Clinical Trial Protocol

	Document Number: **c35307392-04**
EudraCT No. **EU Trial No.**	2021-003041-37
BI Trial No.	1412-0003
BI Investigational Medicinal Product(s)	BI 905711
Title	A phase Ia/Ib, open label, multicentre, dose escalation study of BI 905711 in combination with chemotherapy followed by expansion cohorts in patients with advanced gastrointestinal cancers
Lay Title	A study to find the best dose of BI 905711 in combination with chemotherapy and to test whether this dose helps people with advanced gastrointestinal cancers.
Clinical Phase	Ia/Ib
Clinical Trial Leader	[redacted] Telephone: [redacted] Fax: [redacted]
Coordinating Investigator	[redacted] Phone: [redacted]
Current Version and Date	Final Version 4 27 APR 2023
Original Protocol Date	23 JUN 2021

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Original Protocol date	23 JUN 2021
Revision date	27 APR 2023
BI trial number	1412-0003
Title of trial	A phase Ia/b, open label, multicentre, dose escalation study of BI 905711 in combination with chemo-therapy followed by expansion cohorts in patients with advanced gastrointestinal cancers
Coordinating Investigator	[redacted]
Trial site(s)	Multi-centre
Clinical phase	Ia/Ib
Trial rationale	BI 905711 is a tetravalent bispecific antibody targeting both TRAILR2 and CDH17 and is designed to selectively induce apoptosis in CDH17 expressing tumour cells via CDH17- dependent clustering of TRAILR2. The combination of TRAILR2/CDH17 antibody with chemotherapy aims to increase the apoptotic signal by the activation of both the intrinsic and the extrinsic apoptosis pathways in cancer cells. In relevant preclinical GI cancer models including colorectal cancer and pancreatic adenocarcinoma, BI 905711 showed efficacy as single agent and in combination with chemotherapy agents like capecitabine, irinotecan, paclitaxel and oxaliplatin. Moreover, pro-apoptotic priming with irinotecan followed 24 hours later by BI 905711 led to a synergistic effect as compared to co-administration on the same day (data on file). These data are consistent with published data demonstrating that pre-treatment with chemotherapy eg. cisplatin and irinotecan, sensitizes cancer cells to TRAILR2 agonistic antibodies and the sequential administration might overcome resistance (see section 1.3 for more details). The first-in-human trial 1412-0001 is assessing BI 905711 as monotherapy in patients with advanced or metastatic GI cancers. In Phase Ia, 45 patients (26 with CRC, 19 with non-CRC GI cancers) have received BI 905711 (dose range 0.02–4.8 mg/kg). No safety concerns or dose-limiting toxicities have been observed to date and the MTD was not reached.Based on safety, pharmacokinetic, and pharmacodynamic profiles, as well as preliminary antitumor activity of BI 905711, three dose levels (0.6 mg/kg, 1.2 mg/kg and 2.4 mg/kg) given biweekly or one dose level (0.6 mg/kg) given weekly were selected for assessment of BI 905711 monotherapy in 1412-0001 expansion phase 1b.
Trial objective(s)	Phase Ia: • To determine the maximum tolerated dose (MTD) and the recommended dose for expansion (RDE) of BI 905711 in

	combination with FOLFIRI regimen plus bevacizumab in CRC patients based on the frequency of patients experiencing dose limiting toxicities (DLT) during the MTD evaluation period. • To explore pharmacokinetics/pharmacodynamics, and efficacy to guide the determination of a MTD or a potentially effective dose in the absence of MTD, of BI 905711 in combination with FOLFIRI plus bevacizumab. Phase Ib • To evaluate the efficacy and safety of BI 905711 in combination with FOLFIRI plus bevacizumab in the CRC cohort, and define RP2D. • To evaluate the efficacy and safety of BI 905711 in combination with FOLFIRI (or Liposomal Irinotecan Plus 5-FU/Leucovorin) in PDAC cohort, and define RP2D.
Trial endpoints	Primary endpoints: <u>Phase Ia</u> • Maximum tolerated dose (MTD) defined as the highest dose with less than 25% risk of the true DLT rate being equal or above 33% during the MTD evaluation period. • Number of patients with DLTs in the MTD evaluation period. <u>Phase Ib</u> • Confirmed objective response (OR) as assessed by the investigator based on Response Evaluation Criteria in Solid Tumors (RECIST 1.1) in patients with measurable disease, defined as the best overall response of complete response (CR) or partial response (PR), from the first administration of trial medication until the earliest of progressive disease (PD), death or last evaluable tumor assessment before start of subsequent anti-cancer therapy. • In PDAC cohort safety run-in part: number of patients with DLTs during the MTD evaluation period assessed in the first 6 patients. Secondary endpoints: <u>Phase Ia</u> • The following PK parameters will be calculated after study treatment administration, as measured during the first cycle and after multiple cycles: - C_{max}: Maximum measured plasma concentration of BI 905711. - AUC_{0-t2}: Area under the concentration-time curve in plasma

	of BI 905711 Phase Ib • Progression-Free Survival (PFS) defined from date of start of treatment to the date of disease progression or death, whichever is earlier as assessed by the investigator according to RECIST 1.1. • Radiological (CT Scan) tumor shrinkage, defined as the difference between the minimum post-baseline sum of longest diameters of target lesions and the baseline sum of longest diameters of the same set of target lesions according to RECIST 1.1. • The duration of OR is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or PD is objectively documented (taking as reference for PD the smallest measurements recorded on study) according to RECIST 1.1. • Disease control, defined as CR, PR, or stable disease (SD) lasting at least 16 weeks according to RECIST 1.1 from the start of treatment until the earliest of PD, death or last evaluable tumor assessment and before start of subsequent anti-cancer therapy. • The following PK parameters will be calculated after study treatment administration, as measured during the first cycle and after multiple cycles: - C_{max}: Maximum measured plasma concentration of BI 905711 in plasma. - AUC_{0-t2}: Area under the concentration-time curve for BI 905711 in plasma.
Trial design	Phase Ia is an open-label, non-randomized dose escalation study of BI 905711 in combination with FOLFIRI and bevacizumab in patients with CRC. Dose escalation will be guided by a Bayesian logistic regression model (BLRM) with overdose control. Pharmacokinetics (PK) and efficacy will be evaluated to guide determination of the MTD/RDE. Phase Ib is an open label study with the main objective to assess the safety and efficacy of BI 905711 in combination with chemotherapy in 2 expansion cohorts. PK will be further characterised and the RP2D will be confirmed. Phase Ib will consist of 2 cohorts of patients with 2 different tumor types as described below. Randomized CRC expansion cohort: CRC cohort is an open label, randomized cohort of CRC patients. Patients will be randomized in a 2:1 ratio into either

	• Arm A = FOLFIRI plus bevacizumab plus BI 905711 at the RDE from Phase Ia or • Arm B = FOLFIRI plus bevacizumab without BI 905711 <u>Single Arm PDAC expansion cohort:</u> This is an open label single arm cohort of patients with advanced or metastatic PDAC. A safety run-in will be included in which the first 6 patients will be treated with FOLFIRI (or Liposomal Irinotecan plus 5-FU/Leucovorin) plus BI 905711 at the RDE determined in Phase Ia to confirm the RDE based on DLTs assessed during the first two 14-day treatment cycles prior to enrolling further patients.
Total number of patients treated	Up to approximately 100 patients
Number of patients per treatment group	Phase Ia (dose escalation): approximately 20 evaluable CRC patients. Phase Ib (dose expansion); approximately 60 evaluable CRC patients and 20 evaluable PDAC patients.
Diagnosis	The patient with histologically or cytologically confirmed advanced unresectable or metastatic CRC (Phase Ia and Ib), and CDH17 positive PDAC (Phase Ib only).
Main inclusion and exclusion criteria	**Inclusion Criteria** <u>Applicable to both Phase Ia and Phase Ib Cohorts:</u> 1. Signed and dated written informed consent in accordance with ICH-GCP and local legislation prior to admission to the trial. 2. Of legal adult age (according to local legislation) at screening. 3. Histologically or cytologically confirmed, advanced unresectable or metastatic colorectal adenocarcinoma 4. CRC Patients who have disease progression (PD) after prior oxaliplatin-based first line therapy or within 6 months after the end of oxaliplatin-based adjuvant therapy. 5. Eastern Cooperative Oncology Group (ECOG) performance status ≤ 1 6. Life expectancy ≥ 3 months in the opinion of the investigator 7. Availability and willingness to provide tumor tissue (fresh biopsy or archival) for biomarker analysis. Only non-significant risk procedures per the investigator's judgment will be used to obtain any biopsies specified in this study. In case a fresh tumor biopsy cannot be obtained, the recruitment of the patient may proceed on a case-by-case basis after agreement between the investigator and BI. In such a case, an archived tumor tissue specimen must be submitted. 8. Adequate hepatic, pancreatic, renal and bone marrow functions as defined below: o Total bilirubin ≤ 1.5 x institutional upper level of normal (ULN) o Alanine transaminase (ALT) and Aspartate

transaminase (AST) ≤2.5 x institutional ULN or ≤5 x institutional ULN for patients with known liver metastases
- Serum creatinine ≤1.5x institutional ULN. If creatinine is > 1.5 x ULN, patient is eligible if concurrent creatinine clearance ≥ 50 ml/min (≥ 0.05L/min) (measured or calculated by CKD-EPI formula or Japanese version of CKD-EPI formula for Japanese patients)
- Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L, ≥ 1.5 x 10^3/µL, or ≥ 1500/mm^3
- Platelets ≥ 100 x 10^9/ L, ≥ 100 x 10^3/µL, or ≥ 100 x 10^3/mm^3
- Hemoglobin (Hb) ≥ 8.5 g/dl, ≥ 85 g/L, or ≥ 5.3 mmol/L (without transfusion within previous week)
- Serum lipase ≤ 1.5 institutional ULN (Only for CRC cohort); >1.5 - 2.0 x ULN or asymptomatic >2.0 - 5.0 x ULN if related to PDAC (Only for PDAC cohort)

9. Recovery, from any adverse events (AEs) of previous anti-cancer therapies, to Common Terminology Criteria for Adverse Events (CTCAE) v5.0 (CTCAE) grade 1 except for CTCAE grade 2 alopecia or peripheral sensory neuropathy, or other CTCAE grade 2 AEs considered not clinically significant in the investigator's opinion.
10. 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. A list of contraception methods meeting these criteria is provided in Section 4.2.3.3.

Additionally, criterion #11 is applicable to Phase Ia cohort only:

11. Patient with either measurable or non-measurable disease.

Additionally, criterion #12-14 is applicable to Phase Ib cohorts only:

12. At least one target lesion that can be accurately measured per RECIST 1.1

PDAC Patients must meet the following:

13. Histologically or cytologically confirmed, advanced unresectable or metastatic CDH17 positive pancreatic adenocarcinoma.

14. Patients who have PD after prior platin and/or gemcitabine-based first line therapy.

Exclusion criteria

	Applicable to both Phase Ia and Phase Ib cohorts 1. Any prior irinotecan-based therapy in the metastatic setting. 2. Previous systemic anti-cancer therapy within the specified timeframe from the last dose intake to the first dose of trial treatment as follows: o Any non-investigational drug, including anti-angiogenic agents (bevacizumab or ramucirumab or aflibercept) and anti-EGFR antibodies (cetuximab or panitumumab), within 14 days. o Any investigational drug or other antibodies including immune checkpoint inhibitors, within 28 days. 3. Currently enrolled in another investigational device or drug trial. Patients who are in follow-up/observation for another clinical trial are eligible. 4. Radiation therapy within 4 weeks prior to start of treatment. However, palliative radiotherapy for symptomatic metastasis is allowed if completed within 2 weeks prior to start of treatment. 5. Any serious concomitant disease or medical condition affecting compliance with trial requirements or which are considered relevant for the evaluation of the efficacy or safety of the trial drug, such as neurologic, psychiatric, infectious disease or active ulcers (gastro-intestinal 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. 6. Known pathological condition of GI tract, liver and pancreas, excluding the disease under study, that may interfere with assessment of drug safety or may increase the risk of toxicity: a. inflammatory bowel disease b. chronic pancreatitis c. other serious GI pathological conditions by judgment of the investigator e.g. autoimmune disease with GI involvement, unexplained active diarrhea CTCAE v5.0 grade ≥2. 7. Known history of human immunodeficiency virus (HIV) infection. 8. Any of the following laboratory evidence of hepatitis virus infection. Test results obtained in routine diagnostics are acceptable if done within 14 days before the informed consent date: o Positive results of hepatitis B surface (HBs) antigen o Presence of HBc antibody together with HBV-DNA o Presence of hepatitis C RNA 9. Previous or concomitant malignancies, other than the one treated in this trial within the last 2 years with the exception of the following:

	○ Effectively treated non-melanoma skin cancers ○ Effectively treated carcinoma in situ of the cervix ○ Effectively treated ductal carcinoma in situ ○ Other effectively treated malignancy that is considered cured by local treatment 10. Chronic alcohol or drug abuse or any condition that, in the investigator's opinion, makes the patient an unreliable trial participant or unlikely to comply with the protocol requirements or not expected to complete the trial as scheduled. 11. Women who are pregnant, nursing, or who plan to become pregnant while in the trial; female patients who do not agree to the interruption of breast feeding from the start of study treatment through 6 month after the last study treatment. 12. Presence of uncontrolled or symptomatic brain or subdural metastases. Inclusion of patients with brain metastases who have completed local therapy and are considered stable by the investigator, or with newly identified asymptomatic brain metastases at screening will be allowed. Use of corticosteroids is allowed if the dose was stable for at least 1 week before the baseline MRI. 13. Patients who are under judicial protection and patients who are legally institutionalized. 14. Major surgery (major according to the investigator's assessment) performed within 28 days prior to treatment start or planned within 3 months after screening, e.g. hip replacement. 15. Any of the following cardiac criteria: a. Resting corrected QT interval (QTc) >470 msec, based on local assessment b. Any clinically important abnormalities (as assessed by the Investigator) in rhythm, conduction, or morphology of resting Electrocardiograms (ECGs), e.g., complete left bundle branch block, third degree heart block. c. Patients with an ejection fraction (EF) <50% or the lower limit of normal of the institutional standard will be excluded. Only in cases where the Investigator (or the treating physician or both) suspects cardiac disease with negative effect on the EF, will the EF be measured during screening using an appropriate method according to local standards to confirm eligibility (e.g., echocardiogram, multi-gated acquisition scan). A historic measurement of EF no older than 6 months prior to first administration of study drug can be accepted provided that there is clinical evidence that the EF value has not worsened since this measurement in the opinion of the Investigator or of the treating physician or both. d. Patients with a history of stroke or myocardial infarction within 6 months prior to screening are not permitted.

	16. Known hypersensitivity to the trial medications or their excipients. 17. The patient has any known history or clinical evidence of Gilbert's Syndrome, or is known to have any of the following genotypes: UGT1A1*6/*6, UGT1A1*28/*28, or UGT1A1*6/*28 18. Any contradictions to the proposed background therapy according to the current approved local labels.
Test product(s)	BI 905711
dose	Phase Ia: starting dose of 0.6 mg/kg on Day 3 of each 14-day cycle Phase Ib: RDE from phase Ia
Duration of treatment	BI 905711 will be administered until disease progression, unacceptable toxicity, or other reasons requiring treatment discontinuation.
mode of administration	Intravenous
Combination product(s)	Irinotecan Liposomal Irinotecan (PDAC cohort only) Leucovorin (or Levoleucovorin) Fluorouracil Bevacizumab (CRC cohort only)
Dose and Duration of background treatment	• Bevacizumab: 5 mg/kg IV over 30 minutes on Day 1 of each 14-day cycle. • Irinotecan: 180 mg/m^2 IV over 1.5 hours on Day 1 of each 14-day cycle. • Liposomal Irinotecan: 70 mg/m^2 IV over 1.5 hours on Day 1 of each 14-day cycle. • Leucovorin: 400 mg/m^2 IV (in Japan, Levoleucovorin: 200 mg/m^2) over 2 hours on Day 1 of each 14-day cycle. • Fluorouracil: 400 mg/m^2 IV bolus on Day 1 of each 14-day cycle. • Fluorouracil: 2400 mg/m^2 IV 46 hours continuous infusion starting on Day 1 of each 14-day cycle.
mode of administration	All Intravenous
Statistical methods	Phase Ia: Dose escalation is guided by a BLRM with overdose control that will be fitted to binary toxicity outcomes (DLTs). The estimate of parameters will be updated as data are accumulated using the BLRM. Available safety data from BI Study 1412-0001 can be incorporated into the prior derivation meta-analytic predictive (MAP) approach. Phase Ib: Primary and secondary endpoints will be analyzed descriptively. If additional DLTs are observed during the safety run-in phase, a separate BLRM with overdose control will be used to re-estimate the recommended dose for PDAC cohort.

FLOW CHARTS

FLOW CHART 1 PHASE IA -NO LONGER APPLICABLE PER CTP V4.0

		Treatment Period																		Post-Treatment			
Visit	**SCR**	**Cycle 1 * (14 days)**					**Cycle 2 * (14 days)**			**Cycle 3 * (14 days)**					**Cycle 4 * (14 days)**			**Cycle 5 and beyond ***		**EoT****	**EOR*** (FUP #1)**	**FUP for PD##**	**FUP for OS status ##**
Day (visit window)	**-28 - 1**	**1**	**3**	**4**	**5**	**10 (±2)**	**1 (+2)**	**3**	**4**	**1 (+2)**	**3**	**4**	**5**	**10 (±2)**	**1 (+2)**	**3**	**4**	**1 (+2)**	**3**	**Day 0-14 after discontinuation**	**30 (+5) days after last dose**		
Informed Consent[1]	x																						
Demographics + Medical History	x																						
In- /Exclusion Criteria[2]	x[16]	x																					
Eligibility for re-treatment[2]							x			x					x			x					
Physical Examination[3,4]	x	x					x			x					x			x		x	x	x	
ECOG performance score[5]	x	x					x			x					x			x		x	x	x	
Pregnancy test[6]	x	x								x								x		x			
12-lead-ECG[7]	x									x											x		
Infusion of BI 905711[8]			x					x			x					x			x				
Infusion of FOLFIRI with bevacizumab[8.1]		x					x			x					x			x					
Vital Signs	x	x	x				x	x		x	x				x	x		x	x	x	x	x	
Safety lab testing[9]	x	x	x	x		x	x	x		x	x				x			x		x	x	x	
Pharmacokinetics[10]			x	x	x	x		x	x		x	x	x	x		x	x	x[10]		x	x		
ADA sampling[10]			x					x			x									x	x		
Nab sampling[10]			x					x			x									x	x		
Circulating free DNA[10]		x				x				x					x					x			

Flow Chart 1 Phase Ia (cont.) -NO LONGER APPLICABLE PER CTP V4.0

		Treatment Period																		Post-Treatment			
Visit	**SCR**	**Cycle 1*** **(14 days)**					**Cycle 2 *** **(14 days)**			**Cycle 3 *** **(14 days)**					**Cycle 4 *** **(14 days)**			**Cycle 5 and beyond ***		**EoT****	**EOR***** **(FUP #1)**	**FUP for PD##**	**FUP for OS status ##**
Day (visit window)	**-28 - 1**	**1**	**3**	**4**	**5**	**10 (±2)**	**1 (+2)**	**3**	**4**	**1 (+2)**	**3**	**4**	**5**	**10 (±2)**	**1 (+2)**	**3**	**4**	**1 (+2)**	**3**	**Day 0-14 after discontinuation**	**30 (+5) days after last dose**		
Plasma for cell death biomarkers[10]	x	x	x	x	x	x		x	x		x	x	x	x		x	x						
Tumor tissue collection	x[11]																						
[^{18}F]FDG-PET/CT [13]	x																	x					
Adverse Events[14]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Concomitant Therapy	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Tumor assessment by CT/MRI RECIST 1.1[15] and tumor marker measurement	x[15]	x[15]																					
Termination of all trial medication																				x			
Patient status																							x

FLOW CHART 2 PHASE IB -NO LONGER APPLICABLE PER CTP V4.0

		Treatment Period																		Post-Treatment			
Visit	**SCR**	**Cycle 1* (14 days)**					**Cycle 2 * (14 days)**			**Cycle 3 * (14 days)**					**Cycle 4 * (14 days)**			**Cycle 5 and beyond ***		**EoT****	**EOR*** (FUP #1)**	**FUP for PD##**	**FUP for OS status ##**
Day (visit window)	**-28 - 1**	**1**	**3**	**4**	**5**	**10 (±2)**	**1 (+2)**	**3**	**5**	**1 (+2)**	**3**	**4**	**5**	**10 (±2)**	**1 (+2)**	**3**	**4**	**1 (+2)**	**3**	**Day 0-14 after discontinuation**	**30 (+5) days after last dose**		
Informed Consent[1]	x																						
Demographics + Medical History	x																						
In- /Exclusion Criteria[2]	x[16]	x																					
Eligibility for re-treatment[2]							x			x					x			x					
Physical Examination[3,4]	x	x					x			x					x			x		x	x	x	
ECOG performance score[5]	x	x					x			x					x			x		x	x	x	
Pregnancy test[6]	x	x								x								x		x			
12-lead-ECG[7]	x									x											x		
Infusion of BI 905711[8]			x					x			x					x			x				
Infusion of FOLFIRI (or Liposomal Irinotecan plus 5-FU/Leucovorin (PDAC only)) with or without bevacizumab [8.1]		x					x			x					x			x					
Vital Signs	x	x	x				x	x		x	x				x	x		x	x	x	x	x	
Safety lab testing[9]	x	x	x	x		x	x	x		x	x				x			x		x	x		
Pharmacokinetics[10]			x	x	x	x		x	x		x	x	x	x		x	x	x[10]		x	x		
ADA sampling[10]			x					x			x									x	x		
Nab sampling[10]			x					x			x									x	x		
Circulating free DNA[10]		x					x													x			

Flow Chart 2 Phase Ib (cont.) -NO LONGER APPLICABLE PER CTP V4.0

		Treatment Period																		**Post-Treatment**			
Visit	**SCR**	**Cycle 1*** **(14 days)**					**Cycle 2 *** **(14 days)**			**Cycle 3 *** **(14 days)**					**Cycle 4 *** **(14 days)**			**Cycle 5 and beyond ***		**EoT****	**EOR***** **(FUP #1)**	**FUP for PD##**	**FUP for OS status ##**
Day (visit window)	**-28 - 1**	**1**	**3**	**4**	**5**	**10 (±2)**	**1 (+2)**	**3**	**5**	**1 (+2)**	**3**	**4**	**5**	**10 (±2)**	**1 (+2)**	**3**	**4**	**1 (+2)**	**3**	**Day 0-14 after discontinuation**	**30 (+5) days after last dose**		
Plasma for cell death biomarkers[10]	x	x	x	x	x	x		x	x		x	x	x	x		x	x						
Tumor tissue collection	x[11]								**x[12]**											**x[12]**			
[^{18}F]FDG-PET/CT [13]	x																	x					
Adverse Events[14]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Concomitant Therapy	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Tumor assessment by CT/MRI RECIST 1.1[15] and tumor marker measurement	x[15]	x[15]																					
Termination of all trial medication																				x			
Patient status																							x
PRO-CTCAE[17]		x				x	x			x				x	x			x[17]					

Footnotes pertaining to both Flowchart 1 and 2 -NO LONGER APPLICABLE PER CTP V4.0

(*) Each treatment Cycle has a duration of 14 days.
(**) Patients who discontinue trial treatment should undergo the End of Treatment (EoT) visit as soon as possible (Day 0-14 after treatment discontinuation).
If assessments due at EoT are not completed, they may be performed at the End of Residual Effect Period (EoR) visit, which is also considered the first Follow-Up (FUP) Visit.
(***) The End of Residual Effect Period (EoR) visit (FUP #1) should occur 30 (+5) days after the last dose of treatment (see Section 6.2.3.2).

