic blood pressure as well as pulse rate (electronically or by palpation, count for 1 minute) will be measured after 5 minutes of rest in the seated position. In Part 1, the blood pressure measurement should be performed three times at each time point and the values of these measurements will be entered in the eCRF. In Part 2, only a single blood pressure measurement is required at each time point.
Rationale for change		Adaptions regarding needed information for Part 2
Section to be changed		5.2.4
Description of change		Changed from: • At days of administration two time points will be evaluated: 1. pre-dose (-60 min. to -5 min.), 2. shortly before the end of the infusion of trial medication. To: • <u>For the part 1:</u> 1. pre-dose (-60 min. to -5 min.) 2. shortly before the end of the infusion of trial medication For the part 2: 1. 1st cycle pre and post treatment. Cycle 2,3 and 4 only one ECG pre treatment and then on ECG at pre treatment performed every second cycle (cycle 6,8, 10…etc) 2. shortly before the end of the infusion of trial medication (only at cycle 1).
Rationale for change		Adaption to the new requirements
Section to be changed		5.2.6.1:11 Dose Limiting Toxicities (according to CTCAE V5.0) (cont'd)
Description of change		Changed from: • any grade ≥ 2 pneumonitis of any duration To: • Grade ≥ 2 pneumonitis of any duration Info added: ○ Grade 3 nausea or Grade 3 vomiting will be defined as DLT when it persists at Grade 3 longer than 48 hours despite adequate medical intervention.

Rationale for change		Clarifications to DLTs
Section to be changed		5.2.7.1
Description of change		Changed from: Immune-related AEs are AEs associated with immunotherapy treatments that appear to be associated with the immune therapy's mechanism of action. These adverse reactions, which can be severe, may involve the gastrointestinal, skin, liver, endocrine, respiratory, renal, or other organ systems. The sponsor has defined a list of potential irAEs (Appendix 10.3). These irAEs must be reported as AESIs. If an Investigator determines another event (not on the list) should be a potential irAE, the Investigator may also report that event as an AESI. To: Immune-related adverse events (irAE) Immune-related AEs are AEs associated with immunotherapy treatments that appear to be associated with the immune therapy's mechanism of action. These adverse reactions, which can be severe, may involve the gastrointestinal, skin, liver, endocrine, respiratory, renal, or other organ systems. Although all irAEs are to be reported as AEs, only clinically important irAEs need to be reported as AESIs as defined by the sponsor in Appendix 10.3. If an Investigator determines that a Grade 3 adverse event that is not included in Appendix 10.3 is an irAE, that event should also be reported as an AESI.
Rationale for change		Clarification to Immune related events
Section to be changed		5.3.1.
Description of change		Changed from: Pharmacokinetic profiles of BI 836880 and BI 754091 in plasma will be investigated after the first and after the fourth infusion cycle. Standard plasma PK parameters as specified in Section 2.1.3 will be calculated. To: Pharmacokinetic profiles of BI 836880 and BI 754091 in plasma will be investigated within this trial. Standard plasma PK parameters as specified in Section 2.1.3 will be calculated.
Rationale for change		Clarification Pharmacokinetic profiles

Section to be changed		5.4
Description of change		• Changed from: • Determination of myeloid-derived suppressor cells (MDSCs), PD1+ and LAG3+ T-cells, PD-L1+ monocytes, as well as activated T-effector memory cells and activated dendritic cells in blood (PBMCs; see Section 5.4.2.1) • Mechanism-related cytokines (e.g. ANG2, VEGF; IL-2, IFN-γ), as well as exploratory immune-related cytokines in blood (cytokines; see Section 5.4.2.2) • The ratio of kynurenine: tryptophan will be determined in blood (KYN:TRP; section see Section 5.4.2.2) • PD-L1, PD-1, CD-8 positive cells in tumour biopsies taken baseline and on treatment (dose escalation Part 1 only) (other markers may be added if scientific rationale arises; see Section 5.4.2.3). To: Determination of myeloid derived suppressor cells (MDSCs), PD1+ and LAG3+ T-cells, PD-L1+monocytes, as well as regulatory T cells and activated T-effector memory and potentially PBMC subsets in blood (PBMCs; see Section 5.4.2.1) • Mechanism-related cytokines (e.g. ANG2, VEGF; IL-2, IFN-γ), as well as exploratory immune-related cytokines in blood (cytokines; see Section 5.4.2.2) . For the HCC cohort, AFP will also be measured as a marker for disease severity. • The ratio of kynurenine: tryptophan will be determined in blood (KYN:TRP; section see Section 5.4.2.2) • PD-L1, PD-1, CD-8 positive cells in tumour biopsies taken at baseline and on treatment (dose escalation Part 1 and cohorts E & F Part 2) (other markers may be added if scientific rationale arises; see Section 5.4.2.3).
Rationale for change		Adaption to the new requirements
Section to be changed		5.4.1.

Description of change		Change from: The following tumour biopsies will be mandatory for **all patients in Part 1** (if possible from the same lesion): - the equivalent of 2 fine needle biopsies freshly taken during screening after IC signed and before first trial medication administration. - the equivalent of 2 fine needle biopsies on treatment before start of Cycle 3 (6 weeks after treatment start). The following tumour biopsies **in Part 2,** will be: - **Mandatory**: A minimum of 2 fine needle biopsies should be freshly taken during screening after IC signed and before first trial medication administration. In case a fresh baseline biopsy cannot be obtained (e.g. inaccessible lesions or patient safety concern), the equivalent of 2 archival fine needle biopsies, or 22 archival 4 µm sections from an archival block, if taken within 6 months of trial start with no intermediate therapy, have to be provided. - **Optional**: The equivalent of 2 fine needle biopsies on treatment before start of Cycle 3. To: The following tumour biopsies will be mandatory for **all patients in Part 1** (if possible from the same lesion): - the equivalent of two 14-16G needle biopsies freshly taken during screening after IC signed and before first trial medication administration. - the equivalent of two 14-16G fine needle biopsies on treatment before start of Cycle 3 (6 weeks after treatment start). The following tumour biopsies **in Part 2,** will be: - **Mandatory**: A minimum of two 14-16G fine needle biopsies should be freshly taken during screening after IC signed and before first trial medication administration. In case a fresh baseline biopsy cannot be obtained (e.g. inaccessible lesions or patient safety concern), the equivalent of 2 archival 14-16G needle biopsies, or 26 archival 4 µm sections from an archival block, if taken within 6 months of trial start with no intermediate therapy, have to be provided (except for cohort D). For cohorts E and, F, a fresh on-treatment biopsy is mandatory at C3D1, if possible from the same lesion as the pre-treatment biopsy.

		- **Optional**: The equivalent of two 14 -16 G needle biopsies on treatment before start of Cycle 3 for cohorts A-C.
Rationale for change		Adaption to the new requirements
Section to be changed		[redacted]
Description of change		
Rationale for change		
Section to be changed		
Description of change		
Rationale for change		
Section to be changed		
Description of change		

		[redacted]
Rationale for change		
Section to be changed		
Description of change		
Section to be changed		6.1
Rationale for change		Added: During the treatment phase, after administration of BI 836880 and BI 754091, patients are required to be hospitalized (refers only to Part 1, see Section 1.4) under close surveillance with access to intensive care for at least 48 hours after administration of trial medication to allow close monitoring for infusion-related reactions or other adverse events and availability of patients for PK visits
Description of change		Clarification to Part 2 procedure
Rationale for change		Adaption to the new requirements
Section to be changed		6.2.2
Description of change		Changed from: During cycle 1 and 4 intensive PK-sampling will be conducted and patients have to be observed closely for any adverse events. Therefore patients have to come to the clinic during the first four cycles every week to the clinic. Additional visits are needed at day 2 for cycles 1, 2 and 4 and at day 3 for cycle 1. In cycles 5 and 6 the patient is requested to come to the clinic on day 8 after administration of study drug. From cycle 7 onwards no additional visits, beside day 1 including drug administration, are requested by protocol. Disease response assessment by CT/MRI will be performed at the end of every other cycle (CT to be performed every 6 weeks starting from first trial medication administration). Follow up period and trial completion

		To: During cycle 1 (for Part 1 and 2) and 4 (only for Part 1) intensive PK-sampling will be conducted and patients have to be observed closely for any adverse events. Therefore patients have to come to the clinic during the first four cycles every week to the clinic. In Part 1 additional visits are needed at day 2 for cycles 1, 2 and 4 and at day 3 for cycle 1. In cycles 5 and 6 the patient is requested to come to the clinic on day 8 after administration of study drug. From cycle 7 onwards no additional visits, beside day 1 including drug administration, are requested by protocol. In For Part 2 tumour assessment should be done every 6 weeks (in accordance to local requirements). Assessments are always done prior to the start of the new treatment cycle. At EOT and EOR only when applicable (see section 5.1) For Part 1 disease response assessment by CT/MRI will be performed at the end of every other cycle (CT to be performed every 6 weeks starting from first trial medication administration). Follow up period and trial completion. For Part 2 tumour assessment should be done every 6 weeks (in accordance to local requirements). Assessments are always done prior to the start of the new treatment cycle. At EOT and EOR only when applicable (see section 5.1)
Rationale for change		Adaption to the new requirements
Section to be changed		7.1
Description of change		Changed from: This is Phase I, open-label, dose-escalating trial to determine the Recommended Phase 2 Dose (RP2D) of BI 836880 in combination with BI 754091 in patients with locally advanced or metastatic non-squamous NSCLC who progressed during or after first line platinum-based treatment. In addition, the safety and efficacy of BI836880 combination with BI 754091 will be assessed. To: This is Phase I, open-label, dose-escalating trial to determine the Recommended Phase 2. Dose (RP2D) of BI 836880 in combination with BI 754091 in patients with locally advanced or metastatic non-squamous NSCLC during or after first line platinum-based chemotherapy or CPI monotherapy treatment or the combination of CPI and chemotherapy.
Rationale for change		Clarification to the wording

Section to be changed		7.1.2
Description of change		Changed from: Part 2 of the trial will be designed as Open label, non-randomized expansion phase to assess efficacy and safety of BI 836880 in combination with BI 754091 in patients with locally advanced or metastatic non-squamous PD-L1 high and PD-L1 low, check point inhibitor naive NSCLC. The analyses of the safety and efficacy for this portion of the trial will be descriptive and exploratory in nature. To: To effectively use the information from these patients' cohorts in the assessment of the efficacy, a Bayesian hierarchical model (BHM) approach (R13-4803), which assumes full exchangeability of model parameters and allows borrowing information across patients' cohorts, will be used to analyse the response rate endpoints. The BHM has 2 main components: a data model and a parameter model, as well as priors for the parameter model. The data model is a binomial sampling model $r_j \mid n_j \sim \text{Binomial}\left(n_j, p_j\right), j = 1, 2, 3, \ldots$ where n_j and r_j are the number of patients and the corresponding number of patients with response in each patient cohort. The parameter model for the log-odds parameters, including an adjustment for the target rates $\theta_j = log\left(\frac{p_j}{1-p_j}\right) - log\left(\frac{\tilde{p}_j}{1-\tilde{p}_j}\right)$ is specified as $\theta_j \mid \mu, \tau \sim N(\mu, \tau^2), j = 1, 2, 3, \ldots$ where $\tilde{p}_j$ is the target response rate, μ denotes the "overall" mean of θ_j and τ determines the inter-cohort heterogeneity. **Prior distribution** A non-informative normal distribution with mean 0 and standard deviation of 2 is specified for the mean μ. For the inter-cohort heterogeneity parameter τ, a half normal distribution with parameter 1 is used which is a very conservative assumption regarding between-cohort variability and hence leads to only little borrowing of data across patient cohorts because there is little prior information on the strength of the correlation between the treatment effects across cohorts
Rationale for change		Adaption to the new requirements

Section to be changed		7.3.1.1 and 7.3.1.2
Description of change		Change from: 7.3.1.1 Primary endpoint analyses for Part 1 In order to identify the MTD(s) and the recommended dose(s) for Part 2 of the trial, the number of patients with DLTs at each dose combination during the Part 1 MTD evaluation period (the first cycle of the BI 836880 plus BI 754091 combination) must be presented by descriptive statistics. Patients who discontinue during the first treatment cycle for reasons other than a DLT will be excluded from the determination of the MTD. In addition, the number of patients with DLTs that occurred during the entire treatment period, including Part 1 and Part 2, will be summarised at each dose level. The BLRM will be rerun to re-evaluate the MTD and RPIID together with all relevant data collected during Part 2. To: 7.3.1.1 Primary endpoint analyses for Part 1 In order to identify the MTD(s) and the recommended dose(s) for Part 2 of the trial, the number of patients with DLTs at each dose combination during the Part 1 MTD evaluation period (the first cycle of the BI 836880 plus BI 754091 combination) must be presented by descriptive statistics. Patients who discontinue during the first treatment cycle for reasons other than a DLT will be excluded from the determination of the MTD. In addition, the number of patients with DLTs that occurred during the entire treatment period will be summarised at each dose level. The BLRM will be rerun to re-evaluate the MTD and RP2D together with all relevant data collected during Part 2. 7.3.1.2 Primary endpoint analyses for Part 2 The primary endpoint for Part 2 of the trial is OR defined by confirmed CR or PR according to RECIST 1.1 as assessed by the Investigator. Overall response will be analyzed in terms of OR rate (ORR), defined as the proportion of patients with best overall response of CR or PR determined and confirmed by RECIST 1.1.
Section to be changed		7.3.1.2 Primary endpoint analyses for Part 2
Description of change		Change from: The primary endpoint for Part 2 of the trial is OR defined by confirmed CR or PR according to RECIST 1.1 as assessed by the Investigator. Overall response will be analyzed in terms OR rate (ORR), defined as the proportion of patients with best overall response of CR or PR determined and confirmed by RECIST 1.1.

		To: The primary endpoint for Part 2 of the trial is OR defined by confirmed CR or PR according to RECIST 1.1 as assessed by the Investigator. Overall response will be analyzed in terms of the shrinkage estimator of the OR rate (ORR) based on BHM.
Rationale for change		New information regarding Part 2
Rationale for change		Clarification for Part 1 and new information regarding Part 2
Section to be changed		7.3.2.1
Description of change		[redacted]
Rationale for change		Adaption to the new requirements
Section to be changed		7.4
Description of change		Changed from: Interim safety evaluations will be performed as considered necessary. The dose-escalation design dictates that the sponsor and the SMC perform regular safety evaluations. Safety evaluations will be performed after each dose cohort by the SMC. The SMC will recommend the next dose level as well as the corresponding cohort size. SMC will recommend the RP2D that will be used in Part 2. SMC meeting minutes and outputs provided for these SMC meetings will be documented and archived. Exploratory analyses of PK/PD may be performed at the end of Part 1 and additionally if considered informative for the study. To: **Part 1** Interim safety evaluations will be performed as considered necessary. The dose-escalation design dictates that the sponsor and the SMC perform regular safety evaluations. Safety evaluations will be performed after each dose cohort by the SMC. The SMC will recommend the next dose level as well as the corresponding cohort size. SMC will recommend the RP2D that

		will be used in Part 2. SMC meeting minutes and outputs provided for these SMC meetings will be documented and archived. Exploratory analyses of PK/PD may be performed at the end of Part 1 and additionally if considered informative for the study. **Part 2:** In Part 2 we are randomizing 200 patients. 40 patients for the each of the cohorts A and B, and 30 patient for each of the cohorts C, D, E and F. An interim futility analysis will be performed for cohort C, D, E and F in Part 2. Until any decision from the futility analysis is done, the enrolment of next patient will not be stopped. The two-stage design is planned to stop further recruitment of patient if the defined efficacy boundary (see Table 7.7.2: 1) is not met at the first stage. The interim analyses for each cohort will be conducted after 15th patients in that cohort have completed their two on-treatment imaging assessment (i.e. end of cycle 4). In addition, if considered necessary interim analysis may be performed for evaluation of the efficacy and safety aspects as each cohort is finished
Rationale for change		Adaption to the new requirements
Section to be changed		7.7.1
Description of change		Change from: For Part 1, no formal statistical power calculations of sample size were performed. Approximately 20-25 patients will be expected for the dose finding part and confirmation of RP2D. Fewer patients might be needed based on the recommendation of the SMC and the actual number of cohorts tested. To: For Part 1, no formal statistical power calculations of sample size were performed. Approximately 12-18 patients will be expected for the dose finding part and confirmation of RP2D. Fewer patients might be needed based on the recommendation of the SMC and the actual number of cohorts tested.
Rationale for change		Adaption to the new requirements
Section to be changed		7.7.2

Description of change		Changed from: For Part 2, it is assumed that BI 836880 in combination with BI 754091 will have an ORR of at least 30% in patients with locally advanced or metastatic non-squamous NSCLS with low PD-L1 expression. For a cohort with 30 evaluable patients, an ORR of greater than 25% would be observed with a probability of approximately 72% assuming a true response rate of 30%. The probability of observing a false positive signal, i.e., to observe an ORR of more than 25% if the underlying true ORR is 10%, is around 1%. In patients with high PD-L1 expression, it is assumed that BI 836880 in combination with BI 754091 will have an ORR of at least 50%. For a cohort with 30 evaluable patients, an ORR of greater than 45% would be observed with a probability of approximately 71% assuming a true response rate of 50%. The probability of observing a false positive signal, i.e., to observe an ORR of greater than 45% if the underlying true ORR is 30%, is around 4%. Table 7.7.2: 1 summarizes the probability of observing certain ORRs based on different assumption of the underlying ORR. Table 7.7.2: 1 Probabilities of observing certain objective response rates *Table not shown because of format reasons* To: For Part 2, below cohorts are assume: • Cohort A: patients with locally advanced or metastatic non-squamous Non-Small Cell Lung Cancer with CPI monotherapy • Cohort B: patients with locally advanced or metastatic non-squamous Non-Small Cell Lung Cancer pre-treated with a combination of platinum-based chemotherapy and checkpoint inhibitor • Cohort C: patients with locally advanced or metastatic Small Cell Lung Cancer, with no more than one line of chemotherapy • Cohort D: patients with histologically confirmed recurrent glioblastoma (primary), with no more than one line of chemotherapy (concurrent and adjuvant temozolomide based chemotherapy) • Cohort E: patients with histologically confirmed, unresectable, Stage IV metastatic melanoma, with least one line of any kind of immune therapy • Cohort F: patients with locally advanced or metastatic and/or unresectable Hepatocellular Carcinoma (HCC) who were intolerant or progressed during 1st line sorafenib or lenvatinib treatment; subsequent CPI therapy is allowed as the most recent anticancer treatment. A total of approximate 200 patients will be enrolled for these 6 cohorts. 40 patients each are planned for cohort A and B and 30 patients each are planned for cohort C to F.

For cohorts A, B, and E (MLN), there is no literature available for the target patients. As there are no treatments of proven efficacy for this population, it is assumed around 5% ORR with background therapy. The futility boundary for cohort E is set as 7% at planned interim futility analysis timing. The early stopping probabilities are shown in Table 7.7.2: 1.

For cohort C (SCLC), around 20% ORR with anti-PD-1 antibody monotherapy is assumed. In Checkmate-032 (R19-1713) which is an open label phase I/II trial of Nivolumab in pateints with SCLC who experienced disease progression after platinum-based chemotherapy, the ORR was 12% [95%CI, 6.5-19.5] (N=109). In KEYNOTE-158 (R19-1713), which is a phase II basket study of Pembrolizumab, patient with advanced SCLC had an ORR of 18.7% [95%CI, 11.8-27.4] (N=107). In KEYNOTE-028 (R19-1713), which is a phase Ib basket trial, patients with extensive-stage SCLC showed an ORR of 33% [95%CI, 16-55] (N=24). Based on above result, the futility boundary for cohort C is set as 20% at planned interim futility analysis timing.

For cohort D (GBM), around 25% ORR with Bevacizumab is assumed. In AVF3708 (R11-2708), which is an open-label study in patients with glioblastoma who had progressed following initial treatment with temozolomide and radiation, the ORR was 28% [95%CI, 19-40] (N=85). Based on above results, the futility boundary for cohort D is set as 25% at planned interim futility analysis timing.

For cohort F (HCC), around 15% ORR with anti-PD-1 antibody monotherapy is assumed. In Checkmate-040 (R17-3829) which is an open label phase I/II trial of Nivolumab in patients with advanced hepatocellular carcinoma, the ORR was 20% [95%CI, 15-26] (N=50) in dose expansion phase and 15% [95% CI, 6-28] (N=10) in the dose escalation phase. In KEYNOTE-224 (R19-0168) which is a phase 2 study of Pembrolizumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib , the ORR was 17% [95% CI, 11-26] (N=104). Based on above result, the futility boundary for cohort F is set as 15% at planned interim futility analysis timing.

Different homogeneous scenarios and heterogeneous scenarios as well as different sample sizes are considered in the simulations to assess the frequentist operating characteristics of the BHM approach. The simulation results as shown in Table 7.7.2: 2 below show that, with the proposed cohort size, the BHM approach has reasonable probability of reaching the pre-specified response rate under a wide range of scenarios.