(##) FUP visits For Progressive Disease (PD)
If a patient does not have documented progression prior to or at the EoR visit he/she will continue to have regular FUP visits for PD which will occur per the imaging schedule. Assessments will be performed as indicated in the Flow Chart.
The FUP visits for PD will end at the earliest once one of the following events is met:

- Confirmation of Disease progression
- Start of a new anti–cancer therapy
- Death
- Lost to Follow-Up
- End of whole trial as specified in Section 8.6.

The following will be obtained and/or performed during the FUP visits for progression.

- Perform tumor assessment including physical examination and imaging.
- ECOG performance score
- Treatment date with any subsequent anti-cancer drug / therapy including the name and type of the anti-cancer drug and/or best supportive care (if applicable).
- Outcome (date of and reason for death [if applicable], in case the patient had PD the actual date of PD shall be recorded)

(##) FUP for survival status

Once the FUP visits for progression end for patients with either a confirmation of disease progression or have started a new anti-cancer therapy, the FUP for survival status will start and be performed approximately every 12 weeks (+/-7 days) in person, by telephone or via written correspondence until death, lost to follow-up, withdrawal of consent, or end of the whole trial (see Section 6.2.3.3 and 8.6).
The following patient status information will be collected during the FUP timepoints for survival status:

- Date of contact
- Further anti-cancer treatment including surgery and radiotherapy: regimen and drug name, start and stop dates.
- For each reportable serious adverse event / AESI, the investigator should provide the information with regard to concomitant medication and the medication administered to treat the adverse events on the appropriate CRF pages and the SAE form including trade name, indication and dates of administration

- Outcome event (e.g. death: Record date of and reason for outcome event / death [if applicable])

1. Written informed consent must be obtained before any protocol specific screening assessments are performed. Re-consenting may become necessary when new relevant information becomes available and should be conducted according to the Sponsor's instructions. Separate consent is to be obtained for optional biomarker sampling

2. Cycle 1, Day 1: Inclusion and exclusion criteria must be confirmed prior to first dose.
From Cycle 2 Day 1 onwards: Eligibility for further treatment should be confirmed prior to each dosing day (Day 1 of each cycle) by confirming the patient has not met any criteria for protocol discontinuation as described in section 3.3.4.1 and absence of any adverse event requiring treatment delay or discontinuation (section 4.1.5.2 and 4.2.3).

3. A full physical exam is inclusive of vitals, body weight and height. With the exception of height (performed only at Screening), a full physical is to be performed at Screening, at Day 1 of each cycle, at EoT, EoR and at further FUP visits for progression if applicable. Physical exam does not need to be repeated at Cycle 1 Day 1 if completed within the previous 24hours. See Section 4.1.5.1 for additional timepoints for assessing signs and symptoms of IRR and CRS on drug administration days. Patients should also be assessed for any new neurological signs and symptoms. See section 4.2.4.5.

4. For all cycles including cycle 1, weight can be collected up to 3 days prior to the visit. If the patient's weight changes by ≤10% compared to the reference weight, the dose (in mg) may remain the same for subsequent cycles. If the weight changes by >10% the dose will be recalculated and the new weight will be used as the reference weight.

5. ECOG assessment to be performed at Screening, and Day 1 of each cycle, at EoT, EoR and at further FUP visits for progression if applicable. ECOG does not need to be repeated at Cycle 1 Day 1 if screening ECOG was completed within 72hours of Cycle 1 Day 1.

6. A urine pregnancy test is mandatory for female patients of childbearing potential and must be performed within 72 hours prior to start of study treatment (Day 1) at every 2 cycles and at EoT. If a urine pregnancy test is positive, a serum pregnancy test must be performed and resulted as negative prior to trial drug administration.

7. ECG to be performed at Screening, Day 1 of Cycles 3 and at EoR. An ECG can be added as well as repeated as clinically indicated per investigator's discretion.

8. Dispensing of BI 905711 will be performed via the Interactive Response Technology (IRT). **BI 905711 dose administrations must always be at least 14 days apart.** Patients will remain under surveillance for at least 6 hours after the end of infusion during the first, second and third administrations of BI 905711. During the post-infusion observation period, body temperature, pulse rate and blood pressure will be measured at the end of the infusion and every 2 hours (± 15 minutes) thereafter.
See Section 4.1.5.1 for additional details of this observation period.
8.1. The infusion of FOLFIRI (or Liposomal Irinotecan plus 5-FU/Leucovorin (PDAC only)) with or without bevacizumab will be done per local labels (See section 4 for more details of background administration)

9. Safety Lab testing will be performed locally and includes blood for Hematology, Biochemistry, Hepatitis and Coagulation, as well as Urinalysis. Refer to protocol Section 5.2.3 for specific laboratory requirements.

- Safety lab tests performed during screening do not need to be repeated at Cycle 1 Day 1 if performed within 10 days prior to treatment start and there is no clinical reason to repeat lab tests.
- During Cycle 1, safety labs should be performed on Day 3 (pre-dose), 4-6 hours post BI 905711 administration, on Day 4 (24 hr timepoint), and on Day 10.
- During subsequent Cycles, safety labs on Day 1 should be performed within 48 hours prior to Day 1. During Cycle 2 and 3, safety lab should be performed on Day 1 and Day 3.
- All safety lab tests can be repeated at any other time points, if clinically indicated, at investigator's discretion.
- Safety labs are also performed at EoT and EoR visit and may be repeated if clinically indicated.
- At the Screening visit only, patients are to be tested for Hepatitis B Virus (HBV) and Hepatitis C Virus (HCV) infection which includes hepatitis B surface antigen (HbsAg), Hepatitis B core antibody (anti-HBc), HBV-DNA, as well as HCV RNA. Results for hepatitis virus infection obtained in routine diagnostics are acceptable if done within 14 days before the informed consent date. Also refer to exclusion criteria for criteria for active infection.

10. For detailed information about pharmacokinetics (PK), Anti-drug antibodies (ADA), Neutralizing anti-drug antibodies (Nab), cell death biomarkers, and circulating tumor DNA (cfDNA) sampling timepoints and handling procedures, refer to Appendix 10.2. ADA sampling may be amended based on available data. If the patient will not continue treatment in the next cycle, pre-dose sampling scheduled for Day 3 of the next cycle (see Appendix 10.2) needs to be performed at the EoT visit. For cfDNA, first sample should be collected at baseline (Cycle 1, Day 1) before start of trial treatment. For subsequent cfDNA sample collection refer to Section 5.4.1 and Appendix 10.2 for more details on collection time points.

11. Tumor tissue collection during Screening:

For Phase Ia-

- **For all patients**: Provision of an archived tumor tissue specimen is mandatory during screening. A fresh biopsy is only mandatory for patients who do not have archival tissue.

For Phase Ib-

- **For all patients**: Provision of archival tumor tissue or fresh biopsy is mandatory for all patients prior to treatment start on Day 1. Fresh biopsy sample should be provided if the archival tissue tested is greater than 6 months old from collection to start of treatment on this study. Even if fresh biopsy conducted, provision of an archived tumor tissue is recommended. **For Non-CRC patients**, CDH17 expression measurement by archival tumor tissue or fresh biopsy sample must be completed prior to treatment start on Day 1.

Only non-significant risk procedures per the investigator's judgment will be used to obtain any biopsies specified in this study. For CRC patients only, in case a fresh tumor biopsy cannot be obtained, the recruitment of the patient may proceed on a case-by-case basis after agreement between the investigator and BI. In such a case, an archived tumor tissue specimen needs to be submitted.

12. **For Phase Ib only:** On-treatment tumor tissue collection at Cycle 2 Day 5, 48 h±4 after administration of BI 905711(optional) and/or at disease progression (EOT) (optional) for a patient in which a fresh biopsy has been successfully obtained before first study treatment.

13. CRC patients only: [^{18}F]FDG-PET/CT should be performed during screening and no later than 14 days (±7 days) prior to treatment start (Cycle 1 Day 1) after eligibility has been confirmed. A second [^{18}F]FDG-PET/CT will be performed at the 8-week (±7 days) tumor assessment timepoint. It may be performed together with standard CT assessment if feasible. See section 5.4.2.6 for additional [^{18}F]FDG-PET/CT details including patient fasting and voiding requirements.

14. After the patient's end of trial, the investigator does not need to actively monitor the patient for new AEs but should report any occurrence of cancer and trial drug related SAEs and trial drug related AESIs of which the investigator may become aware of by any means of communication, e.g. phone call. Those AEs should be reported on the BI SAE form but not on the CRF, see Section 5.2.6.2.1.

15. Tumor assessment should include CT scans or MRI of the chest, abdomen, pelvis and, if clinically indicated, imaging of any other known or suspected sites of disease (e.g. brain, bone). The same radiographic procedure must be used throughout the study. Tumor assessment does not need to be performed at the Screening visit if there are valid results available from assessments which were performed as part of routine clinical practice within 28 days prior to start of treatment. Repeat tumor assessment will be performed every 8 weeks (± 7 days) until progression or start of further treatment for disease.
In the event of early discontinuation for reasons other than progressive disease or interruption/delay of treatment, the tumor assessment schedule should not be changed. If the patient finishes study treatment without having progressive disease, tumor assessment/imaging must be performed at the time of treatment discontinuation, unless it has been done within the past 4 weeks.
CEA, CA19.9, etc., tumor marker levels should be obtained at baseline, **every 2 cycles** and at every protocol-specified tumor assessment timepoint in CRC and PDAC patients, respectively.

16. Only in cases where the Investigator (or the treating physician or both) suspects cardiac disease with negative effect on the EF, will the EF be measured during screening using an appropriate method according to local standards to confirm eligibility (e.g., echocardiogram, multi-gated acquisition scan). A historic measurement of EF no older than 6 months prior to first administration of study drug can be accepted provided that there is clinical evidence that the EF value has not worsened since this measurement in the opinion of the Investigator or of the treating physician or both.

17. PRO-CTCAE should be conducted on Day 1 (allowance -1 day) of each cycle until Cycle 5, and Day 10 (allowance ±2 day) of cycle 1 and cycles 3. From Cycle 5, PRO-CTCAE should be conducted on Day 1 (allowance -1 day) of every 2 cycles (Cycle 7, 9, 11 and so on).

FLOW CHART 3 PHASE 1A/B – BIWEEKLY - REDUCED SCHEDULE PER CTP V4.0 – ONGOING PATIENTS

	Treatment Cycle		**Post-Treatment**	
Visit	**CxD1[a]**	**CxD3[a]**	**EOT****	**EOR / EOS*****
Day (day range)	**1 (+2)**	**3**	**Day 0-14 after discontinuation**	**30 (+5) days after last dose**
Physical Examination and Vital Signs	Per institutional practice			
Safety lab parameters	Per institutional practice			
Tumor assessment by CT/MRI RECIST 1.1[1]	Per institutional practice			
Pregnancy test[2]	Per institutional practice			
12-lead-ECG	Per institutional practice			
Body weight	x			
Infusion of FOLFIRI with bevacizumab	x			
Infusion of BI 905711[3]		x		
Adverse Events[4]	x	x	x	x
Concomitant therapy[5]	x	x	x	x
Termination of study medication			x	

After implementation of protocol version 04, the patient will have assessments as medically indicated to monitor the safety at the discretion of the investigator. These assessments may include: physical examination, vital sign, safety lab and ECG at a frequency decided by the investigator. The study treatment is administered and the administration information will be documented in the eCRF. Tumour assessment will be performed according to standard of care based on medical opinion of the investigator.

The results of any assessments will be documented in the source data, but will not be collected in the eCRF, except tumor assement (overall response and progression date).

Findings which qualify as an (S)AE will be reported in the eCRF and in case of an SAE, on the SAE form (timelines and distribution requirements for SAEs apply).

The data collection is required only for the following items:
- Adverse events
- Concomitant medications that are used to treat adverse events
- Drug admistration information
- Dose changes
- Tumor assessment (overall response and progression date).
- At EOT visit: visit date, end of treatment – BI 905711, and subject retention
- At safety follow-up visit: visit date and end of study page
- Death details (if applicable)

(*) Each treatment Cycle has a duration of 14 days
(**) Patients who discontinue trial treatment prematurely should undergo the End of Treatment (EOT) visit as soon as possible. If assessments due at EOT are not completed, they may be performed at the 30-Day Safety FUP (i.e. EOR) Visit.
(***) This combined visit is the End of Residual Effect Period visit (EOR) which must happen at the earliest 30 (+ 5) days after the last dose of treatment (see Section 6.2.3.2).

[a]X is the number of the treatment cycle

[1]Tumor assessment will be performed according to institutional practices. Images no longer need to be sent to imaging vendor. The overall response and progression date will be collected in the electronic CRF.
[2]Serum and/or urine pregnancy testing to be performed for female patients of childbearing potential as per institutional practice within 72 hours prior to start of study treatment infusion, every odd number cycle starting at Cycle 3 and at EOT.
[3] Dispensing of BI 905711 will be performed via the IRT. Assessment for signs and symptoms of infusion-related reactions and Cytokine Release Syndrome (CRS) is described in Sections 4.2.4.1 and 4.2.4.2.
[4] After the individual patient's end of trial: the investigator does not need to actively monitor for new AEs but should only report any occurrence of cancer of new histology, trial drug related SAEs and trial drug related AESIs of which the investigator may become aware of and only via the SAE form, see Section 5.2.6.2.1.
[5]Concomitant medications that are used to treat adverse events.

TABLE OF CONTENTS

ABBREVIATIONS AND DEFINITIONS

AE	Adverse Event
AESI	Adverse Event of Special Interest
ADA	Anti-drug Antibodies
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
AP	Alkaline phosphatase
aPTT	Activated Partial Thromboplastin Time
AxMP	Auxiliary Medicinal Products
AST	Aspartate Aminotransferase
AUC	Area under the Curve
BI	Boehringer Ingelheim
BLRM	Bayesian Logistic Regression Model
BLQ	Below the limit of quantification
BUN	Blood Urea Nitrogen
CDH17	Cadherin 17
cfDNA	Circulating free DNA
C_{max}	Maximum Plasma Concentration
C_{min}	Minimum Plasma Concentration
CRA	Clinical Research Associate
CRF	Case Report Form, paper or electronic (sometimes referred to as “eCRF”)
CRC	Colorectal adenocarcinoma
CRS	Cytokine release syndrome
ctDNA	Circulating tumor DNA
CRO	Contract Research Organisation
CTCAE	Common Terminology Criteria for Adverse Events
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
DRC	Data Review Committee
DILI	Drug Induced Liver Injury
DLT	Dose Limiting Toxicity
ECG	Electrocardiogram

ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EF	Ejection Fraction
EOI	End of infusion
EoR	End of Residual Effect Period
EoT	End of Treatment
EudraCT	European Union Drug Regulating Authorities Clinical Trials Database
EWOC	Escalation with Overdose Control
[^{18}F]FDG-PET	[^{18}F]Fluorodeoxyglucose-Positron Emission Tomography
FIH	First In Human
FUP	Follow-up
GCP	Good Clinical Practice
GI	Gastrointestinal
GMP	Good Manufacturing Practice
IB	Investigator's Brochure
ICH	International Council on Harmonisation
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
IRR	Infusion Related reactions
IRT	Interactive Response Technology
ISF	Investigator Site File
IUD	Intrauterine Device
IUS	Intrauterine Hormone-Releasing System
LPLT	Last patient last treatment
MedDRA	Medical Dictionary for Drug Regulatory Activities
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
Nab	Neutralizing Anti-drug Antibodies
NCI	National Cancer Institute
NCCN	National Comprehensive Cancer Network
NOA	Not to the lag phase

NOR	No valid result
NOS	No Sample
OR	Objective Response
OS	Overall Survival
OPU	Operative Unit
PDAC	Pancreatic Ductal Adenocarcinoma
p.o.	per os (oral)
PK	Pharmacokinetics
PD	Progressive disease
PFS	Progression Free Survival
PR	Partial Response
PRO	Patient Reported Outcome
PT	Prothrombin Time
RBC	Red Blood Cell
RDE	Recommended Dose for Expansion
RECIST	Response Evaluation Criteria in Solid Tumors
REP	Residual effect period
RP2D	Recommended Phase 2 Dose
SAE	Serious Adverse Event
SCR	Screening
SD	Stable Disease
SOI	Start of infusion
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reactions
TLS	Tumor Lysis Syndrome
t_{max}	Timepoint of maximum plasma concentration
TRAIL	TNF Related Apoptosis-Inducing Ligand
TSAP	Trial Statistical Analysis Plan
ULN	Upper limit of normal
WBC	White Blood Cell
WHO	World Health Organisation
WOCBP	Woman of childbearing potential

5-FU	Fluorouracil

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Tumor cell death and apoptosis can be induced by activation of the extrinsic apoptosis pathway via targeting TRAIL (TNF Related Apoptosis-Inducing Ligand) receptors (R16-1878). TRAILR2 represents a valid target for anti-cancer treatment, but conventional TRAILR2 antibodies have not been successful in the clinic so far due to insufficient agonistic properties or liver toxicity (P16-04691) (R17-2985).

Published data suggest that activation of TRAIL receptor depends not only on binding of the ligand to the receptor but requires also a hyperclustering of the receptor that is critical for apoptosis induction (R17-2986). Agonistic properties of TRAILR2 antibodies can be highly enhanced by antibody immobilisation via binding of their Fc part on the solid surface *in-vitro* or FcR cross-linking on membrane of the tumor infiltrating immune cells *in-vivo* (R17-2987).

1.2 DRUG PROFILE

Mode of action

BI 905711 is a tetravalent bispecific molecule targeting both TRAILR2 and Cadherin 17 (CDH17), and it is designed to selectively induce apoptosis in CDH17 expressing tumor cells via the CDH17-dependent clustering of TRAILR2 (R17-4112). CDH17 is a cell surface molecule expressed in gastrointestinal (GI) adenocarcinomas (R18-1615) (R17-4114).
In humans, CDH17 is also present on normal cells of the stomach, intestine, pancreas and gall bladder, but it is not expressed in normal liver tissue. Normal GI tissues were shown to be resistant to TRAILR2-induced apoptosis (R16-4563) while liver tissue may be sensitive to TRAILR2 activation (R16-1795).

The L234A/L235A mutations were incorporated into the BI 905711 molecule to specifically avoid CDH17-independent cross-linking by ablating binding to FcγR and complements. BI 905711 has the potential to avoid hepatotoxicity associated with clustering of TRAILR2 and apoptosis induction in the liver (R16-1795) due to the lack of detectable CDH17 protein in normal liver tissue (R17-2598). Moreover, the non-neoplastic tissues with CDH17 expression as listed above, should be spared from apoptosis and tissue damage due to their low sensitivity to TRAILR2 activation (R17-4113, R16-4563). For a more detailed description of the BI 905711 pharmacologic profile, refer to the current Investigator's Brochure (IB) (c16856466).

Key pharmacokinetic (PK) characteristics

Preliminary PK results from the Phase I FIH study 1412-0001, using planned PK sampling timepoints, were available for patients treated in at dose levels 1-8 (0.02 mg/kg-4..8 mg/kg,

total N=42 patients in 1412-0001 clinical trial. Following intravenous administration of BI 905711, peak plasma concentrations occurred around the end of the infusion at 0.5 h. Terminal Half life was about 3 days at 1.2 mg/kg dose and above. Inter-patient variability was evident. The maximum plasma concentrations (Cmax) were comparable between cycle 1 and cycle 3.
The systemic exposure (AUC_{0-336}) values of BI 905711 were comparable between cycle 1 and cycle 3. Thus, no accumulation was seen between cycle 1 and cycle 3 at the analyzed dose levels between cycle 1 and cycle 3.

Distribution
No dedicated distribution studies have been performed.

Metabolism
BI 905711 is a protein and is expected to undergo protein catabolism in humans to peptides and amino acids. Dedicated metabolism studies were not conducted for BI 905711.

Excretion
The molecular weight of BI 905711 is approximately 201 kDa, which is above the renal filtration cut-off threshold (approximately 60 kDa). Dedicated excretion studies were not conducted.

Pharmacokinetic drug-drug interactions
BI 905711 is a protein, and its clearance is through protein catabolism. BI 905711 is not an immune modulator and is not expected to impact expression and production of cytochrome P450 enzyme or certain drug transporters that may affect indirectly the exposure of co-administered small molecules. Therefore, pharmacokinetic drug-drug interaction between BI 905711 and co-administered small molecules is not expected.

Residual Effect Period (REP)

The expected REP of BI 905711 is 30 days (+ 5 days). This is the period after the last dose with measurable drug levels and/or pharmacodynamic effects still likely to be present.

Data from non-clinical studies

BI 905711 demonstrated high preclinical anti-tumor activity in-vitro and in-vivo in CDH17 positive tumor cell lines. A short summary is given below. For more details, refer to the current IB (c16856466).

The sensitivity to BI 905711 of a panel of 24 CDH17-positive CRC cell lines was evaluated and is shown in Figure 1.2: 1. A V-shaped dose-response is predicted for this bi-specific antibody where concentrations above the optimum will favour individual target recruitment, thus preventing TRAILR2 cross-linking and therefore reducing efficacy. Within the range of concentrations tested, different cell lines showed a reduced efficacy when using higher than optimal doses. Importantly, despite differences in CDH17 and TRAILR2 protein expression levels and the intrinsic sensitivity to TRAILR2 agonists among these cells, there was a common concentration range inducing the maximal effect in all tested cells (Figure 1.2: 1)

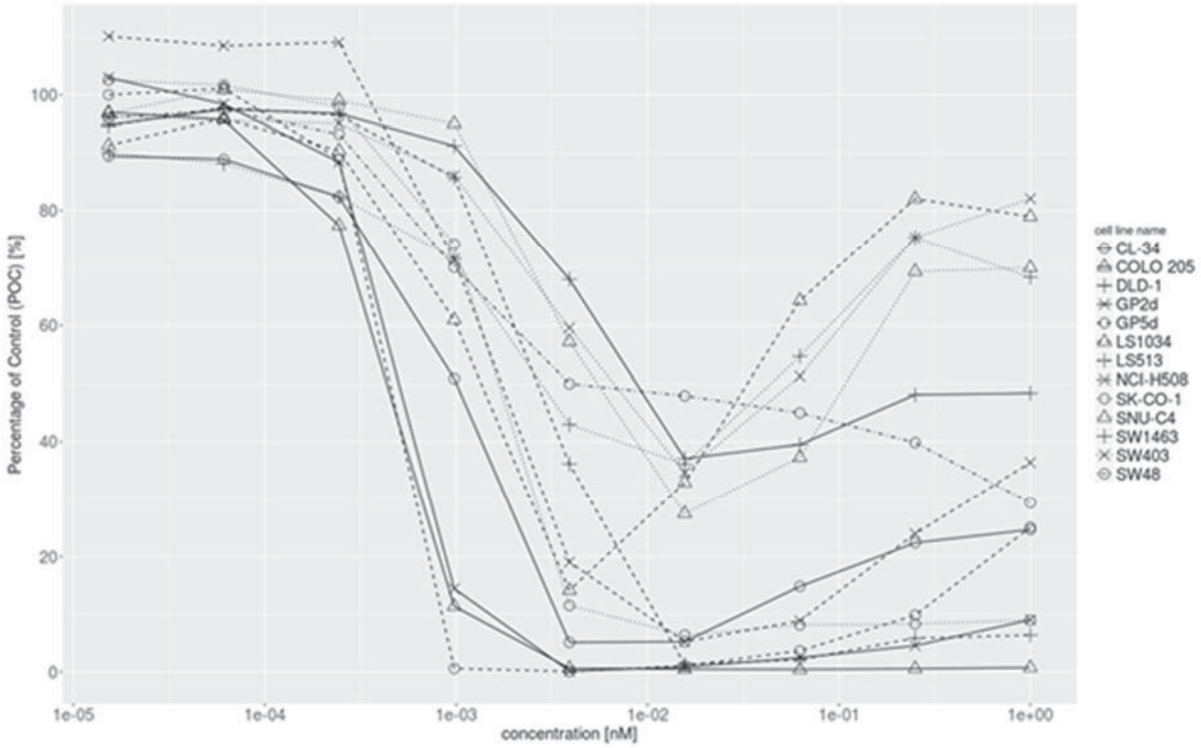

Figure 1.2:1 Sensitivity to BI 905711 of a panel of 24 CDH17-positive CRC cell lines

BI 905711 was also tested in CDH17 negative liver-derived cells, and Hep G2 was used as a surrogate for TRAIL sensitive hepatocytes. In Hep G2 cells, no significant effect of BI 905711 decreasing cell viability was observed. The potent tetrameric nanobody agonist targeting TRAILR2 (EX 77749) was used as a reference for sensitivity to TRAILR2 agonists. As expected for a CDH17-independent molecule, a significant effect of EX 77749 decreasing cell viability was observed independently of the absence of CDH17 membrane expression (Figure 1.2: 2).

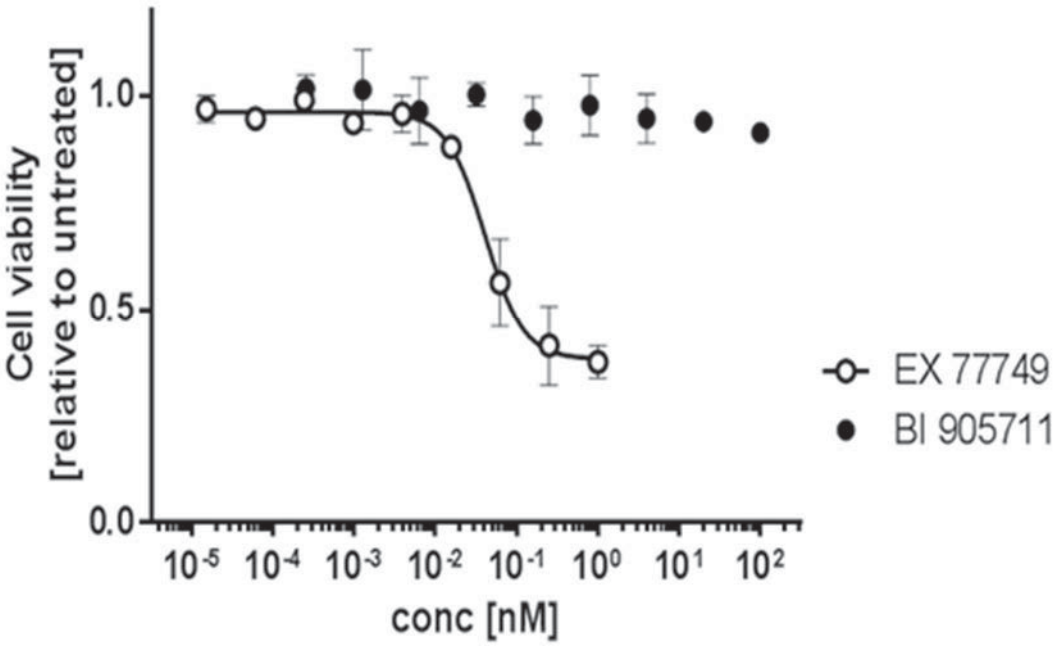

Figure 1.2: 2 Representative graph of concentration response curves as determined in the 72h Hep G2 Cell Titer-Glo assay (c16856466).

BI 905711 *in vivo* efficacy was demonstrated in the COLO 205 xenograft tumor model, where a single dose administration (0.3, 1, 5 and 15 mg/Kg) led to significant growth inhibition for all treatment groups. The GP2d cell line was selected as a second CRC xenograft tumor model for *in vivo* profiling of BI 905711. Compared to COLO 205 derived tumor samples, CDH17 distribution in GP2d derived tumor samples was more similar to those of metastatic CRC patients. BI 905711 was initially administered at doses of 1.67, 5 and 15 mg/kg. After a single dose, BI 905711 administered at 1.67 mg/kg led to sustained tumor regressions for most of the tumors from day 6 until day 36 (end of the experiment). In a follow up study, BI 905711 was administered at lower doses (0.05, 0.2, 0.8, and 1.67 mg/kg). Similar to the 1.67mg/kg group, BI 905711 administered at 0.8 mg/kg as a single dose led to sustained tumor regressions for most of the tumors from day 3 until day 29. The minimal efficacious dose was defined as 0.2 mg/kg with only a few regressions as compared to the 1.67 and 0.8 mg/kg groups but still demonstrated statistically significant tumor growth inhibition at the end of the experiment.

To evaluate the combination potential of BI 905711 with chemotherapeutics, *in vivo* efficacy experiments in several CRC and gastric-esophageal xenograft tumor models were performed (P19-11314, P20-10420). Combination of BI 905711 with irinotecan or paclitaxel or oxaliplatin, resulted in a statistically significant tumor growth control, as compared with vehicle and either compound as monotherapy.

Preclinical toxicology
Preclinical toxicology is fully described in the IB (c16856466). BI 905711 intravenously administered once per week to cynomolgus monkeys for 6 weeks up to dose levels of 100 mg/kg produced no overt adverse effects. No changes in clinical pathology (hematology, clinical chemistry, urinalysis), ophthalmology, or immunophenotyping were observed, nor were any alterations to body weight or food consumption apparent. The majority of treated monkeys displayed ADAs to BI 905711 at the end of the 6-week drug phase, which slightly reduced total exposure (AUC_{0-168}) when compared to the first administration.

BI 905711-related effects in the 6-week monkey study were limited to microscopic findings in the brain (choroid plexus, meninges of the cerebrum, and/or cerebral cortex) at ≥ 30 mg/kg, and in the spinal cord (meninges, gray matter) and kidney (glomerulus) at 100 mg/kg. Changes in the brain and spinal cord were characterized by minimal to mild perivascular mononuclear cell infiltrates that contained admixed eosinophils. In animals allowed a 4-week recovery phase, changes in the choroid plexus and meninges of the brain remained apparent, but no findings were noted in the spinal cord. The perivascular accumulation of mononuclear cell infiltrates may represent immune responses originating within the Virchow-Robin space, continuous with the subarachnoid space and outside of the blood-brain barrier. In the kidney, glomerulopathy was observed in monkeys at the end of treatment and recovery phases and was considered related to BI 905711 administration, although no alterations to serum blood urea nitrogen and creatinine or urinary protein were observed. Immunohistochemical (IHC) staining of affected tissues revealed granular deposits containing human IgG (BI 905711) and/or monkey IgG in the kidneys of animals displaying glomerulopathy. These deposits are consistent with immune complex formation, deposition, and clearance in monkeys that have generated ADA in response to administration of a heterologous protein. An immune complex-mediated basis for the perivascular mononuclear cell infiltrates with admixed eosinophils in the brain and/or spinal cord could not be confirmed by IHC staining.
No hemolytic or local effects due to BI 905711 intravenous injection were noted. BI 905711 did not cause *in vitro* cytokine release (c16856466).

Data from clinical studies
The first-in-human trial 1412-0001 assessing BI 905711 as monotherapy in patients with treatment-refractory GI cancers has been initiated in several countries and is currently ongoing.

For a more detailed description of the BI 905711 profile (limited clinical data are available so far), refer to the current IB (c16856466).

1.3 RATIONALE FOR PERFORMING THE TRIAL

Efficacy of current standard of care therapies for GI cancers at advanced or metastatic stage is limited. The majority of these patients die due to resistance to therapy, thus there is a need to develop new treatment approaches.

BI 905711 is a tetravalent bispecific antibody targeting both TRAILR2 and CDH17, and is designed to selectively induce apoptosis in CDH17 expressing tumour cells via CDH17-dependent clustering of TRAILR2. CDH17 is a membrane protein that is expressed only in

GI tissues including GI cancers but not in normal hepatic cells. Thus, BI 905711 has the potential to avoid liver toxicity.

The potential indications for BI 905711 include GI adenocarcinomas expressing CDH17 including but not limited to: CRC, gastric, oesophageal, pancreatic and biliary tract cancers as indicated in Table 1.3: 1. CRC consistently expresses CDH17 at a high or intermediate level by immunohistochemistry (IHC) in both primary tumors and metastatic sites (R17-2598, R18-1615). High CDH17 expression in metastatic CRC samples was confirmed in a BI prevalence study and showed CDH17 expression in 100 % of the samples analyzed (n=39), and 97% of the samples showed CDH17 expression on over 50% of the tumor cells (77% of samples with >90% positive cells). Expression of CDH17 in gastric, oesophageal, and pancreatic adenocarcinomas and biliary tract cancers is more variable.

Table 1.3: 1 Gastrointestinal cancers expressing CDH17. The percentage indicates the relative number of positive tumors for CDH17 by IHC/IF* according to tumor origin and histology type

	Altree-Tacha et al, 2017 (R18-2263)	Panarelli et al, 2012 (R18-1615)	BI's Prevalence study (data on file)
Colon adenocarcinoma	97%	100%	100%[#]
Esophageal adenocarcinoma	39%	82%	48%
Gastric adenocarcinoma	64%	90%	84%
Pancreatic ductal adenocarcinoma	39%	50%	70%
Cholangiocarcinoma	33%	53%	

* Method and threshold for CDH17-positivity by IHC vary between reports.
[#] Only metastatic samples

BI 905711 can potentially activate TRAILR2 on both CDH17 positive tumor cells and adjacent tumor cells (cis- and trans-activation). BI 905711 can therefore induce TRAILR2 activation in the CDH17 negative cells if surrounded by CDH17 positive cells.

BI 905711 showed efficacy in relevant GI cancer preclinical models as single agent and in combination with chemotherapy agents like capecitabine, irinotecan, paclitaxel and oxaliplatin.

Chemotherapy combinations commonly used in first- and second-line treatment of CRC include leucovorin calcium, fluorouracil (5-FU) and irinotecan (FOLFIRI regimen), or leucovorin, 5-FU and oxaliplatin (FOLFOX regimen) with or without an anti- angiogenic agents such as bevacizumab, or, if RAS wild type, an EGFR antibody.

Second-line treatment options in metastatic pancreatic cancer depend on the therapies previously given in the first-line setting and the patient's performance status, and include:

FOLFIRI or FOLFIRINOX/mFOLFIRINOX (preferred option for patients who progressed on prior gemcitabine-based treatment), gemcitabine plus nab-paclitaxel, FOLFOX, or single agent gemcitabine or 5-FU, (R20-3885).

Chemotherapy induces apoptosis via activation of the intrinsic pathway while TRAILR2/CDH17 antibody induces apoptosis via the activation of the extrinsic pathway. Thus, the combination of BI 905711 with FOLFIRI (+/- bevacizumab) should increase the apoptosis signal by the activation of both intrinsic and extrinsic apoptosis pathways in cancer cells. An increased efficacy of BI 905711 in combination with chemotherapy has been observed in CRC GP2d xenograft models (c16856466). BI 905711 plus irinotecan or oxaliplatin showed increased efficacy in the CRC GP2d xenograft models as compared to single agents. The combination with irinotecan showed the deepest and longest tumor growth control. Moreover, the efficacy of the sequential administration of irinotecan and BI 905711 was analysed in preclinical models by measuring the induction of caspase cleavage in tumor tissue at baseline and at several timepoints on treatment. The results showed that pro-apoptotic priming with irinotecan followed, 24 hours later, by the administration of BI 905711 led to the highest synergistic effect (cCasp3 activation) as compared to co-administration on the same day (data on file). These data are consistent with published data demonstrating that pre-treatment with chemotherapy eg. cisplatin or irinotecan, sensitizes cancer cells to TRAILR2 agonistic antibodies and the sequential administration might overcome resistance (R21-2020, R21-2040, R21-2041).

The first-in-human trial 1412-0001 is assessing BI 905711 as monotherapy in patients with advanced or metastatic GI cancers. In Phase Ia, 45 patients (26 with CRC, 19 with non-CRC GI cancers) have received BI 905711 (dose range 0.02–4.8 mg/kg). No safety concerns or dose-limiting toxicities have been observed to date (c16856466) and the MTD was not reached. Based on safety, pharmacokinetic, and pharmacodynamic profiles, as well as preliminary antitumor activity of BI 905711, three dose levels (0.6 mg/kg, 1.2 mg/kg and 2.4 mg/kg) given biweekly or one dose level (0.6 mg/kg) given weekly were selected for assessment of BI 905711 monotherapy in 1412-0001 expansion phase 1b.

As of Apr 2022, 37 out of 45 (82.2%) patients treated with BI 905711 monotherapy (dose range 0.02 mg/kg-4.8 mg/kg) experienced at least 1 adverse event (AE). Most of the reported AEs were consistent with known signs and symptoms of advanced colorectal, biliary and pancreatic cancers. 15 out of 45 patients experienced grade 1-3 drug-related AEs consisting of general disorders and administration site conditions, and gastrointestinal disorders. A total of 11 patients experienced SAEs, and 2 events were considered drug-related by the investigators.

There were no dose-limiting toxicities identified and there was no pattern of any anticipated adverse effects (see section 7 of the current BI 905711 investigator's brochure). There were 4 AEs leading to dose reduction and/or discontinuations of study medication. In addition, there was no evidence of any dose/(adverse) effect relationship regarding both frequency as well as severity.

There were 2 cases of hepatic laboratory abnormalities suspicious for drug induced liver injury (DILI) which meeting to Hy's law criteria, and there was no evidence indicative for (laboratory) tumor lysis syndrome or cytokine release syndrome (CRS). 3 patients experienced Grade 1-2 infusion related reaction (IRR).

In order to address future scientific questions, patients will be asked to voluntarily donate biospecimens for banking (please see Section 5.5). If the patient agrees, banked samples may be used for future biomarker research and drug development projects, e.g. to identify patients that are more likely to benefit from a treatment or to experience an adverse event (AE), or to gain a mechanistic or genetic understanding of drug effects and thereby better match patients with therapies.

Based on available preliminary data from phase I clinical studies (1412.1 and 1412.3), the decision was made to terminate BI 905711 (TRAILR2/CDH17) development program. This decision is not related to any safety concerns or unfavorable benefit/risk balance, but to the lack of predictive biomarkers and the limited efficacy particularly in the context of the evolving treatment landscape for advanced CRC and other GI cancers.

The purpose of CTP v4.0 is to reduce the study related activities to the minimum required to monitor patient safety and to avoid undue burden on patients.

1.4 BENEFIT - RISK ASSESSMENT

1.4.1 Benefits

Most patients with advanced or metastatic GI cancers have limited effective treatment options, develop resistance to currently available therapies, and succumb to their disease. BI 905711 in combination with chemotherapy (+/- bevacizumab) can potentially provide a new therapeutic option for these patients as suggested by its efficacy in relevant preclinical GI cancer models and further supported by extensive pharmacology and toxicology preclinical data.

1.4.2 Risks

TRAILR2 agonistic antibodies, both as single agents and in combination with chemotherapy, have been extensively tested in the clinic and showed a good safety profile with the exception of TAS266 (R16-1795). The majority of these compounds did not induce dose limiting toxicities (DLTs) in phase I trials with no established maximum tolerated dose (MTD). Treatment-related adverse events (AEs) reported with these compounds mostly included GI AEs (nausea, vomiting, diarrhea, stomatitis, decreased appetite) and elevation of aspartate aminotransferase (AST), alanine aminotransferase (ALT) and pancreatic amylase (R16-1793, R16-1794, R17-2590, R17-2600, R17-2601, R16-4524, R17-2606, R18-2222). There is limited clinical experience with the second generation of compounds inducing TRAILR2 clustering independently of FcR interactions. Phase I data of the TRAILR2 binding tetramer (TAS 266) reported reversible liver toxicity at the first administered dose level leading to TAS 266 discontinuation from further development (R16-1795). Published pre-clinical and

clinical data suggest that a relatively high exposure at the starting dose in the phase I trial may have contributed to the observed liver toxicity (R16-1800, R18-2222). Another TRAILR2 agonist (ABBV-621) currently under clinical investigation reported mainly liver and GI AEs with no defined MTD, and 1 partial response out of 24 patients each in CRC and pancreatic cancer patients (R18-2222). A bi-specific compound targeting TRAILR2 and FAP (RG 7386) has completed phase I with no reported DLTs and MTD (R18-1695).