		Table 7.7.2: 1 Early stopping probabilities at interim based on observed ORR under different scenarios Table 7.7.2: 2 Operating characteristics of the Bayesian Hierarchical Modelling approach for final analysis under different scenarios with interim analysis based on observed ORR *Tables not shown because of format reasons*
Rationale for change		Adaption to the new requirements
Section to be changed		9.2
Description of change		Added information c23621412-01 [redacted] A First in human Phase I, non-ramdomized, open label multi-center dose escalation trial of BI 836880 administered by repeated intravenous infusions in patietns with solid tumors. 1336.1 30 April 2019
Rationale for change		New available information
Section to be changed		9.1.
Description of change		Added information: R11-2708 Friedman HS, Prados MD, Wen PY, Mikkelsen T, Schiff D, Abrey LE, Yung WKA, Paleologos N, Nicholas MK, Jensen R, Vredenburgh J, Huang J, Zheng M, Cloughesy T. Bevacizumab alone and in combination with irinotecan in recurrent glioblastoma. J Clin Oncol 27 (28), 4733 - 4740 (2009) R12-0948 Llovet JM, Pena CEA, Lathia CD, Shan M, Meinhardt G, Bruix J, SHARP Investigators Study Group. Plasma biomarkers as predictors of outcome in patients with advanced hepatocellular carcinoma. Clin Cancer Res, (2012) R17-3829 El-Khoueiry AB, Sangro B, Yau T, Crocenzi TS, Kudo M, Hsu C, et al Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial. Lancet 389, 2492 - 2502 (2017)

<table>
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<tr><td>R19-0168</td><td>Zhu AX, Finn RS, Edeline J, Cattan S, Ogasawara S, Palmer D, et al, KEYNOTE-224 Investigators
Pembrolizumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib (KEYNOTE-224): a non-randomised, open-label phase 2 trial.
Lancet Oncol 19, 940 - 952 (2018)</td></tr>
<tr><td>R19-1712</td><td>Wu X, Giobbie-Hurder A, Liao X, Connelly C, Connolly EM, Li J, et al. Angiopoietin-2 as a biomarker and target for immune checkpoint therapy. Cancer Immunol Res 5 (1), 17 - 28 (2016)</td></tr>
<tr><td>R19-1713</td><td>Ready N, Farago AF, Braud F de, Atmaca A, Hellmann MD, Schneider JG, et al. Third-line nivolumab monotherapy in recurrent SCLC: CheckMate 032. J Thorac Oncol 14 (2), 237 - 244 (2019)</td></tr>
<tr><td>R19-1714</td><td>Horn L, Mansfield AS, Szczesna A, Havel L, Krakowski M, Hochmair MJ, et al, IMpower133 Study Group. First-line atezolizumab plus chemotherapy in extensive-stage small-cell lung cancer. N Engl J Med 379 (23), 2220 - 2229 (2018)</td></tr>
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<tr><td>Rationale for change</td><td></td><td>New available information</td></tr>
<tr><td>Section to be changed</td><td></td><td>10.3 IMMUNE-RELATED ADVERSE EVENTS OF SPECIAL INTEREST</td></tr>
<tr><td>Description of change</td><td></td><td>New added table:
Table 10.3: 1 irAEs which must be reported as AESIs.
<table>
<tr><td>Immune-related adverse events of special interest</td></tr>
<tr><td>Pneumonitis (reported as an AESI if ≥ Grade 2)</td></tr>
<tr><td>• Acute interstitial pneumonitis
• Interstitial lung disease
• Pneumonitis</td></tr>
<tr><td>Colitis (reported as an AESI if ≥ Grade 2 or any grade resulting in dose modification or use of systemic steroids to treat the AE)</td></tr>
<tr><td>• Intestinal obstruction
• Colitis
• Colitis microscopic
• Enterocolitis
• Enterocolitis haemorrhagic
• Gastrointestinal perforation
• Necrotizing colitis
• Diarrhea</td></tr>
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Endocrine (reported as an AESI if ≥ Grade 3 or ≥ Grade 2 and resulting in dose modification or use of systemic steroids to treat the AE)
• Adrenal insufficiency • Hyperthyroidism • Hypophysitis • Hypopituitarism • Hypothyroidism • Thyroid disorder • Thyroiditis • Hyperglycaemia, if ≥ Grade 3 and associated with ketosis or metabolic acidosis
Endocrine (reported as an AESI)
• Type 1 diabetes mellitus (if new onset)
Hematologic (reported as an AESI if ≥ Grade 3 or any grade resulting in dose modification or use of systemic steroids to treat the AE)
• Autoimmune haemolytic anaemia • Aplastic anaemia • Thrombotic thrombocytopenic purpura • Idiopathic (or immune) thrombocytopenia purpura • Disseminated intravascular coagulation • Haemolytic-uraemic syndrome • Any Grade 4 anaemia regardless of underlying mechanism
Hepatic (reported as an AESI if ≥ Grade 2, or any grade resulting in dose modification or use of systemic steroids to treat the AE**)**
• Hepatitis • Autoimmune hepatitis • Transaminase elevations (ALT and/or AST)
Infusion Reactions (reported as an AESI)
• Allergic reaction • Anaphylaxis • Cytokine release syndrome • Serum sickness • Infusion reactions • Infusion-like reactions

		Neurologic (reported as an AESI) • Autoimmune neuropathy • Guillain-Barre syndrome • Demyelinating polyneuropathy • Myasthenic syndrome **Ocular (report as an AESI if ≥ Grade 2 or any grade resulting in dose modification or use of systemic steroids to treat the AE)** • Uveitis • Iritis **Renal (reported as an AESI if ≥ Grade 2)** • Nephritis • Nephritis autoimmune • Renal failure • Renal failure acute • Creatinine elevations (report as an irAE if ≥Grade 3 or any grade resulting in dose modification or use of systemic steroids to treat the AE) **Skin (reported as an AESI)** • Dermatitis exfoliative • Erythema multiforme • Stevens-Johnson syndrome • Toxic epidermal necrolysis **Skin (reported as an AESI if ≥ Grade 3)** • Pruritus • Rash • Rash generalized • Rash maculopapular • Any rash considered clinically significant in the physician's judgment **Other (reported as an AESI)** • Myocarditis • Pancreatitis • Pericarditis • Any other Grade 3 event that is considered immune-related by the physician
Rationale for change		Clarification to irAEs
Section to be changed		10.5.1

Description of change		Table 10.5.1: 1 info: “for Part 1” added Added: Table 10.5.1: 2 Time schedule for PK blood sampling during treatment cycles for Part 2
Rationale for change		Adaption to the new study requirements

11.4 GLOBAL AMENDMENT 4

Date of amendment		03 Mar 2020
EudraCT number EU number		2017-001378-41
BI Trial number		1336-0011
BI Investigational Product(s)		BI 836880 BI 754091
Title of protocol		An open label phase Ib dose finding study of BI 836880 in combination with BI 754091 to characterize safety, tolerability, pharmacokinetics, pharmacodynamics and efficacy in patients with locally advanced or metastatic non-squamous Non-Small Cell Lung Cancer and in other solid tumors
Global Amendment due to urgent safety reasons		☐
Global Amendment		☒
Section to be changed		Synopsis – Study Design
Description of change		Change from: This is a Phase Ib study, containing two parts; Part 1 (dose escalation of BI 836880 in combination with BI 754091) and Part 2 (expansion phase in 6 cohorts). **Part 1**: Dose escalation of BI 836880 in combination with BI 754091 in check point inhibitor naïve or previously treated patients with locally advanced or metastatic non-squamous NSCLC who progressed during or after completion of at least 2 cycles first line (in case of checkpoint inhibitor naïve patients) platinum-based therapy and patients who progressed during or relapsed after completion of at least 2 cycles (in case of checkpoint inhibitor relapsing patients) of platinum-based chemotherapy and a checkpoint inhibitor treatment (monotherapy or in combination with chemotherapy). **Part 2**: Open label, non-randomized expansion phase to assess efficacy and safety of BI 836880 in combination with BI 754091: **Cohort A (NSCLC):** Patient with pathologically confirmed locally advanced or metastatic non-squamous NSCLC who progressed during or after check-point inhibitor monotherapy treatment as the most recent anticancer treatment.

		Cohort B (NSCLC): Patient with pathologically confirmed locally advanced or metastatic non-squamous NSCLC who progressed during or after **platinum-based chemotherapy and a check-point inhibitor (CPI) combination treatment as the** most recent anticancer treatment. **Cohort C (SCLC):** Patient with pathologically confirmed locally advanced or metastatic Small Cell Lung Cancer (SCLC) **who progressed during or after first line** standard chemotherapy regimen. **Cohort D (Glioblastoma):** Patient with histologically confirmed recurrent glioblastoma with **no more than one previous line of chemotherapy** (concurrent and adjuvant temozolomide based chemotherapy including in combination with another investigational agent is considered one line of chemotherapy). **Cohort E (Melanoma):** Patient with histologically confirmed, unresectable, Stage IV metastatic melanoma who progressed during or after CPI based regimen. **Cohort F (Hepatocellular Carcinoma):** Patient with locally advanced or metastatic and/or unresectable Hepatocellular Carcinoma (HCC) who were intolerant or progressed during 1st line sorafenib or lenvatinib treatment; subsequent CPI therapy is allowed as the most recent anticancer treatment. To: This is a Phase Ib study, containing two parts; Part 1 (dose escalation of BI 836880 in combination with BI 754091) and Part 2 (expansion phase in 7 cohorts). **Part 1**: Dose escalation of BI 836880 in combination with BI 754091 in check point inhibitor naïve or previously treated patients with locally advanced or metastatic non-squamous NSCLC who progressed during or after completion of at least 2 cycles first line (in case of checkpoint inhibitor naïve patients) platinum-based therapy and patients who progressed during or relapsed after completion of at least 2 cycles (in case of checkpoint inhibitor relapsing patients) of platinum-based chemotherapy and a checkpoint inhibitor treatment (monotherapy or in combination with chemotherapy).

		Part 2: Open label, non-randomized expansion phase to assess efficacy and safety of BI 836880 in combination with BI 754091: **Cohort A (NSCLC):** Patient with pathologically confirmed locally advanced or metastatic non-squamous NSCLC who progressed during or after **check-point inhibitor monotherapy treatment**. Patient must also have received treatment with a platinum-based chemotherapy regimen and have progressed or be intolerant, or ineligible, as per applicable local practice. **Cohort B (NSCLC):** Patient with pathologically confirmed locally advanced or metastatic non-squamous NSCLC who progressed during or after **platinum-based chemotherapy and a check-point inhibitor (CPI) combination treatment as the** most recent anticancer treatment. **Cohort C (SCLC):** Patient with pathologically confirmed locally advanced or metastatic Small Cell Lung Cancer (SCLC) with documented intolerance to platinum-based chemotherapy or refractory to platinum-based chemotherapy (progression during treatment or during < 90 days of the last dose of platinum-based chemotherapy). Patients who are platinum-sensitive (progression ≥ 90 days of the last dose of platinum-based chemotherapy) must also have received at least one other prior line of platinum-based chemotherapy, if eligible, with or without combination with CPI as per applicable local treatment country guidelines. **Cohort D (Glioblastoma):** Patient with histologically confirmed recurrent glioblastoma with **no more than two previous lines of chemotherapy** (concurrent and adjuvant temozolomide based chemotherapy including in combination with another investigational agent is considered one line of chemotherapy). **Cohort E (Melanoma):** Patient with histologically confirmed, unresectable, Stage IV metastatic melanoma who progressed during or after CPI based regimen. Patients with a BRAF mutation must have received targeted treatment, or were not eligible, with a BRAF and MEK inhibitor as per applicable local country guidelines. **Cohort F (2nd line Hepatocellular Carcinoma):** Patient with locally advanced or metastatic and/or unresectable Hepatocellular Carcinoma (HCC) who were intolerant or progressed during 1st line sorafenib or lenvatinib treatment; subsequent CPI therapy is allowed as the most recent anticancer treatment.

		Cohort G (1st line Hepatocellular Carcinoma): Patient with locally advanced or metastatic and/or unresectable HCC with no prior systemic treatment. This will be implemented only in countries UK, Korea, Taiwan, Hong Kong, Poland, Ukraine, Russia, Spain, USA, Australia
Rationale for change		Wording of local AMs were included, # of cohorts was adapted, information regarding Cohort D – Glioblastoma and additional Cohort G – naïve HCC was added
[redacted]		
Section to be changed		Synopsis - Endpoints
Description of change		Change from: Primary endpoints: **PART 1:** The primary endpoint is the number of patients with dose limiting toxicity (DLT) within the first cycle of treatment (3 weeks). **PART 2:** The primary endpoint is the shrinkage estimator of objective response (OR) based on BHM. OR is defined as best overall response (RECIST1.1) of complete response (CR) or partial response (PR) from first treatment infusion until the earliest of disease progression, death or last evaluable tumour assessment before start of subsequent anti-cancer therapy, lost to follow-up or withdrawal of consent. **Secondary endpoint(s):** **PART 1:** • Adverse events (AEs), drug related AEs, drug related AEs leading to dose reduction or discontinuation during treatment period. **PART 2:**

- Adverse events (AEs), drug related AEs, drug related AEs leading to dose reduction or discontinuation during treatment period
- Disease control (DC), defined as best overall response of CR, PR, or stable disease (SD) (RECIST1.1) from first treatment infusion until the earliest of disease progression, death or last evaluable tumour assessment before start of subsequent anti-cancer therapy, lost to follow-up or withdrawal of consent.
- Duration of objective response (DoR), defined as the time from first documented CR or PR (RECIST1.1) until the earliest of disease progression or death among patients with OR.
- Progression-free survival (PFS) (RECIST1.1), defined as the time from first treatment infusion until disease progression or death from any cause, whichever occurs earlier.
- Tumour shrinkage (in millimeters), defined as the difference between the minimum post-baseline sum of diameters of target lesions (longest for non-nodal lesions, short axis for nodal lesions) and the baseline sum of diameters of the same set of target lesions.
- Pharmacokinetic parameters Cmax, tmax0-504h after the first and fourth infusion cycle.

To:
Primary endpoints:

PART 1:

The primary endpoint is the number of patients with dose limiting toxicity (DLT) within the first cycle of treatment (3 weeks).

PART 2:

The primary endpoint is the shrinkage estimator of objective response (OR) based on BHM. OR is defined as best overall response (RECIST1.1) of complete response (CR) or partial response (PR) from first treatment infusion until the earliest of disease progression, death or last evaluable tumor assessment before start of subsequent anti-cancer therapy, lost to follow-up or withdrawal of consent. In case of recurrent glioblastoma (GBM) assessment will be based on RANO (Response Assessment in Neuro-Oncology) criteria.

Secondary endpoint(s):

		PART 1: • Adverse events (AEs), drug related AEs, drug related AEs leading to dose reduction or discontinuation during treatment period. • Pharmacokinetic parameters C_{max}, t_{max}, AUC_{0-504h} after the first infusion cycle. **PART 2:** • Adverse events (AEs), drug related AEs, drug related AEs leading to dose reduction or discontinuation during treatment period • Disease control (DC), defined as best overall response of CR, PR, or stable disease (SD) (RANO for GBM & RECIST1.1 for all other cohorts) from first treatment infusion until the earliest of disease progression, death or last evaluable tumor assessment before start of subsequent anti-cancer therapy, lost to follow-up or withdrawal of consent. • Duration of objective response (DoR), defined as the time from first documented CR or PR (RANO for GBM & RECIST1.1 for all other cohorts) until the earliest of disease progression or death among patients with OR. • Progression-free survival (PFS) (RANO for GBM & RECIST1.1 for all other cohorts), defined as the time from first treatment infusion until disease progression or death from any cause, whichever occurs earlier. • Tumour shrinkage (in millimeters), defined as the difference between the minimum post-baseline sum of diameters of target lesions (longest for non-nodal lesions, short axis for nodal lesions) and the baseline sum of diameters of the same set of target lesions in case of RECIST. In GBM, using RANO criteria, tumor shrinkage will be calculated based on the difference between the post-baseline and baseline measurements of the sum of product of the largest bi-dimensional measurements for all target lesions. • Pharmacokinetic parameters C_{max}, t_{max}, AUC_{0-504h} after the first and fourth infusion cycle.
Rationale for change		Information regarding RANO for GBM cohort D was added
Section to be changed		Synopsis – Number of patient entered
Description of change		Changed from:

		A total of 255 patients (28 part 1 plus 227 part 2) approximately will be entered (Part 1 and Part 2) To: A total of 315 patients (22 part 1 plus 293 part 2) approximately will be entered (Part 1 and Part 2)
Rationale for change		Screening failure rate was increased, Part 1 patient # was adapted and additional patient for cohort G were added.
Section to be changed		Synopsis – Number of patients on each treatment
Description of change		Changed from: Part 1: 12 to 18 evaluable patients Part 2: 80 evaluable locally advanced or metastatic non-squamous NSCLC patients (Cohort A and B, 40 patients per cohort) and 30 evaluable paients in each of the other 4 cohorts. In total 200 patients. To: Part 1: 12 to 18 evaluable patients Part 2: 80 evaluable locally advanced or metastatic non-squamous NSCLC patients (Cohort A and B; 40 patients per cohort) and 30 evaluable patients in each of the other 5 cohorts. In total 230
Rationale for change		Patient for new cohort G were added
Section to be changed		Synopsis – Diagnosis cohort F and G
Description of change		Changed from: Cohort F: Patients with hepatocellular carcinoma To: Cohort F: Patients with 2nd line hepatocellular carcinoma Cohort G: Patients with 1st line hepatocellular carcinoma (This will be implemented only in UK, Korea, Taiwan, Hong Kong, Poland, Ukraine, Russia, Spain, USA, Australia.
Rationale for change		Information regarding change study design adapted.
Section to be changed		Synopsis: **Main in- and exclusion criteria Part 2**
Description of change		Change from: Inclusion Criteria: For Part 1: 1. Age ≥ 18 years

2. Pathologically confirmed diagnosis of non-squamous NSCLC
3. Locally advanced (stage IIIb) or metastatic (stage IV) NSCLC
4. Documented disease progression or relapse (based on investigator's assessment) during or after completion of at least 2 cycles of platinum-based chemotherapy as first line treatment of Stage IIIB/IV non- squamous NSCLC or for checkpoint inhibitor experienced patients during or after completion of at least 2 cycles of platinum-based chemotherapy and a checkpoint inhibitor treatment (monotherapy or in combination with chemotherapy). This includes patients relapsing within 6 months of completing (neo)adjuvant/curative-intent chemotherapy/CPI or chemoradiotherapy.
5. At least one target lesion (outside the brain), that can be accurately measured per RECIST v 1.1
6. Availability and willingness to provide a fresh tumour tissue sample obtained after relapse or progression on or after prior therapy.
7. ECOG performance status of 0 or 1
8. Adequate hepatic, renal and bone marrow functions

For Part 2:

1. Of full age (according to local legislation, usually ≥ 18 years) at screening
2. At least one target lesion outside the brain (excluding the glioblastoma patients), that can be accurately measured per RECIST v 1.1
3. ECOG performance status ≤ 1

Inclusion for:

Cohort A (NSCLC):

- Pathologically confirmed locally advanced or metastatic non-squamous NSCLC
- **Prior Check-point inhibitor monotherapy either as 1st or 2nd line** as the last therapy before entering trial**. No more than one regimen of prior chemotherapy.**
- Approximately 10 patients will be recruited who have primary resistance to CPI based therapy which is defined as those advanced or metastatic IIIB/IV non-squamous NSCLC patients who previously received at least 2 cycles of CPI treatment without achieving benefit (SD <6 months or progressive disease in <6 months).

- Approximately 30 patients will be recruited who have secondary resistance to CPI based therapy which is defined as those advanced or metastatic IIIB/IV non-squamous NSCLC patients who had a documented minimum duration of benefit of (minimum of stable disease) 6 months and minimum treatment duration of 2 months on the previous CPI treatment without experiencing disease progression during that period.
- Patients with NSCLC known to harbor an ALK rearrangement, or EGFR mutation are only eligible after experiencing disease progression (during or after treatment) or intolerance to EGFR TKI or ALK TKI therapy.

Cohort B (NSCLC):

- Pathologically confirmed locally advanced or metastatic non-squamous NSCLC
- **1st line Platinum-based chemotherapy and a check-point inhibitor combination treatment** as the most recent therapy before entering trial
- Approximately 10 patients will be recruited who have primary resistance to the combination therapy which is defined as those advanced or metastatic IIIB/IV non-squamous NSCLC patients who previously received at least 2 cycles of platinum-based chemotherapy and CPI treatment without achieving benefit (SD < 8 months or progressive disease in < 8 months).
- Approximately 30 patients will be recruited who have secondary resistance to CPI based therapy which is defined as those advanced or metastatic IIIB/IV non-squamous NSCLC patients who had a documented minimum duration of benefit (minimum of stable disease) of 8 months who received CPI and platinum-based chemotherapy in a first line setting.
- Patients with NSCLC known to harbor an ALK rearrangement, or EGFR mutation are only eligible after experiencing disease progression (during or after treatment) or intolerance to EGFR TKI or ALK TKI therapy.

Cohort C (SCLC):

- Pathologically confirmed locally advanced or metastatic SCLC

		- **No more than one line of chemotherapy** with or without in combination with CPI - Documented disease progression during or after first line standard chemotherapy regimen with or without in combination with CPIs
		Cohort D (recurrent glioblastoma): - Histologically confirmed denovo glioblastoma (primary) - **No more than one line of chemotherapy** (concurrent and adjuvant temozolomide based chemotherapy including in combination with another investigational agent is considered one line of chemotherapy). - Documented first progression after radiotherapy (RT) and concurrent/adjuvant chemotherapy - An interval of at least 12 weeks from the completion of radiation therapy to start of study drug unless there is a new area of enhancement consistent with recurrent tumor outside the radiation field or there is unequivocal histologic confirmation of tumor progression - Patient may have been operated for recurrence. If operated: residual and measurable disease after surgery is required; surgical site must be adequately healed free of drainage or cellulitis, and the underlying cranioplasty must appear intact at the time of randomization
		Cohort E (Melanoma): - Histologically confirmed, unresectable, Stage IV metastatic melanoma - **At least one line of any kind of CPI based regimen as last treatment before entering the study** Documented progression during or after CPI therapy based regimen
		Cohort F (Hepatocellular Carcinoma): - Patients must have diagnosis of locally advanced or metastatic and/or unresectable histologically confirmed advanced hepatocellular carcinoma, not eligible for surgical and/or locoregional therapies - Patients should have progressed or discontinued first line treatment with sorafenib or lenvatinib, due to lack of tolerability. Patients who received 2nd line treatment with

anti-PD1 therapy (but not other therapy) after failure of sorafenib are also eligible.

- Documented virology status of hepatitis, as confirmed by screening hepatitis B surface antigen (HBsAg), antibody to hepatitis B core antigen (anti-HBc), and/or anti-hepatitis C virus (anti-HCV)
- Child-Pugh score class A
- Anti-viral therapy per local standard-of-care if active hepatitis B virus (HBV)

4. Adequate hepatic, renal and bone marrow functions
5. Availability and willingness to provide a fresh tumor tissue sample obtained after relapse or progression on or after prior therapy. In case a fresh biopsy cannot be obtained (e.g. inaccessible lesions or patient safety concern), an archived specimen obtained up to 6 months prior to cycle 1, visit 1 (C1V1) may be submitted in case no systemic antineoplastic therapy has been administered between the biopsy and C1V1 (except for cohort D). For cohorts E and, F, a fresh on-treatment biopsy is mandatory at C3D1, if possible from the same lesion as the pre-treatment biopsy.
6. Life expectancy ≥ 3 months after start of the treatment in the opinion of the investigator

Exclusion Criteria:

Part 2:

1 Not more than one CPI based treatment regimen prior to entering study (eg. anti-Programmed Death receptor-1 (PD-1), anti-Programmed Death-1 ligand-1 (PD-L1), anti-PD-L2, or anti-cytotoxic T lymphocyte associated antigen-4 (anti-CTLA-4) antibody); Exception is for Melanoma cohort (Cohort E)
2 Active hepatitis B virus (HBV) or hepatitis C virus (HCV) infection (exception for patients in HCC cohort Cohort F).
3 Prior treatment with any antiangiogenic treatment (e.g. bevacizumab, cediranib, aflibercept, vandetanib, XL-184, sunitinib, etc) except for sorafenib and lenvatinib in HCC cohort (Cohort F)
4 Patients with known active second malignancy other than non-melanoma skin cancers, non-metastatic prostate cancer, in situ cervical cancer, and ductal or lobular carcinoma in situ of the breast. Patients are not considered to have a currently active malignancy if they have completed anticancer therapy

and have been disease free for greater than 2 years prior to screening

Further exclusion criteria:

Exclusion criteria for Glioblastoma:

5 Tumor primarily localized to the brainstem or spinal cord.
6 Presence of diffuse leptomeningeal disease or extracranial disease.

Exclusion criteria for Melanoma cohort:

7 Uveal or ocular melanoma

Exclusion criteria for HCC cohort:

8 Co-infection with HBV and HCV or or HBV and hepatitis D virus (HDV)
9 Known fibrolamellar HCC, sarcomatoid HCC, or mixed cholangiocarcinoma and HCC
10 History of hepatic encephalopathy
11 Untreated or incompletely treated varices with bleeding or high-risk for bleeding
12 Uuntreated active Hepatitis B virus (HBV)
13 Treatment with any HCV anti-viral therapy within 4 weeks prior to Cycle 1 Day 1

To

<u>For Part 2</u>:

1. Of full age (according to local legislation, usually ≥ 18 years) at screening
2. At least one measurable target lesion outside the brain (excluding the glioblastoma patients), that can be accurately measured per RECIST v 1.1
3. ECOG performance status ≤ 1 (Karnofsky status for GBM)

Inclusion for:

Cohort A (NSCLC):

- Pathologically confirmed locally advanced or metastatic non-squamous NSCLC
- **Prior Check-point inhibitor monotherapy either as 1st or 2nd line. Patient must also have received treatment with a platinum-based chemotherapy regimen and have progressed or be intolerant, or ineligible, as per applicable local practice.**

- Approximately 10 patients will be recruited who have primary resistance to CPI based therapy which is defined as those advanced or metastatic IIIB/IV non-squamous NSCLC patients who previously received at least 2 cycles of CPI treatment and progressed without achieving benefit (SD <4 months or progressive disease in <4 months).
- Approximately 30 patients will be recruited who have secondary resistance to CPI based therapy which is defined as those advanced or metastatic IIIB/IV non-squamous NSCLC patients who had a documented minimum duration of benefit of (minimum of stable disease) 4 months and minimum treatment duration of 2 cycles on the previous CPI treatment without experiencing disease progression during that period.
- Patients with NSCLC known to harbor an ALK rearrangement, or EGFR mutation, or other genomic aberrations (e.g., ROS rearrangement, BRAF V600E mutation), are only eligible after experiencing disease progression (during or after treatment) or intolerance to approved targeted therapy for respective genomic aberrations, as applicable per local country guidelines.
- No more than one prior line of targeted therapy or chemotherapy regimen is allowed.