So far AEs reported were consistent with known signs and symptoms of an end-stage CRC population. A total of11 patients experienced SAEs, and 2 events were considered drug-related by the investigator. There were no dose-limiting toxicities identified and there was no pattern of any anticipated safety topics (acc section 7 of the current BI 905711 investigator's brochure). In addition, there was no evidence of any dose/(adverse) effect relationship regarding both frequency as well as severity.
In addition, there were 2 cases of hepatic laboratory abnormalities suspicious for drug-induced liver injury (DILI) which met Hy's law criteria; and there was no evidence indicative of (laboratory) tumor lysis syndrome or cytokine release syndrome (CRS). 3 patients experienced Grade 1-2 infusion-related reaction (IRR).

The safety data will be closely monitored throughout this trial, and a Data Review Committee (DRC) will be implemented for this purpose.

Table 1.4.2: 1 Overview of trial related risks

Possible or known risks of clinical relevance for this trial	**Summary of data, rationale for the risk**	**Mitigation strategy**
Investigational Medicinal Product: BI 905711 The anticipated AEs based on the BI 905711 mode of action, pharmacological data and results of preclinical toxicology studies are described below; For more details, refer to the IB (c16856466).		
Injury of GI tissues expressing CDH17	BI 905711 may potentially cross-link TRAILR2 to CDH17 in GI tissues and induce apoptosis and injury. No signs of GI injury were observed in preclinical toxicology studies in cynomolgus monkeys up to the highest administered dose. In-vitro data suggest that normal human colon epithelial cells are insensitive to TRAILR2 induced apoptosis, but their sensitivity can be increased during inflammation or viral infection (R16-4563, R17-2592). Based on above considerations, possible anticipated AEs of BI 905711 may include nausea, anorexia, diarrhea, vomiting, pancreatitis, increase in pancreatic amylase, abdominal pain and/or other GI tract related signs/symptoms.	Patients with inflammatory bowel disease or bowel infection, or history of chronic pancreatitis should not participate in clinical trials with BI 905711. Guidelines for management of nausea, diarrhea and vomiting is provided in Section 4.2.4.3.

Table 1.4.2: 1 Overview of trial related risks (cont)

Possible or known risks of clinical relevance for this trial	**Summary of data, rationale for the risk**	**Mitigation strategy**
Drug-induced liver injury	Liver tissue is reported as the most sensitive non-cancerous tissue to TRAILR2 mediated apoptosis (R16-1795, R16-1793). Human hepatocytes do not express CDH17 and in Hep G2 cells used as a surrogate for TRAIL sensitive hepatocytes, no significant effect of BI 905711 on cell viability was observed. However, liver damage cannot be excluded particularly in patients with liver metastases.	Timely detection, evaluation, and follow-up of alterations in selected liver laboratory parameters to ensure patients´safety will be implemented.
Renal Injury	A 6-week GLP toxicology study in monkeys showed glomerulopathy at the highest tested dose of 100 mg/kg. These finding were not accompanied by clinical or biochemical changes in renal function. There was no proteinuria and no increase in serum creatinine or blood urea nitrogen (BUN).	The relevance of these renal findings for humans is unknown. Patients will be monitored for changes in renal functions by routine measurement of creatinine and urea in blood and protein in urine. See section 4.2.4.6
Infusion-related reaction (IRR)	As with any mAb, hypersensitivity reactions with BI 905711 are possible. BI 905711 is a humanized bi-specific antibody with atypical format which may induce IRR via multiple mechanisms. Recent data with a bi-specific antibody targeting TRAILR2 and FAP, and a TRAILR1/R2 agonist (ABBV-261) reported an incidence of 9% and 8% of grade 1-2 infusion reactions respectively but no grade ≥3 (R18-1695, R20-0970).	Patients with a known hypersensitivity to the trial medications or their excipients are excluded. Management guidelines for IRR are provided in Section 4.2.4.1
Cytokine release syndrome (CRS) and immune-mediated reactions	CRS is a supra-physiologic response resulting in the activation or engagement of T cells and / or other immune effector cells, which can be serious or life-threatening. The TRAIL pathway has been implicated in inflammation, in some preclinical experiments, but the clinical relevance of these findings is unknown (R18-2770). BI 905711 did not induce any cytokine release using a standard in vitro assay (c16856466). There was no CRS reported in historical studies with conventional TRAILR2 agonists (R16-1793, R16-1794, R17-2590, R17-2600, R17-2601, R16-4524, R17-2606).	The risk of CRS cannot be excluded, and patients should be followed for possible occurrence of CRS. Guidelines are provided in Section 4.2.4.2

Table 1.4.2: 1 Overview of trial related risks (cont)

Possible or known risks of clinical relevance for this trial	**Summary of data, rationale for the risk**	**Mitigation strategy**
Tumor Lysis Syndrome (TLS)	BI 905711 induces apoptosis within a short time frame in-vitro and leads to tumor regression in-vivo in preclinical models. Theoretically, TLS can occur.	Patients should be monitored for occurrence of TLS particularly after the first administration of BI 905711. Guidelines are provided in Section 4.2.4.4
Neurological adverse events	A six-week GLP toxicology study in monkeys showed minimal to mild perivascular eosinophilic/monocyte cell infiltrations in brain and spine at doses of 30mg/kg and 100mg/kg with no apparent clinical neurological finding in affected animals. More details are described in section 1.2 and the IB (c16856466)	Relevance of these findings for humans is unknown. Human exposure to the highest planned dose of 4.8 mg/kg is estimated to be 3 to 4-fold below exposure in monkeys at the 30 mg/kg (NOAEL). CDH17 is an epithelial protein and it is not expressed in brain tissue. No neurological AE related to BI 905711 have been observed in preclinical studies and in ongoing FIH phase I trial. Thus, BI905711 is not expected to induce neurological adverse events. Patients who develop new neurological symptoms or deficits need to undergo neurological investigations including a brain MRI, and treatment with BI 905711 must be interrupted or discontinued. Guidelines for management of potential neurological toxicities are provided in Section 4.2.4.5 and their relationship to ADA will be assessed in this trial.
ADA (anti-drug antibodies) related adverse reactions	ADA to BI 905711 were observed in monkeys and were considered an immune response to a humanized monoclonal antibody. The presence of ADA in monkeys is not indicative of a similar response in humans (c16856466). BI 905711 may lead to development of ADA in humans, and its occurrence will be explored in this study (see Section 5.3.2). The consequence of ADA on safety is currently unknown, however there is a single preclinical report indicating the possibility of ADA-mediated clustering of TRAILR2 and its potential contribution to liver injury (R17-2603).	Patients will be followed for development of liver injury, and possible contribution of ADA to liver injury will be assessed.

Table 1.4.2: 1 Overview of trial related risks (cont)

Possible or known risks of clinical relevance for this trial	**Summary of data, rationale for the risk**	**Mitigation strategy**
SARS CoV-2 infection	Due to the underlying disease, exposure to intensive anti-cancer treatments and/or immunosuppressive therapies, patients in this trial may be immuno-compromised and at higher risk for infection and/or severe illness from COVID-19.	A Benefit-Risk assessment in the context of the COVID-19 pandemic for patients treated with BI 905711 has been performed. Based on its mode of action, BI 905711 is not expected to have a relevant impact on the susceptibility to or the course of a COVID-19 infection. In case of a confirmed infection, continued use of trial treatment will be left to the investigator's benefit-risk assessment on a case-by-case basis. Withdrawing treatment in a cancer patient who may have few or no alternative treatment options requires a careful, individual evaluation.
Trial procedures		
Tumor Biopsy	There is an added risk for pain, swelling, bleeding for those patients who will undergo tumor biopsies. As the results from the biopsy will provide more information which will assist clinical decisions for future patients, the benefit is assumed to outweigh the risks.	Biopsies will only be performed when deemed safe by the investigator and if the platelet count is sufficient to allow for haemostasis.
Background therapy		
Irinotecan, Leucovorin, Fluorouracil, Bevacizumab	Refer to the most recent approved local labels.	The investigator must review the label for each background therapy and implement any additional required safety monitoring to reduce the risk to the patient.

1.4.3 Discussion

There may be a potential benefit, eg. improved disease control and survival while maintaining quality of life, to patients from the addition of BI 905711 to FOLFIRI (or Liposomal Irinotecan plus 5-FU/Leucovorin) in pancreatic cancer, or to FOLFIRI plus bevacizumab in CRC.

The first in human (FIH) Phase I study of BI 905711 (1412-0001) currently being conducted in Asia, Europe and USA, is investigating the recommended phase 2 dose, safety, tolerability, pharmacokinetics (PK), pharmacodynamics, and preliminary efficacy of BI 905711 as monotherapy in patients with advanced or metastatic GI cancers. At the initiation of trial 1412-0003, the FIH monotherapy study 1412-0001 will be still ongoing, and the available preliminary safety data in monotherapy will serve as a reference for the starting and

subsequent dose levels of BI 905711 in combination with background treatment for the dose escalation phase.
So far AEs reported were consistent with known signs and symptoms of an end-stage CRC population. A total of 11 patients experienced SAEs, and 2 events were considered drug-related by the investigator. There were no dose-limiting toxicities identified and there was no pattern of any anticipated safety topics (acc section 7 of the current BI 905711 investigator's brochure). In addition, there was no evidence of any dose/(adverse) effect relationship regarding both frequency as well as severity.

The DRC will assess trial data to ensure the overall safety of enrolled patients. The DRC will also provide the investigators and the Sponsor with advice about the overall conduct of the trial (refer to Section 8.7).

The Sponsor will continuously assess the risks and benefits based on accumulating data from all clinical trials with BI 905711. Any significant change in risk-benefit ratio will be communicated to investigators and patients.

In summary, this trial will implement multiple safety measures to mitigate possible risks for participating patients. It is assumed that participation in this study and treatment with BI 905711 in combination with the background treatment may potentially provide patients with clinical benefit at an acceptable risk.

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

2.1.1 Main objectives

Phase Ia:

- To determine the maximum tolerated dose (MTD) and the recommended dose for expansion (RDE) of BI 905711 in combination with FOLFIRI regimen plus bevacizumab in CRC patients based on the frequency of patients experiencing dose limiting toxicities (DLT) during the MTD evaluation period (as defined in section 3.1.1).
- To explore pharmacokinetics/pharmacodynamics, and efficacy to guide the determination of a MTD or a potentially effective dose in the absence of MTD, of BI 905711 in combination with FOLFIRI plus bevacizumab.

Phase Ib

- To evaluate the efficacy and safety of BI 905711 in combination with FOLFIRI plus bevacizumab in the CRC cohort, and define RP2D (Recommended phase II dose).
- To evaluate the efficacy and safety of BI 905711 in combination with FOLFIRI (or Liposomal Irinotecan plus 5-FU/Leucovorin) in PDAC cohort, and define RP2D.

2.1.2 Primary endpoint(s)

Phase Ia

- Maximum tolerated dose (MTD) defined as the highest dose with less than 25% risk of the true DLT rate being equal or above 33% during the MTD evaluation period.
- Number of patients with DLTs in the MTD evaluation period.

Phase Ib

- Confirmed objective response (OR) as assessed by the investigator based on Response Evaluation Criteria in Solid Tumors (RECIST 1.1) (R09-0262) in patients with measurable disease, defined as the best overall response of complete response (CR) or partial response (PR), from the first administration of trial treament until the earliest of progressive disease (PD), death or last evaluable tumor assessment before start of subsequent anti-cancer therapy.
- In safety run-in part of PDAC cohort: number of patients with DLTs during the MTD evaluation period assessed in the first 6 patients.

2.1.3 Secondary endpoint(s)

Phase Ia

- The following PK parameters will be calculated after study treatment administration, as measured during the first cycle and after multiple cycles:
  - C_{max}: Maximum measured plasma concentration of BI 905711.
  - AUC_{0-t2}: Area under the concentration-time curve in plasma of BI 905711

Phase Ib

- Progression-Free Survival (PFS) defined from date of start of treatment to the date of disease progression or death, whichever is earlier as assessed by the investigator according to RECIST 1.1.
- Radiological (CT Scan) tumor shrinkage, defined as the difference between the minimum post-baseline sum of longest diameters of target lesions and the baseline sum of longest diameters of the same set of target lesions according to RECIST 1.1.
- The duration of OR is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or PD is objectively documented (taking as reference for PD the smallest measurements recorded on study) according to RECIST 1.1.
- Disease control, defined as CR, PR, or stable disease (SD) lasting at least 16 weeks according to RECIST 1.1 from the start of treatment until the earliest of PD, death or last evaluable tumor assessment and before start of subsequent anti-cancer therapy.
- The following PK parameters will be calculated after study treatment administration, as measured during the first cycle and after multiple cycles:
  - C_{max}: Maximum measured plasma concentration of BI 905711 in plasma.
  - AUC_{0-t2}: Area under the concentration-time curve for BI 905711 in plasma.

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN

This is a phase Ia/b, open label, multicentre, dose escalation study of BI 905711 in combination with chemotherapy (with or without bevacizumab) followed by expansion cohorts in patients with advanced or metastatic CRC and PDAC. The study will consist of two phases: a dose-escalation phase (Phase Ia) and a dose-expansion phase (Phase Ib). The study design is illustrated in Figure 3.1:1.

Recruitment in Phase Ia is complete and recruitment in Phase Ib was discontinued during Phase I expansion, and no PDAC patients were enrolled in this expansion cohort.

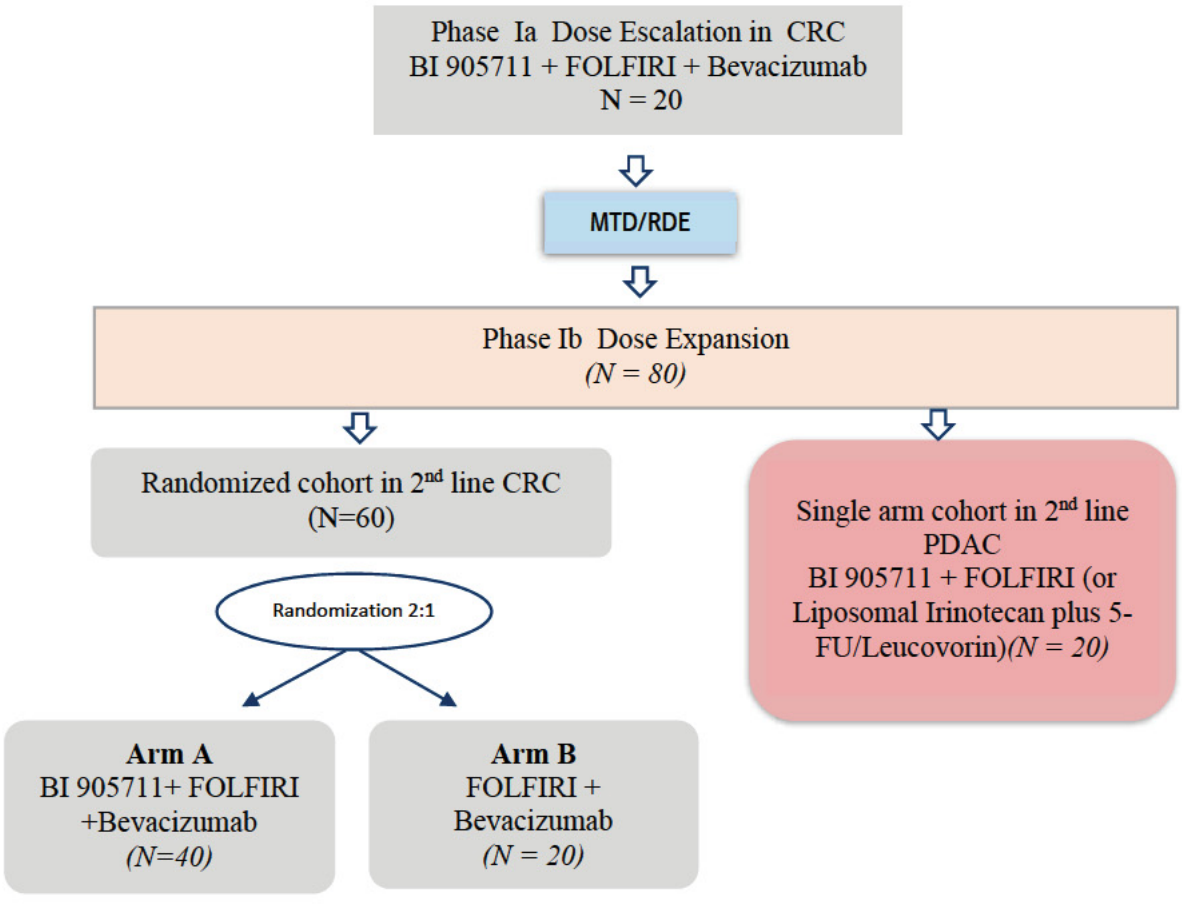

Figure 3.1:1 Overall study design

3.1.1 Dose escalation phase (Phase Ia)

Phase Ia is an open-label, non-randomized dose escalation study of BI 905711 in combination with FOLFIRI and bevacizumab in patients with CRC. Refer to Figure 3.1: 1. The objective of the phase Ia is to determine the MTD/RDE.

A Bayesian logistic regression model (BLRM) with overdose control (R13-4803) will be used to determine the MTD. The BLRM estimates the MTD by updating the probability of observing a DLT for each dose level in each dose escalation cohort. At any time during the trial, it will not be permitted to escalate to a dose which does not fulfil the escalation with overdose control (EWOC) criterion.

The MTD evaluation period is defined as a two 14-day treatment cycle (from cycle 1 Day 1 until the day before cycle 3 Day 1, or end of the REP in case of discontinuation before start of cycle 3).

Patients will receive increasing doses of BI 905711 in combination with FOLFIRI plus bevacizumab until either the MTD or the RDE in the absence of MTD, is reached. Incremental dose increases of BI 905711 in successive patient cohorts will be no more than 100% of the previous dose level.

At each dose level, all patient cohorts will include at least 3 patients. In the case that only 2 out of 3 patients in a cohort are evaluable and neither has experienced a DLT within the MTD evaluation period, dose-escalation can occur based on the data from these 2 patients.

As soon as all patients at a dose level have either experienced a DLT or have completed the MTD evaluation period without experiencing a DLT, a BLRM with overdose control will be re-run with the newly accumulated data. Based on the estimates from the model and on additional information (i.e. PK and PD as available), the DRC will reach a joint recommendation of the next dose level to be investigated, the size of the next cohort, as well as the potential recommendation to expand the size of the recruiting cohort.

If DLTs are observed in the first two consecutive patients of a previously untested dose level, subsequent enrolment to this dose cohort will be stopped. The BLRM will be re-run to confirm whether the dose level still fulfils the EWOC criterion. Based on this information, the DRC will evaluate whether the next patients will be enrolled at the same dose level or at a lower dose level including intermediate dose levels.

No further dose escalation will take place after the criterion for MTD is fulfilled. Further patients may be included to confirm this MTD estimate, i.e. to confirm that the EWOC criterion is still fulfilled. The DRC can declare any dose fulfilling the EWOC criterion as the RDE, independent of the MTD estimate. The RDE will not exceed the MTD. Any DLTs occurring after the MTD evaluation period will be considered for the evaluation of the RDE. If no DLT is observed, the DRC may decide to declare the RDE based on PK/PD and efficacy endpoints, and overall safety profile.

3.1.2 Dose expansion phase (Phase Ib)

Phase Ib is an open label study with the main objective to assess the safety and efficacy of BI 905711 in combination with chemotherapy (with or without bevacizumab) in 2 expansion cohorts. PK will be further characterised and the RP2D will be determined.

Phase Ib will consist of 2 cohorts of patients with 2 different tumor types as described below. Refer to Figure 3.1: 1 for the planned randomized CRC cohort and single arm PDAC cohort.

3.1.2.1 Randomized CRC expansion cohort

This is an open label, randomized cohort of approximately 60 CRC patients. Patients will be randomized in a 2:1 ratio into either:

- Arm A = BI 905711 (at the RDE from Phase Ia) plus FOLFIRI and bevacizumab

or

- Arm B = FOLFIRI plus bevacizumab

3.1.2.2 Single Arm PDAC expansion cohort

This is an open label single arm cohort of approximately 20 patients with CDH17-positive PDAC.
A safety run-in will be included in which the first 6 patients will be treated with BI 905711 (at the RDE from Phase Ia) plus FOLFIRI (or Liposomal Irinotecan plus 5-FU/Leucovorin), to confirm the RDE based on DLTs assessed during the MTD evaluation period as defined for the Phase Ia, prior to enrolling further patients.

3.1.3 Enrolment stopping rules

All safety information will be carefully analysed by the sponsor. Enrolment will be temporarily stopped if a clinically relevant AE occurs which meets both of the following criteria:

- associated with evidence suggesting a reasonable possibility that the investigational drug caused the AE
- occurs at a frequency or with severity that suggest that the risk-benefit profile of the investigational drug should be reassessed

If the DRC determine that the above criteria are met, the enrolment to the trial will be temporarily stopped to allow for in-depth analysis of the safety profile of BI 905711 plus the applicable background treatment. The benefit-risk profile will be re-assessed by the DRC to determine if the trial should be continued as planned, or permanently discontinued or will continue with modification to the trial protocol. The purpose of any modifications to the protocol will be to mitigate patient-risk and ensure that the benefit-risk assessment for continued investigation of BI 905711 plus applicable background treatment remains positive. The DRC will also consider and provide guidance for the management of patients who are already receiving study treatment. The outcome of the analysis and the recommendations will

be shared with all involved Health Authorities prior to a planned re-start of enrolment. In case the benefit-risk assessment is no longer considered positive, the trial will be discontinued.

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

FOLFIRI in combination with Bevacizumab is indicated for first- and second-line treatment of CRC, including those who have progressed on a first-line bevacizumab-containing regimen. FOLFIRI (or Liposomal Irinotecan plus 5-FU/Leucovorin) is a second-line treatment option for patients with PDAC.

In Phase Ia, the selection of dose levels and patient cohort size will be guided by a BLRM with overdose control. An EWOC design will increase the chance of treating patients at efficacious doses while reducing the risk of overdosing. This design is based on practical experience and is an efficient method due to its ability to identify the dose with a desired toxicity rate and its allocation of a greater proportion of patients to doses at, or close to, that desired dose (R13-4802, R13-4804, R13-4805). The use of BLRM for Phase I trials has also been advocated by the EMA guideline on small populations (R07-4856) and by the FDA (R13-4881).

3.3 SELECTION OF TRIAL POPULATION

This is an international multi-center trial.

For phase Ia (dose escalation) approximately 20 patients are planned to be entered at approximately 4-5 sites. The total number of patients will depend on the number of dose levels to be tested and the size of the dose escalation cohorts.

For phase Ib, approximately 80 patients are planned to be entered at sites that participate in the dose escalation part of the study as well as additional sites that will be initiated as needed to fulfill the planned enrolment. If participating sites are unable to recruit patients, additional sites may be opened, and under-performing sites may be closed.

Screening of patients for this trial is competitive, however in Phase Ia, recruitment slots will be assigned by the Sponsor. Screening for the trial will stop at all sites at the same time once a sufficient number of patients has been screened. Investigators will be notified about screening completion and will then not be allowed to screen additional patients for this trial. Any patients already in screening at the time of screening completion, will be allowed to continue to receive treatment if eligible.

A log of all patients enrolled into the trial (i.e. who have signed informed consent) will be maintained in the Investigator Site File (ISF) irrespective of whether they have been treated or not.
If retrospectively it is found that a patient has been entered in error (=did not meet all inclusion criteria or met one or more exclusion criteria), the sponsor or delegate should be contacted immediately. Based on an individual benefit-risk assessment a decision will be made whether continued trial participation is possible or not.

Assessments may be repeated within the screening period if patients do not initially meet the inclusion/exclusion criteria. Eligibility must always be assessed using the latest results available.

A patient who has been declared as a "screening failure" may be re-screened once.
In this situation, patients will be handled as new patients i.e. sign a new informed consent, allocate a new patient number, and undergo full screening assessments to assess eligibility.

3.3.1 Main diagnosis for trial entry

The patient population for this trial includes patients with histologically or cytologically confirmed advanced unresectable or metastatic colorectal adenocarcinoma (CRC), and CDH17 positive pancreatic ductal adenocarcinoma (PDAC) (Phase Ib only).

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

Applicable to both Phase Ia and Phase Ib Cohorts:

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

2. Of legal adult age (according to local legislation) at screening.

3. Histologically or cytologically confirmed, advanced unresectable or metastatic colorectal adenocarcinoma

4. CRC : Patients who have PD after prior oxaliplatin-based first line therapy or within 6 months after the end of oxaliplatin-based adjuvant therapy.

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

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

7. Availability and willingness to provide tumor tissue (fresh biopsy or archival) for biomarker analysis as described in the Flow Chart Footnotes and in Section 5.4.3.1

   Only non-significant risk procedures per the investigator's judgment will be used to obtain any biopsies specified in this study. In case a fresh tumor biopsy cannot be obtained, the recruitment of the patient may proceed on a case-by-case basis after agreement between the investigator and BI. In such a case, an archived tumor tissue specimen must be submitted.

8. Adequate hepatic, pancreatic, renal and bone marrow functions as defined by all of the below:
    - Total bilirubin ≤ 1.5 x institutional upper level of normal (ULN).
    - Alanine transaminase (ALT) and Aspartate transaminase (AST) ≤2.5 x institutional ULN or ≤5 x institutional ULN for patients with known liver metastases.
    - Serum creatinine ≤1.5x institutional ULN. If creatinine is > 1.5 x ULN, patient is eligible if concurrent creatinine clearance ≥ 50 ml/min (≥ 0.05L/min) (measured or calculated by CKD-EPI formula or Japanese version of CKD-EPI formula for Japanese patients).
    - Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L, ≥ 1.5 x 10^3/µL, or ≥ 1500/mm^3
    - Platelets ≥ 100 x 10^9/L, ≥ 100 x 10^3/µL, or ≥ 100 x 10^3/mm^3
    - Hemoglobin (Hb) ≥ 8.5 g/dl, ≥ 85 g/L, or ≥ 5.3 mmol/L (without transfusion within previous week)
    - Serum lipase ≤ 1.5 institutional ULN (Only for CRC cohort); >1.5 - 2.0 x ULN or asymptomatic >2.0 - 5.0 x ULN if related to PDAC (Only for PDAC cohort)

9. Recovery, from any adverse events (AEs) of previous anti-cancer therapies, to Common Terminology Criteria for Adverse Events (CTCAE) v5.0 grade 1 except for CTCAE grade 2 alopecia or peripheral sensory neuropathy, or other CTCAE grade 2 AEs considered not clinically significant in the investigator's opinion.

10. 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. A list of contraception methods meeting these criteria is provided in Section 4.2.3.3.

[1] A woman is considered of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming postmenopausal 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.

Additionally, criterion 11 is applicable to Phase Ia cohort only

11. Patient with either measurable or non-measurable disease.

Additionally, criterion 12-14 is applicable to Phase Ib cohorts only

12. At least one target lesion that can be accurately measured per RECIST 1.1

PDAC Patients must also meet the followings:

13. Histologically or cytologically confirmed, advanced unresectable or metastatic CDH17 positive pancreatic adenocarcinoma

14. Patients who have PD after prior platin and/or gemcitabine-based first line therapy.

3.3.3 Exclusion criteria

Applicable to both Phase Ia and Phase Ib cohorts

1. Any prior irinotecan-based therapy in the metastatic setting.

2. Previous systemic anti-cancer therapy within the specified timeframe from the last dose intake to the first dose of trial treatment as follows:

    - Any non-investigational drug, including anti-angiogenic agents (bevacizumab or ramucirumab or aflibercept) and anti-EGFR antibodies (cetuximab or panitumumab), within 14 days.
    - Any investigational drug or other antibodies including immune checkpoint inhibitors, within 28 days.

3. Currently enrolled in another investigational device or drug trial. Patients who are in follow-up/observation for another clinical trial are eligible.

4. Radiation therapy within 4 weeks prior to start of treatment. However, palliative radiotherapy for symptomatic metastasis is allowed if completed within 2 weeks prior to start of treatment.

5. Any serious concomitant disease or medical condition affecting compliance with trial requirements or which are considered relevant for the evaluation of the efficacy or safety of the trial drug, such as neurologic, psychiatric, infectious disease or active ulcers (gastro-intestinal 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.

6. Known pathological condition of GI tract, liver and pancreas, excluding the disease under study, that may interfere with assessment of drug safety or may increase the risk of toxicity:
    a. inflammatory bowel disease
    b. chronic pancreatitis
    c. other serious GI pathological conditions by judgment of the investigator e.g. autoimmune disease with GI involvement, unexplained active diarrhea CTCAE v5.0 grade ≥2.

7. Known history of human immunodeficiency virus (HIV) infection.

8. Any of the following laboratory evidence of hepatitis virus infection. Test results obtained in routine diagnostics are acceptable if done within 14 days before the informed consent date:
    - Positive results of hepatitis B surface (HBs) antigen
    - Presence of HBc antibody together with HBV-DNA
    - Presence of hepatitis C RNA

9. Previous or concomitant malignancies, other than the one treated in this trial within the last 2 years with the exception of the following:
    - Effectively treated non-melanoma skin cancers
    - Effectively treated carcinoma in situ of the cervix
    - Effectively treated ductal carcinoma in situ
    - Other effectively treated malignancy that is considered cured by local treatment

10. Chronic alcohol or drug abuse or any condition that, in the investigator's opinion, makes the patient an unreliable trial participant or unlikely to comply with the protocol requirements or not expected to complete the trial as scheduled.

11. Women who are pregnant, nursing, or who plan to become pregnant while in the trial; female patients who do not agree to the interruption of breast feeding from the start of study treatment through 6 months after the last study treatment.

12. Presence of uncontrolled or symptomatic brain or subdural metastases. Inclusion of patients with brain metastases who have completed local therapy and are considered stable by the investigator, or with newly identified asymptomatic brain metastases at screening will be allowed. Use of corticosteroids is allowed if the dose was stable for at least 1 week before the baseline MRI.

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

14. Major surgery (major according to the investigator's assessment) performed within 28 days prior to treatment start or planned within 3 months after screening, e.g. hip replacement.

15. Any of the following cardiac criteria:
    a. resting corrected QT interval (QTc) >470 msec based on local assessment
    b. Any clinically important abnormalities (as assessed by the Investigator) in rhythm, conduction, or morphology of resting Electrocardiograms (ECGs), e.g., complete left bundle branch block, third degree heart block.
    c. Patients with an ejection fraction (EF) <50% or the lower limit of normal of the institutional standard will be excluded. Only in cases where the Investigator (or the treating physician or both) suspects cardiac disease with negative effect on the EF, will the EF be measured during screening using an appropriate method according to local standards to confirm eligibility (e.g., echocardiogram, multi-gated acquisition scan). A historic measurement of EF no older than 6 months prior to first

administration of study drug can be accepted provided that there is clinical evidence that the EF value has not worsened since this measurement in the opinion of the Investigator or of the treating physician or both.

d. Patients with a history of stroke or myocardial infarction within 6 months prior to screening are not permitted.

16. Known hypersensitivity to the trial medications or their excipients

17. The patient has any known history or clinical evidence of Gilbert's Syndrome, or is known to have any of the following genotypes: UGT1A1*6/*6, UGT1A1*28/*28, or UGT1A1*6/*28

18. Any contradictions to the proposed background therapy according to the current approved local label.

3.3.4 Discontinuation of patients from treatment or assessments

Patients may discontinue trial treatment or withdraw consent to trial participation as a whole ("withdrawal of consent") with very different implications; please see sections 3.3.4.1 and 3.3.4.2).

Every effort should be made to keep the patients in the trial: if possible on treatment, or at least to collect important trial data.
Measures to control the withdrawal rate include careful patient selection, appropriate explanation of the trial requirements and procedures prior to trial enrolment, as well as the explanation of the consequences of withdrawal.

The decision to discontinue trial treatment or withdraw consent to trial participation and the reason must be documented in the patient files and CRF. If applicable, consider the requirements for Adverse Event collection reporting (please see section 5.2.6)

3.3.4.1 Discontinuation of trial treatment

An individual patient will discontinue trial treatment if:

- The patient wants to discontinue trial treatment, without the need to justify the decision.
- 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 adhere to the trial requirements in the future.
- The patient needs to take concomitant medication that interferes with the investigational medicinal product.
- The patient can no longer receive trial treatment for medical reasons (such as surgery, adverse events, other diseases, pregnancy, or nursing).
- Has radiological (or clinical) documentation of progressive disease on the current treatment (see section 5.1) unless the investigator documents that the patient will continue treatment beyond progression due to clinical benefit.

The patient may continue treatment beyond initial RECIST progression if:

- The patient is clinically benefiting,
- The criteria described below are met,
- It is agreed between the Investigator and the Sponsor,
- The patient has signed an informed consent describing this circumstance.

Criteria required to continue treatment beyond RECIST-defined radiological progression of disease:

- Absence of clinical symptoms or signs indicating clinically significant disease progression
- No decline in performance status
- Absence of rapid disease progression or threat to vital organs or critical anatomical sites [e.g., CNS metastasis, respiratory failure due to tumor compression, spinal cord compression] requiring urgent alternative medical intervention
- No significant, unacceptable or irreversible toxicities related to study treatment

If a patient becomes pregnant during the trial, trial treatment must be stopped immediately. The patient will be followed up until delivery or termination of pregnancy.

If new efficacy/safety information becomes available, Boehringer Ingelheim will review the benefit-risk-assessment and, if needed, pause or discontinue the trial treatment for all patients or take any other appropriate action to guarantee the safety of the trial patients.

Even if the trial treatment is discontinued, the patients remain in the trial and, given their agreement, will undergo the procedures for early treatment discontinuation and follow-up as outlined in the Flow Chart and section 6.2.3.

3.3.4.1.1 Replacement of patients

Patients will be considered non-evaluable for MTD determination in the following circumstances;

- Patients who withdraw consent or who are lost from follow-up or for any other reason other than DLT before completing the first two cycles of study treatment.
- Patients who have received less than 70% of the planned BI 905711 doses during first two cycles of study treatment and does not experience a DLT
- Patients who miss 2 or more partial or complete visits during the first two cycles of study treatment, with missing PK and safety parameters needed to accurately assess DLT and MTD determination.
- Patients found to be non eligible after starting study treatment based on a case by case basis

Non-evaluable patients will be replaced and not included in the primary analysis model whenever additional patients are required in order to ensure there are a sufficient number of evaluable patients in a cohort.
Of note, the dose escalation will be determined based on all the safety information of all treated patients including those who will not be included in the BLRM analysis.

Patients who experience a DLT during the MTD evaluation period as well as patients who withdraw after the MTD evaluation period will not be replaced.

3.3.4.2 Withdrawal of consent to trial participation

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

If a patient wants to withdraw consent, the investigator should be involved in the discussion with the patient and explain the difference between trial treatment discontinuation and withdrawal of consent to trial participation, as well as explain the options for continued follow-up after trial treatment discontinuation, 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. New efficacy or safety information invalidating the earlier positive benefit-risk-assessment, please see Section 3.3.4.1.
3. Deviations from GCP, the trial protocol, or the contract impairing the appropriate conduct of the trial.

Further treatment and follow up of patients affected will occur as described in Section 3.3.4.1.
The investigator / the trial site will be reimbursed for reasonable expenses incurred in case of trial termination (except in case of the third reason).

4. TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

4.1.1 Identity of the Investigational Medicinal Product during Phase Ia

Table 4.1.1: 1 BI 905711

Substance:	BI 905711
Pharmaceutical formulation:	Powder for Solution for Infusion
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	100 mg/vial (10 mg/mL)
Posology:	Single administration every 2 weeks (Day 3 of each 14-day cycle)
Method and route of administration:	Intravenous

See Section 4.2 for AxMP (background therapy) required in Phase Ia.

4.1.2 Identity of the Investigational Medicinal Product during Phase Ib

Table 4.1.2: 1 BI 905711

Substance:	BI 905711
Pharmaceutical formulation:	Powder for Solution for Infusion
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	100 mg/vial (10 mg/mL)
Posology:	Single administration every 2 weeks (Day 3 of each 14-day cycle)
Method and route of administration:	Intravenous

See Section 4.2 for AxMP (background therapy) required in Phase Ib.

4.1.3 Selection of doses in the trial and dose modifications

A dose of 0.6 mg/kg of BI 905711 was selected as a starting dose for this combination trial because this dose level as well as the next dose level (i.e. 1.2 mg/kg) were considered safe and well tolerated (i.e. no observed DLTs or AEs of CTCAE grade >1) as assessed in the monotherapy dose escalation trial 1412-0001 in 4 patients each with CRC (data on file).

The dose of BI 905711 will be escalated in patient cohorts at the provisional dose levels (as shown in Table 4.1.3: 1) until the MTD or the monotherapy recommended dose (as established in trial 1412-0001) is reached. The dose level tested will never exceed the highest dose level deemed safe by the DRC in the monotherapy trial 1412-0001.

BI 905711 dose levels may be escalated up to 4.8 mg/kg which is based upon the pharmacodynamic modeling. Based on the available safety data and statistical model evaluation, exploration of doses higher than 4.8 mg/kg and up to 9 mg/kg, may be considered. The selection of the dose levels higher than 4.8 mg/kg that may be tested will be

defined by the DRC. Intermediate dose levels may be investigated as long as they fulfill the EWOC criterion.

At the end of the MTD evaluation period, BI will convene a meeting with the DRC. At these meetings, the clinical course including all safety information, PK and pharmacodynamics biomarker data as available, for each patient in the current dose cohort, will be described. Updated safety data on other ongoing patients, including data beyond the MTD evaluation period, will be discussed as well. Based on the data, a decision on the next dose level of BI 905711 is made. Incremental dose increases in successive cohorts will be no more than 100% of the previous dose level.

Dose escalation will continue until identification of the MTD or recommended dose for expansion (RDE) in case no MTD is established, or safety concerns arise, or the trial is terminated for other reasons.

Table 4.1.3: 1 Provisional dose levels of BI 905711 and possible cohort size within each escalation group in phase Ia

Dose level	Dose mg/kg	Increment from previous dose	Minimum number of patients
1	0.6	Starting dose	3
2	1.2	100%	3
3	2.4	100%	3
4	3.6	50%	3
5	4.8	33%	3

4.1.3.1 Selection of BI 905711 dose for Phase Ib in combination with FOLFIRI with or without bevacizumab

The BI 905711 dose for phase Ib will be selected by the DRC with the aim to select a safe and potentially effective dose of BI 905711 based on all data collected in phase Ia (including safety, PK, biomarker, efficacy).

4.1.3.2 Selection of FOLFIRI dose regimen and bevacizumab for Phase Ib

The dose of FOLFIRI (or Liposomal Irinotecan plus 5-FU/Leucovorin) regimen in PDAC and FOLFIRI regimen in combination with bevacizumab in CRC will be in accordance to respective NCCN Guidelines (R21-2007, R21-2008).

4.1.4 Method of assigning patients to treatment groups

Recruitment into the trial will be conducted in a controlled manner. Patient numbers will be assigned via Interactive Response Technology (IRT) upon registration of screening.

In both phase Ia and Phase Ib, each eligible patient will be assigned and receive the appropriate dose for their assigned cohort.

In both phases, BI 905711 will be assigned via IRT. Each medication vial will have a unique medication number. The medication number assigned will be documented in the CRF. Note that the medication number is different from the patient number (the latter is generated during screening via the IRT System).

For phase Ib, patients in the CRC expansion cohort, will be randomized via IRT into one of 2 arms; (BI 905711 + FOLFIRI +Bevacizumab arm) or (FOLFIRI +Bevacizumab arm) with 2:1 randomization ratio. The dose level of BI 905711 is determined at phase 1a.

4.1.5 Drug assignment and administration of doses for each patient

BI 905711 will be prepared and handled according to the 1412-0003 ‘Preparation and Handling Instructions” which will be filed in the ISF. Each patient will receive the appropriate trial medication and dose for their assigned dose cohort.

IMP (BI 905711 and background therapy for Phase Ib CRC cohort, if considered as IMP per local regulations) will be assigned via IRT for each treatment cycle. Upon notification that a patient will be treated in the study, the pharmacy will prepare the trial medication at the assigned dosage for administration to the patient.

The Cycle 1 Day 3 dose of BI 905711 will be calculated using the Cycle 1 Day 1 weight or up to 3 days prior as the reference weight. If the patient’s weight changes by ≤10% compared to the reference weight, the dose (in mg) may remain the same for subsequent cycles. If the weight changes by >10% the dose will be recalculated and the new weight will be used as the reference weight.

All IMP as well as background treatment will be given as an intra-venous infusion by authorised site staff in a specialised unit where emergency care can be provided. Appropriate drugs and medical equipment to treat anaphylactic reactions must be immediately available, and study personnel must be trained to recognise and treat anaphylaxis.

No routine premedication will be required for BI 905711 i.v. infusions. (refer to Section 4.2.2.1). Refer to section 4.2.2.1 for premedication for background therapy.

The BI 905711 i.v. infusion should take place over 30 minutes (+/-10 minutes), unless there is a necessity of administration rate reduction according to the protocol (e.g., in case of infusion-related reaction). If a patient’s weight is ≤50 kg, the infusion duration may be less than 30 minutes depending upon the infusion rate and the patient’s condition.

Priming and flushing should not be included in the administration duration. Total storage time for ready-to-use solution at room temperature should not exceed 150 minutes between preparation and end of infusion time.

Observation period for CRS/IRR

- Patients will remain under surveillance for at least 6 hours after the end of infusion after the first, second and third administrations of BI 905711. During the post-infusion observation period, body temperature, pulse rate and blood pressure will be measured at the end of the infusion and every 2 hours (± 15 minutes) thereafter.

- If no adverse signs or symptoms, e.g. infusion-related reactions, are observed during the first 3 administrations, the duration of the post-infusion observation period may be reduced to 4 hours for subsequent administrations. Body temperature, pulse rate and blood pressure will be measured at the end of the infusion, then after 2 and 4 hours (± 15 minutes).

- After 6 administrations in the absence of infusion-related reactions, the post-infusion observation period can be reduced to 2 hours at investigator's discretion. Body temperature, pulse rate and blood pressure will be measured at the end of the infusion, then after 2 hours (± 15 minutes).

4.1.5.1 Administration of FOLFIRI with or without bevacizumab

Background therapy FOLFIRI (or Liposomal Irinotecan plus 5-FU/Leucovorin) in patients with PDAC and FOLFIRI in combination with bevacizumab in patients with CRC will be administered in accordance to respective NCCN Guidelines (R21-2007, R21-2008).

See Section 4.2 for background treatment for dose escalation (Phase Ia) and dose expansion (Phase Ib).

4.1.5.2 Criteria for receiving further treatment

Eligibility for further treatment should be confirmed prior to dosing on Day 1 of each cycle (and on Day 3 prior to administration of BI 905711 for clinical criteria only) by confirming the patient has not met any criteria for protocol discontinuation as described in section 3.3.4.1 and absence of any adverse event requiring treatment discontinuation (section 4.2.3).