Cohort B (NSCLC):

- Pathologically confirmed locally advanced or metastatic non-squamous NSCLC
- **1st line Platinum-based chemotherapy and a check-point inhibitor combination treatment** as the most recent therapy before entering trial
- Approximately 10 patients will be recruited who have primary resistance to the combination therapy which is defined as those advanced or metastatic IIIB/IV non-squamous NSCLC patients who previously received at least 2 cycles of platinum-based chemotherapy and CPI treatment and progressed without achieving benefit (SD < 4 months or progressive disease in < 4 months).
- Approximately 30 patients will be recruited who have secondary resistance to CPI based therapy which is defined as those advanced or metastatic IIIB/IV non-squamous NSCLC patients who had a documented minimum duration of benefit (minimum of stable disease) of 4 months when previously treated with at least 2 cycles of the CPI and platinum-based chemotherapy in a first line setting without experiencing disease progression during that period.

		- Patients with NSCLC known to harbor an ALK rearrangement, or EGFR mutation, or other genomic aberrations (e.g., ROS rearrangement, BRAF V600E mutation), are only eligible after experiencing disease progression (during or after treatment) or intolerance to approved targeted therapy for respective genomic aberrations, as applicable per local country guidelines. No more than one line of targeted therapy is allowed.
		Cohort C (SCLC): - Pathologically confirmed locally advanced or metastatic SCLC - Documented intolerance to platinum-based chemotherapy or refractory to platinum-based chemotherapy (progression during treatment or during < 90 days of the last dose of platinum-based chemotherapy). Patients who are platinum-sensitive (progression ≥ 90 days of the last dose of platinum-based chemotherapy) must also have received at least one other prior line of platinum-based chemotherapy, if eligible, with or without combination with CPI as per applicable local treatment country guidelines.
		Cohort D (recurrent glioblastoma): - Histologically confirmed denovo glioblastoma (primary) at first or second recurrence after initial standard, control or experimental therapy that includes at a minimum RT. - Unequivocal evidence of progressive disease on contrast-enhanced brain CT or MRI as defined by RANO Criteria, or have documented recurrent glioblastoma on diagnostic biopsy. - **No more than two lines of prior chemotherapy** (concurrent and adjuvant temozolomide based chemotherapy including in combination with another investigational agent is considered one line of chemotherapy). - Only first and second recurrences of GBM are eligible - An interval of at least 12 weeks from the completion of radiation therapy to start of study drug unless there is a new area of enhancement consistent with recurrent tumor outside the radiation field or there is unequivocal histologic confirmation of tumor progression - Patient may have been operated for recurrence. If operated: residual and measurable disease after surgery is required; surgical site must be adequately healed free of drainage or

		cellulitis, and the underlying cranioplasty must appear intact at the time of randomization - Karnofsky performance status (KPS) ≥ 70 - MRI within 14 days prior to start of study drug - Patients should be immunocompetent (i.e. no concomitant treatment with dexamethasone (or equivalent), or receive stable/decreasing steroid levels not exceeding 2 mg/day dexamethasone (or equivalent) during the last 3 days prior to clinical screening; no severe lymphopenia).
		Cohort E (Melanoma): - Histologically confirmed, unresectable, Stage IV metastatic melanoma. - Patients with a BRAF mutation must have received targeted treatment, or were not eligible, with a BRAF and MEK inhibitor as per applicable local country guidelines. In such a case no more than one line of targeted therapy is allowed. - **At least one line of any kind of CPI based regimen as last treatment before entering the study** - Documented progression during or after CPI therapy based regimen.
		Cohort F (2nd line Hepatocellular Carcinoma): - Patients must have diagnosis of locally advanced or metastatic and/or unresectable histologically confirmed advanced hepatocellular carcinoma, not eligible for surgical and/or locoregional therapies - Patients should have progressed on or after first line treatment with sorafenib or lenvatinib or discontinued sorafenib or lenvatinib due to lack of tolerability after receiving at least two weeks of treatment. Reason for discontinuation must be documented.~~Patients who received 2nd line treatment with anti-PD1 therapy (but not other therapy) after failure of sorafenib or lenvatinib are also eligible.~~ - Documented virology status of hepatitis, as confirmed by screening hepatitis B surface antigen (HBsAg), antibody to hepatitis B core antigen (anti-HBc), HBV DNA, anti-hepatitis C virus (anti-HCV) and HCV RNA as applicable. - Child-Pugh score class A - Anti-viral therapy per local standard-of-care if active hepatitis B virus (HBV). HBV DNA to be <500IU/ml and

patients on anti HBV therapy for >4 weeks before entering the study.

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- **Cohort G (1st line Hepatocellular Carcinoma):** (To be implemented only in UK, Korea, Taiwan, Hong Kong, Poland, Ukraine, Russia, Spain, USA, Australia))The subject should have have diagnosis of locally advanced or metastatic and/or unresectable histologically confirmed advanced hepatocellular carcinoma that is not amenable to a curative treatment approach (eg, transplant, surgery, ablation therapy) or locoregional therapy (eg, TACE).
- No prior systemic therapy for HCC. Previous use of herbal therapies/traditional Chinese medicines with anti-cancer activity included in the label is allowed, provided that these medications are discontinued prior to randomization.
- Child-Pugh Score of A.
- Documented virology status of hepatitis, as confirmed by screening hepatitis B surface antigen (HBsAg), antibody to hepatitis B core antigen (anti-HBc), HBV DNA, anti-hepatitis C virus (anti-HCV) and HCV RNA as applicable.
- Anti-viral therapy per local standard-of-care if active hepatitis B virus (HBV). HBV DNA to be <500IU/ml and patients on anti HBV therapy for >4 weeks before entering the study.

4. Adequate hepatic, renal and bone marrow functions
5. Availability and willingness to provide a fresh tumor tissue sample obtained after relapse or progression on or after prior therapy. In case a fresh biopsy cannot be obtained (e.g. inaccessible lesions or patient safety concern), an archived specimen obtained up to 6 months prior to cycle 1, visit 1 (C1V1) may be submitted in case no systemic antineoplastic therapy has been administered between the biopsy and C1V1 (except for cohort D). For cohorts E, F and G, a fresh on-treatment biopsy is mandatory at C3D1, if possible from the same lesion as the pre-treatment biopsy.
6. Life expectancy ≥ 3 months after start of the treatment in the opinion of the investigator

Exclusion Criteria:

Part 2:

1 Not more than one CPI based treatment regimen prior to entering study (eg. anti-Programmed Death receptor-1 (PD-1),

		anti-Programmed Death-1 ligand-1 (PD-L1), anti-PD-L2, or anti-cytotoxic T lymphocyte associated antigen-4 (anti-CTLA-4) antibody) unless combination CPIs approved by the local regulatory agencies; For eg., Melanoma cohort (Cohort E) 2 Active hepatitis B virus (HBV) or hepatitis C virus (HCV) infection (exception for patients in HCC cohorts; Cohort F & cohort G). 3 Prior treatment with any antiangiogenic treatment (e.g. bevacizumab, cediranib, aflibercept, vandetanib, XL-184, sunitinib, etc) except for sorafenib and lenvatinib in 2nd line HCC cohort (Cohort F). 4 Patients with known active second malignancy other than non-melanoma skin cancers, non-metastatic prostate cancer, in situ cervical cancer, and ductal or lobular carcinoma in situ of the breast. Patients are not considered to have a currently active malignancy if they have completed anticancer therapy and have been disease free for greater than 2 years prior to screening Further exclusion criteria: Exclusion criteria for Glioblastoma: 5 Tumor primarily localized to the brainstem or spinal cord. 6 Presence of diffuse leptomeningeal disease or extracranial disease. 7 Is known to have IDH mutant variety of recurrent glioblastoma. 8 Any prior treatment with prolifeprospan 20 with carmustine wafer. 9 Any prior treatment with an intracerebral agent. Exclusion criteria for Melanoma cohort: 10 Uveal or ocular melanoma Exclusion criteria for HCC cohorts (Cohorts F & G): 11 Co-infection with HBV and HCV or HBV and hepatitis D virus (HDV) 12 Known fibrolamellar HCC, sarcomatoid HCC, or mixed cholangiocarcinoma and HCC 13 History of hepatic encephalopathy 14 Untreated or incompletely treated varices with bleeding or high-risk for bleeding 15 Untreated active Hepatitis B virus (HBV) 16 Treatment with any HCV anti-viral therapy within 4 weeks prior to Cycle 1 Day 1

Rationale for change		Adapting the information regarding implemented local AMs and changes to cohort D, F and G
Section to be changed		Synopsis - Dose
Description of change		Added Information: **Part 2**: RP2D of BI 836880 and BI 754091 BI 836880: 720 mg BI 754091: 240 mg
Rationale for change		Dose which was found to be used for Part 2
Section to be changed		Flowchart Part 2
Description of change		• EoR 42 days, was changed to "Safety Follow-op" visit (SFV) 30 days after last IMP administration • Karnofsky performance was added • Infection screening was added • Height and weight on SFV was added • Disease response assessment deleted for cycle 1 • Tumor biopsy info adjusted from cycle 1 to screening period Footnote information changed to: 1 See Appendix 10.2 for BP and HR should be measured before and after study drugs have been administered. Please follow the BP monitoring and study drug administration guidelines in Appendix 10.2.1. 2 ECG for all patients according to flowchart schedule.- Cycle 1 to 4 pre and post treatment (within 60 min after completion of administration of BI 836880) and thereafter ECG at pre- and post treatment of BI 836880 performed every second cycle (cycle 6,8, 10…etc 3 Echocardiography to be done within 21 days before treatment start and at EOT. 4 Safety lab to be done at local lab according to the Flowchart (up to 72 hours before treatment start) but should be more frequent in case of relevant findings based on medical opinion of the investigator.(Section 5.2.3~~).~~ 5 Complete physical examination must be performed at screening and before start of treatment and EoT andSafety Follow-up visit. For further time points, at minimum the actual health status of the patient should be assessed (see Section 5.2.1). 6 more details about AE are provided in Section 5.2.7 7 For medication number allocation it's possible to conduct IRT call ahead of the planned visit (= day of administration). Start with administration of BI 754091 and 15 min (+/- 10 min) after the end of this infusion, BI836880 should be administered (***see Instructions for Pharmacist provided in the ISF***) 8 Tumour assessments should be done according to RECIST v1.1 and iRECIST for all cohorts except GBM. RANO criteria to be followed for GBM cohort. Assessments should include computed tomography (CT) scans of the chest and abdomen and, if clinically indicated, imaging of any other known or suspected sites of disease (e.g., pelvis, brain) using an appropriate method (CT scan or magnetic resonance imaging [MRI]). The same radiographic procedure must be used throughout the trial. Baseline evaluation must be performed as close as possible to the treatment start and no more than 28 days before start of treatment (For GBM – 14 days prior to treatment).. Tumour assessment should be done every 6 weeks (in accordance to local

		requirements). Assessments are always done prior to the start of the new treatment cycle (window is up to minus 7 days).
		At EOT and Safety Follow-up visit only when applicable (see Section 5.1).
		9, 10 and 11: see Appendix 10.5 Table 10.5.1: 2
		12: Cohort F & G (HCC cohort): only C1D1 sample to be collected. NO on-treatment samples.
		13: ONLY Cohort F & G (HCC) cohort
		14: Cohort F & G (HCC) cohort: NO samples collected
		§ Women of child-bearing potential must have a serum beta human chorionic gonadotropin (β-HCG) pregnancy test at screening. Thereafter, this test can be done in either serum or urine on Day 1 of each cycle, and at the EOT visit. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
		$ Hepatitis B surface antigen (HBsAg; qualitative), hepatitis B core antibody (anti-HBc; qualitative), Hep B DNA, hepatitis C antibodies (Anti-HCV; qualitative), Hep C RNA, hepatitis D antibodies (Anti-HDV; qualitative) human immunodeficiency virus (HIV)-1 and HIV-2 antibody (at the discretion of the Investigator where clinically indicated) will be performed.
		@ Karnofsky performance status (KPS) to be implemted for GBM cohort
		
		• [a] **Part 2/ Tumour biopsy**
		  • **Mandatory pretreatment biopsy for cohort A, B, C, E, F , G:** - The equivalent of 2 14 -16 G (cohorts A-C: 3 18 G) needle biopsies should be freshly taken during screening after IC signed and before first trial medication administration, In case a fresh baseline biopsy cannot be obtained (e.g. inaccessible lesions or patient safety concern), 26 archival 4 µm sections from an archival block, taken within 6 months of trial start with no intermediate therapy have to be provided.
		  • **Mandatory for cohorts E, F and G, a fresh on-treatment biopsy**: - The equivalent of 2 14-16 G needle biopsies at C3D1 (-/+ 7 days) if possible from the same lesion as the pre-treatment biopsy. Treatment to be initiated only after ensuring patient is stable and bleeding has stopped completely after biopsy.
		  • **Optional for cohorts A-C:** - The equivalent of 3 18 G needle biopsies on treatment before start of Cycle 3 (-/+ 7 days, 6 weeks after treatment start)
		Note for on treatment biopsies: Biopsy to be performed on a lesion different than target lesion and if there is only one lesion than biopsy may be skipped in that patient.

Rationale for change		Adding and adapting information regarding new procedures and changes
Section to be changed		1.1 Medical background
Description of change		Added: . Currently multiple phase III studies of CPI in combination with anti-angiogenics is being conducted in 1st line HCC.
Rationale for change		Updating the information.
Section to be changed		1.2 Drug Profile
Description of change		This several parts for both compounds were updated
Rationale for change		The information was updated regarding the latest information for both compound regarding drug development and IB information.
Section to be changed		1.4 Risk Benefit Assessment

Description of change		Change from: Two Phase I trial testing BI 836880 monotherapy given i.v. in an every 1 or 3 week schedule are ongoing. Interim safety analysis of BI836880 phase I trials confirm the expected safety profile of the compound with hypertension, asthenia, nausea, vomiting, diarrhea and constipation being the most commonly reported AEs. Most of these reported AEs were grade 1-2 (CTCAE version 4.03). In total, 5 dose limiting toxicities were reported. In trial 1336.1 one patient treated on the highest dose level (1000mg) experienced a pulmonary embolism. In trial1336.6 4 patients experienced DLTs (proteinuria, proteinuria and hypertension, hypertension and respiratory distress one patient each) . (See BI 836880 IB section 6.3). To: Three Phase I trial testing BI 836880 monotherapy given i.v. in an every 1 or 3 week schedule are ongoing. Interim safety analysis of BI836880 phase I trials confirm the expected safety profile of the compound with hypertension, asthenia, nausea, vomiting, diarrhea and constipation being the most commonly reported AEs. Most of these reported AEs were grade 1-2 (CTCAE version 4.03). In total, 5 dose limiting toxicities were reported. In trial 1336.1(q3w dosing) one patient treated on the highest dose level (1000mg) experienced a pulmonary embolism. In trial1336.6 (q1w) 4 patients experienced DLTs (proteinuria, proteinuria and hypertension, hypertension and respiratory distress one patient each). Additionally, monotherapy trial in Japanese patients (1336.12) is also ongoing. In the Part-1 of 1336-0011 trial 1 DLT was reported at 360 mg dose cohort. (See BI 836880 IB section 6.3). Change from: In Part 2, hospitalization is optional. Furthermore, Patients with uncontrolled hypertension, with history of severe haemorrhage or thromboembolism are not allowed to participate to this study. Other side effects 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. To: In Part 2, hospitalization is optional. The period of surveillance after study drug administration depends on the medical assessment of the investigator, and is at the investigator´s discretion. Please refer to Sections 5.2.1, 5.2.2, and 5.2.3.

		Patients enrolled in Part 2 will continue to be excluded if they have uncontrolled hypertension (defined as BP > 140/90 mmHg) at baseline, and/or a history of severe haemorrhage or thromboembolism. Other side effects 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.
Rationale for change		Update because of the latest available information.
Section to be changed		2.1.2 Primary Endpoints
Description of change		Change from: **PART 2:** The primary endpoint is the shrinkage estimator of Objective Response (OR) based on Bayesian Hierarchical Model (BHM) defined as best overall response of complete response (CR) or partial response (PR) from first treatment infusion until the earliest of disease progression, death or last evaluable tumour assessment before start of subsequent anti-cancer therapy, lost to follow-up, withdrawal of consent. To: **PART 2:** The primary endpoint is the shrinkage estimator of Objective Response (OR) based on Bayesian Hierarchical Model (BHM) defined as best overall response (RECIST 1.1) of complete response (CR) or partial response (PR) from first treatment infusion until the earliest of disease progression, death or last evaluable tumour assessment before start of subsequent anti-cancer therapy, lost to follow-up, withdrawal of consent. In case of recurrent glioblastoma (GBM) assessment will be based on RANO (Response Assessment in Neuro-Oncology) criteria.
Rationale for change		Adapting the endpoints regarding the Glioblastoma Cohort D
Section to be changed		2.1.3 Secondary Endpoints – Part 2
Description of change		Change from: **PART 2:** • Adverse events (AEs), drug related AEs, drug related AEs leading to dose reduction or discontinuation during treatment period

		• Disease control (DC), defined as best overall response of CR, PR, or stable disease (SD) by RECIST1.1 criteria from first treatment infusion until the earliest of disease progression, death or last evaluable tumour assessment before start of subsequent anti-cancer therapy, lost to follow-up or withdrawal of consent. • Duration of objective response (DoR), defined as the time from first documented CR or PR by RECIST1.1) until the earliest of disease progression or death among patients with OR. • Progression-free survival (PFS) (RECIST1.1), defined as the time from first treatment infusion until disease progression or death from any cause, whichever occurs earlier. • Tumour shrinkage (in millimeters), defined as the difference between the minimum post-baseline sum of diameters of target lesions (longest for non-nodal lesions, short axis for nodal lesions) and the baseline sum of diameters of the same set of target lesions. • Pharmakinetic parameters C_{max}, t_{max}, $AUC_{0\text{-}504h}$ after the first and fourth infusion cycle. To: **PART 2:** • Adverse events (AEs), drug related AEs, drug related AEs leading to discontinuation during treatment period • Disease control (DC), defined as best overall response of CR, PR, or stable disease (SD) by RECIST1.1 (RANO for the GBM cohort) from first treatment infusion until the earliest of disease progression, death or last evaluable tumour assessment before start of subsequent anti-cancer therapy, lost to follow-up or withdrawal of consent. • Duration of objective response (DoR), defined as the time from first documented CR or PR by RECIST1.1 (RANO for the GBM cohort) until the earliest of disease progression or death among patients with OR. • Progression-free survival (PFS) (RANO for the GBM cohort & RECIST1.1 for all other cohorts), defined as the time from first treatment infusion until disease progression or death from any cause, whichever occurs earlier. • Tumour shrinkage (in millimeters), defined as the difference between the minimum post-baseline sum of diameters of target

		lesions (longest for non-nodal lesions, short axis for nodal lesions) and the baseline sum of diameters of the same set of target lesions. In GBM, using RANO criteria, tumor shrinkage will be calculated based on the difference between the post-baseline and baseline measurements of the sum of product of the largest bi-dimensional measurements for all target lesions. • Pharmacokinetic parameters C_{max}, t_{max}, $AUC_{0\text{-}504h}$ after the first infusion cycle.
Rationale for change		Adapting the Cohort D regarding RANO measurements
Section to be changed		[redacted]
Description of change		
Rationale for change		
Section to be changed		
Description of change		

		[redacted]
Rationale for change		
Section to be changed		3.1 Overall Study design Plan
Description of change		Changed from: The eligible patient population will be CPI naïve and experienced patients with locally advanced or metastatic non - squamous NSCLC who progressed during or after first line platinum-based chemotherapy or CPI monotherapy treatment or the combination of CPI and chemotherapy. The trial will consist in 2 Parts; Part 1 and part 2: The eligible patient population will be CPI naïve and experienced patients with locally advanced or metastatic non - squamous NSCLC who progressed during or after first line platinum-based chemotherapy or CPI monotherapy treatment or the combination of CPI and chemotherapy. The trial will consist in 2 Parts; Part 1 and part 2: To: The eligible patient population will be CPI naïve and experienced patients with locally advanced or metastatic non - squamous NSCLC who progressed during or after first line platinum-based chemotherapy

		or CPI monotherapy treatment or the combination of CPI and chemotherapy in Part 1. Part-2 will have additional expansion cohorts. Additional was the information regarding the new cohort added and two trial design overview graphics adapted and information was changed to: It is foreseen to enroll up to 230 patients of full age (according to local legislation, usually ≥ 18 years) at screening in different indications: Patients with locally advanced or metastatic 2nd or 3rd line CPI resistant non-squamous Non-Small Cell Lung Cancer (NSCLC) and ≥2nd line Small Cell Lung Cancer (SCLC) and recurrent glioblastoma and IO failure metastatic melanoma,1st line HCC patients or HCC patients who were intolerant or progressed during or after standard first line treatment with sorafenib or lenvatinib. Patients who received 2nd line treatment with anti-PD1 therapy (but not other therapy) after failure of sorafenib or lenvatinib are also eligible (see image below – **please note the cohorts will run in parallel, not sequential**) (see Figure 3.1: 1). 1st line HCC cohort will be implemented only in countries UK, Korea, Taiwan, Hong Kong, Poland, Ukraine, Russia, Spain, USA, Australia. Additional added: As described in Section 6.1 of the protocol, the period of surveillance during the treatment phase after administration of BI 836880 and BI 754091 is at the investigator´s discretion. Management guidelines have been provided for infusion related reactions (Section 5.2.7.1) and hypertension episodes (Appendix 10.2.1).
Rationale for change		The study design was adapted regarding the additional cohort D and the increase number of patients.
Section to be changed		3.2 Discussion of trial design, including the choice of control Groups
Description of change		Information was adapted to: Part 2 is an open-label expansion phase to assess efficacy and safety of BI 836880 in combination with BI 754091 in pretreated or naïve check point inhibitor patients with locally advanced or metastatic non-squamous NSCLC, small cell lung cancer, recurrent glioblastoma, malignant melanoma and 1st and 2nd line hepatocellular carcinoma. Once RP2D is determined in Part 1, it is planned to randomize up to 230 patients as described in Section 3.1 for Part 2

Rationale for change		HCC patient cohorts were adapted according to the needs
Section to be changed		3.3 Selection of trial population
Description of change		Change from: Approximately 80 patients will be enrolled in the NSCLC cohort and 30 patients each in the SCLC, metastatic melanoma, recurrent glioblastoma and HCC cohorts. To: Approximately 80 patients will be enrolled in the NSCLC cohort and 30 patients each in the SCLC, metastatic melanoma, recurrent glioblastoma, 1st and 2nd line HCC cohorts. 1st line HCC will be implemented only in countries UK, Korea, Taiwan, Hong Kong, Poland, Ukraine, Russia, Spain, USA, Australia.
Rationale for change		Adaption regarding additional HCC cohort G
Section to be changed		3.3.1 man diagnosis for trial entry – Part2
Description of change		Change from: For the part 2 we look for patients with locally advanced or metastatic 2nd line CPI resistant NSCLC and 2nd line SCLC, recurrent glioblastoma, IO failure metastatic melanoma and HCC pts who are intolerant or failed the first line treatment with sorafenib or lenvatinib. Patients who received 2nd line treatment with anti-PD1 therapy (but not other therapy) after failure of sorafenib or lenvatinib are also eligible. Please refer to Section 8.3.1 (Source Documents) for the documentation requirements pertaining to the in- and exclusion criteria. For the part 2 we look for patients with locally advanced or metastatic 2nd line CPI resistant NSCLC and 2nd line SCLC, recurrent glioblastoma, IO failure metastatic melanoma and HCC pts who are intolerant or failed the first line treatment with sorafenib or lenvatinib. Patients who received 2nd line treatment with anti-PD1 therapy (but not other therapy) after failure of sorafenib or lenvatinib are also eligible. Please refer to Section 8.3.1 (Source Documents) for the documentation requirements pertaining to the in- and exclusion criteria. To For the part 2 we look for patients with locally advanced or metastatic 2nd and 3rd line CPI resistant NSCLC and 2nd line SCLC, recurrent glioblastoma, IO failure metastatic melanoma, 1st line HCC patients and HCC patients who are intolerant or failed the first line treatment

		with sorafenib or lenvatinib. HCC patients who received 2nd line treatment with anti-PD1 therapy (but not other therapy) after failure of sorafenib or lenvatinib are also eligible. Please refer to Section 8.3.1 (Source Documents) for the documentation requirements pertaining to the in- and exclusion criteria.
Rationale for change		Adaption regarding additional HCC cohort
Section to be changed		3.3.2 Inclusion Criteria Part 1 - # 13
Description of change		Change from: Male or female patients. Women of childbearing potential (WOCBP) and men able to father a child must be ready and able to use highly effective methods of birth control per ICH M3 (R2) that result in a low failure rate of less than 1% per year when used consistently and correctly, starting with the screening visit and through 150 days after the last dose of BI 836880 and BI 754091 treatment, respectively. A list of contraception methods meeting these criteria is provided in the patient information. For further detail refer to Section 4.2.2.3. Note: Female patients of childbearing potential must have a negative urine or serum pregnancy test within 72 hours prior to taking study medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required. The serum pregnancy test must be negative for the patient to be eligible. To: Male or female patients. Women of childbearing potential (WOCBP) and men able to father a child must be ready and able to use highly effective methods of birth control per ICH M3 (R2) that result in a low failure rate of less than 1% per year when used consistently and correctly, starting with the screening visit and through 6 months after the last dose of BI 836880 and BI 754091 treatment, respectively. A list of contraception methods meeting these criteria is provided in the patient information. For further detail refer to Section 4.2.2.3. Note: Female patients of childbearing potential must have a negative serum pregnancy test within 72 hours prior to taking study medication during the screening period. At the following visits according to the flowchart a urine and/or serum pregnancy test is required. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required. The serum pregnancy test must be negative for the patient to be eligible.
Rationale for change		Correction of wrong information

Section to be changed		3.3.2 main Inclusion criteria for all Cohorts – Part 2
Description of change		Changed from: 2. At least one measurable untreated lesion according to RECIST v1.1 3. ECOG performance status ≤ 1 4.Adequate organ function as all of the following (all screening labs should be performed at local lab within 10 days prior to treatment initiation) To: 2: At least one measurable target lesion outside the brain (excluding the glioblastoma patients), that can be accurately measured per RECIST v 1.1 3. ECOG performance status ≤ 1 (For glioblastoma cohort Karnofsky status is applicable; see below) 4. Adequate organ function as all of the following (all screening labs should be performed at local lab within approximately 72 hours prior to treatment initiation): Change from: #9 Male or female patients. Women of childbearing potential (WOCBP) and men able to father a child must be ready and able to use highly effective methods of birth control per ICH M3 (R2) that result in a low failure rate of less than 1% per year when used consistently and correctly, starting with the screening visit and through 150 days after the last dose of BI 836880 and BI 754091 treatment, respectively. A list of contraception methods meeting these criteria is provided in the patient information. For further detail refer to Section 4.2.2.3. Note: Female patients of childbearing potential must have a negative urine or serum pregnancy test within 72 hours prior to taking study medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required. The serum pregnancy test must be negative for the patient to be eligible. To: 9. Male or female patients. Women of childbearing potential (WOCBP) and men able to father a child must be ready and able to use highly effective methods of birth control per ICH M3 (R2) that result in a low failure rate of less than 1% per year when used consistently and correctly, for the entire duration of the trial treatment intake and for 6 months after the end of the trial treatment. A list of contraception methods

		meeting these criteria is provided in the patient information. For further detail refer to Section 4.2.2.3. Note: Female patients of childbearing potential must have a negative serum pregnancy test within 72 hours during the screening period. At the following visits according to the flowchart, a urine and/or serum pregnancy test is required. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required. The serum pregnancy test must be negative for the patient to be eligible Change for the different cohorts to:
Section to be changed		3.3.2 Inclusion criteria Part 2 Cohort A
Description of change		Change from: **Cohort A (NSCLC):** - Pathologically confirmed locally advanced or metastatic IIIB/IV non-squamous NSCLC - **Prior Check-point inhibitor monotherapy either as 1st or 2nd line** as the last therapy before entering trial**. No more than one regimen of prior chemotherapy.** - Approximately 10 patients will be recruited who have primary resistance to CPI based therapy which is defined as those advanced or metastatic IIIB/IV non-squamous NSCLC patients who previously received at least 2 cycles of CPI treatment without achieving benefit (RECIST v1.1 SD <6 months or progressive disease in <6 months). - Approximately 30 patients will be recruited who have secondary resistance to CPI based therapy which is defined as those advanced or metastatic IIIB/IV non-squamous NSCLC patients who had a documented minimum duration of benefit of (minimum of stable disease) 6 months and minimum treatment duration of 2 months on the previous CPI treatment without experiencing disease progression during that period. - Patients with NSCLC known to harbor an ALK rearrangement, or EGFR mutation are only eligible after experiencing disease progression (during or after treatment) or intolerance to EGFR TKI or ALK TKI therapy. To: **Inclusion for:** **Cohort A (NSCLC):** - Pathologically confirmed locally advanced or metastatic IIIB/IV non-squamous NSCLC - Prior Check-point inhibitor monotherapy either as 1st or 2nd line. Patient must also have received treatment with a

		platinum-based chemotherapy regimen and have progressed or be intolerant, or ineligible, as per applicable local practice. - Approximately 10 patients will be recruited who have primary resistance to CPI based therapy which is defined as those advanced or metastatic IIIB/IV non-squamous NSCLC patients who previously received at least 2 cycles of CPI treatment and progressed without achieving benefit (RECIST v1.1 SD <4 months or progressive disease in <4 months). - Approximately 30 patients will be recruited who have secondary resistance to CPI based therapy which is defined as those advanced or metastatic IIIB/IV non-squamous NSCLC patients who had a documented minimum duration of benefit of (minimum of stable disease) 4 months and minimum treatment duration of 2 cycles on the previous CPI treatment without experiencing disease progression during that period. - Patients with NSCLC known to harbor an ALK rearrangement, or EGFR mutation, or other genomic aberrations (e.g., ROS rearrangement, BRAF V600E mutation), are only eligible after experiencing disease progression (during or after treatment) or intolerance to approved targeted therapy for respective genomic aberrations, as applicable per local country guidelines. - No more than one prior line of targeted therapy or chemotherapy regimen is allowed.
Rationale for change		Adaption to requests from the authorities in different countries
Section to be changed		3.3.2 Inclusion criteria Part 2 Cohort B
Description of change		Change from: - **Cohort B (NSCLC):** - Pathologically confirmed locally advanced or metastatic IIIB/IV non-squamous NSCLC - **1st line Platinum-based chemotherapy and a check-point inhibitor combination treatment** as the most recent therapy before entering trial - Approximately 10 patients will be recruited who have primary resistance to the combination therapy which is defined as those advanced or metastatic IIIB/IV non-squamous NSCLC patients who previously received at least 2 cycles of platinum-based chemotherapy and CPI treatment without achieving benefit (RECIST v1.1 SD < 8 months or progressive disease in < 8 months). - Approximately 30 patients will be recruited who have secondary resistance to CPI based therapy which is defined as those advanced or metastatic IIIB/IV non-squamous NSCLC

		patients who had a documented minimum duration of benefit (minimum of stable disease) of 8 months who received CPI and platinum-based chemotherapy in a first line setting. - Patients with NSCLC known to harbor an ALK rearrangement, or EGFR mutation are only eligible after experiencing disease progression (during or after treatment) or intolerance to EGFR TKI or ALK TKI therapy. To: - **Cohort B (NSCLC):** - Pathologically confirmed locally advanced or metastatic IIIB/IV non-squamous NSCLC - **1st line Platinum-based chemotherapy and a check-point inhibitor combination treatment** as the most recent therapy before entering trial - Approximately 10 patients will be recruited who have primary resistance to the combination therapy which is defined as those advanced or metastatic IIIB/IV non-squamous NSCLC patients who previously received at least 2 cycles of platinum-based chemotherapy and CPI treatment and progressed without achieving benefit (RECIST v1.1 SD < 4 months or progressive disease in < 4 months). - Approximately 30 patients will be recruited who have secondary resistance to CPI based therapy which is defined as those advanced or metastatic IIIB/IV non-squamous NSCLC patients who had a documented minimum duration of benefit (minimum of stable disease) of 4 months when previously treated with at least 2 cycles of the CPI and platinum-based chemotherapy in a first line setting without experiencing disease progression during that period. - Patients with NSCLC known to harbor an ALK rearrangement, or EGFR mutation, or other genomic aberrations (e.g., ROS rearrangement, BRAF V600E mutation), are only eligible after experiencing disease progression (during or after treatment) or intolerance to approved targeted therapy for respective genomic aberrations, as applicable per local country guidelines. No more than one line of targeted therapy is allowed.
Rationale for change		Adaption to requests from the authorities in different countries
Section to be changed		3.3.2 Inclusion criteria Part 2 Cohort C
Description of change		Changed from: **Cohort C (SCLC):** - Pathologically confirmed locally advanced or metastatic SCLC

		- **No more than one line of chemotherapy** with or without combination with CPI - Documented disease progression during or after first line standard chemotherapy regimen with or without combination with anti-PD (L)1 To: **Cohort C (SCLC):** - Pathologically confirmed locally advanced or metastatic SCLC. - Documented intolerance to platinum-based chemotherapy or refractory to platinum-based chemotherapy (progression during treatment or during < 90 days of the last dose of platinum-based chemotherapy). Patients who are platinum-sensitive (progression ≥ 90 days of the last dose of platinum-based chemotherapy) must also have received at least one other prior line of platinum-based chemotherapy, if eligible, with or without combination with CPI as per applicable local treatment country guidelines.
Rationale for change		Adaption to requests from the authorities in different countries
Section to be changed		3.3.2 Inclusion criteria Part 2 Cohort D
		Changed from: **Cohort D (recurrent glioblastoma):** - Histologically confirmed denovo glioblastoma (primary) - **No more than one line of chemotherapy** (concurrent and adjuvant temozolomide based chemotherapy including in combination with another investigational agent is considered one line of chemotherapy). - Documented first progression after radiotherapy (RT) and concurrent/adjuvant chemotherapy - An interval of at least 12 weeks from the completion of radiation therapy to start of study drug unless there is a new area of enhancement consistent with recurrent tumor outside the radiation field or there is unequivocal histologic confirmation of tumor progression - Patient may have been operated for recurrence. If operated: residual and measurable disease after surgery is required; surgical site must be adequately healed free of drainage or cellulitis, and the underlying cranioplasty must appear intact at the time of randomization To: **Cohort D (recurrent glioblastoma):**

		- Histologically confirmed denovo glioblastoma (primary) at first or second recurrence after initial standard, control or experimental therapy that includes at a minimum RT. - Unequivocal evidence of progressive disease on contrast-enhanced brain CT or MRI as defined by RANO Criteria, or have documented recurrent glioblastoma on diagnostic biopsy. - **No more than two lines of prior chemotherapy** (concurrent and adjuvant temozolomide based chemotherapy including in combination with another investigational agent is considered one line of chemotherapy). - Only first and second recurrences of GBM are eligible. - An interval of at least 12 weeks from the completion of radiation therapy to start of study drug unless there is a new area of enhancement consistent with recurrent tumor outside the radiation field or there is unequivocal histologic confirmation of tumor progression - Patient may have been operated for recurrence. If operated: residual and measurable disease after surgery is required; surgical site must be adequately healed free of drainage or cellulitis, and the underlying cranioplasty must appear intact at the time of randomization1 - Karnofsky performance status ≥ 70 - MRI within 14 days prior to start of study drug. - Patients should be immunocompetent (i.e. no concomitant treatment with **Description of change** dexamethasone (or equivalent), or receive stable/decreasing steroid levels not exceeding 2 mg/day dexamethasone (or equivalent) during the last 3 days prior to clinical screening; no severe lymphopenia)
Rationale for change		Adaption regarding adequate way to evaluate this population
Section to be changed		3.3.2 Inclusion criteria Part 2 Cohort E
Description of change		Change from: **Cohort E (Melanoma):** - Histologically confirmed, unresectable, Stage IV metastatic melanoma - **At least one line of any kind of CPI based regimen as last treatment before entering the study** - Documented progression during or after CPI therapy based regimen To: **Cohort E (Melanoma):** - Histologically confirmed, unresectable, Stage IV metastatic melanoma

		- Patients with a BRAF mutation must have received targeted treatment, or were not eligible, with a BRAF and MEK inhibitor as per applicable local country guidelines. In such a case no more than one line of targeted therapy is allowed. - **At least one line of any kind of CPI based regimen as last treatment before entering the study**
Rationale for change		Adaption to requests from the authorities in different countries
Section to be changed		3.3.2 Inclusion criteria Part 2 Cohort F
Description of change		Change from: To **Cohort F (Hepatocellular Carcinoma):** - Patients must have diagnosis of locally advanced or metastatic and/or unresectable histologically confirmed advanced hepatocellular carcinoma, not eligible for surgical and/or locoregional therapies - Patients should have progressed or discontinued first line treatment with sorafenib or lenvatinib, due to lack of tolerability. Patients who received 2nd line treatment with anti-PD1 therapy (but not other therapy) after failure of sorafenib are also eligible. - Child-Pugh score class A - Documented virology status of hepatitis, as confirmed by screening hepatitis B surface antigen (HBsAg), antibody to hepatitis B core antigen (anti-HBc), and/or anti-hepatitis C virus (anti-HCV) - Anti-viral therapy per local standard-of-care if active hepatitis B virus (HBV) To: **Cohort F (2nd line HepatocellularCarcinoma):** - Patients must have diagnosis of locally advanced or metastatic and/or unresectable histologically confirmed advanced hepatocellular carcinoma, not eligible for surgical and/or locoregional therapies - Patients should have progressed on or after first line treatment with sorafenib or lenvatinib or discontinued sorafenib or lenvatinib due to lack of tolerability after receiving at least two weeks of treatment. Reason for discontinuation must be documented. - Documented virology status of hepatitis, as confirmed by screening hepatitis B surface antigen (HBsAg), antibody to hepatitis B core antigen (anti-HBc), HBV DNA, anti-hepatitis C virus (anti-HCV) and HCV RNA as applicable. - Child-Pugh score class A

		- Anti-viral therapy per local standard-of-care if active hepatitis B virus (HBV). HBV DNA to be <500IU/ml and patients on anti HBV therapy for >4 weeks before entering the study.
Rationale for change		Adaption regarding the differentiation from the cohort G and request from local authorities
Section to be changed		3.3.2 Inclusion criteria Part 2 Cohort G
Description of change		Added new cohort G: **Cohort G (1st line Hepatocellular Carcinoma): To be implemented only in countries** UK, Korea, Taiwan, Hong Kong, Poland, Ukraine, Russia, Spain, USA, Australia. - The subject should have have diagnosis of locally advanced or metastatic and/or unresectable histologically confirmed advanced hepatocellular carcinoma that is not amenable to a curative treatment approach (eg, transplant, surgery, ablation therapy) or locoregional therapy (eg, TACE). - No prior systemic therapy for HCC. Previous use of herbal therapies/traditional Chinese medicines with anti-cancer activity included in the label is allowed, provided that these medications are discontinued prior to randomization. - Child-Pugh Score of A. - Documented virology status of hepatitis, as confirmed by screening hepatitis B surface antigen (HBsAg), antibody to hepatitis B core antigen (anti-HBc), HBV DNA, anti-hepatitis C virus (anti-HCV) and HCV RNA as applicable. - Anti-viral therapy per local standard-of-care if active hepatitis B virus (HBV). HBV DNA to be <500IU/ml and patients on anti HBV therapy for >4 weeks before entering the study.
Rationale for change		Additional population to the trial
Section to be changed		3.3.3 Exclusion Criteria Part 2
Description of change		Change from: 2.) Not more than one CPI based treatment regimen prior to entering study (eg. anti-Programmed Death receptor-1 (PD-1), anti-Programmed Death-1 ligand-1 (PD-L1), anti-PD-L2, or anti-cytotoxic T lymphocyte associated antigen-4 (anti-CTLA-4) antibody); Exception is for Melanoma cohort (Cohort E) 4.) Active hepatitis B virus (HBV) or hepatitis C virus (HCV) infection (exception for patients in HCC cohort). 6.) Immunosuppressive corticosteroid doses (> 10 mg prednisone daily or equivalent) within 4 weeks prior to the first dose of trial medication.

		7.) Current or prior treatment with any systemic anti-cancer therapy either within 28 days or a minimum of 5 half-lives, whichever is longer before start of treatment. 17.) No Vitamin K antagonist and other anticoagulation allowed; LMWH allowed only for prevention not for curative treatment. 23.) Women who are pregnant, nursing, or who plan to become pregnant in the trial 24.) Uncontrolled pleural effusion, pericardial effusion, or ascites To: 2.) Not more than one CPI based treatment regimen prior to entering study (eg. anti-Programmed Death receptor-1 (PD-1), anti-Programmed Death-1 ligand-1 (PD-L1), anti-PD-L2, or anti-cytotoxic T lymphocyte associated antigen-4 (anti-CTLA-4) antibody) unless combination CPIs approved by the local regulatory agencies; For eg., Melanoma cohort (Cohort E). 4.) Active hepatitis B virus (HBV) or hepatitis C virus (HCV) infection (exception for patients in HCC cohorts; Cohorts F& G). 6.) Immunosuppressive corticosteroid doses (> 10 mg prednisone daily or equivalent) within 4 weeks prior to the first dose of trial medication except for control of cerebral edema in case of recurrent glioblastoma (cohort D). 7.) Current or prior treatment with any systemic anti-cancer therapy (including radiotherapy) either within 28 days or a minimum of 5 half-lives, whichever is shorter before start of treatment 17.) History of pneumonitis (non-infectious) within the last 5 years 23.) Symptomatic pleural effusion, pericardial effusion, or ascites 24.) Prior treatment with any antiangiogenic treatment (e.g. bevacizumab, cediranib, aflibercept, vandetanib, XL-184,

		sunitinib, etc) except for sorafenib and lenvatinib in 2nd line HCC cohort (Cohort F)
Rationale for change		Changes required to new cohort definition
Section to be changed		3.3.3 Exclusion Criteria
Description of change		**Added information:** **Exclusion criteria for Glioblastoma cohort:** 3. Is known to have IDH mutant variety of recurrent glioblastoma. 4. Any prior treatment with prolifeprospan 20 with carmustine wafer. 5. Any prior treatment with an intracerebral agent.
Rationale for change		Additional request needed for Gliobastoma population
Section to be changed		3.3.3 Exclusion Criteria
Description of change		Change from: Exclusion criteria for HCC cohort: 1. Co-infection with HBV and HCV or HBV and hepatitis D virus (HDV) 2. Known fibrolamellar HCC, sarcomatoid HCC, or mixed cholangiocarcinoma and HCC 3. History of hepatic encephalopathy To: **Exclusion criteria for HCC cohorts (cohorts F & G):** 1. Co-infection with HBV and HCV or HBV and hepatitis D virus (HDV) 2. Known fibrolamellar HCC, sarcomatoid HCC, or mixed cholangiocarcinoma and HCC 3. Untreated active Hepatitis B virus (HBV)
Rationale for change		Changes required for HCC population cohort F and G
Section to be changed		4.1.2.2 Part 2

Description of change		Change from: Once at least 6 patients have received at least 1 cycle at the maximum dose level, a safety evaluation of all patients treated in Part 1 will be performed. Based on all this safety data, the SMC may approve the selected BI 836880 dose (RP2D) to be used in combination with BI 754091 for Part 2 of the trial. This data will be supported with the PK and PD analysis of at least 3 patients in each dose cohort. To: Once at least 6 patients have received at least 1 cycle at the maximum dose level in Part 1, a safety evaluation of all patients treated in Part 1 will be performed. Based on all available data, the SMC may approve the selected BI 836880 dose (RP2D) to be used in combination with BI 754091 for Part 2 of the trial. The RP2D assessment will be supported with the PK and PD analysis of at least 3 patients in each dose cohort. *Update after SMC decision:* *The SMC selected the dose BI 836880 720 mg and for BI 754091 240 mg as dose for the Part 2 of this trial.*
Rationale for change		Added information regarding Part 2 dase according to SMC decision
Section to be changed		4.1.4
Description of change		Change from: If symptoms of an infusion-related reaction CTCAE grade 2 or higher, but not qualifying as DLT according to Section 5.3.1 occur, the infusion should be temporarily stopped. Upon recovery, it should be infused at 50% of the rate at which the reaction occurred. To: If symptoms of an infusion-related reaction CTCAE grade 2 or higher, the infusion should be temporarily stopped. The intensity and prolongation of vital sign monitoring should be considered. Upon recovery, the study drug should be infused at 50% of the rate at which the reaction occurred.
Rationale for change		Adaption regarding new available data.
Section to be changed		4.1.4
Description of change		*Re-treatment criteria* – was renamed to: **Drug re-administration criteria after the first cycle has been completed for Part 1**:

		And information regarding Part 2 was added: **Drug re-administration criteria after the first cycle has been completed in Part 2**: Before initiating a new treatment cycle the current health status of the patient will be assessed according to the Flow Chart. To continue treatment with further cycles, all of the following criteria must be met: 1. Pre-infusion SBP should be < 160 mmHg and pre-infusion DBP should be < 100 mmHg; study drug administration of both study drugs should be temporarily delayed until BP < 160/100. Please see **Table 10.2.1:1 in Appendix 10.2.1**, which describes the guidelines for BP management and study drug administration. 2. QTcF <=480 ms (according to Exclusion-Criterion #8) 3. Echocardiography if clinically indicated (based on investigators judgment) with Left Ventricular Ejection Fraction (LVEF) ≥ 50% 4. Acceptable tolerability (in case of an adverse event at the planned start of a treatment cycle patients may continue therapy only after recovery to a level which would allow further therapy in the opinion of investigator). In case the above mentioned criteria 2, 3, and 4 are not fulfilled the patient should be re-evaluated as needed. Any case of a delay in treatment cycle should be communicated to the Clinical Monitor at Boehringer Ingelheim. The investigator in agreement with the Clinical Monitor will decide about further treatment of individual patient, based on known risk/benefit of BI 836880 and BI 754091.
Rationale for change		Changes refers to feedback from authorities and CTP development
Section to be changed		4.1.4 Dose reduction guidelines Part 2
Description of change		Information was changed to: Part 2: Dose escalations of BI 836880 or BI 754091 in any patient is not allowed. Dose reductions are not allowed for BI 754091 in any patient.