To continue treatment the following criteria must be met:

- Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L, $\geq 1.5 \times 10^3$/µL, or ≥ 1500/mm^3
- Platelets $\geq 75 \times 10^9$/L, $\geq 75 \times 10^3$/µL, or ≥ 75000/mm^3
- Adequate renal function: for bevacizumab, proteinuria should be monitored per local site practice.

- Absence of worsening (any CTCAE grade) or new neurological signs/symptoms CTCAE grade > 1.
- Absence of progressive disease unless the investigator documents that the patient will continue treatment beyond progression due to clinical benefit and after agreement with Sponsor).

If the criteria are not met but the patient is recovering, the patient should continue to be assessed regularly and the next dose of treatment may be delayed for up to 28 days until the criteria are met. Dose modification may be appropriate (see Section 4.1.5.3).

4.1.5.3 Dose modifications

Individual patients must not receive a higher dose than assigned to them at the start of the trial. Dose escalation is allowed in cases where the dose has been reduced in error. At the time the recommended doses for expansion are determined by DRC, patients that are on any other dose levels may be adapted to the recommended dose at investigator's discretion. The dose cannot be escalated if the dose has been previously reduced for toxicity reason.

Dose modification of BI 905711 and FOLFIRI (or Liposomal Irinotecan plus 5-FU/Leucovorin (PDAC only)) regimen should be based on the worst preceding toxicity. Dose adjustment should not be considered for bevacizumab and leucovorin.

Subsequent doses should be adjusted as suggested in Table 4.1.5.3:1.

Table 4.1.5.3:1 Dose modifications of BI 905711 and background therapy

Agents	Starting dose	Dose level -1	Dose level -2
Irinotecan	180	150	120
Liposomal Irinotecan	70	50	43
5-FU (bolus)	400	200	0
5-FU (infusion)	2400	1920	1440
BI 905711	Current DL	DL-1 per protocol	DL-2 per protocol
Bevacizumab and Leucovorin	No dose adjustment.		

Recommendations on dose modification of irinotecan (refer latest local package insert), liposomal irinotecan (refer latest local package insert) and 5-FU (refer latest local package insert), and BI 905711 are summarized in Table 4.1.5.3:2.

Table 4.1.5.3:2 Dose modification for FOLFIRI (or Liposomal Irinotecan plus 5-FU/Leucovorin) regimen and BI 905711

CTC Grade (Value)	**Action on FOLFIRI (or Liposomal Irinotecan plus 5-FU/Leucovorin) at the Start of Subsequent Cycles**	**BI 905711**
Neutropenia	Each drug should be delayed until ANC >1500/µl and platelet count >100 000/µl.	Delay as for FOLFIRI (or Liposomal Irinotecan plus 5-FU/Leucovorin) Resume at same dose
1 (1500 to 1999/mm3)	Maintain dose level of both Irinotecan and 5-FU	
2 (1000 to 1499/mm3)	Maintain dose level of both Irinotecan and 5-FU	
3 (500 to 999/mm3)	↓ 1 dose level of both Irinotecan and 5-FU	
4 (<500/mm3)	↓ 2 dose levels of both Irinotecan and 5-FU	
Neutropenic fever	Omit irinotecan or Liposomal Irinotecan dose until resolved, then ↓ 2 dose levels	
Other hematologic toxicities	Dose modifications for leukopenia or thrombocytopenia during a cycle of therapy and at the start of subsequent cycles of therapy are also based on NCI toxicity criteria and are the same as recommended for neutropenia above.	
Diarrhea	Withhold treatment until resolution of diarrhea for at least 24 hours off all antidiarrheal medications.	Withhold treatment until resolution of diarrhea for at least 24 hours off all antidiarrheal medications. For diarrhea grade ≥ 3 restart at one lower dose level.
1 (2-3 stools/day > pretx)	Maintain dose level of irinotecan	
2 (4-6 stools/day > pretx)	Maintain dose level of irinotecan	
3 (7-9 stools/day > pretx)	1 lower dose level of irinotecan	
4 (≥10 stools/day > pretx)	2 lower dose levels of irinotecan	
	Withhold 5-FU for diarrhea ≥grade 2 and restart at reduced dose by 20% after resolution.	
Other nonhematologic toxicities (except alopecia, anorexia or asthenia)	If grade 3 or 4, hold treatment until ≤grade 1 or baseline value. Decrease the dose of 5FU by 20%.	Hold treatment if FOLFIRI (or Liposomal Irinotecan plus 5-FU/Leucovorin) is on hold. If the AE is grade 3 or 4 and deemed related to BI 905711 in the investigator's judgement**, restart at 1 lower dose level.**
1	Maintain dose level of irinotecan	
2	Maintain dose level or irinotecan	
3	1 lower dose level of irinotecan	
4	2 lower dose levels of irinotecan	
Skin/mucosal toxicities	Withhold 5-FU for ≥ grade 2 PPE*, ≥grade3 mucositis/stomatitis and resume 5-FU at a 20% reduced dose after improvement to ≤ grade 1 or baseline value.	No change
Interstitial lung disease	Permanently discontinue liposomal irinotecan	Discontinue treatment if FOLFIRI (or Liposomal Irinotecan plus 5-FU/Leucovorin) is on hold.
Anaphylactic Reaction	Permanently discontinue liposomal irinotecan	Discontinue treatment if FOLFIRI (or Liposomal Irinotecan plus 5-FU/Leucovorin) is on hold.

*PPE - Palmar-Plantar Erythrodysesthesia (hand-foot syndrome)

Recommendations on dosage modification of bevacizumab (refer local package insert) are summarized in Table 4.1.5.3:3.

Table 4.1.5.3:3 Dose adjustment for bevacizumab (refer to local package insert)

Dosage Modifications for Adverse Reactions	**Severity**	**Dosage Modification**
Gastrointestinal Perforations and Fistulae	• Gastrointestinal perforation, any grade • Tracheoesophageal fistula, any grade • Fistula, grade 4 • Fistula formation involving any internal organ	Discontinue Bevacizumab
Wound Healing Complications	• Wound healing complications requiring medical intervention • Necrotizing fasciitis	Discontinue Bevacizumab
Hemorrhage	• Grade 3 or 4	Discontinue Bevacizumab
	• Recent history of hemoptysis of 1/2 teaspoon (2.5 mL) or more	Withhold Bevacizumab
Thromboembolic Events	• Arterial thromboembolism, severe	Discontinue Bevacizumab
	• Venous thromboembolism, grade 4	Discontinue Bevacizumab
Hypertension	• Hypertensive crisis • Hypertensive encephalopathy	Discontinue Bevacizumab
	• Hypertension, severe	Withhold Bevacizumab if not controlled with medical management; resume once controlled
Posterior Reversible Encephalopathy Syndrome	• Any	Discontinue Bevacizumab
Renal Injury and Proteinuria	• Nephrotic syndrome	Discontinue Bevacizumab
	• Proteinuria ≥2 grams per 24 hours in absence of nephrotic syndrome	Withhold Bevacizumab until proteinuria less than 2 grams per 24 hours
Infusion-Related Reactions	• Severe	Discontinue Bevacizumab
	• Clinically significant	Interrupt infusion; resume at a decreased rate of infusion after symptoms resolve
	• Mild, clinically insignificant	Decrease infusion rate
Congestive Heart Failure	Any	Discontinue Bevacizumab

- No more than two dose reductions are allowed for each study drug.
- Trial treatment, or individual drugs of background therapy or BI 905711 may be discontinued or withheld depending on the type and severity of related adverse effects.
- Any trial drug should be discontinued permanently in case the related adverse events (as detailed in the table above) do not recover to grade ≤1 or baseline after 28 days.

4.1.6 Blinding and procedures for unblinding

4.1.6.1 Blinding

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

4.1.6.2 Unblinding and breaking the code

Not applicable.

4.1.7 Packaging, labelling, and re-supply

All IMP 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.
For details of background treatment see section 4.2.1.

4.1.8 Storage conditions

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

4.1.9 Drug accountability

The investigator or designee will receive the investigational drugs delivered by the sponsor or delegate 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 or delegate 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 (for USA).

Investigational drugs are not allowed to be used outside the context of this protocol. They must not be forwarded to other investigators or clinics.
The investigator or designee must maintain records of the product's delivery to the trial site, the inventory at the site, the use by each patient, and the return to the sponsor or warehouse /

drug distribution centre or alternative disposal of unused products. If applicable, the sponsor or warehouse / drug distribution centre will maintain records of the disposal.

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

4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

4.2.1 Background treatment for dose escalation (Phase Ia) and dose expansion (Phase Ib)

The following required background treatment, considered as AxMP are commercially available and locally supplied by sites according to local regulations. Documentation of administered background treatment must be noted in the patient's source and the CRF.

4.2.1.1 FOLFIRI regimen and Liposomal Irinotecan plus 5-FU/Leucovorin (PDAC only)

FOLFIRI in combination with bevacizumab will be administered to the CRC patients in Phase Ia and Phase Ib, FOLFIRI (or Liposomal Irinotecan plus 5-FU/Leucovorin) to PDAC patients in the expansion phase (Phase Ib), in accordance with NCCN Guidelines as described below (R21-2007, R21-2008):

FOLFIRI regimen to be administered on Day 1 of each 14-day treatment cycle:

- Irinotecan:180 mg/m^2 IV over 1.5 hours on Day 1 of each 14-day cycle.
- Leucovorin: 400 mg/m^2 IV (in Japan, Levoleucovorin: 200 mg/m^2) over 2 hours on Day 1 of each 14-day cycle.
- Fluorouracil: 400 mg/m^2 IV bolus on Day 1 of each 14-day cycle.
- Fluorouracil: 2400 mg/m^2 IV 46 hours continuous infusion starting on Day 1 of each 14-day cycle.

Liposomal Irinotecan plus 5-FU/Leucovorin (PDAC only) regimen to be administered on Day 1 of each 14-day treatment cycle:

- Liposomal Irinotecan: 70 mg/m^2 IV over 1.5 hours on Day 1 of each 14-day cycle.
- Leucovorin: 400 mg/m^2 IV (in Japan, Levoleucovorin: 200 mg/m^2) over 2 hours on Day 1 of each 14-day cycle.
- Fluorouracil: 2400 mg/m^2 IV 46 hours continuous infusion starting on Day 1 of each 14-day cycle.

4.2.1.2 Bevacizumab

Bevacizumab will be administered to CRC patients in Phase Ia and Phase Ib at 5 mg/kg IV over 30 minutes on day 1 before start of chemotherapy and repeated every 14 days, in combination with FOLFIRI regimen, in accordance with NCCN guidelines (R21-2007).

4.2.2 Other treatments and emergency procedures

There are no special emergency procedures to be followed.
Rescue medications to reverse the actions of BI 905711 or FOLFIRI (or Liposomal Irinotecan plus 5-FU/Leucovorin) and bevacizumab are not available. Potential adverse events should be treated symptomatically with concomitant medications to provide adequate supportive care as clinically necessary. Section 4.2.4 provides guidance for management of adverse events.

Radiotherapy for local symptom control of non-target lesions may be allowed if agreed between the investigator and Sponsor.

4.2.2.1 Premedication

No routine premedication will be required for BI 905711 i.v. infusions.
See Section 4.2.4.1 for pre-medication requirements for all subsequent treatment infusions of BI 905711 after symptoms of an IRR ≥ grade 2 occur.

Pre-medication for background therapy must be given in accordance with the local approved label, which includes but not limited to;

- Anti-emetics prior to irinotecan infusion

4.2.3 Restrictions

4.2.3.1 Restrictions regarding concomitant treatment

Anti-cancer treatment

No experimental or approved anti-cancer treatment including chemotherapy, targeted therapy, immunotherapy, hormone therapy (except as stated below), or radiotherapy is allowed throughout the study treatment period. Radiotherapy for local symptom control of non-target lesions may be allowed if agreed between the investigator and Sponsor.

Gonadotropin-releasing hormone or luteinizing hormone releasing hormone analogs for patients with prostate cancer or breast cancer can be continued but should not be initiated during trial.

Anticoagulants

Therapy with factor Xa inhibitors, direct thrombin inhibitors, and warfarin is allowed. Patients receiving warfarin must have their INR values closely monitored according to institutional guidelines.

The use of heparin (including flushing and locking of intravenous catheters) or LMWH is permitted during study treatment. However, the following restrictions must be applied:

- BI 905711 and heparin should not be mixed or infused through the same IV line
- If the same IV line has to be used, flush thoroughly with 0.9% saline prior to and following BI 905711 infusion.

If a catheter will be locked with heparin, this must be flushed thoroughly with 0.9% saline prior to and following BI 905711 infusion.

Hematopoietic growth factors

Hematopoietic growth factor agents are not allowed for use as primary prevention during the first two 14-day cycles. Thereafter hematopoietic growth factor agents may be used according to institutional standard.

Erythropoietic therapy is allowed when used in accordance with the American Society of Clinical Oncology/American Society of Hematology or the National Comprehensive Cancer Network (NCCN) guidelines. In Japan, erythropoietic therapy is not approved for anemia caused by cancer chemotherapies.

COVID-19 Vaccination and other preventive measures

The decision on COVID-19 vaccination of a BI study patient must be taken based on an individual Benefit-Risk Assessment by the investigator after thorough discussion with the patient. This assessment should consider the approved labels of the respective vaccines as well as the provisions given in the protocol, including the time point when the vaccination should be given or a potential delay of the vaccination or of the study treatment.

The package insert for approved COVID-19 vaccinations should be carefully reviewed for local guidance considering acute moderate/severe febrile illness, and the risk of an anaphylactic reaction to the vaccine. Furthermore, the diminished response to the vaccine needs to be considered for immunocompromised conditions which may be observed in BI 905711 treated patients.

It is important to encourage to continue taking precautions such as wearing a mask, maintaining social distancing and washing hands frequently, even after a patient receives a COVID-19 vaccine. These precautions will be necessary until public health experts advise otherwise.

4.2.3.2 Restrictions on diet and lifestyle

There are no restrictions regarding diet and lifestyle.

4.2.3.3 Contraception requirements

WOCBP (for the definition please refer to section 3.3.3) and men able to father a child must use two medically approved methods of birth control throughout the trial, and for a period of at least 6 months after last trial drug intake, one barrier method, and one highly effective non-barrier method.

Men (trial participant or partner of a trial participant) must be vasectomised with documented absence of sperm or use a condom if their sexual partner is a WOCBP.

WOCBP (trial participant or partner of a trial participant) must use a highly effective method of birth control per ICH M3 (R2) that results in a low failure rate of less than 1% per year when used consistently and correctly if their sexual partner is a man able to father a child.

- Combined (estrogen and progestogen containing) hormonal birth control that prevents ovulation (oral [approved in Japan], intravaginal [unapproved in Japan], transdermal [unapproved in Japan]).
- Progestogen-only hormonal birth control that prevents ovulation (oral, injectable, implantable) [unapproved in Japan].
- Intrauterine device (IUD) or intrauterine hormone-releasing system (IUS).
- Bilateral tubal occlusion

Or

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

Breast feeding should be interrupted from the start of study treatment through 6 month after the last study treatment

4.2.4 Dose modification and management of adverse events

4.2.4.1 Management of infusion-related reactions

Infusion-related reactions (IRR) involve the immune system; however, they can have different mechanisms. Some are allergic in nature and are usually mediated by immunoglobulin E while others are not classical allergic reactions (so-called anaphylactoid reactions e.g. caused by cytokine release). Although infusional reactions can be allergic or nonallergic, clinical symptoms are difficult to distinguish and require rapid assessment and immediate management to avoid severe adverse events, including fatality.

If an infusion-related reaction of ≥ CTCAE Grade 3 occurs, trial treatment must be permanently discontinued.

If symptoms of an infusion-related reaction of CTCAE Grade 2 occur, which do not qualify as DLT according to Section 5.2.7 the infusion should be temporarily stopped. Institute medical management (e.g. glucocorticoids, epinephrine, bronchodilators, or oxygen) for infusion reactions as needed. Upon recovery, the following guidance must be followed.

- If at least 50% of the planned dose of BI 905711 was administered, no further BI 905711 will be administered until the next scheduled dose.
- If less than 50% of the planned dose of BI 905711 was administered due to an infusion-related reaction, a further dose of 50% of the intended total dose may be administered on the following day and after recovery to baseline for at least 24 hours. Administration may occur within up to 2 days after the original planned dose (Subsequent treatments, FOLFIRI+bevacizumab + BI905711 or FOLFIRI (or Liposomal Irinotecan plus 5-FU/Leucovorin) + BI 905711 should be also delayed so that the interval between BI 905711 is 14 days). Refer to Appendix 10.2 for details regarding PK collection. Remaining solution from the original dose must be discarded, and a new kit must be dispensed to prepare the dose of 50% of the intended total dose.
- During the first re-exposure, patients must remain under observation for at least 6 hours post start of infusion. If required, patients may be hospitalised for a longer observation period at the investigator's discretion.
- Premedication must be used for all subsequent treatment infusions. The recommended premedication is:
    - Acetaminophen/Paracetamol 650 mg - 1000 mg p.o., or equivalent
    - Antihistamine p.o. or i.v., equivalent to Diphenhydramine 50 mg i.v.
    - Glucocorticoid i.v., equivalent to prednisolone 50-100 mg
- The infusion rate for further treatment cycles may be adapted according to Investigator decision, but any adaption of the infusion rate must be agreed with the sponsor. Total storage time for ready-to-use solution at room temperature should not exceed 150 minutes between preparation and end of infusion time. See section 4.1.5

If infusion reactions and/or hypersensitivity reactions occur in a substantial proportion of treated patients without premedication, the DRC may decide that all future patients treated in the trial must receive premedication (as described above) prior to BI 905711 infusion; the dosage and schedule of premedication will be aligned and will take into account any local clinical standards. Such a decision will be communicated to all investigators in writing. Premedications should be recorded in the eCRF.

For bevacizumab refer to table 4.1.5.3.3 for guidance in case of infusion reactions and/or hypersensitivity reactions.
For irinotecan, liposomal irinotecan and 5-FU refer to local approved label for guidance in case of infusion reactions and/or hypersensitivity reactions.

4.2.4.2 Management of CRS, other IRRs and events with similar signs/symptoms

CRS is a supra-physiologic response following any therapy that results in the activation or engagement of endogenous or infused T cells and/or other immune effector cells. Symptoms can be progressive, include fever at the onset, and may include hypotension, hypoxia, capillary leak syndrome and end organ dysfunction. Other signs/symptoms of CRS can be e.g. tachypnea, headache, tachycardia, rash, nausea, vomiting, increased transaminases, and increased bilirubin. CRS can be serious or life threatening.

CRS signs/symptoms may occur quickly during or after administration, or after several hours or days. Occurrence of such signs/symptoms temporally related to administration of trial medication, requires immediate management and rapid diagnosis to avoid severe complications.

The manifestations of CRS overlap with those of other types of IRRs, infection, capillary leak syndrome and haemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS). IRRs can be allergic or non-allergic (due to release of histamine or cytokines, respectively). Mixed type reactions may occur. CRS, other IRRs and events with similar signs/symptoms are difficult to distinguish.

Patients must remain under observation for potential signs and symptoms of CRS (e.g. hypotension, rash, tachypnea, hypoxia, tachycardia, fever, nausea, fatigue, headache, myalgias and malaise) for at least 6 hours following the end of infusion of BI 905711. If no signs or symptoms of CRS are observed during the first 3 administrations, the duration of observation may be reduced to 4 hours for subsequent administrations. After 6 administrations, in the absence of potential signs and symptoms of CRS, the observation period can be reduced to 2 hours at investigator's discretion. During all post infusion observation periods, body temperature, pulse rate and blood pressure must be monitored as described in section 4.1.5.

In case of CRS, other IRRs or events with similar signs/symptoms, appropriate measures depending on the type and severity of the reaction should be taken by the investigator according to international standards (R19-0311, R20-2020), best medical judgement, and local guidelines. Supportive therapy including antipyretics, intravenous fluids, and low dose vasopressors may be used. In patients who do not respond to these treatments, corticosteroids and/or interleukin 6 receptor antagonists (R15-0031, R18-1685, R18-1686) may be required and patients should be monitored closely, preferably in an intensive care unit.

In the event of CTCAE ≥ Grade 3 CRS, study treatment must be permanently discontinued. In the event of CTCAE Grade 2 CRS, the guidance for handling a CTCAE Grade 2 infusion-related reaction must be followed (Section 4.2.4.1).

Appropriate drugs and medical equipment to treat CRS, other IRRs and events with similar signs/symptoms must be immediately available, and trial personnel must be trained to recognise and treat such events. 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.

4.2.4.3 Management of diarrhea, nausea and vomiting

The occurrence, severity and duration of diarrhea, vomiting and nausea, and the outcomes of these events will be documented in detail in the eCRF. Further tests and examinations e.g. colonoscopy, gastroscopy should be performed according to the severity of the symptoms in order to document and obtain more information about the extent of possible injury due to BI 905711. If severe injury to GI tissues is excluded, these events could be managed symptomatically according to Tables 4.2.4.3: 1 and 4.2.4.3: 2.