		In the dose expansion study, only dose reductions are allowed for BI 836880. Table 4.1.4: 3 Dose reduction recommendations for BI 836880 in Part 2 BI 836880 received dose | BI 836880 reduced dose 720 mg | 480 mg A dose reduction of BI 836880 from 720 mg to 480 mg is allowed, if investigator can attribute the AE unequivocally to the BI 836880 (for eg., hypertension). If the reduced dose is still intolerable, the dose maybe delayed (please see below the sub-section "Delay of treatment") . Where deemed in the best interest of the patient, the investigator may restart at the originally assigned dose of 720 mg of BI 836880 as soon as deemed clinically appropriate. Delay of Treatment: During combination therapy, if treatment is held or discontinued due to an AE(s), both BI 836880 and BI 754091 will be held or discontinued together. If treatment is to be restarted after resolution (≤ Grade 1 or baseline) of the AE, both BI 836880 and BI 754091 must be started together. ~~The combination therapy may be delayed for up to 6 weeks because of AEs, following discussion with the sponsor.~~
Rationale for change		Changes refer to the possibility to down dithrate the dose for the patients in case of AEs.
Section to be changed		4.2.2 Restrictions
Description of change		Changed from: • Concomitant anti-cancer therapy is not allowed. Radiotherapy for local symptom control of non-target lesions can be allowed after consulting the investigator and sponsor. To: Concomitant anti-cancer therapy is not allowed. Radiotherapy for local symptom control of non-target lesions can be allowed after consulting the investigator and sponsor. Palliative radiotherapy will not be allowed during the first cycle for any lesion. Palliative radiotherapy is allowed only for non-target lesions, following discussion with the Medical Monitor, provided that the reason for radiotherapy does not reflect PD and does not interfere with response assessment. Lesions that have been exposed to radiotherapy are no longer evaluable, and may not be included in the assessment of the non-target lesions and the overall assessment. Unless in emergency

		situations, the Medical Monitor should be contacted prior to the administration of palliative radiotherapy in the expansion phase.
Rationale for change		Clarification to explain the specific restrictions
Section to be changed		4.2.2.3 Restrictions regarding women of childbearing potential
Description of change		Change to: 4.2.2.3 Restrictions regarding women of childbearing potential Women of childbearing potential must use the contraception methods described in the patient information. Due to the advanced stage of disease of Phase I trial patient populations and the high medical need, females of childbearing potential can be included in this trial provided that they agree to use a highly-effective contraception method. These are methods of birth control per the International Committee on Harmonisation (ICH) M3 (R2) that result in a low failure rate of less than 1% per year when used consistently and correctly. Highly-effective methods of contraception include: • Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation, Oral, intravaginal, transdermal • Progestogen-only hormonal contraception associated with inhibition of ovulation: oral, injectable, implantable • Intrauterine device • Intrauterine hormone-releasing system • Bilateral tubal occlusion • Vasectomised partner o provided that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomised partner has received medical assessment of the surgical success. • Sexual abstinence o defined as refraining from heterosexual intercourse during the entire period (stated above) of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject. Details of these contraception methods are described in the patient information in the ICF. Women of childbearing potential must follow these methods during the trial and for at least 6 months after the end of the trial treatment. Although use of a contraceptive pill is considered a highly-effective method of birth control, women of childbearing potential taking a contraceptive pill must use an additional barrier method for the entire duration of the trial treatment intake and for 6 months after the end of the trial treatment intake.

		Male patients with partners of childbearing potential must agree to use condoms and ensure their partner is using an additional highly-effective method of birth control, during the trial and until at least 6 months after the end of the trial treatment.
Rationale for change		Adaption to clarify the information regarding restrictions regarding women of childbearing potential.
Section to be changed		5.1 Assessment of Efficacy
Description of change		Added information: The same method of assessment and the same technique should be used also in follow up of identified and reported lesions. Lesions in previously irradiated areas may not be used as target lesions (except recurrent glioblastoma after a period of 12 weeks). Baseline evaluation must be performed as close as possible to the treatment start and no more than 28 days before start of treatment. Efficacy endpoints will be assessed every 2 cycles (6 weeks) as specified in the FC. An additional evaluation at EoT is only applicable; when patient has no PD documented, will not continue with regular imaging in Follow-up period and did not have imaging within the last 4 weeks before EoT. At Safety Follow-up visit, in case a patient has discontinued due to PD one additional tumor assessment should be done in case no other cancer treatment has been initiated. All measurements must be recorded in metric notation. All tumor imaging performed in this trial will be collected by authorized CRO and stored until shipment to Boehringer Ingelheim. The CRO will not be implicated in tumor response evaluation. This collected data may be considered for central review at a later time point. Additionally added: 5.1.1 Tumor response assessments using RECIST 1.1 5.1.2 Tumor response assessments using RANO Including the RANO criteria
Rationale for change		To address the evaluation regarding the Glioblastoma cohort
Section to be changed		5.2.1 Physical examination
Description of change		Change from: A complete physical examination (including cardiac, neurological, dermatological, pulmonological etc.), record of height (only at screening visit), weight and ECOG performance score will be performed at screening and before start of treatment and EoT and EoR. At further time points specified in the FC not a complete PE must be done, but at minimum the actual health status of the patient

		should be assessed (incl. evaluation of BP, ECG, lab values, AE, Concomitant Treatments, ECOG as applicable). During the physical examination, the patient should be assessed for possible AEs. To: A complete physical examination (including cardiac, neurological, dermatological, pulmonological etc.), record of height (only at screening visit), weight and ECOG /Karnofsky performance score will be performed at screening and before start of treatment and EoT and Safety Follow-up. At further time points specified in the FC not a complete PE must be done, but at minimum the actual health status of the patient should be assessed (incl. evaluation of BP, ECG, lab values, AE, Concomitant Treatments, ECOG/Karnofsky as applicable). During the physical examination, the patient should be assessed for possible AEs.
Rationale for change		Updating the information regarding Gliostoma cohort evaluation and the re-wording of the EoR to Saftey Follow-up visit.
Section to be changed		5.2.2 Vital signs
Description of change		Adapted to: Vital signs (blood pressure, heart rate and body temperature) will be recorded at every visit indicated in the FC. In Part 1, on days of study drug administration, blood pressure and heart rate will be evaluated at three time points: 1. Pre-dose (-60 min. to -5 min.), before infusion of BI 754091 2. 5 to 10 minutes before infusion of BI 836880, 3. 5 to 10 minutes after infusion of BI 836880.In case of an infusion-related reaction, the Investigator should decide whether to intensify or prolong monitoring of vital signs of the patient. In Part 2, on days of study drug administration, blood pressure and heart rate will be evaluated at two time points: 1. Pre-dose (-60 min. to -5 min.), before infusion of BI 754091; the results should be assessed using the BP management and study drug administration guidelines in Appendix 10.3 2. 5 to 10 minutes after infusion of BI 836880. In case of an infusion-related reaction, the Investigator should decide whether to intensify or prolong monitoring of vital signs of the patient. **Frequency of blood pressure measurements at each time point**

		Systolic and diastolic blood pressure as well as pulse rate (electronically or by palpation, count for 1 minute) will be measured after 5 minutes of rest in the seated position. In Part 1, the blood pressure measurement should be performed three times at each time point and the values of these measurements will be entered in the eCRF. In Part 2, only a single blood pressure measurement is required at each time point. Further details on the procedure for blood pressure measurements are given in Appendix 10.2.
Rationale for change		Information specified for Part1 and Part2 and adapted for the new settings
Section to be changed		5.2.3 Safety laboratory parameters
Description of change		Changed from: …Therefore it's possible to take blood sample a valuable time ahead (usually the day before treatment). Safety laboratory examinations will include hematology, biochemistry, coagulation and urine analysis: To: Therefore it's possible to take blood sample a valuable time ahead (usually the day before treatment but possible up to approximately 72 hours before). Safety laboratory examinations will include hematology, biochemistry, coagulation and urine analysis: Change from: Biochemistry — Glucose, sodium, potassium, calcium, magnesium, inorganic phosphate, creatinine, AST, ALT, alkaline phosphatase (AP), lactate dehydrogenase (LDH), bilirubin, urea, total protein, albumin, uric acid, CK, CK-MB Serum immunoglobulin levels (IgG, IgM, IgA; IgE) and direct antiglobulin test have to be measured at Screening and at occurrence of infusion related reactions. To Biochemistry — Glucose, sodium, potassium, calcium, magnesium, inorganic

			phosphate, creatinine, AST, ALT, alkaline phosphatase (AP), lactate dehydrogenase (LDH), bilirubin, serum urea nitrogen (or urea), thyroid panel [TSH, free T4, and free T3]), urinalysis total protein, albumin, uric acid, CK, In case of pathological CK elevated, then CK-MB, additional troponin, and myoglobin as available should be reactively tested and the findings documented.
		Serum immunoglobulin levels (IgG, IgM, IgA; IgE) and direct antiglobulin test have to be measured at Screening and at occurrence of infusion related reactions. Change from: Pregnancy test obtained at the time patients of childbearing To: Pregnancy test Added information: Screening for Infections	A serum pregnancy test needs to be points indicated in the Flow Chart in potential. A pregnancy test needs to be obtained at the time points indicated in the Flow Chart in patients of child bearing potential. A beta human chorionic gonadotropin (β-HCG) pregnancy test in serum will be performed for women of childbearing potential (WOCBP) at screening. Thereafter, this test may be done in serum or urine on Day 1 of each cycle, at the EOT visit. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required. HIV-1 and HIV-2 antibody (qualitative, as per applicable

		local regulations, at the discretion of the Investigator where clinically indicated). Hepatitis B serology (HBsAg, anti-HBc qualitative) and Hepatitis C serology (anti-HCV qualitative) for screening active Hepatitis B and Hepatitis C. For HCC cohorts (cohorts F & G) additional tests may include HBV DNA (if needed), HCV RNA (if needed) and Hepatitis D (anti-HDV qualitative).
Rationale for change		To clarify needed safety lab parameters
Section to be changed		5.2.4 Electrocardiogram
Description of change		Changed from: For the part 2: 1. 1st cycle pre and post treatment. Cycle 2,3 and 4 only one ECG pre treatment and then on ECG at pre treatment performed every second cycle (cycle 6,8, 10…etc) 2. shortly before the end of the infusion of trial medication (only at cycle 1). To: <u>For the part 2</u>: 1. Cycle 1 to 4 pre and post treatment (within 60 min after completion of administration of BI 836880) and thereafter ECG at pre- and post treatment of BI 836880 performed every second cycle (cycle 6,8, 10…etc)
Rationale for change		Clarification to the Part 2 ECGs
Section to be changed		5.2.5 Echocardiography
Description of change		Change from: Echocardiography have to be conducted at screening (not older than 7 days) and at EoT-visit. During treatment phase it has only to be done when clinically indicated. To:

		Echocardiography have to be conducted at screening (not older than 21 days before treatment start) and at EoT-visit. During treatment phase it has only to be done when clinically indicated.
Rationale for change		More relaxed time window was introduced to help the sites in multiple countries manage Echocardiography based on their local practices. Based on data from Part 1 there are no concerns to having a relaxed window.
Section to be changed		5.2.6.1 Dose limiting toxicities (DLTs)
Description of change		Added: Once the dose escalation part of the study has been completed (Part 1), DLTs no longer need to be reported (i.e. Part 2).
Rationale for change		To clarify of no DLTs in Part 2 of the trial.
Section to be changed		5.2.7 Assessment of adverse events
Description of change		Different changes in the wording: From: Dose Limiting Toxicities All DLTs are considered to be AESIs, and must be reported as such. The definition of DLT is presented in Section 5.2.6.1. Severe Hypertension A hypertensive episode will be considered an AESI if: • SBP >= 140 mmHg or DBP >= 90 mmHg which persists longer than 2 days despite either he initiation of antihypertensive agent(s) in a patient without prior history of hypertension, or the intensification / addition of new antihypertensive agents in a patient with prior history of hypertension. Immune-related adverse events (irAE) Immune-related AEs are AEs associated with immunotherapy treatments that appear to be associated with the immune therapy's mechanism of action. These adverse reactions, which can be severe, may involve the gastrointestinal, skin, liver, endocrine, respiratory, renal, or other organ systems. Although all irAEs are to be reported as AEs, only clinically important irAEs need to be reported as AESIs as defined by the sponsor in Appendix 10.3. If an Investigator determines that a Grade 3 AE that is not included in Appendix 10.3 is an irAE, that event should also be reported as an AESI.

Recommendations for the management of irAEs are presented in Appendix 10.4.

Infusion-related reactions
In the event of an infusion-related reaction ≥ Grade 2, the infusion rate of BI 836880 or BI 754091 may be decreased by 50% or interrupted until resolution of the event and re-initiated at 50% of the initial rate until completion of the infusion. In patients experiencing infusion-related reactions ≥ Grade 2, subsequent infusions may be administered at 50% of the initial rate.

If a patient experiences an infusion-related reaction, acetaminophen and/or an antihistamine (e.g., diphenhydramine) and/or corticosteroid or equivalent medication per institutional standard may be administered prior to subsequent infusions at the discretion of the Investigator for secondary prophylaxis of infusion-related reactions. If an infusion-related reaction is Grade 4 or higher in severity at any point during the study, treatment with BI 836880 or BI 754091 will be permanently discontinued.

As with any mAb, allergic reactions to BI 754091 administration are possible. Appropriate drugs and medical equipment to treat acute anaphylactic reactions must be immediately available, and trial personnel must be trained to recognize and treat anaphylaxis. The trial site must have immediate access to emergency resuscitation teams and equipment in addition to the ability to admit patients to an intensive care unit if necessary.

The following events 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 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 must report that event as an AESI.

Potential Hepatic injury

A potential hepatic injury is defined by the following alterations of hepatic laboratory

- Parameters:

  - **For patients with normal aminotransferase levels at baseline**: 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 without evidence of cholestasis, OR aminotransferase elevations ⩾10 fold ULN
  - **For patients with abnormal aminotransaminase levels at baseline >1 and <2.5 x ULN at baseline:** An elevation of AST and/or ALT ⩾3 fold the baseline value combined with an elevation of bilirubin ⩾2 fold ULN and the baseline value in the same blood sample; OR Aminotransferase elevations ⩾5 fold the baseline value.
  - **For patients with abnormal aminotransaminase levels at baseline >=2.5 and <=5 x ULN at baseline** (patients with liver metastases only)**:** An elevation of AST and/or ALT ⩾2 fold the baseline value combined with an elevation of bilirubin ⩾2 fold ULN and the baseline value in the same blood sample; OR Aminotransferase elevations ⩾3 fold the baseline value.

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 potential 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 analyzed, 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

To:
Dose Limiting Toxicities
All DLTs are considered to be AESIs, and must be reported as such. The definition of DLT is presented in Section 5.2.6.1. DLTs are no longer applicable in Part 2 of the study, therefore are no longer AESIs in Part 2.

Persistent hypertension despite treatment
A hypertensive episode will be considered an AESI if:

- SBP >= 140 mmHg or DBP >= 90 mmHg which persists longer than 2 days despite either he initiation of

antihypertensive agent(s) in a patient without prior history of hypertension, or the intensification / addition of new antihypertensive agents in a patient with prior history of hypertension.

Immune-related adverse events (irAE)
Although all irAEs are to be reported as AEs, only clinically important irAEs need to be reported as AESIs as defined by the sponsor in Appendix 10.3. Non-clinically important irAEs, such as mild to moderate rash and hypothyroidism, for example, do not need to be reported as AESIs. If an Investigator determines that a severe irAE or other clinically significant irAE that is not included in Appendix 10.3 is medically significant, the investigator may, also report this irAE as an AESI.

Recommendations for the management of irAEs are presented in Appendix 10.4.

Infusion-related reactions
All infusion-related reactions need to be reported as AESIs.

In the event of an infusion-related reaction ≥ Grade 2, the infusion rate of BI 836880 or BI 754091 may be decreased by 50% or interrupted until resolution of the event and re-initiated at 50% of the initial rate until completion of the infusion. In patients experiencing infusion-related reactions ≥ Grade 2, subsequent infusions may be administered at 50% of the initial rate.

If a patient experiences an infusion-related reaction, acetaminophen and/or an antihistamine (e.g., diphenhydramine) and/or corticosteroid or equivalent medication per institutional standard may be administered prior to subsequent infusions at the discretion of the Investigator for secondary prophylaxis of infusion-related reactions. If an infusion-related reaction is Grade 4 or higher in severity at any point during the study, treatment with BI 836880 or BI 754091 will be permanently discontinued.

As with any mAb, allergic reactions to BI 836880 and BI 754091 administration are possible. Appropriate drugs and medical equipment to treat acute anaphylactic reactions must be immediately available, and trial personnel must be trained to recognize and treat anaphylaxis. The trial site must have immediate access to emergency resuscitation teams and equipment in addition to the ability to admit patients to an intensive care unit if necessary.
The following events 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 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 must report that event as an AESI. Potential DILI A potential DILI is defined by the following alterations of hepatic laboratory • Parameters: • **For patients with normal aminotransferase levels at baseline**: 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 without evidence of cholestasis, OR aminotransferase elevations ⩾10 fold ULN • **For patients with abnormal aminotransaminase levels at baseline >1 and <2.5 x ULN at baseline:** An elevation of AST and/or ALT ⩾3 fold the baseline value combined with an elevation of bilirubin ⩾2 fold ULN and the baseline value in the same blood sample; OR Aminotransferase elevations ⩾5 fold the baseline value. • **For patients with abnormal aminotransaminase levels at baseline >=2.5 and <=5 x ULN at baseline** (patients with liver metastases only)**:** An elevation of AST and/or ALT ⩾2 fold the baseline value combined with an elevation of bilirubin ⩾2 fold ULN and the baseline value in the same blood sample; OR Aminotransferase elevations ⩾3 fold the baseline value. These lab findings constitute a potential DILI alert and the patients experiencing these lab abnormalities need to be followed up according to the "DILI checklist" provided in the ISF, unless an underlying other than study drug(s) cause has been determined
Rationale for change		Adapted wording to the part 2 and the clarification of DILI and infusion related reactions.

Section to be changed		5.2.7.2 Adverse event collection and reporting
Description of change		Change from: … • After the end of the REP until individual patient's end of trial: any new occurrence of cancer of new histology, all related SAEs and all related AESIs. … The **Residual Effect Period** (REP) is defined as 42 days after the last trial medication administration …. **AE reporting to sponsor and timelines** The investigator must report SAEs, AESIs, and non-serious AEs which are relevant for the reported SAE or AESI, on the BI SAE form via fax immediately (within 24 hours) to the sponsor's unique entry point (country specific contact details will be provided in the ISF). To: • After the end of the REP (Safety Follow up visit) until individual patient's end of trial: any new occurrence of cancer of new histology, all related SAEs and all related AESIs. … The **Residual Effect Period** (REP) is defined as 30 days after the last trial medication administration …. **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 reporting process will be provided in the ISF).
Rationale for change		Updating the SAE collection information, reducing the REP from 42 to 30 days.
Section to be changed		5.3.2 Methods of sample collection
Description of change		Change from: For quantification of analyte plasma concentrations, samples will be drawn at the time points listed in the Flow Chart under PK sampling and specified in PK time schedules in Appendix 10.4. Plasma will be divided into duplicate aliquots for each analyte (in total 4 aliquots) and stored frozen at about -70°C at the participating sites or logistics CRO until shipment on dry ice to the bioanalytical laboratory of Boehringer Ingelheim or a Boehringer Ingelheim selected and authorized CRO. To:

		For quantification of analyte plasma concentrations, samples will be drawn at the time points listed in the Flow Chart under PK sampling and specified in PK time schedules in Apendix 10.5. The provided sampling timepoints are depicted as planned timepoints, however according to Section 4.1.4, the infusion time may be adapted. In this case, the PK sampling referring to the "end" time of the infusion should be performed shortly after the end of infusion including flushing of the tubes, no matter the duration of the infusion. The subsequently requested PK sampling should be drawn as planned. Do not adapt the time because of the variation of the duration of the infusion schema.
Rationale for change		Clarifictaion to the PK sample collections timepoints
Section to be changed		5.4 ASSESSMENT OF BIOMARKER(S)
Description of change		[redacted]

Rationale for change		Clarification regarding biopsies and biomarker assessment
Section to be changed		5.4.1.Methods of sample collection –Part 2
Description of change		[redacted]

	[redacted]
Rationale for change	Clarification on needed Biopsy material.
Section to be changed	[redacted]
Description of change	
Rationale for change	
Section to be changed	
Description of change	

	[redacted]
Section to be changed	
Section to be changed	5.5.1 Immunogenicity assessments
Description of change	Change from: Methods of ADA sample collection For the determination of anti-drug antibodies (ADA), approximately 3 mL of blood will be taken from a forearm vein in a K2 EDTA (ethylendiaminetetraacetic acid) anticoagulant blood drawing tube at those time points specified in the Flow Chart and in Appendix 10.4. EDTA plasma will be divided into duplicate aliquots into 2 mL cryovials and stored frozen at approximately -70°C or below at the investigator sites or logistics CRO until shipment on dry ice to the bioanalytical laboratory. The second aliquot will be shipped only after the acknowledgement of receipt of the first aliquot. Details about sample collection, preparation, storage and shipment are described in the laboratory manual. [redacted]

		To: For ADA assessments (BI 836880 and BI 754091), the specified blood volume will be drawn into blood-drawing tubes at the time points listed in the flow chart and Appendix 10.5. Details on sample characteristics, processing, handling, and shipment are provided in the Laboratory Manual. [redacted]
Rationale for change		Clarification regarding the us e of ADAs in this trial.
Section to be changed		6.1 Visit Schedule
Description of change		Added information: During the treatment phase of Part 2, hospitalization is not required, and the period of surveillance is left at the discretion of the investigator. Investigators should consider that although infusion reactions to any monoclonal antibody typically develops within 30 minutes to two hours after the initiation of drug infusion, symptoms may be delayed for up to 24 hours. Some patients may also develop severe hypertensive episodes, and treatment should be considered accordingly. Please see Section 4.1.4 for the required criteria to administer study drugs after the first cycle. Please see Section 5.2.7.1 for guidelines on how to report and manage infusions related reactions, and Appendix 10.2.1 for BP management and study administration guidelines
Rationale for change		Clarification regarding hospitalization in the Part 2.
Section to be changed		6.2.1 Screening and run-in period(s
Description of change		Changed from: The examinations required for the screening visit may be conducted within a time interval of 21 days prior to the first study drug administration. Prior to any other study related procedure, written informed consent must be obtained from the patient. CT/MRI images obtained prior to study participation can be used within the study as long as they are not older than 28 days at day of first treatment.

		Echocardiography must be obtained within 7 days before start of treatment. If for administrative or medical reasons, the patient is not entered within the defined screening period, re-assess of eligibility parameter could be allowed after discussion with Clinical Monitor. This should be considered as exceptional situation and not a general rule. If the patient has been determined eligible by the investigator to enter the trial (refer to Section 3.3), the investigator will assign one or more medication number(s) to the patient through the IRT system at Visit 1 (Section 4.1.3). First dose of BI 836880+ BI 75091 will be administered at the beginning of Visit 1 at the trial site (Day 1, cycle 1). To: The examinations required for the screening visit may be conducted within a time interval of 21 days prior to the first study drug administration. Prior to any other study related procedure, written informed consent must be obtained from the patient. CT/MRI images obtained prior to study participation can be used within the study as long as they are not older than 28 days at day of first treatment. For Glioblastoma patient only, MRI 14 days before treatment start is required Echocardiography must be obtained within 7 days before start of treatment. I possible to take blood sample a valuable time ahead (usually the day before treatment but possible up to 72 hours before). For cohort D (Glioblastoma) patient the base line status on IDH and MGMT methylation need to be captured in the eCRF if available. If for administrative or medical reasons, the patient is not entered within the defined screening period, re-assess of eligibility parameter could be allowed after discussion with Clinical Monitor. This should be considered as exceptional situation and not a general rule. If the patient has been determined eligible by the investigator to enter the trial (refer to Section 3.3), the investigator will assign one or more medication number(s) to the patient through the IRT system at Visit 1 (Section 4.1.3). First dose of BI 836880+ BI 754091 will be administered at the beginning of Visit 1 at the trial site (Day 1, cycle 1)

Rationale for change		Clarification and adding of Cohort D specific procedures.
Section to be changed		6.2.2.Treatment period
Description of change		Change from: For Part 2 tumour assessment should be done every 6 weeks (in accordance to local requirements). Assessments are always done prior to the start of the new treatment cycle. At EOT and EOR only when applicable (see Section 5.1) To: For Part 2 tumour assessment should be done every 6 weeks (in accordance to local requirements with a window of minus 7days). Assessments are always done prior to the start of the new treatment cycle. At EOT and Safety Follow-up visit only when applicable (see Section 5.1)
Rationale for change		Adapted wording to the change of the EOR visit to Safety Follow-up visit
Section to be changed		6.2.4 Residual effect period (REP)
Description of change		Changed from: The REP is defined in Section 5.2.7.2. The End of REP (EoR) visit should not be performed earlier than 42 days after permanent discontinuation of the trial medication. In case the patient discontinued due to PD by RECIST 1.1, one additional tumour assessment should be done at EOR visit. The information collected at this visit should include all new AEs that occurred after EOT and a follow-up of adverse events ongoing at EOT. Any subsequent anti-cancer therapy administered between EoT and EoR should be reported To: The REP is defined in Section 5.2.7.2. The End of REP the Safety Follow-up visit should not be performed earlier than 30 days after permanent discontinuation of the trial medication (last day medication was administered). In case the patient discontinued due to PD by RECIST 1.1/RANO, one additional tumor assessment should be done at the Safety Follow-up visit or time close according to requested 6 weeks interval for images. The information collected at this visit should include all new AEs that occurred after EOT and a follow-up of adverse events ongoing at EOT. Any subsequent anti-cancer therapy administered between EoT and EoR should be reported.
Rationale for change		Adaption, to wording, new RANO assessment and different time window.