Table 4.2.4.3: 1 Management of diarrhea

CTCAE Grade	Action for anti-diarrheal treatment
Grade 1	Anti-diarrheal treatment according to the local standard e.g. loperamide p.r.n. and hydration
Grade 2 > 7 days despite optimal medical management	Anti-diarrheal treatment according to the local standard e.g. loperamide p.r.n, and hydration
Grade ≥3	Anti-diarrheal treatment according to the local standard e.g. loperamide p.r.n, and hydration

Table 4.2.4.3: 2 Management of nausea and vomiting

CTCAE Grade	Anti-emetic treatment
Nausea Grade 1	Anti-emetic treatment may be considered according to the local standard e.g. metoclopramide p.r.n.
Nausea Grade 2 and/or vomiting Grade 1	Start anti-emetic treatment according to local standard of care e.g. metoclopramide or 5-HT_3 receptor antagonist. If ineffective, patients should be treated according to treatment of vomiting ≥2 or nausea CTCAE Grade ≥ 3 as shown below.
Vomiting Grade ≥2 and/or nausea Grade ≥ 3	Anti-emetic treatment according to local standard of care e.g.: with 5-HT_3 receptor antagonist and/or corticosteroid

4.2.4.4 Tumor lysis syndrome

All patients have to be assessed for clinical or laboratory suspicion of tumor lysis syndrome. To prevent tumor lysis syndrome, patients should remain appropriately hydrated throughout the administration period. For details of laboratory assessment, refer to Section 5.2.3. In case tumor lysis syndrome (TLS) is observed, patients should be managed according to local or available guidelines (R10-4517).

4.2.4.5 Neurological adverse events

Toxicology studies in cynomolgus monkeys showed that BI 905711 at high doses induced minimal to mild monocytic/eosinophilic cells infiltrates in CNS (c16856466). Clinical significance of these findings for humans is currently unknown. Human exposure to the highest planned dose of 4.8 mg/kg is estimated to be 3 to 4-fold below exposure in monkeys at the 30 mg/kg. As CDH17 is not expressed in brain tissue, BI905711 is not expected to induce neurological adverse events. No neurological AE related to BI905711 or background therapy have been observed so far. Patients shall be monitored for possible neurological toxicity. Patients who develop worsening or new neurological signs/symptoms CTCAE grade ≥ 2 should undergo full neurological investigation including a brain MRI. Treatment with BI 905711 must be interrupted or permanently discontinued unless alternative etiology is documented e.g. new metastases in the CNS, metabolic disturbances, sepsis, infection, hypoxia, tumor lysis syndrome, trauma, adverse effect of concomitant medications. Additional workup may be performed if clinically indicated e.g. lumbar puncture.

4.2.4.6 Renal adverse events

Toxicology studies in cynomolgus monkeys showed that BI 905711 at high doses induced minimal to mild glomerulopathy with no proteinuria or increase of serum creatinine and urea (c16856466). Clinical significance of these findings for humans is currently unknown. Patients will be followed periodically for kidney function by measurement of serum creatinine and a qualitative urine protein.
Patients with a 2+ or greater protein reading on a urine dipstick should be followed by a 24 hour urine collection for a quantitative protein.
Patients with proteinuria ≥ CTCAE grade 3 (>3.5 g/24 hours) should interrupt BI 905711. Continuation of treatment with BI 905711 at a reduced dose may be considered if proteinuria recovers to ≤ grade 1 within 3 weeks.

Patients receiving bevacizumab should suspend administration for urine protein levels ≥2 g/24 hours and resume when proteinuria is <2 gm/24 hours. Bevacizumab must be permanently discontinued in patients with nephrotic syndrome.

4.3 TREATMENT COMPLIANCE

BI 905711 and background therapy will be administered as an intravenous infusion at the clinical site under the supervision of trained site personnel. Therefore, actual dosing is expected to follow the protocol. The doses administered will be recorded in the eCRF and any irregularities in dosing will also be documented in the eCRF by the investigator or designee.

5. ASSESSMENTS

5.1 ASSESSMENT OF EFFICACY

Tumor response and progression will be evaluated by investigator review in this study according to Response Evaluation Criteria in Solid Tumors (RECIST) guideline (Version 1.1) (R09-0262).

Tumor assessment will be performed per institutional practice. Only the overall response and disease progression will be collected in the eCRF.

Tumor assessments should include computed tomography (CT) scans or MRI of chest, abdomen, and pelvis. If clinically indicated, imaging of any other known or suspected sites of disease (e.g. brain, bone) should be performed.

5.2 ASSESSMENT OF SAFETY

Safety will mainly be evaluated by severity and incidence of AEs, graded according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 (R18-1357). Criteria for DLT are described in Section 5.2.7.

5.2.1 Physical examination

A complete physical examination will be performed as per institutional practice. It includes at a minimum general appearance, neck, lungs, cardiovascular system, abdomen, extremities, and skin.
Measurement of height (cm) and body weight (kg) and the evaluation of ECOG performance score will be performed at the time points specified in the flowchart.
The results must be included in the source documents available at the site.

5.2.1.1 Body Weight

Body weight measurements should be done on the same scale for each patient. In order to get comparable body weight values, body weight measurements should be performed per the following:

- shoes and coat/jackets should be taken off
- pockets should be emptied of heavy objects (i.e. keys, coins etc)

5.2.2 Vital signs

Vital signs will be evaluated as per institutional practice, prior to blood sampling.
This includes systolic and diastolic blood pressure, body temperature and pulse rate (electronically or by palpation count for 1 minute) in a seated position after 2 minutes of rest.
The results must be included in the source documents available at the site.

5.2.3 Safety laboratory parameters

Safety laboratory parameters to be assessed are listed in Table 5.2.3: 1 and will be performed by a local laboratory as per institutional practice
The site will file the respective reference ranges in the ISF.

Patients do not have to be fasted for the blood sampling for the safety laboratory.

It is the responsibility of the investigator to evaluate the laboratory reports. Clinically relevant abnormal findings as judged by the investigator will be reported as adverse events (please refer to section 5.2.6).
In case a treatment course is delayed due to an adverse event, the patient should visit the site at least once a week for assessment of safety laboratory and adverse events. More frequent visits may be appropriate as assessed by the investigator.

Additional parameters may be measured if they are part of the standard panel of the institution laboratory. The sponsor and investigator may discuss and agree that individual parameters will not be measured if they are not part of the standard panel of the institution laboratory. The investigator should complete additional evaluations of laboratory tests as clinically indicated. Any abnormal and clinically relevant finding from these investigations will be reported as an Adverse Event.

In case the criteria for hepatic injury are fulfilled, a number of additional measures will be performed (please see Section 5.2.6.1.4 and the DILI Checklist provided in the eDC system and ISF. The amount of blood taken from the patient concerned will be increased due to this additional sampling.

Table 5.2.3: 1 Safety laboratory tests

Functional lab group	**Test name**
Haematology	Haematocrit, Haemoglobin, Red blood cell (RBC) count, White blood cell (WBC) count including differential (absolute) RBC indices, Reticulocytes, Platelet count
Coagulation	Activated partial thromboplastin time (aPTT), Prothrombin Time (PT) or if applicable, International Normalises Ratio (INR)
Biochemistry	Glucose, Blood urea nitrogen (BUN), Creatinine, Inorganic Phosphate, Sodium, Potassium, Calcium, Total Protein, Albumin, Uric Acid, Lipase, Amylase, Total Bilirubin (indirect and direct in case of elevated total or if required per local guidelines) Aspartate aminotransferase (AST), Alanine aminotransferase (ALT), Alkaline phosphatase (AP), Lactate dehydrogenase (LDH) Note: Creatinine can be assessed by any of these methods: • CREE (enzymatic serum creatinine assay), • CREJIDMS (IDMS standardized Jaffe), or • CREJ (non-IDMS standardized Jaffe).

Table 5.2.3: 1 Safety laboratory tests (cont)

Functional lab group	Test name
Pregnancy testing	A Human Chorionic Gonadotropin urine pregnancy test needs to be obtained at the time points indicated in the Flowchart in patients of childbearing potential. A serum pregnancy test should be performed at screening if urine test is positive.
Urinalysis	pH, glucose, erythrocytes, leukocytes, protein, nitrite will be analyzed by routine analysis and reported as semiquantitative measurements. In case of pathological findings, further evaluation should be performed and results documented.[2]
Infectious disease[1]	Hepatitis B: Hepatitis B surface (HBs) antigen (qualitative), HBcAb (qualitative), HBV-DNA (quantitative) Hepatitis C: HCV-RNA. (qualitative) Results for hepatitis virus infection obtained in routine diagnostics are acceptable if done within 14 days before the informed consent date.

1. At Screening visit, patients are to be tested for hepatitis B and C virus infection. See Section 3.3.3 for hepatitis exclusion criteria.
2. In case of a 2+ or greater urine protein by urine dipstick is found, a 24-hours urine should be collected for a quantitative protein

Table 5.2.3: 2 Exclusionary laboratory tests

Functional lab group	Test name
Infectious disease	• Positive Hepatitis B surface (HBs) antigen • Positive HBc antibody together (qualitative) with HBV-DNA (quantitative) • Positive Hepatitis C (HCV-RNA)- qualitative
Hepatic, renal and bone marrow functions	• Total bilirubin >1.5 x ULN. • Alanine transaminase (ALT) and Aspartate transaminase (AST) > 2.5 x ULN or > 5 x ULN for patients with known liver metastases. • Serum creatinine > 1.5 x ULN. If creatinine is > 1.5 x ULN, patient is eligible if concurrent creatinine clearance ≥ 50 ml/min (measured or calculated by CKD-EPI formula or Japanese version of CKD-EPI formula for Japanese patients). • Absolute neutrophil count (ANC) < 1.5 x 10^9/L, < 1.5 x 10^3/µL, or < 1500/mm^3 • Platelets < 100 x 10^9/ L, < 100 x 10^3/µL, or < 100 x 10^3/mm^3 • Hemoglobin (Hb) < 8.5 g/dl, < 85 g/L, or < 5.3 mmol/L (without transfusion within previous week) • Serum lipase > 1.5 ULN

5.2.4 Electrocardiogram

The 12-lead ECGs will be performed per institutional pracctice. The investigator or a designee will evaluate whether the ECG is normal or abnormal and assess clinical relevance. ECGs may be repeated for quality reasons and a repeated recording used for analysis. Additional ECGs may be recorded for safety reasons. Dated and signed printouts of ECG with findings should be documented in patient's medical record.

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

5.2.5 Other safety parameters

Not Applicable

5.2.6 Assessment of adverse events

5.2.6.1 Definitions of AEs

5.2.6.1.1 Adverse event

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

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

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

- Worsening of the underlying disease if certain conditions are met – refer to section 5.2.6.2.4
- Worsening of pre-existing conditions other than the underlying disease.
- Changes in vital signs, ECG, physical examination and laboratory test results, if they are judged clinically relevant by the investigator.

If such abnormalities already exist prior to trial inclusion, they will be considered as baseline conditions and should be collected in the eCRF only.

5.2.6.1.2 Serious adverse event

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

- results in death,
- is life-threatening, which refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if more severe,
- requires inpatient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability or incapacity,
- is a congenital anomaly / birth defect,
- is deemed serious for any other reason if it is an important medical event when based on appropriate medical judgement which may jeopardise the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the

above definitions. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation or development of dependency or abuse.

For Japan only: An event that possibly leads to disability will be handled as 'deemed serious for any other reason' and, therefore, reported as an SAE.

5.2.6.1.3 AEs considered "Always Serious"

In accordance with the European Medicines Agency initiative on Important Medical Events, Boehringer Ingelheim has set up a list of 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. A copy of the latest list of "Always Serious AEs" will be provided upon request. These events should always be reported as SAEs as described in section 5.2.6.2.
Every occurrence of cancer of new histology must be classified as a serious event regardless of the time since the discontinuation of the trial medication and must be reported as described in 5.2.6.2, subsections "AE Collection" and "**AE reporting to sponsor and timelines**".

5.2.6.1.4 Adverse events of special interest

The term adverse events of special interest (AESI) relates to any specific AE that has been identified at the project level as being of particular concern for prospective safety monitoring and safety assessment within this trial, e.g. the potential for AEs based on knowledge from other compounds in the same class. AESIs need to be reported to the sponsor's Pharmacovigilance Department within the same timeframe that applies to SAEs, please see Section 5.2.6.2.2.
The following are considered as AESIs:

Potential Severe DILI
A potential severe Drug Induced Liver Injury (DILI) that requires follow-up is defined by the following alterations of hepatic laboratory parameters:

For patients with normal ALT and AST levels at baseline:
- An elevation of AST (Aspartate Aminotransferase) and / or ALT (Alanine Aminotransferase) ≥3-fold ULN combined with an elevation of total bilirubin ≥2-fold ULN measured in the same blood sample, or in samples drawn within 30 days of each other, or
- ALT and / or AST elevations ≥10-fold ULN.

For patients with abnormal aminotransaminase levels between >1 and <3 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 or ≥2-fold the baseline value (if bilirubin is

elevated at baseline), measured in the same blood sample, or in samples drawn within 30 days of each other; or;
- Aminotransferase elevations ≥5-fold the baseline value.

For patients with abnormal aminotransaminase levels between ≥3 x ULN and <5 x ULN at baseline:
- An elevation of AST and / or ALT ≥2-fold the baseline value combined with an elevation of bilirubin ≥2-fold ULN or ≥2-fold the baseline value (if bilirubin is elevated at baseline); measured in the same blood sample or in samples drawn within 30 days of each other; 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 hepatic injury (icterus, unexplained encephalopathy, unexplained coagulopathy, right upper quadrant abdominal pain, etc.) without lab results (ALT, AST, total bilirubin) available, the investigator should make sure these parameters are analysed, if necessary, in an unscheduled blood test. Should the results meet the criteria of hepatic injury alert, the procedures described in the DILI checklist should be followed.

For further details see figure 5.2.6.1.4: 1 below.

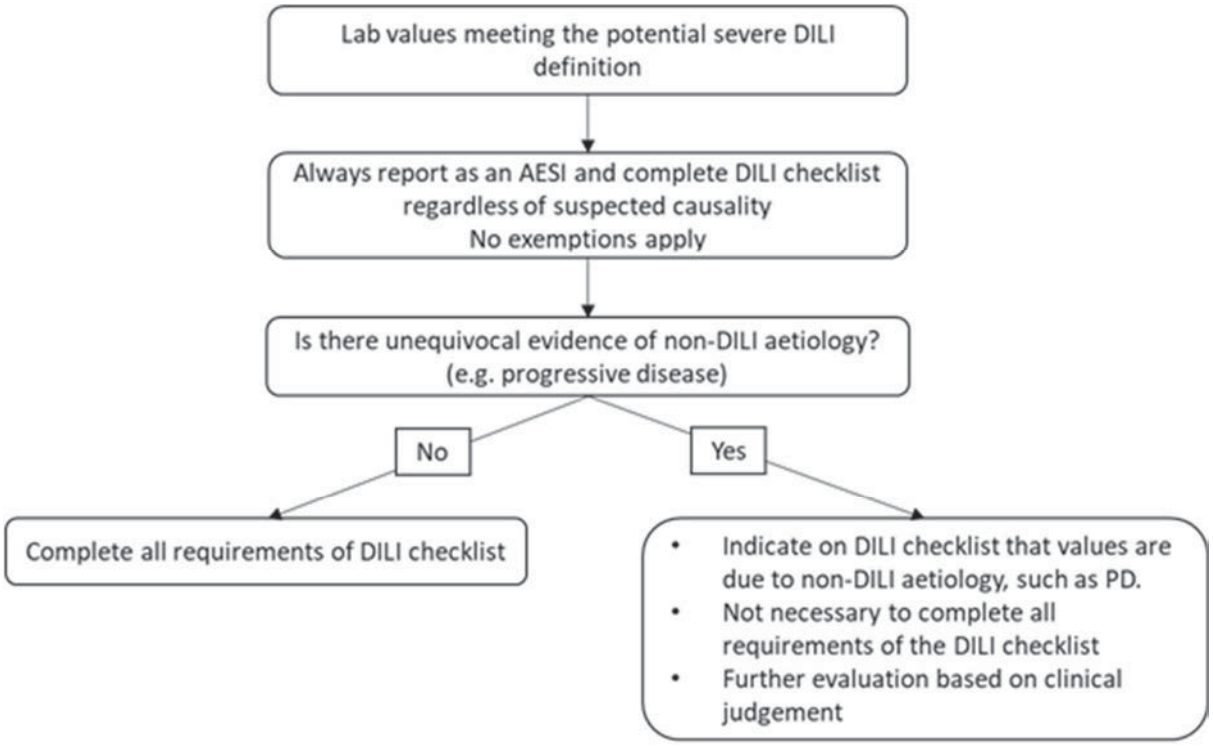

Figure 5.2.6.1.4: 1 Potential severe DILI reporting

Dose Limiting Toxicity
Any medical event fulfilling the criteria of DLT (see Section 5.2.7) should be reported as an AESI.

Infusion-related reactions
The following AEs, when occurring with a temporal relationship to the infusion, are considered as potential infusion-related reactions and should be reported as AESIs, regardless of their CTCAE grade:

- Infusion-related reaction (synonyms: infusion reactions, infusion-like reactions)
- Allergic reaction
- Anaphylaxis
- Cytokine-release syndrome
- Any other event which the investigator considers as a potential infusion-related reaction.

5.2.6.1.5 Intensity (severity) of AEs

The intensity (severity) of AEs should be classified and recorded in the CRF according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 (R18-1357).

5.2.6.1.6 Causal relationship of AEs

Medical judgement should be used to determine the relationship between the adverse event and the BI investigational compound, 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 trial 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 reduced).

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 trial 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.
- There is an alternative explanation, e.g. situations where other drugs or underlying diseases appear to provide a more likely explanation for the observed event than the drug concerned.
- Disappearance of the event even though the trial drug treatment continues or remains unchanged.

5.2.6.2 Adverse event collection and reporting

5.2.6.2.1 AE Collection

The investigator shall maintain and keep detailed records of all AEs in the patient files.

The following must be collected and documented on the appropriate CRF(s) by the investigator:

- From signing the informed consent onwards until the individual patient's EoR visit (FUP #1)): all AEs (non-serious and serious) and all AESIs.
- After the individual patient's EoR visit until the individual patient's end of trial: cancers of new histology and exacerbations of existing cancer, all trial drug related SAEs and all trial drug 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 only report any occurrence of cancer of new histology and trial drug related SAEs and trial drug related AESIs of which the investigator may become aware of by any means of communication, e.g. phone call. Those AEs should be reported on the BI SAE form (see Section 5.2.6.2.2), but not on the CRF.

The rules for Adverse Event Reporting exemptions still apply, please see Section 5.2.6.2.4.

5.2.6.2.2 AE reporting to the 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 to the sponsor's unique entry point within 24 hours of becoming aware of the event, the country specific process will be specified 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 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. All (S)AEs, including those persisting after individual patient's end of trial must

be followed up until they have resolved, have been assessed as “chronic” or “stable” , or no further information can be obtained.

5.2.6.2.3 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 written consent of the pregnant partner. Reporting and consenting must be in line with local regulations. The ISF will contain the trial specific information and consent for 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 Studies (Part B).
The ISF will contain the Pregnancy Monitoring Form for Clinical Studies (Part A and B).

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

5.2.6.2.4 Exemptions to AE reporting

Collection and reporting of PD
The outcome progressive disease (PD) is used to assess trial endpoints for the analysis of efficacy. It will be recorded on the appropriate page of the eCRF.

If the disease progression does not meet standard seriousness criteria (see section 5.2.6.1.2), then it is exempt from AE reporting, and will only be recorded on the appropriate page of the eCRF.

For example, asymptomatic disease progression detected on a routine scan would be exempt from AE reporting, even if disease progression is on the “always serious” list.
However if there is evidence suggesting a causal relationship between the investigational drug(s) and the progression of the underlying malignancy, the event must be recorded as an SAE on the AE page in the eCRF and reported as an SAE on the SAE Form.

If disease progression meets the standard seriousness criteria (see section 5.2.6.1.2) it will be recorded on the AE page in the eCRF and on the SAE form and SAE reporting process will be followed.

Lab values meeting the potential severe DILI definition in section 5.2.6.1.4 must always be reported as AESI, even if the most likely cause is disease progression. No exemption to AE reporting applies.

Clinical symptoms and/or signs of PD will be recorded on the AE page in the eCRF. If signs and symptoms of disease progression of the patient's underlying malignancy meet standard seriousness criteria, they will additionally be reported as SAEs on the SAE form and SAE reporting procedures will be followed. If signs and symptoms are attributable to a diagnosis, reporting the diagnostic term is preferable e.g. pulmonary embolism rather than dyspnoea, intestinal obstruction rather than abdominal pain.
Exempted events are reviewed at appropriate intervals by the Sponsor and the DRC.

5.2.7 Dose limiting toxicities

Any of the following AEs will be classified as DLTs, unless unequivocally due to underlying malignancy or an extraneous cause:

Table 5.2.7: 1 Dose limiting toxicities

Category	Criteria and CTC AE Grade defining a DLT
Treatment delay*	• Any toxicity that result in a treatment delay >14 days
Hematologic laboratory*	• Grade 4 neutropenia lasting >7 days. • Grade ≥ 3 neutropenia with documented infection. • Grade ≥ 3 febrile neutropenia defined as ANC <1000/mm^3 (< 1.0 x10^9//L, < 1.0 x10^3 /µL) and a single temperature of ≥ 38.3 degrees C (101 degrees F) or a sustained temperature of ≥ 38 degrees C (100.4 degrees F) for more than one hour; or where there are life-threatening consequences or urgent intervention indicated. • Grade 3 thrombocytopenia <50,000/m^3 (< 50 x10 ^{9} /L, < 50 x10^3/ µL) associated with bleeding excluding grade 1 epistaxis. • Grade 4 thrombocytopenia (platelet count <25,000/m^3 (< 25 x 10^9 /L, < 25 x 10^3 / µL) . • Thrombocytopenia or anemia requiring transfusion per local or international guidelines. • Neutropenia that requires administration of hematopoietic growth factor agents per local or international guidelines.
Non-hematologic laboratory*	• Any Grade 3 or Grade 4 non-hematologic laboratory value if: - Medical intervention is required to treat the patient, or - The abnormality is a serious adverse event, or - The abnormality persists >1 week, and considered significant enough to be qualified as DLT in the investigator's opinion, and confirmed by the DRC. • An elevated AST or ALT value ≥ 3 x the upper limit of normal (ULN) and an elevated total bilirubin value ≥ 2 x ULN measured in the same blood draw sample and, at the same time, an alkaline phosphatase value < 2 x ULN, as determined by way of protocol-specified lab testing or unscheduled lab testing. • An elevated AST or ALT value ≥ 5 x ULN and an elevated total bilirubin value ≥ 2 x ULN measured in the same blood draw sample, with the exclusion of causes due to underlying diseases (for patients with elevated liver enzymes at baseline).

*Except if the event is considered due to background therapy only.

Table 5.2.7: 1 Dose limiting toxicities (cont)

Category	Criteria and CTC AE Grade defining a DLT
	• Any Grade 4 non laboratory toxicity possibly related to study therapy, irrespective of whether patient received maximal supportive therapy. • Any Grade 3 non laboratory toxicities despite the use of adequate/maximal medical interventions and/or prophylaxis as dictated by local institutional clinical practices or the judgment of the investigator, except for: - Fatigue/ asthenia present at baseline that worsens on study and lasts less than 7 days. - New onset of Grade 3 nausea or Grade 3 vomiting lasting ≤ 48 hours, and which resolved to ≤ Grade 1 either spontaneously or with conventional medical intervention. - Nausea or vomiting present at baseline that worsens on-study, and resolves with treatment within 24 hours. - Grade 3 diarrhea not requiring hospitalization, lasting ≤ 48 hours, and which resolved to ≤ Grade 1 either spontaneously or with conventional medical intervention. • Any other toxicity considered significant enough to be qualified as DLT in the opinion of the investigator, and confirmed by the DRC, will be reported as a DLT. • Any toxicity Grade ≥ 2 leading to dose reduction will be considered as a DLT. • Any death not clearly due to the underlying disease or extraneous causes.

Dose-limiting toxicities (DLTs) will be recorded throughout the trial. Any DLT must be reported to the Sponsor's Pharmacovigilance Department by the Investigator or designee within 24 hours of first knowledge regardless of the relationship to the study drug. All DLTs will be agreed upon by the DRC after review of the data from each cohort. Only DLTs occurring in the first two cycles are necessary for dose-escalation decisions made by the DRC. DLTs observed during the MTD evaluation period will be considered for MTD determination. However, all AEs and SAEs meeting criteria of DLT observed in all treatment cycles will be considered for determining a RP2D.

Replacement of patients for DLT evaluation during MTD evaluation period

For the definition of DLT, it is essential that patients are sufficiently treated according to supportive care standards described in Section 4.1.5.1. Patients with treatable AEs (eg. nausea, vomiting, and diarrhea) that are not sufficiently treated do not qualify for DLT and need to be replaced, if this occurs in the first two Cycles. Dose escalation will be determined based on all safety information of all treated patients including those who do not complete the first two cycles for reasons other than a DLT. Criteria for replacement of patients during the MTD evaluation period is described in Section 3.3.4.1.1.

5.3 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

5.3.1 Assessment of pharmacokinetics

The evaluation of BI 905711 concentrations will be performed according to BI standards and processes.

Pharmacokinetic (PK) profiles of BI 905711 will be investigated after the first and after repeated doses. Standard PK parameters as listed in Appendix 10.1 will be calculated, if data allows and if scientifically reasonable. Noncompartmental PK parameters will be calculated based on actual sampling times using a validated PK software (Phoenix® WinNonlin® 6.3).

Individual concentration data and the PK parameters calculated thereof will be tabulated and graphically displayed. Statistical analyses will be performed as described in Section 7.3. A patient's PK data will be flagged and excluded from the statistical analyses in case of protocol deviations relevant to the evaluation of PK (to be decided no later than in the Blinded Report Planning Meeting) or in case of PK non-evaluability (as revealed during data analysis, based on internal procedures). Reasons for exclusion of a patient's data will be documented in the Clinical Trial Report (CTR). PK data may be additionally analyzed using a population PK approach. If required, modelling activities will be planned and documented separately according to internal and external guidelines and SOPs.

Preliminary PK and Immunogenicity analyses can be performed as necessary e.g. as additional information for the DRC. In contrast to the final PK and Immunogenicity analysis, the preliminary analyses will be based on planned sampling times rather than on actual times; no supplementary patient information, e.g. on AEs or concomitant medication, will be used in these analyses, and the outputs will not be validated. Minor numerical discrepancies between preliminary and final results may therefore occur.

The presence of ADA to BI 905711 will be assessed at pre-dose and regularly during treatment according to the sampling scheme in Appendix 10.2

5.3.2 Methods of sample collection

Effective from CTP v4.0, PK and ADA/Nab samples are no longer collected for ongoing patients.

Details of the sample collection, preparation, storage and shipment are described in the ISF/laboratory manual.

The timepoints for collection of PK and ADA/Nab samples are given in Appendix 10.2.
Date and clock time of drug administration(s) and PK sampling will be recorded in the CRFs.
Exact time points of plasma sampling will be documented in the CRFs or sent as electronic files to the Trial Data Manager.
The samples may be used for further methodological investigations, (e.g. stability testing for PK, or to further characterise ADA/Nabs response or to address Health authority questions

regarding the results/methodology) however, only data related to the analyte and ADAs/Nabs will be generated by these additional investigations.
After analysis of PK samples, leftover samples may be used to explore the effect of high mannose glycoforms on the PK of BI 905711. It is not intended to include the results from such analysis in the clinical trial report. The results may be provided in a stand-alone report.

The study samples will be discarded after completion of additional investigations including high mannose assessment but not later than 5 years after the final study report has been signed.

[redacted]

5.3.4 Pharmacokinetic - pharmacodynamic relationship

No formal analysis of a pharmacokinetic/pharmacodynamic relationship is planned. Exploratory PK/PD relationship may be investigated depending on the suitability of the data. In addition, exploratory correlation may also be made between drug concentration and AEs. If required, modeling activities will be planned and documented separately according to internal and external guidelines and SOP.

5.4 ASSESSMENT OF BIOMARKER(S)

Effective from CTP v4.0, biomarker samples, tumor biopsies samples and [^{18}F]FDG-PET are no longer collected for ongoing patients.

This section refers to exploratory biomarkers. Established biomarkers of efficacy and safety are described and discussed in Sections 5.1 and 5.2.

The study of biomarkers will be mostly exploratory hypothesis-generating and will be used to expand our understanding of the disease and trial drug. The following biomarkers are planned to be examined in this trial (for detailed sampling times, refer to Appendix 10.2 and Flowchart):

- Determination of CDH17 expression (see Section 5.4.2.1).
- Determination of cell death biomarkers in plasma and tumor tissue, including but not limited to: activated caspase 3/7, at screening, baseline and on treatment as an indicator for apoptosis induction in the body (see Section 5.4.2.2).
- Quantification of cell-free tumor DNA levels in patients plasma at baseline and after treatment as an indicator for apoptotic tumor cells and tumor burden (see Section 5.4.2.3).
- Measurement of gene expression in tumor biopsies taken at baseline and on treatment addressing a potential correlation with treatment response (see Section 5.4.2.5).

- Determination of correlation of cancer-related mutations/biomarkers with clinical signals and/or PD biomarker modulation and/or mRNA gene expression via Next Generation Sequencing (NGS). (see Section 5.4.2.5)
- Determination of change in tumor cell glucose uptake by [^{18}F]FDG-PET as surrogate to assess tumor cell apoptosis induced by the study drug (see Section 5.4.2.6)

As medical knowledge in this field is constantly evolving, other tissue/blood biomarkers that may become relevant e.g. as predictive markers of treatment response may also be explored via available tissues/blood. The list of biomarkers planned to be studied during the trial may change based on assay validity, new information in the literature or insights from early analyses.

The biomarker analyses will be performed by Boehringer Ingelheim or laboratories authorized by Boehringer Ingelheim.

Data obtained from the biomarker analysis will not be disclosed to patients because the analysis is exploratory. If consent is withdrawn, all data that had already been collected up to the time of withdrawal of consent will still be used.

5.4.1 Drug interaction biomarkers

Please refer to Section 1.2

5.4.2 Pharmacodynamics and patient selection biomarkers

5.4.2.1 Determination of CDH17 protein/mRNA expression

CDH17 protein expression will be measured in an IHC assay using FFPE tumor material. Where feasible samples will also be evaluated for CDH17 mRNA expression using appropriate technologies.

After eligibility has been confirmed, all CRC patients will be enrolled in the trial irrespective of CDH17 expression. Where feasible, the CDH17 expression data from all patients will be used for retrospective correlation with treatment response or clinical outcome in phase Ia and phase Ib and will help to determine a threshold for possible patients´ selection based on CDH17 expression.

For Non-CRC patients CDH17 expression will be used as part of the enrolment criteria in phase Ib. Only non CRC patients showing positive CDH17 expression will be entered in the trial. Where feasible, the CDH17 expression data will be used for retrospective correlation with treatment response or clinical outcome in order to refine the threshold of expression that could be used for patient selection.

Due to science continually evolving, it may be necessary to perform additional biomarker assessments using tumor tissue material remaining after completion of assessments described in Section 5.4.2. Such assessments may include but are not limited to the measurement of proteins relevant to TRAILR2 engagement in the tumors.

5.4.2.2 Determination of activated cell death biomarker levels in plasma

Caspase 3/7 activity in plasma will be measured at screening, baseline and on treatment. Possible other cell death biomarkers in plasma, including but not limited to e.g. caspase-cleaved CK18 (M30) and/or total CK18 (M65) may also be measured.

5.4.2.3 Quantification of cell-free tumor DNA levels in plasma

Analysis of cell-free DNA (cfDNA), including ctDNA (circulating tumor DNA) provides a non-invasive technique that may help early detection of tumor response. Quantification and mutation analysis will be performed in cfDNA extracted from pre-treatment, on treatment and post-treatment plasma samples prepared from whole blood.

5.4.2.4 Immunohistochemical analysis of apoptosis induction and tumor cell proliferation in tumor tissue

Protein expression in tumor tissue collected pre and on treatment will be assessed by Immunohistochemistry in Phase Ib to indicate potential treatment effects on tumor cell apoptosis and proliferation. Protein markers to be analyzed include, but are not limited to, cleaved caspase 3 and Ki67.

5.4.2.5 Assessment of gene expression and cancer-related gene mutation in tumor biopsies

Gene-expression analysis and assessment of cancer-related gene mutation will be performed in tumor biopsies. The purpose of this analysisis to study the biology of the tumors at baseline (prior to first treatment). If feasible data will be used for retrospective correlation with treatment response or clinical outcome in phase Ia and phase Ib. Furthermore, should on treatment samples be attained changes induced by the treatment intervention will be investigated via gene expression analysis.

Details on biopsy sample collection and shipment will be provided in the Laboratory Manual and the ISF.

5.4.2.6 [^{18}F]FDG-PET/CT

To evaluate tumor cell death and apoptosis induced by BI 905711, [^{18}F]FDG-PET/CT is intended to be used as a sensitive non-invasive PD marker measuring drug-induced changes in metabolic activity of the tumor. [^{18}F]FDG-PET/CT will be performed in CRC patients in both phase Ia and phase Ib.

Two scans will be performed during the study; one during screening (baseline) and one on treatment (at the 8 week ($\pm$ 7 days) tumor assessment timepoint). The PET scan may be performed together with CT scan if feasible. The PET scan at screening should preferably be performed no later than 14 days (±7 days) prior to first treatment.

[^{18}F]FDG-PET/CT examination procedure

To undergo a [^{18}F]FDG-PET/CT examination, patients should fast before i.v. injection of [^{18}F]FDG. At the time point of [^{18}F]FDG injection, plasma glucose level of the patient will be assessed. Immediately after [^{18}F]FDG injection, patients must be advised to remain seated or to lie down and relax for approximately one hour before start of PET/CT scanning. Patients should be asked to void immediately prior to the PET/CT scan to reduce bladder activity.

Radiation dosimetry
The effective dose of [^{18}F]FDG is 0.019 mSv/MBq (approximately 6-8 mSv per scan) (R18-3386). The organ receiving the largest radiation dose is the bladder (0.13 mGy/MBq) (R18-3386). National regulations must be complied with in regard to the administration of radioactive substances and the CT exposure for the purpose of this study.

Image analysis
Visual, semi-quantitative and quantitative image interpretation will be performed (SUV parameters). Treatment response will be scored according to standard guidelines e.g. EORTC response criteria (R14-1470).

Further details regarding [^{18}F]FDG-PET/CT imaging will be outlined in the Imaging Manual.

5.4.3 Methods and timing of sample collection

Detailed instructions on sampling, preparation, processing, shipment and storage are provided in the laboratory manual. For sampling timepoints see Appendix 10.2 and Flow Chart.

5.4.3.1 Tumor Tissue collection

For fresh biopsies always use the equivalent of at least two core needle biopsies (18 gauge or greater). Tissue needs to be provided as formalin-fixed and paraffin-embedded tissue block. Potential prioritization of the biomarker analyses might be made according to the available tissue amount. In case a tissue block cannot be collected as indicated, the site needs to contact the Sponsor for agreement regarding fresh biopsy collection.

Archival tumor tissue samples should be provided as FFPE. For samples collected during screening mounted tissue sections (at least 19 sections of 4-5 µm thickness), where feasible under RNase free conditions, should be prepared and shipped. For all samples to be provided post-confirmation of eligibility an embedded FFPE block is preferable. Please refer to the Flow Chart for sampling timepoints.

Tumor tissue collection in Phase Ia

- Provision of an archived tumor tissue specimen is mandatory during screening for all patients. A fresh biopsy is only mandatory for those patients who do not have archival tissue.

Tumor Tissue collection in Phase Ib

- **For all patients**: Provision of archival tumor tissue or fresh biopsy is mandatory for all patients prior to treatment start on Day 1. Fresh biopsy sample should be provided if the archival tissue tested is greater than 6 months old from collection to start of

treatment on this study. Even if fresh biopsy conducted, provision of an archived tumor tissue is recommended. **For Non-CRC patients**, CDH17 expression measurement by archival tumor tissue or fresh biopsy sample must be completed prior to treatment start on Day 1.

- On-treatment biopsies should be taken on Cycle 2 Day 5, 48h after administration of BI 905711 (optional) and/or at disease progression (optional) for a patient in which a fresh biopsy has been successfully obtained before first study treatment.

Only non-significant risk procedures per the investigator's judgment will be used to obtain any biopsies specified in this study.
In case a fresh pre-treatment tumor biopsy cannot be obtained, an archived tumor tissue specimen must be submitted (mandatory).

Timepoints for fresh tumor biopsy collection are detailed in the Flowchart.

Left over tumor samples will be biobanked (Section 5.5). For patients who do not consent to biobanking, remaining samples will be disposed of at the latest 5 years after the final trial report has been signed. Until then, samples will be stored at Boehringer Ingelheim or a designated CRO.

5.4.3.2 Plasma samples

Plasma for cell death biomarkers
Cell death biomarkers will be measured. (see Flowcharts and Appendix 10.2).
Collection of plasma for analysis of cell death biomarkers is mandatory.

cfDNA (including ctDNA)
Additional blood/plasma samples will be collected from all patients (see Flowchart and Appendix 10.2).

Collection of one blood sample (baseline only) and up to four plasma samples for analysis of cfDNA is mandatory.

All samples must be adequately labelled by the trial site personnel. Further details about tumor tissue and blood sample collection, plasma preparation, required tubes, labelling of tubes, storage and shipment (frequency and addresses) will be provided in the laboratory manual and the ISF.

5.5 BIOBANKING

Participation in biobanking is voluntary and not a prerequisite for participation in the trial. Biobanking will only occur after a separate biobanking informed consent has been given in accordance with local ethical and regulatory requirements. China will not participate to this biobanking.

The following biomarker samples specified in section 5.4, Assessment of Biomarkers, will be banked: pre-treatment and post-treatment biopsies, fixed in formalin and embedded in paraffin (From Phase Ia/Ib, and both archival/fresh).

5.6 OTHER ASSESSMENTS

5.6.1 Patient-reported outcomes

Patient-reported outcomes (PRO) are considered important to prescribers, patients and health care decision-makers when evaluating the clinical utility of medical intervention. The information collected using PRO instruments can lend supportive arguments to the clinical activity or tolerability of a therapy and describe the extent to which patients' physical, emotional and social well-being are affected by treatment.
Patient-reported symptom data will be measured with the Patient Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) (R18-2068)

Questionnaires will be completed at the time points specified in the Flow Chart. Paper questionnaires should be completed at the site by patients prior to seeing the clinician, prior to clinical assessment, prior to any treatment at the clinic, and before provision of any new information about their disease status so that the responses are not influenced (biased). The responses recorded on the questionnaires will not be recorded as adverse events. Adverse events are collected during protocol specified study visits with the clinician.

The questionnaire generally takes about 10 minutes to complete. Patients will receive the questionnaire in their native language in countries where validated translations exist. The answered questionnaires will be entered into the CRF by the site personnel.

PRO-CTCAE

PRO-CTCAE is a patient-reported outcome measure developed to evaluate symptomatic toxicity in patients in cancer clinical trials. It was designed to be used as a companion to the CTCAE criteria, the standard lexicon for adverse event reporting in cancer trials.

5.7 APPROPRIATENESS OF MEASUREMENTS

All methods used are standard. Determination of MTD is based on toxicities graded according to CTCAE version 5.0 (R18-1357). The CTCAE criteria are commonly used in the assessment of AEs in cancer patients. RECIST 1.1 (R09-0262) is used for evaluation of response. These criteria are well-established and scientifically accepted.

PRO-CTCAE has been developed and validated in accordance with FDA and EMA guidance for patient-reported outcome measures.

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

Patients must satisfy all inclusion and exclusion criteria prior to treatment administration (see Section 3.3). Details of any patient who is screened for the study but is found ineligible must be entered in an enrolment log (see ISF) and documented in the eCRF. All patients are to adhere to the visit schedule as specified in the Flowchart.

If a patient misses a visit during which there is no treatment administration planned, the visit should be rescheduled as soon as possible and the delayed visit documented with the actual date and the reason for the delay. The scheduling of subsequent visits must not be altered, so if it is not possible to reschedule prior to the next planned visit, the missed visit should be skipped.

If a patient is hospitalised for administrative reasons to allow treatment and PK sampling this will not be considered an SAE, unless any other criteria for an SAE are fulfilled.

In addition to the scheduled assessments, unscheduled visits and unscheduled assessments for safety reasons may be performed at any time according to clinical need.

In the event of force majeure or other disruptive circumstances (e.g. pandemic), sites should adhere to the required protocol procedures as close as possible, however the investigational plan as per this clinical trial protocol may not be feasible at a site. The patient may also be unable or unwilling to attend a clinic visit. The investigator must assess the risk-benefit for the individual patient and in agreement with the Sponsor may decide to implement alternative solutions (i.e. virtual patient visits and assessments) if this is in the best interest of the patient. Patient safety must be ensured when determining if a visit may be remote. The implementation of any alternative solutions 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

Refer to the Flow Charts and Section 5 for details on the procedures performed at each visit.

6.2.1 Screening period

Following informed consent, the patient will undergo screening assessments as indicated in the Flowchart.The assessments required during the screening period do not need to be conducted on the same day but must be conducted within a time interval of 28 days prior to the Cycle 1 Day1.
Screening assessments may be repeated as long as they fall within the 28 day screening visit window. If more than one screening assessment is available, the latest assessment prior to the start of treatment must be used to assess eligibility.

Rescreening for non CRC patients will be allowed if CDH17 positivity is confirmed.
A patient who has been declared as a "screening failure" may be re-screened once.
In this situation patients will be handled as new patients i.e. sign a new informed consent, allocate a new patient number, and undergo full screening assessments to assess eligibility.

Tumor assessments performed prior to informed consent as part of routine clinical practice can be accepted if they meet the requirements of the protocol. For example, during the screening period, a tumor assessment does not need to be performed if there are valid results available from assessments which were performed within 28 days prior to start of treatment.

Demographics to be collected during the screening period

- During the screening visit, demographics information will be collected. This includes: age on the day of informed consent (in years).
- Sex (male, female in order to describe the subject`s sex at birth),
- Gender identity (male, female, other in order to describe how the subject self-identifies regardless of their genotypic or phenotypic sex)
- For women: of childbearing potential yes / no in order to characterize the patient population and as a basis for contraception requirements.
- Ethnicity and race in order to sufficiently characterize the patient population and to support possible subgroup analyses unless not acceptable according to local regulations.

Baseline Conditions
Baseline conditions and concomitant therapies present during screening will be recorded in the eCRF.

Medical History:
A general medical history and a detailed oncological disease history will be collected.
The oncological history to be reported on the eCRF will include:

- Date of first histological diagnosis
- The primary tumor site
- Staging