Section to be changed		7.3 Planned Analyses
Description of change		Changed from: For the determination of the MTD, only MTD-evaluable patients will be considered. For the analysis of secondary and further endpoints, all patients in the treated set (i.e., patients treated with at least one dose of trial medication) will be included in the analysis. Any other analysis To: For the determination of the MTD, only MTD-evaluable patients will be considered. For the analysis of secondary and further endpoints in Part 1, all patients in the treated set (i.e., patients treated with at least one dose of trial medication) will be included in the analysis. All analyses planned in Part 2 will be based on the treated set.
Rationale for change		Adapted wording regarding Part 2.
Section to be changed		7.3.1.2 Primary endpoint analyses for Part 2
Description of change		Change from: The primary endpoint for Part 2 of the trial is OR defined by confirmed CR or PR according to RECIST 1.1 as assessed by the Investigator. Overall response will be analyzed in terms of the shrinkage estimator of the OR rate (ORR) based on BHM. To: The primary endpoint for Part 2 of the trial is OR defined by confirmed CR or PR according to RECIST 1.1 for all cohorts except GBM as assessed by the Investigator. OR in GBM cohort will be evaluated using RANO criteria. Overall response will be analyzed in terms of the shrinkage estimator of the OR rate (ORR) based on BHM.
Rationale for change		Adaption for the Glioblastoma Cohort D and the RANO criteria
Section to be changed		7.3.2.2 Secondary endpoint analyses for Part 2
Description of change		Change From: Disease control (DC) will be analyzed in terms of DC rate (DCR), defined as the proportion of patients with best overall response of CR, PR, or SD according to RECIST 1.1. Proportions will be presented with 95% two-sided confidence interval using the exact Clopper-Pearson method. Duration of objective response (DoR) - for all patients with an OR, the duration of OR is defined as time from first documented CR or PR to the earliest of disease progression or death among patients with OR. If a patient did not die or progress until the last visit in the study, this

		patient will be censored at the last time point known to be alive and progression-free. The outcome will be assessed according to RECIST 1.1. To: Disease control (DC) will be analyzed in terms of DC rate (DCR), defined as the proportion of patients with best overall response of CR, PR, or SD according to RANO for GBM & RECIST1.1 for all other cohorts. Proportions will be presented with 95% two-sided confidence interval using the exact Clopper-Pearson method. Duration of objective response (DoR) - for all patients with an OR, the duration of OR is defined as time from first documented CR or PR to the earliest of disease progression or death among patients with OR. If a patient did not die or progress until the last visit in the study, this patient will be censored at the last time point known to be alive and progression-free. The outcome will be assessed according to RANO for GBM & RECIST1.1 for all other cohorts.
Rationale for change		Adaption for the Glioblastoma Cohort D and the RANO criteria
Section to be changed		[redacted]
Description of change		
Rationale for change		
Section to be changed		7.4 Interim Analysis – Part 2
Description of change		Change from: In Part 2 we are randomizing 200 patients. 40 patients for the each of the cohorts A and B, and 30 patient for each of the cohorts C, D, E and F. An interim futility analysis will be performed for cohort C, D, E and F in Part 2. Until any decision from the futility analysis is done,

		the enrolment of next patient will not be stopped. The two-stage design is planned to stop further recruitment of patient if the defined efficacy boundary (see Table 7.7.2: 1) is not met at the first stage. The interim analyses for each cohort will be conducted after 15th patients in that cohort have completed their two on-treatment imaging assessment (i.e. end of cycle 4). In addition, if considered necessary interim analysis may be performed for evaluation of the efficacy and safety aspects as each cohort is finished. To: In Part 2, 230 patients are planned to be treated. 40 patients each are planned for cohorts A and B, and 30 patients each are planned for cohorts C, D, E, F, and G. An interim futility analysis will be performed for cohorts C, D, E, F, and G in Part 2. The interim analyses for each cohort are planned to be conducted after 15 patients in that cohort have completed their two on-treatment imaging assessments (i.e., end of cycle 4). For each cohort, timing of the interim analysis may be adjusted according to actual recruitment rate to facilitate or avoid delay of the trial conduct. Until any decision from the futility analysis is done, the enrollment of next patient will not be stopped. The two-stage design is planned to stop further recruitment of patients if the defined efficacy boundary (see Table 7.7.2: 1) is not met at the first stage.
Section to be changed		Adaptions regarding new cohort
Section to be changed		7.7.2 Determination of sample size for Part 2
Description of change		Change from: • Cohort F: patients with locally advanced or metastatic and/or unresectable Hepatocellular Carcinoma (HCC) who were intolerant or progressed during 1st line sorafenib or lenvatinib treatment; subsequent CPI therapy is allowed as the most recent anticancer treatment. ….. For cohort D (GBM), around 25% ORR with Bevacizumab is assumed. In AVF3708 (R11-2708), which is an open-label study in patients with glioblastoma who had progressed following initial treatment with temozolomide and radiation, the ORR was 28% [95%CI, 19-40] (N=85). Based on above results, the futility boundary for cohort D is set as 25% at planned interim futility analysis timing.

		For cohort F (HCC), around 15% ORR with anti-PD-1 antibody monotherapy is assumed. In Checkmate-040 (R17-3829) which is an open label phase I/II trial of Nivolumab in patients with advanced hepatocellular carcinoma, the ORR was 20% [95%CI, 15-26] (N=50) in dose expansion phase and 15% [95% CI, 6-28] (N=10) in the dose escalation phase. In KEYNOTE-224 (R19-0168) which is a phase 2 study of Pembrolizumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib , the ORR was 17% [95% CI, 11-26] (N=104). Based on above result, the futility boundary for cohort F is set as 15% at planned interim futility analysis timing. Different homogeneous scenarios and heterogeneous scenarios as well as different sample sizes are considered in the simulations to assess the operating characteristics of the BHM approach. The simulation results as shown in Table 7.7.2: 2 below show that, with the proposed cohort size, the BHM approach has reasonable probability of reaching the pre-specified response rate under a wide range of scenarios. To: Cohort F (2nd line HCC): patients with locally advanced or metastatic and/or unresectable Hepatocellular Carcinoma who were intolerant or progressed during 1st line sorafenib or lenvatinib treatment~~; subsequent CPI therapy is allowed as the most recent anticancer treatment~~. • Cohort G (1st line HCC): patients with locally advanced or metastatic and/or unresectable HCC with no prior systemic treatment A total of approximately 230 patients will be enrolled for these 7 cohorts. 40 patients each are planned for cohorts A and B, and 30 patients each are planned for cohorts C to G …. For cohort D (GBM), around 20% ORR with Bevacizumab is assumed. In a recent phase II study (R22-0513) comparing standard dose bevacizumab versus low dose bevacizumab plus lomustine, in patients with recurrent glioblastoma following standard radiation and temozologmide, the ORR was 19% [95% CI, 8-36] (N = 36) based on RANO criteria for the standard dose bevacizumab arm. Based on above results, the futility boundary for cohort D is set as 20% at planned interim futility analysis timing. For cohort F (2nd line HCC), around 15% ORR with anti-PD-1 antibody monotherapy is assumed. In Checkmate-040 (R17-3829) which is an open label phase I/II trial of Nivolumab in patients with advanced hepatocellular carcinoma, the ORR was 20% [95% CI, 15-26] (N=50) in dose expansion phase and 15% [95% CI, 6-28] (N=10) in the dose escalation phase. In KEYNOTE-224 (R19-0168) which is

		a phase 2 study of Pembrolizumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib, the ORR was 17% [95% CI, 11-26] (N=104). Based on above result, the futility boundary for cohort F is set as 15% at planned interim futility analysis timing. For cohort G (1st line HCC), around 20% ORR with target monotherapies is assumed. In REFLECT (R20-3051), which is a Phase 3 study comparing Lenvatinib vs. Sorafenib, the ORR was 19% [95%, CI 17-21] (N = 478) for Lenvatinib and 7% [95%, CI 6-8] (N = 476) for Sorafenib. In IMbrave150 (R22-0533), which is a Phase III trial comparing Atezolizumab plus Bevacizumab vs. Sorafenib, the ORR for Sorafenib arm observed was 12% [95% CI, 7-17] (N = 165). In Checkmate-459 (R22-0532), which is a phase III study comparing Nivolumab vs. Sorafenib, the observed ORR was 7% [95% CI, 4-10] (N = 372)). Based on above result, the futility boundary for cohort G is set as 20% at planned interim futility analysis timing. Proposed sample size will provide accumulative safety and tolerability data for the investigational combination across different tumor types. Different homogeneous scenarios and heterogeneous scenarios as well as different sample sizes are considered in the simulations to assess the operating characteristics of the BHM approach. The simulation results as shown in Table 7.7.2: 2 below show that, with the proposed cohort size and interim futility analysis in SCLC, MLN, GBM and HCC cohorts, the BHM approach has reasonable probability of reaching the pre-specified response rate under a wide range of scenarios. The probability of observing a $\geq$ 15% increase in the shrinkage estimator of the ORR under negative scenario is well controlled on cohort level (< 1%). Desirable true positive probabilities (~> 60%) and false negative probabilities (<2%) are also demonstrated under nugget scenarios for each cohort on proposed sample size. Additional update of: Table 7.7.2: 1 Early stopping probabilities at interim for cohorts C-G based on observed ORR under different scenarios Table 7.7.2: 2 Operating characteristics of the Bayesian Hierarchical Modelling approach for final analysis under different scenarios with futility evaluation at the interim
Rationale for change		Adaptions regarding new cohort and patient numbers.
Section to be changed		9.1
Description of change		Added information:

		R11-0753 Wen PY, Macdonald DR, Reardon DA, Cloughesy TF, Sorensen AG, Galanis E, DeGroot J, Wick W, Gilbert MR, Lassman AB, Tsien C, Mikkelsen T, Wong ET, Chamberlain MC, Stupp R, Lamborn KR, Vogelbaum MA, Bent MJ van den, Chang SM. Updated response assessment criteria for high-grade gliomas: Response Assessment in Neuro-Oncology Working Group. J Clin Oncol 2010 ; 28(11) ; 1963-1972. R22-0513 Weathers S-P, Han X, Liu DD, Conrad CA, Gilbert MR, Loghin ME, et al. A randomized phase II trial of standard dose bevacizumab versus low dose bevacizumab plus lomustine (CCNU) in adults with recurrent glioblastoma. J Neurooncol 129 (3), 487 - 494 (2016) R20-3051 Kudo, M, Finn RS, Qin S, Han K-H, Ikeda K, Piscaglia F, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. The Lancet 391 (10126), 1163 - 1173 (2018) R22-0533 ESMO 2019 oncology news: atezolizumab in combination with bevacizumab provides superior outcome compared with sorafenib in unresectable HCC (date: 23 Nov 2019). esmo.org/oncology-news/atezolizumab-in-combination-with-bevacizumab-provides-superior-outcome-compared-with-sorafenib-in-unresectable-hcc (access date: 28 Jan 2020) 2019 R22-0532 ESMO 2019 press release: clinical benefit with first-line immunotherapy in advanced hepatocellular carcinoma (date: 27 Sep 2019). esmo.org/newsroom/press-office/esmo-congress-hepatocellular-carcinoma-cancer-checkmate459-yau (access date: 28 Jan 2020) 2019 R20-0571 Okada H, Weller M, Huang R, Finocchiaro G, Gilbert MR, Wick W, et al. Immunotherapy response assessment in neuro-oncology: a report of the RANO working group. Lancet Oncol 2015 ; 16; e534-e542.
Rationale for change		New available information
Section to be changed		10.2 BLOOD PRESSURE MEASUREMENT PROCEDURE
Description of change		Change from: In Part 2, only a single blood pressure measurement is required per scheduled time point measurement.

		In case of a suspected "white coat effect" it is recommended to repeat the measurement in a pleasant condition after sufficient rest. Values from self-blood pressure measurements (SBPM) communicated from patient to investigator are not considered valuable for study related decisions. To: In Part 2, only a single blood pressure measurement is required per scheduled time point, i.e. one measurement before the study drugs have been administered, and one measurement after the study drugs are administered. Please see Section 5.2.2 for further details, and Appendix 10.2.1 for management guidelines. ~~In case of a suspected "white coat effect" it is recommended to repeat the measurement in a pleasant condition after sufficient rest. Values from self-blood pressure measurements (SBPM) communicated from patient to investigator are not considered valuable for study related decisions.~~ Table was added: Table 10.2.1: 1 BP management and study drug administration guidelines following completion of cycle 1, based on pre-infusion SBP and DBP measured on study drug administration visits.
Rationale for change		Adaption to the new blood pressure measurement guideline for this trial
Section to be changed		10.3
Description of change		Change of chapter title: IMMUNE-RELATED ADVERSE EVENTS OF SPECIAL INTEREST To: IMMUNE-RELATED ADVERSE EVENTS AS ADVERSE EVENTS OF SPECIAL INTEREST
Rationale for change		To specify the immune related events regarding events of special interest.
Section to be changed		10.5.1 Time Schedule for Pharmacokinetic (PK) and Pharmacodynamic Blood Sampling
Description of change		Added information: According to Section 4.1.4 of the protocol, the infusion time may be adapted. In this case, the PK sampling referring to the "end" time of the infusion should be performed shortly after the end of infusion including flushing of the tubes, no matter the duration of the infusion.

The subsequently requested PK sampling should be drawn as planned. Do not adapt the time because of the variation of the duration of the infusion schema.

Table 10.5.1:1 was modified

Change from:
According to Section 4.1.4 of the protocol, the infusion time may be adapted. In this case, the PK sampling referring to the" start" and "end" time of the infusion should be performed shortly after the end of infusion, no matter the duration of the infusion.
The subsequently requested PK sampling should be drawn as planned. Do not adapt the time because of the variation of the duration of the infusion schema.

To:

The time for PK plasma sampling in Table 10.5.1: 1 and 10.5.1: 2 are nominal times and should be adhered if possible. However, as actual sampling times will be recorded and used for the determination of pharmacokinetic parameters, there is some flexibility. A guidance for allowed time windows for PK plasma sample collection is provided in Table 10.5.1: 3.

Table 10.5.1: 3 Allowed time windows for PK plasma sample collection

Samples	Time Windows	Explanation
pre-dose Cycle 1		Before start of first infusion
1:00, 2:15	Within 15 min after end of each infusion	This time point refers to suggested infusion time of 1 hour for each compound. If the infusion time is adapted please collect the sample within 15 min after the end of the infusion + flushing, when the full dose was administered
6:00	± 1 h	
24:00, 168:00, 336:00	± 5 h	
-0:05 (pre-dose) all other Cycle besides Cycle 1	- 5 h	But before start of next infusion

Rationale for change

Windows for the PK sample collection have been added

Section to be changed		10.7APPENDIX - PERFORMANCE STATUS CRITERIA
Description of change		Added information: 10.7APPENDIX - PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally	20	Very sick, hospitalization indicated. Death not imminent.

			confined to bed or chair.	10	Moribund, fatal processes progressing rapidly.
		5	Dead.	0	Dead.
Rationale for change		Clarifying the performance status criteria regarding the Cohort D and the Karnofsky Performance scale			

11.5 GLOBAL AMENDMENT 5

Date of amendment		18 Nov 2020
EudraCT number EU number		2017-001378-41
BI Trial number		1336-0011
BI Investigational Product(s)		BI 836880 BI 754091
Title of protocol		An open label phase Ib dose finding study of BI 836880 in combination with BI 754091 to characterize safety, tolerability, pharmacokinetics, pharmacodynamics and efficacy in patients with locally advanced or metastatic non-squamous Non-Small Cell Lung Cancer and in other solid tumors
Global Amendment due to urgent safety reasons		☐
Global Amendment		☒
Section to be changed		Synopsis – Study Design and Main in- and exclusion criteria
Description of change		Change from: **Cohort C (SCLC):** Patient with pathologically confirmed locally advanced or metastatic Small Cell Lung Cancer (SCLC) with documented intolerance to platinum-based chemotherapy or refractory to platinum-based chemotherapy (progression during treatment or during < 90 days of the last dose of platinum-based chemotherapy). Patients who are platinum-sensitive (progression ≥ 90 days of the last dose of platinum-based chemotherapy) must also have received at least one other prior line of platinum-based chemotherapy, if eligible, with or without combination with CPI as per applicable local treatment country guidelines. To: **Cohort C (SCLC):** Patient with pathologically confirmed locally advanced or metastatic Small Cell Lung Cancer (SCLC) with documented intolerance to platinum-based chemotherapy or refractory to platinum-based

		chemotherapy (progression during treatment or during < 90 days of the last dose of platinum-based chemotherapy). Patients who are platinum-sensitive (progression ≥ 90 days of the last dose of platinum-based chemotherapy) must also have received one additional prior line of platinum-based chemotherapy, if eligible, with or without combination with CPI as per applicable local treatment country guidelines
Rationale for change		Clarification to understand the inclusion criteria of cohort C SCLC better.
Section to be changed		Synopsis - Number of patients entered:
Description of change		Change from: A total of 315 patients (22 part 1 plus 293 part 2) approximately will be entered (Part 1 and Part2) To: A total of approximately 315 patients (22 in Part 1 plus 293 in Part 2) will be entered.
Rationale for change		Clarification of the wording.
Section to be changed		Synopsis - Number of patients on each treatment
Description of change		Change from: Part 1: 12 to 18 evaluable patients Part 2: 80 evaluable locally advanced or metastatic non-squamous NSCLC patients (Cohort A and B; 40 patients per cohort) and 30 evaluable patients in each of the other 5 cohorts. In total 230 patients To: Part 1: 12 to 18 evaluable patients Part 2: 80 evaluable locally advanced or metastatic non-squamous NSCLC patients (Cohort A and B; 40 patients per cohort) and 30 evaluable patients in each of the other 5 cohorts for a total of 230 patients.
Rationale for change		Clarification of the wording.
Section to be changed		Synopsis - **Main in- and exclusion criteria**
Description of change		Change from: Exclusion Criteria: Part 2: 1 Not more than one CPI based treatment regimen prior to entering study (eg. anti-Programmed Death receptor-1 (PD-1),

		anti-Programmed Death-1 ligand-1 (PD-L1), anti-PD-L2, or anti-cytotoxic T lymphocyte associated antigen-4 (anti-CTLA-4) antibody) unless combination CPIs approved by the local regulatory agencies; For eg., Melanoma cohort (Cohort E) To: 1 Not more than one CPI based treatment regimen prior to entering study (e.g., anti-Programmed Death receptor-1 (PD-1), anti-Programmed Death-1 ligand-1 (PD-L1), anti-PD-L2, or anti-cytotoxic T lymphocyte associated antigen-4 (anti-CTLA-4) antibody). In case of CPIs combination, they need to be approved by the local regulatory agencies (e.g., Melanoma cohort (Cohort E)).
Rationale for change		Clarification for a better understanding of the exclusion criteria.
Section to be changed		Flowchart Part2
Description of change		Change of Safety Follow-up visit period from 30 to 42 day Change the Disease response assessment field Addding to footnote $: HCC cohorts (cohorts F & G) additional tests may include HBV DNA (if needed), HCV RNA (if needed) and Hepatitis D (anti-HDV qualitative). HIV-1 and HIV-2 Ab and r local applicable guidelines. HBsAg, anti-HBc qualitative, anti-HCV qualitative. If positive: test HBV DNA + HCV RNA, anti HDV qualitative
Rationale for change		The change of the residual period was an requirement of the MHRA. The change of the Disease response field is a clarification for a better understanding of the CTP requirements. The adding of the additional wording should clarify the already required hepatitis testing.
Section to be changed		1.1 Medical Backgrounds
Description of change		Added: The planned inclusion of a cohort of patients with locally advanced or metastatic and/or unresectable hepatocellular carcinoma (HCC) with no prior systemic treatment is based on an understanding of the mechanisms involved in the proposed combination therapy, and the available evidence supporting the expectation of enhanced activity with the added inhibition of Ang2 signaling. Hepatocellular carcinoma (HCC) is a vascular tumor and angiogenesis is believed to play an

important role in its progression. The role of anti-VEGF is well established in HCC.
Multikinase inhibitors targeting VEGFR like sorafenib and lenvatinib have been approved as
a first-line treatment in HCC. Given its high immunogenicity, immune checkpoint inhibitors (ICI), targeting the programmed cell death-1 (PD-1) axis have been approved either as monotherapies or in combination with other ICI, such as cytotoxic T lymphocyte antigen-4 (CTLA-4).
Combination therapies involving antiangiogenics and ICI show improved response over antiangiogenic monotherapy (IMbrave 150 trial). It is hypothesized that this is due to the complementary mechanisms involved.
The phase III IMbrave150 study conducted in the previously untreated HCC patients supported the combination of atezolizumab (anti-PDL1) with Bevacizumab (anti-VEGF). Overall response rate was 27% with atezolizumab plus bevacizumab vs 12% compared to sorafenib based on independent assessment using RECIST 1.1 criteria. Median progression-free survival (PFS) was also significantly increased (median 6.8 vs 4.3 months, HR = 0.59; 95% CI = 0.47– 0.76, P < .0001).
The combination therapy being investigated in this trial addresses both mechanisms described above. It combines an anti-PD-1 agent (BI 754091) with a bispecific nanobody (BI 836880) that blocks VEGF and in addition Ang2. Data suggests that this added activity against Ang2 may add to the overall response seen with the combination of ICI and anti-VEGF alone. The rationale for this is described below.
Ang2 leads to immune suppression by distinct mechanisms compared to VEGF. VEGF plays a key role in suppressing tumor immune response by negatively affecting the antigen presenting cells (APCs)[1] and effector T-cells[2,3] while augmenting the effects of immune suppressive cells such as T-regulatory cells (T-regs)[4] and myeloid derived suppressor cells (MDSCs)[5].
Ang-2 increases the neutrophil recruitment and adhesion of both neutrophils and TEMs to endothelium[6] and increases the conversion to M2-like macrophage phenotype[7]. Ang-2 further can stimulate TEMs to secrete IL-10, which can promote the expansion of T-regs and the inhibition of effector T-cells. The Sorafenib HCC Assessment Randomized Protocol (SHARP) trial demonstrated that angiogenesis biomarkers Ang2 and VEGF were independent predictors of survival in patients with advanced HCC[8]. Furthermore, treatment with CTLA-4 and PD-1 blockade in patients with high pre-treatment serum Ang-2 and increased Ang-2 titers post-treatment were found to have worse clinical outcomes compared to patients with lower pre-treatment titers and treatment with immune checkpoint inhibitors can induce

		functional Ang-2 antibodies especially in patients who derive clinical benefits from ICIs[9,10]. Based on the distinct role of Ang-2 in immune suppression of the tumor microenvironment and its role in conferring resistance to therapy targeting only VEGF, we believe selective triple inhibition of anti-VEGF, anti-Ang2 and PD-1 may confer a distinct advantage in the treatment of HCC patients. This is supported by preclinical data from a LL/2 (lewis lung) syngeneic tumour pre-clinical study (please refer to section 5.1.1.4 "Combining BI 836880 with immune checkpoint inhibition" of the IB).
Rationale for change		Adding of new information which supports the medical background of the study.
Section to be changed		**1.4.1 Benefit-Risk Assessment in context of COVID-19 pandemic for patients participating in clinical trials investigating BI 836880 in combination with BI 754091**
Description of change		Adding of: **1.4.1 Benefit-Risk Assessment in context of COVID-19 pandemic for patients participating in clinical trials investigating BI 836880 in combination with BI 754091** Considering the mechanism of action of VEGF/Ang2 inhibition and PD-1receptor blockade, there is no evidence to suggest an increased risk of infection. Based on available data, treatment with BI 836880 alone and in combination with a PD-1 inhibitor is not anticipated to pose a higher risk of acquiring a COVID-19 infection in cancer patients. Overlapping toxicity with VEGF/Ang2 combined with PD1 with an increased risk of infection has not been observed. Considerations around drug-drug interactions are not included in this benefit-risk assessment – this information is provided in the protocol, Investigator's Brochure and the most recent label of the respective medication(s) used for treatment of COVID-19 infection. **BENEFITS AND RISKS CONCLUSIONS AND RECOMMENDATIONS** Patients in clinical trials with BI 836880 and BI 754091 have advanced late stage cancer with limited treatment options. Given the life threatening nature of the underlying disease, the approach recommended by professional oncology organizations (e.g. ASCO, ESMO) remains to treat patients with cancer as under normal circumstances. No consensus on recommendations exist regarding holding chemotherapy or immunotherapy or delaying adjuvant therapy

		or radiotherapy treatment in cancer patients with no signs of a COVID-19 infection. Withdrawing treatment in a cancer patient who may have few or any alternative treatment options requires a careful, individual evaluation. To date, there is no evidence suggesting a link between susceptibility to COVID-19 infections and the inhibition of VEGF-A and Ang2 targeted by BI 836880. Also, there is no evidence suggesting a link between susceptibility to COVID-19 infections and the inhibition of PD-1/PDL-1. Available non-clinical and clinical data from completed clinical trials have not shown an increased risk of infections with BI 836880 and BI 754091. Considering the limited and sparse data on immune activation and the role of inflammation as well as other underlying factors that may increase the severity and mortality from COVID-19 infection, there may be some factors representing the risk for using VEGF/Ang2 or PD1 that are currently still unknown. The information about the risk factors, the severity and the activity of immune response in patient with COVID-19 infections will be constantly monitored as it evolves. All up-to-date information about the investigational compounds (preclinical, clinical, clinical pharmacology) is included in the trial documentation, including IB, clinical trial protocol for the guidance of the investigator. The latter also outlines the pre-cautionary eligibility criteria, measures for management of associated AEs, required dose reductions etc. The protocol-defined trial procedures themselves do not impose any increased risk to study participants in developing COVID-19 infection. The risk mitigation measures currently in place within the clinical trial protocols are a sufficient safeguard, as patients are frequently monitored with comprehensive safety evaluations. Based on laboratory data and any adverse event that may occur, clinical trial protocols include guidance for the continuation, interruption, dose reduction, and discontinuation of study drugs. Therefore, assuming the protocol-defined requirements for continued study drug administration are met, the decision about concomitant use of experimental anti-cancer therapy with VEGF/Ang2 and PD1 with COVID-19 treatment in case of contracted COVID-19 infection will be left to the investigator's benefit-risk assessment on a case-by-case basis. The investigators will take the totality of information related to each single patient and the local COVID-19 situation into consideration

		when performing the individual benefit-risk assessment on a case-by-case basis. Considering all aspects, the investigator will decide upon each patient's (continued) participation in the planned trials. BI as the sponsor, recommend to adhere to the trial protocol and where required, will support the investigator in their decision finding, where this protects the safety, wellbeing and/or is in the best interest of the patient.
Rationale for change		Additing of the risk/ benefit assessment in context of the covid-19
Section to be changed		[redacted]
Description of change		
Rationale for change		
Section to be changed		3.1. OVERALL TRIAL DESIGN AND PLAN – Part 2
Description of change		Change from: It is foreseen to enroll up to 230 patients of full age (according to local legislation, usually ≥ 18 years) at screening in different indications: Patients with locally advanced or metastatic 2nd or 3rd line CPI resistant non-squamous Non-Small Cell Lung Cancer (NSCLC) and ≥2nd line Small Cell Lung Cancer (SCLC) and recurrent glioblastoma and IO failure metastatic melanoma,1st line HCC patients or HCC patients who were intolerant or progressed during or after standard first line treatment with sorafenib or lenvatinib. Patients who received 2nd line treatment with anti-PD1 therapy (but not other therapy) after failure of sorafenib or lenvatinib are also eligible (see image below – **please note the cohorts will run in parallel, not sequential**) (see Figure 3.1: 1). 1st line HCC cohort will be implemented only in

		countries UK, Korea, Taiwan, Hong Kong, Poland, Ukraine, Russia, Spain, USA, Australia To: It is foreseen to treat up to 230 patients of full age (according to local legislation, usually ≥ 18 years) at screening in different indications: patients with locally advanced or metastatic 2nd or 3rd line CPI resistant non-squamous Non-Small Cell Lung Cancer (NSCLC), ≥2nd line Small Cell Lung Cancer (SCLC), recurrent glioblastoma, IO failure metastatic melanoma, 1st line HCC patients or HCC patients who were intolerant or progressed during or after standard first line treatment with sorafenib or lenvatinib. **Please note that the cohorts will run in parallel, not sequentially** (see Figure 3.1: 1). The 1st line HCC cohort will be implemented only in countries: UK, Korea, Taiwan, Hong Kong, Poland, Ukraine, Russia, Spain, USA, Australia, Japan. Figure 3.1:1 adapted
Rationale for change		Clarification of wording and adding of Japan as a country which 1st line HCC will be implemented.
Section to be changed		**3.3.1. Main diagnosis for trial entry**
Description of change		Change from: For the part 1 we look for patients with advanced/metastatic non squamous NSCLC who have progressed during or after first line (in case of naïve patients) of platinum-based therapy and patients who relapsed after completion of at least 2 cycles (in case of relapsed patients) of a CPI treatment alone or in combination with platinum-based chemotherapy (monotherapy or in combination with chemotherapy). Patients included in Part1 are not eligible to participate in Part 2. For the part 2 we look for patients with locally advanced or metastatic 2nd and 3rd line CPI resistant NSCLC and 2nd line SCLC, recurrent glioblastoma, IO failure metastatic melanoma, 1st line HCC patients and HCC patients who are intolerant or failed the first line treatment with sorafenib or lenvatinib. HCC patients who received 2nd line treatment with anti-PD1 therapy (but not other therapy) after failure of sorafenib or lenvatinib are also eligible. Please refer to Section 8.3.1 (Source Documents) for the documentation requirements pertaining to the in- and exclusion criteria. To: In Part 1, the following patients are allowed for trial entry: patients with advanced/metastatic non squamous NSCLC who have progressed during or after first line (in case of naïve patients) of platinum-based

		therapy and patients who relapsed after completion of at least 2 cycles (in case of relapsed patients) of a CPI treatment alone or in combination with platinum-based chemotherapy (monotherapy or in combination with chemotherapy). Patients included in Part 1 are not eligible to participate in Part 2. In Part 2, the following patients are allowed for trial entry: patients with locally advanced or metastatic as 2nd and 3rd line CPI resistant NSCLC and 2nd line SCLC, recurrent glioblastoma, IO failure metastatic melanoma, 1st line HCC patients and HCC patients who are intolerant or failed the first line treatment with sorafenib or lenvatinib.
Rationale for change		Clarification for a better understanding.
Section to be changed		**3.3.2: Inclusion criteria – Part 2** **Main Inclusion Criteria for all cohorts**
Description of change		Change from: 2. At least one measurable target lesion outside the brain (excluding the glioblastoma patients), that can be accurately measured per RECIST v 1.1 **Cohort C (SCLC):** - Pathologically confirmed locally advanced or metastatic SCLC. Documented intolerance to platinum-based chemotherapy or refractory to platinum-based chemotherapy (progression during treatment or during < 90 days of the last dose of platinum-based chemotherapy). Patients who are platinum-sensitive (progression ≥ 90 days of the last dose of platinum-based chemotherapy) must also have received at least one other prior line of platinum-based chemotherapy, if eligible, with or without combination with CPI as per applicable local treatment country guidelines. To: 3. At least one measurable target lesion outside the brain (excluding the glioblastoma patients where brain lesions are allowed), that can be accurately measured per RECIST v 1.1 or RANO. **Cohort C (SCLC):** - Pathologically confirmed locally advanced or metastatic SCLC. Documented intolerance to platinum-based chemotherapy or refractory to platinum-based chemotherapy (progression during treatment or during < 90 days of the last dose of platinum-based chemotherapy). Patients who are platinum-sensitive (progression ≥ 90

		days of the last dose of platinum-based chemotherapy) must also have received one additional prior line of platinum-based chemotherapy, if eligible, with or without combination with CPI as per applicable local treatment country guidelines. Adding of Japan for the countries where Cohort G- 1st line HCC will be implemented.
Rationale for change		Clarification of the main inclusion criteria #2 and the cohort C- SCLC and adding of Japan to the countries where Cohort G will be implemented.
Section to be changed		3.3.3 – Exclusion criteria Part 2 - #2
Description of change		Change from: Not more than one CPI based treatment regimen prior to entering study (eg. anti-Programmed Death receptor-1 (PD-1), anti-Programmed Death-1 ligand-1 (PD-L1), anti-PD-L2, or anti-cytotoxic T lymphocyte associated antigen-4 (anti-CTLA-4) antibody) unless combination CPIs approved by the local regulatory agencies; For eg., Melanoma cohort (Cohort E). To: Not more than one CPI based treatment regimen prior to entering study (eg. anti-Programmed Death receptor-1 (PD-1), anti-Programmed Death-1 ligand-1 (PD-L1), anti-PD-L2, or anti-cytotoxic T lymphocyte associated antigen-4 (anti-CTLA-4) antibody).In case of CPIs combination, they need to be approved by the local regulatory agencies; for e.g., Melanoma cohort (Cohort E).
Rationale for change		Clarification of exclusion criteria #2 for a better understanding
Section to be changed		**4.1.4. Drug assignment and administration of doses for each patient**
Description of change		Change from: The expected infusion time is 60 minutes for BI 754091 and same for BI 836880; BI 754091 will be administered first, then 15 minutes (+/- 10 min) after the end of this infusion BI 836880 will be administered. In case no relevant infusion reactions are observed, this can be shorten to about 30 minutes for BI836880 only but should not be prolonged to more than 6 hours for BI 836880 and should not be prolonged to more than 2 hours for BI 754091, also in case of technical issues. Appropriate drugs and medical equipment to treat anaphylactic reactions must be immediately available and study personnel must be trained to recognize and treat anaphylaxis.

		If symptoms of an infusion-related reaction CTCAE grade 2 or higher, the infusion should be temporarily stopped. The intensity and prolongation of vital sign monitoring should be considered. Upon recovery, the study drug should be infused at 50% of the rate at which the reaction occurred. Depending on the time of occurrence and the severity of the reaction, the investigator may consider administering additional supportive medication, e.g. corticosteroids for re-introduction. Infusion rate and premedication for further treatment cycles should be adapted according to Investigator decision, but adaption of administration scheme need to be agreed with sponsor. To: The expected infusion time is 60 minutes for BI 754091 and same for BI 836880; BI 754091 will be administered first, then 15 minutes (+/- 10 min) after the end of this infusion BI 836880 will be administered. In case of technical issues or complications during infusion, the total infusion time (including stop time and flushing) for BI836880 should not exceed 360 minutes. <u>For BI 754091, in case of technical issues or complications during infusion</u>, the total infusion time (including stop time) should not exceed 180 minutes. Appropriate drugs and medical equipment to treat anaphylactic reactions must be immediately available, and study personnel must be trained to recognize and treat anaphylaxis. In the event of an infusion-related reaction ⩽ Grade 2, the infusion rate of BI 754091 may be decreased by 50% or interrupted until resolution of the event and re-initiated at 50% of the initial rate until completion of the infusion. In patients experiencing infusion-related reactions ⩽ Grade 2, subsequent infusions may be administered at 50% of the initial rate. Depending on the time of occurrence and the severity of the reaction, the investigator may consider administering additional supportive medication, e.g. corticosteroids for re-introduction. Infusion rate and premedication for further treatment cycles should be adapted according to Investigator decision, but adaption of administration scheme need to be agreed with sponsor. If an infusion related reaction is Grade 3 or higher in severity at any point during the study, treatment with BI 754091 has to be permanently discontinued. Adding of:

		Rescreening is generally not allowed. In individual cases, rescreening can be considered in alliance with the sponsor.
Rationale for change		Change of the administration time for BI 836880 and adding of wording regarding the new available information for infusion related reaction in line with the new wording for Appendix 10.4. Adding for wording regarding rescreening of patients.
Section to be changed		4.2.2. Restrictions
Description of change		Adding of wordin G: …For patients in the cohort D (Glioblastoma) higher doses of corticosteroids may be allowed as defined in the cohort-specific eligibility criteria.
Rationale for change		Adding to use higher corticosteroids for Cohort D Glioblastoma patient-
Section to be changed		5.1 Assessment of efficacy
Description of change		Change from: … Efficacy endpoints will be assessed every 2 cycles (6 weeks) as specified in the FC. An additional evaluation at EoT is only applicable; when patient has no PD documented, will not continue with regular imaging in Follow-up period and did not have imaging within the last 4 weeks before EoT. At Safety Follow-up visit, in case a patient has discontinued due to PD one additional tumor assessment should be done in case no other cancer treatment has been initiated. All measurements must be recorded in metric notation. All tumor imaging performed in this trial will be collected by authorized CRO and stored until shipment to Boehringer Ingelheim. The CRO will not be implicated in tumor response evaluation. This collected data may be considered for central review at a later time point. To: Efficacy endpoints will be assessed every 2 cycles (6 weeks) as specified in the FC. An additional evaluation at EoT is only applicable; when patient has no PD documented, will not continue with regular imaging in Follow-up period and did not have imaging within the last 4 weeks before EoT. In case a patient has discontinued due to PD one additional tumor assessment should be done according to iRECIST in case no other cancer treatment has been initiated (confirming image should be done 4 – 6 weeks after the last image). For Glioblastoma patients, an additional image according to iRANO should be taken 3 month after PD. All measurements must be recorded in metric notation.

		All tumor imaging performed in this trial will be collected by authorized CRO and stored until shipment to Boehringer Ingelheim. The CRO will not be implicated in tumor response evaluation. This collected data might be considered for central review at a later time point.
Rationale for change		Calrification regarding the required use f iRANO and iRecist in the trial.
Section to be changed		5.2.3 Safety laboratory parameters – infection screening
Description of change		Adding of wording: HIV-1 and HIV-2 Ab and HBsAg, anti-HBc qualitative, anti-HCV qualitative for all patients. as per local applicable guidelines. HBsAg, anti-HBc qualitative, anti-HCV qualitative. If positive: test HBV DNA + HCV RNA, anti HDV qualitative.
Rationale for change		Clarification which parameters for the infection screening for which cohort are needed.
Section to be changed		
Description of change		Change from: <u>Infusion-related reactions</u> All infusion-related reactions need to be reported as AESIs. In the event of an infusion-related reaction ≥ Grade 2, the infusion rate of BI 836880 or BI 754091 may be decreased by 50% or interrupted until resolution of the event and re-initiated at 50% of the initial rate until completion of the infusion. In patients experiencing infusion-related reactions ≥ Grade 2, subsequent infusions may be administered at 50% of the initial rate. If a patient experiences an infusion-related reaction, acetaminophen and/or an antihistamine (e.g., diphenhydramine) and/or corticosteroid or equivalent medication per institutional standard may be administered prior to subsequent infusions at the discretion of the Investigator for secondary prophylaxis of infusion-related reactions. If an infusion-related reaction is Grade 4 or higher in severity at any point during the study, treatment with BI 836880 or BI 754091 will be permanently discontinued. To: <u>Infusion-related reactions</u> All infusion-related reactions need to be reported as AESIs. In the event of an infusion-related reaction ⩽ Grade 2, the infusion rate of BI 836880 or BI 754091 may be decreased by 50% or interrupted until resolution of the event and re-initiated at 50% of the

		initial rate until completion of the infusion. In patients experiencing infusion related reactions ⩽ Grade 2, subsequent infusions may be administered at 50% of the initial rate. If a patient experiences an infusion-related reaction, acetaminophen and/or an antihistamine (e.g., diphenhydramine) and/or corticosteroid or equivalent medication per institutional standard may be administered prior to subsequent infusions at the discretion of the Investigator for secondary prophylaxis of infusion-related reactions. If an infusion-related reaction is Grade 3 or higher in severity at any point during the study, treatment with BI 836880 or BI 754091 will be permanently discontinued.
Rationale for change		Adapted wording because of new program related information.
Section to be changed		5.2.7.2 Adverse event collection and reporting
Description of change		Change from: … **<u>AE reporting to sponsor and timelines</u>** 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 reporting process 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. To: **<u>AE reporting to sponsor and timelines</u>** 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 reporting process 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 send the BI SAE form.

Rationale for change		Adaption needed as of new distribution possibilities in some countries.
Section to be changed		5.4 Assessment of Biomarkers
Description of change		[redacted]
Rationale for change		Wording needed to be adapted for the use of radiomics
Section to be changed		[redacted]
Description of change		
Rationale for change		
Section to be changed		
Description of change		

		[redacted]
Rationale for change		
Section to be changed		**6.2.1 Screening and run-in period(s)**
Description of change		Change from: The examinations required for the screening visit may be conducted within a time interval of 21 days prior to the first study drug administration. Prior to any other study related procedure, written informed consent must be obtained from the patient. To: The examinations required for the screening visit may be conducted within a time interval of 21 days prior to the first study drug administration. Prior to any other study related procedure, written informed consent must be obtained from the patient. ECOG and Physical examination can be performed the day prior to the start of treatment cycle.
Rationale for change		Allowing a bigger window for certain pre-treatment assessments.
Section to be changed		**6.2.4 Residual effect period (REP)**
Description of change		Change from: The REP is defined in Section 5.2.7.2. The End of REP the Safety Follow-up visit should not be performed earlier than 30 days after permanent discontinuation of the trial medication (last day medication was administered).

		To: The REP is defined in Section 5.2.7.2. The End of REP the Safety Follow-up visit should not be performed earlier than 42 days after permanent discontinuation of the trial medication (last day medication was administered).
Rationale for change		MHRA requestde change back from 30 to 42 days.
Section to be changed		7.4 Interim Analyse
Description of change		Change from: **Part 2:** In Part 2, 230 patients are planned to be treated. 40 patients each are planned for cohorts A and B, and 30 patients each are planned for cohorts C, D, E, F, and G. An interim futility analysis will be performed for cohorts C, D, E, F, and G in Part 2. The interim analyses for each cohort are planned to be conducted after 15 patients in that cohort have completed their two on-treatment imaging assessments (i.e., end of cycle 4). For each cohort, timing of the interim analysis may be adjusted according to actual recruitment rate to facilitate or avoid delay of the trial conduct. Until any decision from the futility analysis is done, the enrollment of next patient will not be stopped. The two-stage design is planned to stop further recruitment of patients if the defined efficacy boundary (see Table 7.7.2: 1) is not met at the first stage. In addition, if considered necessary, interim analysis may be performed for evaluation of the efficacy and safety aspects as each cohort is finished. To: **Part 2:** In Part 2, 230 patients are planned to be treated. 40 patients each are planned for cohorts A and B, and 30 patients each are planned for cohorts C, D, E, F, and G. The Sponsor may pause enrollment in any cohort at any time to carefully evaluate the safety and efficacy data of patients already enrolled in a given cohort. An interim futility analysis will be performed for cohorts C, D, E, F, and G in Part 2. The interim analyses for each cohort are planned to be conducted after 15 patients in that cohort have completed their two on-treatment imaging assessments (i.e., end of cycle 4 or later depending on the cohort). For each cohort, timing of the interim analysis may be adjusted according to actual recruitment rate to facilitate or avoid delay of the trial conduct. The Sponsor may pause enrollment in a

		cohort before making any decisions from the interim futility analysis. The two-stage design is planned to stop further recruitment of patients if the defined efficacy boundary (see Table 7.7.2: 1) is not met at the first stage.
Rationale for change		Adding possibility to pause a cohort before making any decision from the interim futility analysis.
Section to be changed		**7.7.2 Determination of sample size for Part 2**
Description of change		Change fropm: • Cohort C: - patients with locally advanced or metastatic Small Cell Lung Cancer, with no more than one line of chemotherapy • Cohort D: - patients with histologically confirmed recurrent glioblastoma (primary), with no more than one line of chemotherapy (concurrent and adjuvant temozolomide based chemotherapy) To: • Cohort C: - patients with locally advanced or metastatic Small Cell Lung Cancer, with no more than one line of chemotherapy, except platinum sensitive patients. • Cohort D: - patients with histologically confirmed recurrent glioblastoma (primary), **No more than two lines of prior chemotherapy** (concurrent and adjuvant temozolomide based chemotherapy including in combination with another investigational agent is considered one line of chemotherapy).
Rationale for change		Clarification of the CTP v5.0.
Section to be changed		**10.4 MANAGEMENT OF IMMUNE-RELATED ADVERSE EVENTS**
Description of change		Change of the complete appendix section
Rationale for change		As of new available program information the section was accordantly adapted.
Section to be changed		Table 10.5.1: 2 change of footnote**
Description of change		Change from: **For the HCC cohorts, only the Cycle 1 Day 1 sample will be collected for ANG/VEGF, but no on-treatment samples, and NO KYN:TRP samples To:

		**For the HCC cohorts, only the Cycle 1 Day 1 pre-treatment sample will be collected for ANG/VEGF, but no on-treatment samples, and NO KYN:TRP samples
Rationale for change		Clarification for the collection of the biomarker samples.
Section to be changed		**6. Investigational Plan**
Description of change		Added wording: In the event of force majeure or other disruptive circumstances (e.g. pandemic, war) the investigational plan as per this clinical trial protocol may not be feasible at a site. With the consent of the patient, sponsor and investigator may agree on alternative, back-up or rescue methodology. The implementation of these measures will depend on patient's consent, operational feasibility, local law and regulations. If alternative methodology is implemented, the deviations from the original plan will be precisely documented.
Rationale for change		Adaption to handle crisis which may occur and affect the trial and patient safety.

11.6 GLOBAL AMENDMENT 6

Date of amendment		16 Aug 2021
EudraCT number **EU number**		2017-001378-41
BI Trial number		1336-0011
BI Investigational Product(s)		BI 836880 (anti-VEGF/Ang2) Ezabenlimab (BI 754091 [anti-PD-1])
Title of protocol		An open label phase Ib dose finding study of BI 836880 in combination with ezabenlimab to characterize safety, tolerability, pharmacokinetics, pharmacodynamics and efficacy in patients with locally advanced or metastatic non-squamous Non-Small Cell Lung Cancer and in other solid tumors
Global Amendment due to urgent safety reasons		☐
Global Amendment		☒
Section to be changed		All sections
Description of change		Change from: BI 754091 To: Ezabenlimab
Rationale for change		Name registered for BI 754091.
Section to be changed		Cover page
Description of change		Change from: BI 836880 BI 754091 To: BI 836880 (anti-VEGF/Ang2) Ezabenlimab (BI 754091 [anti-PD-1])
Rationale for change		Adding information regarding the molecules
Section to be changed		CLINICAL TRIAL PROTOCOL SYNOPSIS 3.1 OVERALL TRIAL DESIGN AND PLAN 3.3 SELECTION OF TRIAL POPULATION
Description of change		Change from:

		Cohort G to be implemented only in countries UK, Korea, Taiwan, Hong Kong, Poland, Ukraine, Russia, Spain, USA, Australia. To: Cohort G to be implemented only in countries where this cohort is approved.
Rationale for change		Additional countries could be added to contribute to cohort G recruitment.
Section to be changed		CLINICAL TRIAL PROTOCOL SYNOPSIS Flowchart Part 2 3.1 OVERALL DESIGN AND PLAN 3.3 SELECTION OF TRIAL POPULATION 5.2.3 Safety Laboratory Parameters 5.4.1 Methods of sample collection 7.4 INTERIM ANALYSES 7.7.2 Determination of sample size for Part 2
Description of change		Cohort H added, including number of patients to be enrolled, patient population, inclusion/exclusion criteria, applicable procedures and statistical considerations
Rationale for change		Adding cohort H for further exploration of preliminary efficacy and safety among 2nd line HCC patients
Section to be changed		CLINICAL TRIAL PROTOCOL SYNOPSIS (Primary endpoints):
Description of change		Change from: The primary endpoint is the shrinkage estimator of objective response (OR) based on BHM. OR is defined as best overall response (RECIST 1.1) of complete response (CR) or partial response (PR) from first treatment infusion until the earliest of disease progression, death or last evaluable tumor assessment before start of subsequent anti-cancer therapy, lost to follow-up, or withdrawal of consent. To: The primary endpoint is Objective Response (OR) defined as best overall response (RECIST 1.1) of complete response (CR) or partial response (PR) from first treatment infusion until the earliest of disease progression, death or last evaluable tumor assessment before start of subsequent anti-cancer therapy, lost to follow-up, or withdrawal of consent.
Rationale for change		Consistency with Section 2.1.2
Section to be changed		CLINICAL TRIAL PROTOCOL SYNOPSIS (Secondary endpoints):

Description of change		Change from: **PART 1:** • Pharmacokinetic parameters C_{max}, t_{max}, AUC_{0-504h} after the first infusion cycle. **PART 2:** • - Pharmacokinetic parameters C_{max}, t_{max}, AUC_{0-504h} after the first and fourth infusion cycle. To: **PART 1:** • Pharmacokinetic parameters C_{max}, t_{max}, AUC_{0-504h} after the first and fourth infusion cycle. **PART 2:** • Pharmacokinetic parameters C_{max}, t_{max}, AUC_{0-504h} after the first infusion cycle.
Rationale for change		Updated timepoints to be in line with section 2.
Section to be changed		CLINICAL TRIAL PROTOCOL SYNOPSIS 3.1 OVERALL TRIAL DESIGN AND PLAN 3.3 SELECTION OF TRIAL POPULATION 7.4 INTERIM ANALYSES 7.7.2 Determination of sample size for Part 2
Description of change		Number of patients updated from 293 to 420 screened and from 230 to 290 evaluable patients (treated) in Part 2.
Rationale for change		Number of patients updated due to the addition of cohort H and 30 additional patients in cohort F.
Section to be changed		FLOW CHART (PART 2) 2.2.2 Further endpoints 6.2.5.2 Follow up for Overall Survival
Description of change		Adding Overall Survival as a further enpoint and the Follow up for Overall Survival status visit
Rationale for change		Data collection for new Further endpoint in Part 2
Section to be changed		FLOW CHART (PART 2) 10.5.1:2 Time schedule for PK blood sampling during treatment cycles for Part 2
Description of change		PK, ADA and Biomarker sample collection timepoints have been updated (from visits 2 to 12 to visits 2 - onwards).
Rationale for change		Further sample analysis planned for all treatment visits.
Section to be changed		Flowchart (PART 2) - footnotes

Description of change		Change from: 8 Tumour assessments should be done according to RECIST v1.1 and iRECIST for all cohorts except GBM. RANO/iRANO criteria to be followed for GBM cohort. Assessments should include computed tomography (CT) scans of the chest and abdomen only, if clinically indicated, imaging of any other known or suspected sites of disease (e.g., pelvis, brain) using an appropriate method (CT scan or magnetic resonance imaging [MRI]). The same radiographic procedure must be used throughout the trial. Baseline evaluation must be performed as close as possible to the treatment start and no more than 28 days before start of treatment (For GBM – 14 days prior to treatment). Tumour assessment should be done every 6 weeks (in accordance to local requirements). Assessments are always done prior to the start of the new treatment cycle (window is up to minus 7 days).. To: 8 Tumour assessments should be done according to RECIST v1.1 and iRECIST for all cohorts except GBM. RANO/iRANO criteria to be followed for GBM cohort. Assessments should include computed tomography (CT) scans of the chest and abdomen only, if clinically indicated, imaging of any other known or suspected sites of disease (e.g., pelvis, brain) using an appropriate method (CT scan or magnetic resonance imaging [MRI]). The same radiographic procedure must be used throughout the trial. Baseline evaluation must be performed as close as possible to the treatment start and no more than 28 days before start of treatment (For GBM – 14 days prior to treatment). Tumour assessment should be done every 6 weeks (± 7 days) (in accordance to local requirements). Assessments are always done prior to the start of the new treatment cycle.
Rationale for change		Allowing a wider window for tumour assesments
Section to be changed		Flowchart (PART 2) 5.4.1 Methods of sample collection
Description of change		Change from 14-16 G to 16G and 3 18G to 4 18 G needle biopsies to be obtained. Change from 26 to 20 archival 4 µm sections from archival block to be provided.
Rationale for change		Modifying needle size to have enough material for analysis.
Section to be changed		ABBREVIATIONS
Description of change		Adding EMA, FDA, EWOC, OS
Rationale for change		Inclusion of the new abbreviations used in the main text
Section to be changed		1.1 MEDICAL BACKGROUND 1.3 RATIONALE FOR PERFORMING THE TRIAL
Description of change		Addition of introduction and rationale to include HCC patients in second line (atezo-bev failures)
Rationale for change		Adding justification for the addition of cohort H.

Section to be changed		1.4 BENEFIT – RISK ASSESSMENT
Description of change		Updated information regarding the number of treated patients and adverse events observed.
Rationale for change		Updating information according to the last Investigator Brochure
Section to be changed		[redacted]
Description of change		
Rationale for change		
Section to be changed		3.1 OVERALL TRIAL DESIGN AND TRIAL POPULATION 7.1.2 Statistical design – Part 2 (dose expansion cohorts) 7.2 NULL AND ALTERNATIVE HYPOTHESES 7.3.1 Primary endpoint analyses 7.7.2 Determination of sample size for Part 2 7.7.3 Determination of additional sample size for stage II in cohort F
Description of change		Addition of 30 patients in cohort F: justification and statistical considerations and justification and statistical considerations for the adding of 30 patients to cohort H.
Rationale for change		Observed response rates in cohort F have triggered the decision to add 30 more patients in the cohort F and to add the new cohort H for the same patient pool, but pretreated with the new standard of care,
Section to be changed		4.1.4 Drug assignment and administration of doses for each patient
Description of change		Text added: In some cases, in discussions with the Sponsor, treatment with one of the two investigational drugs can be allowed if there is an AE reported which can be clearly attributed to one of the two drugs and further warrants a temporary discontinuation of this drug in the interest of the patient.
Rationale for change		Allow certain flexibility to continue treatment with one drug only.
Section to be changed		5.3.1 Assessment of pharmacokinetics 7.4 INTERIM ANALYSES
Description of change		Change from: Exploratory pharmacokinetic analyses can be performed as necessary for safety review as well as for dose selection in part 2 of the trial, but require sufficient lead time to collect samples, measure plasma concentrations, analyze data and prepare meaningful outputs. … In contrast to the final PK analysis, the exploratory analyses will be based on planned sampling times rather than on actual times; no

		supplementary subject information, e.g. on adverse events of concomitant medication, will be used in these analyses, and the outputs will not be validated. Minor discrepancies between interim and final results may therefore occur. To: Exploratory pharmacokinetic and ADA analyses can be performed as necessary for safety review, for dose selection in part 2 of the trial as well as further project planning, but require sufficient lead time to collect samples, measure plasma concentrations, analyze data and prepare meaningful outputs. Exploratory data may also be used for modelling activities. … In contrast to the final PK analysis, the exploratory analyses will be based on planned sampling times rather than on actual times; the outputs will not be validated. Minor discrepancies between interim and final results may therefore occur. Additional text: Exploratory analyses of PK/PD may be additionally performed during Part 2 and if considered informative for the study
Rationale for change		Addition of ADA and allowing model set up for part 2 data.
Section to be changed		8.6 TRIAL MILESTONES
Description of change		Change from: **The end of the trial** is defined as the date of the last visit of the last patient in the whole trial (“Last Patient Out”). To: **The end of the trial** is defined as the date of the last visit of the last patient in the whole trial (“Last Patient Out”), or when all patients have been discontinued from study treatment and followed up for overall survival for at least 12 weeks after treatment discontinuation.
Rationale for change		End of trial definition updated due to the addition of overall survival.
Section to be changed		9. PUBLISHED REFERENCES
Description of change		References added or updated
Rationale for change		Adding references that support the protocol updates.

Section to be changed		Minor editorial changes were done across the protocol
Description of change		
Rationale for change		Clarification
Section to be changed		1.2 DRUG PROFILE
Description of change		Information for BI 836880 and Ezabenlimab was adapted.
Rationale for change		The CTP was adapted according to the latest available IB information regarding the profiles of the two IMP compounds.

11.7 GLOBAL AMENDMENT 7

Date of amendment		01 Mar 2022
EudraCT number EU number		2017-001378-41
BI Trial number		1336-0011
BI Investigational Product(s)		BI 836880 (anti-VEGF/Ang2) Ezabenlimab (BI 754091 [anti-PD-1])
Title of protocol		An open label phase Ib dose finding study of BI 836880 in combination with ezabenlimab to characterize safety, tolerability, pharmacokinetics, pharmacodynamics and efficacy in patients with locally advanced or metastatic non-squamous Non-Small Cell Lung Cancer and in other solid tumors
Global Amendment due to urgent safety reasons		☐
Global Amendment		☒
Section to be changed		Cover
Description of change		From: [redacted] Phone: [redacted] Fax: [redacted] To: [redacted]

		[redacted] Phone: [redacted] Fax: [redacted]
Rationale for change		New CTL contact details updated
Section to be changed		Synopsis – Duration of treatment
Description of change		From: Treatment will continue until disease progression, undue toxicity or Informed consent withdrawn To: Treatment may continue until disease progression, undue toxicity, withdrawal of patient consent, or 53 cycles [approximately 3 years] from the start of first treatment administration, whichever occurs first. Patients will be allowed to stay on treatment also in the case of initial radiological PD, until progression is confirmed or up to 53 cycles from the start of first treatment administration if the investigator considers that the treatment is beneficial for the patient
Rationale for change		Treatment period limitation added due to the program discontinuation
Section to be changed		Flow chart Part 1 and Flow chart Part 2
Description of change		Total number of cycles limited to 53
Rationale for change		Treatment period limitation added due to the program discontinuation
Section to be changed		Flow chart Part 1 and Flow chart Part 2
Description of change		Central lab samples collection discontinuation
Rationale for change		To reduce patient burden due to the program discontinuation for the remaining visits
Section to be changed		Flow chart Part 1 and Flow chart Part 2 (footnotes)
Description of change		From: Tumour assessment every 6 weeks (in accordance to local requirements) starting from first trial medication infusion. At EOT and EOR only when applicable (see Section 5.1). To: Tumour assessment can be performed according to institutional practices and SOC from the data cut-off date for interim database lock forward, starting from first trial medication infusion.
Rationale for change		Imaging adjusted to standard of care to reduce patient burden after program discontinuation decision on December 2021.
Section to be changed		Flow chart Part 2

Description of change		Biopsies removed
Rationale for change		To reduce patient burden after program discontinuation decision on December 2021.
Section to be changed		Flow chart Part 2
Description of change		FUP for survival status removed
Rationale for change		Program discontinuation decision from December 2021.
Section to be changed		ABBREVIATIONS
Description of change		Addition of SOC
Rationale for change		Inclusion of new abbreviation used in the main text.
Section to be changed		1.1 MEDICAL BACKGROUND
Description of change		Update in the number of treated patients.
Rationale for change		Updated information.
Section to be changed		1.1 MEDICAL BACKGROUND
Description of change		Last paragraph with preliminary responses removed: Although available data from the ongoing clinical program for the ezabenlimab + BI 836880 combination indicate a positive benefit risk ratio, with signs of antitumor activity and manageable safety profile, BI decided in December 2021 to discontinue further development with this combination due to evolving standards of care in the indications under investigation. As a part of this decision, any patients still ongoing will be allowed to continue to receive treatment with the investigational regimen until progression or 53 cycles [approximately 3 years] from the start of first treatment administration until treatment expires in early 2025, whichever comes first.
Rationale for change		Information outdated.
Section to be changed		1.2. DRUG PROFILE
Description of change		Safety update according to IB BI 836880 version 17 Aug 2021 and ezabenlimab IB version 19 Jan 2022
Rationale for change		New safety information available.
Section to be changed		1.3 RATIONALE FOR PERFORMING THE TRIAL

Description of change		Addition: DECISION TO TERMINATE THE TRIAL Although a preliminary assessment of the available data from the ongoing clinical program for the ezabenlimab + BI 836880 combination exhibit signs of antitumor activity and a manageable safety profile for an overall positive benefit risk ratio, careful review of the full data set performed in the context of the current standards of care for the indications under study has led to the decision taken by the sponsor in December 2021 to discontinue recruitment in study 1336.11, and terminate further expansion of the study. An important consideration in the review process was whether the investigational combination treatment under study, namely BI 836880 plus ezabenlimab, had demonstrated benefit that delivered clear improvement over the current standards of care, some of which had evolved over the course of the study. The measure used to evaluate efficacy was the Objective Response Rate (ORR) which was the primary efficacy endpoint of the trial. It is important to note that at the time of this evaluation all cohorts had completed planned enrolment, and sufficient data had been collected to support a well-informed decision. Based on this evaluation, the efficacy observed in the different indications did not show clear improvement over the standards of care relative to published efficacy results in the different indications, with the one possible promising result in the 2L HCC cohort. This finding, however, was confounded by the population studied. The 2L HCC cohort enrolled patients that had received prior 1L treatment with monotherapy anti-angiogenic TKi (i.e., either sorafenib or lenvatinib). Given the evolution of the standard of care for 1L HCC, from monotherapy anti-angiogenic TKi treatment to combination treatment with immune checkpoint inhibitor plus an anti-angiogenic agent, it was determined that this cohort was not representative of what is expected to be the 2L HCC patient population moving forward. Based on this evaluation, the decision was taken to terminate the trial. As a part of this decision, for patients still under active treatment, treatment with BI 836880 plus ezabenlimab may continue until disease progression, undue toxicity, withdrawal of patient consent, or 53 cycles [approximately 3 years] from the start of first treatment administration, whichever occurs first (see Section 4.1.4, “Treatment duration” for full details).

Rationale for change		To include information regarding the program discontinuation decision.
Section to be changed		3.1 OVERALL TRIAL DESIGN AND PLAN 3.2 DISCUSSION OF TRIAL DESIGN, INCLUDING THE CHOICE OF CONTROL GROUP(S) 3.3 SELECTION OF TRIAL POPULATION
Description of change		Addition:
Rationale for change		As of the decision of Boehringer Ingelheim in Dec 2021 no additional patients will be further included to the trial.
Section to be changed		To include information regarding the program discontinuation decision.
Description of change		Deletion: BI 836880 + ezabenlima will be administered (infusion every 3 weeks. In the case the patient shows a stable disease or response, the administration of BI 836880 and Ezabenlimab can be continued up o desease progression or until intolerable toxicity has been observed.
Rationale for change		Information moved to Section 4.1.4
Section to be changed		4.1 INVESTIGATIONAL TREATMENTS (tables 4.1.1: 1 and 4.1.1: 2)
Description of change		From: BI836880. Duration of use: until progression or unacceptable toxicity BI 754091 Duration of use: until progression or unacceptable toxicity To: BI836880. Duration of use: until progression, unacceptable toxicity, or up to a maximum of 53 cycles BI 754091 Duration of use: until progression, unacceptable toxicity, or up to a maximum of 53 cycles
Rationale for change		Treatment period limitation added due to the program discontinuation
Section to be changed		4.1.4 Drug assignment and administration of doses for each patient
Description of change		From:

		Dose escalations of BI 836880 or ezabenlimab in any patient is not allowed. Dose reduction are not allowed for Ezabenlimab in any patient. In the dose expansion study, only dose reductions are allowed for BI 836880. To: Dose reductions or escalations are not allowed for ezabenlimab in any patient. In the dose expansion study, only dose reductions/re-escalations are allowed for BI 836880.
Rationale for change		Clarification: only BI 836880 dose can be reduced/re-escalated in part 2.
Section to be changed		4.1.4 Drug assignment and administration of doses for each patient
Description of change		Addition: <u>Treatment duration:</u> Treatment with BI 836880 plus ezabenlimab may continue until disease progression, undue toxicity, withdrawal of patient consent, or 53 cycles [approximately 3 years] from the start of first treatment administration, whichever occurs first. Patients will be allowed to stay on treatment also in the case of initial radiological PD, until progression is confirmed or up to 53 cycles from the start of first treatment administration if the investigator considers that the treatment is beneficial for the patient. Investigators may consider discontinuing BI 836880 and continue therapy with ezabenlimab for up to 53 cycles from the start of the first treatment administration if the patient has been on therapy ≥ 6 months, has achieved at least SD by RECIST 1.1 and can tolerate the therapy, and if the investigator considers this to be in the best interest of the patient. For any patient still on treatment with the investigational combination of BI 836880 plus ezabenlimab 53 cycles from the start of the first treatment administration, treatment extension will be considered on a case-by-case basis upon request by the investigator for a maximum additional 6 cycles, to complete no later than 30 April 2025, if the investigator considers this to be in the best interest of the patient. After this date treatment with the investigational combination BI 836880 plus ezabenlimab will no longer be available.

		Investigators are requested to prepare for discontinuation of patients from the current investigational treatment of BI 836880 plus ezabenlimab and to switch them to alternative available treatment options outside of the current protocol no later than by the final availability date of 30 April 2025.
Rationale for change		Treatment period limitation added due to the program discontinuation
Section to be changed		5.1 ASSESSMENT OF EFFICACY
Description of change		From: Efficacy endpoints will be assessed every 2 cycles (6 weeks) as specified in the FC. An additional evaluation at EoT is only applicable; when patient has no PD documented, will not continue with regular imaging in Follow-up period and did not have imaging within the last 4 weeks before EoT. In case a patient has discontinued due to PD one additional tumor assessment should be done according to iRECIST in case no other cancer treatment has been initiated (confirming image should be done 4 – 6 weeks after the last image). For Glioblastoma patients, an additional image according to iRANO should be taken 3 month after PD. All measurements must be recorded in metric notation To: Efficacy endpoints will be assessed according to institutional practices and SOC from data cut-off date for interim database lock (iDBL) forward as specified in the flowchart.
Rationale for change		To reduce patient burden after program discontinuation decision on December 2021.
Section to be changed		5.1.2 Tumour response assessments using RANO
Description of change		From: Response assessments in GBM will be performed every 6 weeks using the objective status categories per RANO and iRANO criteria. To: Response assessment in GBM will be performed according to institutional practices and SOC from data cut-off date for interim database lock (iDBL) forward using the objective status categories per RANO and iRANO criteria.
Section to be changed		5.3.1 Assessment of pharmacokinetics
Description of change		Addition: As of the decision of Boehringer Ingelheim in December 2021 no additional blood samples for pharmacokinetics will be collected

Rationale for change		To reduce patient burden after program discontinuation decision on December 2021.
Section to be changed		5.4 ASSESSMENT OF BIOMARKER(S)
Description of change		From: The list of biomarkers planned to be studied during the trial may change or based on new information in the literature or early analyses. To: Planned exploratory biomarker analyses during the trial may be changed or stopped based on new information in the literature or early analyses.
Rationale for change		Clarification
Section to be changed		5.4.1 Methods of sample collection
Description of change		Addition: As of the decision of Boehringer Ingelheim in December 2021 no additional biopsies will be collected.
Rationale for change		To reduce patient burden after program discontinuation decision on December 2021.
Section to be changed		6.2.2 Treatment period(s)
Description of change		From: For Part 1 disease response assessment by CT/MRI will be performed at the end of every other cycle (CT to be performed every 6 weeks starting from first trial medication administration). Follow up period and trial completion For Part 2 tumour assessment should be done every 6 weeks (in accordance to local requirements with a window of +/- 7 days). Assessments are always done prior to the start of the new treatment cycle. At EOT and Safety Follow-up visit only when applicable (see Section 5.1). To: For Part 1 and Part 2 disease response assessment by CT/MRI will be performed according to institutional practices and SOC.
Rationale for change		To reduce patient burden after program discontinuation decision on December 2021.
Section to be changed		6.2.5.1 Follow-up for progression
Description of change		Deletion: - Sampes for PK, ADA and plasma biomarker at first Follow up (FU1)
Rationale for change		To reduce patient burden after program discontinuation decision on December 2021.

Section to be changed		6.2.5.2 Follow up for Overall Survival
Description of change		Complete instruction removed and replaced with: Sponsor has decided that as of this protocol amendment acknowledgement no further survival status follow-up will be collected.
Rationale for change		Overall survival follow-up will no longer be performed.
Section to be changed		8.6 TRIAL MILESTONES
Description of change		From: **The end of the trial** is defined as the date of the last visit of the last patient in the whole trial ("Last Patient Out"), or when all patients have been discontinued from study treatment and followed up for overall survival for at least 12 weeks after treatment discontinuation. To: **The end of the trial** is defined as the date of the last visit of the last patient in the whole trial ("Last Patient Out"), or when all patients have been discontinued from study treatment and followed up for overall survival until the end of REP
Rationale for change		Clarification
Section to be changed		10.5.1 Time Schedule for Pharmacokinetic (PK) and Pharmacodynamic Blood Sampling
Description of change		Addition: From December 2021, no further blood samples should be obtained for central lab shipments, and no biopsies should be performed.
Rationale for change		To reduce patient burden after program discontinuation decision on December 2021.
Section to be changed		Minor editorial changes were done across the protocol
Description of change		
Rationale for change		Clarification

11.8 GLOBAL AMENDMENT 8

Date of amendment		03 May 2023
EudraCT number **EU number**		2017-001378-41
BI Trial number		1336-0011

BI Investigational Product(s)		BI 836880 (anti-VEGF/Ang2) Ezabenlimab (BI 754091 [anti-PD-1])
Title of protocol		An open label phase Ib dose finding study of BI 836880 in combination with ezabenlimab to characterize safety, tolerability, pharmacokinetics, pharmacodynamics and efficacy in patients with locally advanced or metastatic non-squamous Non-Small Cell Lung Cancer and in other solid tumors
Global Amendment due to urgent safety reasons		☐
Global Amendment		☒
Section to be changed		4.1.1 Identity of the Investigational Medicinal Products
Description of change		From: Substance: Ezabenlimab (BI 754091) Pharmaceutical formulation: Solution for infusion Source: Boehringer Ingelheim Pharma GmbH & Co. KG Unit strength: 20 mg /mL (15 mL vial) Posology: rate controlled infusion on Day 1 of each 3-week cycle Route of administration: i.v. Duration of use: until progression, unacceptable toxicity, or up to a maximum of 53 cycles To: Substance: Ezabenlimab (BI 754091) Pharmaceutical formulation: Solution for Infusion or Concentrate for solution for infusion Source: Boehringer Ingelheim Pharma GmbH & Co. KG Unit strength: 20 mg /mL (15 mL vial) or 20 mg /mL (12 mL vial) Posology: rate controlled infusion on Day 1 of each 3-week cycle Route of administration: i.v.

		<table><tr><td>Duration of use:</td><td>until progression, unacceptable toxicity, or up to a maximum of 53 cycles</td></tr></table>
Rationale for change		Update new formulation of ezabenlimab.
Section to be changed		4.1.7 Storage conditions
Description of change		From: BI 836880 vials (old and new formulation) and ezabenlimab vials must be stored in their original packaging. To: BI 836880 vials (old and new formulation) and ezabenlimab vials (solution and concentrate for solution) must be stored in their original packaging.
Rationale for change		Addition of the concentrate for solution

APPROVAL / SIGNATURE PAGE

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

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Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Trial Statistician	[redacted]	18 May 2023 15:51 CEST
Author-Clinical Trial Leader		18 May 2023 15:55 CEST
Approval-Clinical Program Leaders		22 May 2023 09:33 CEST
Approval-Clinical Trial Leader		22 May 2023 15:27 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed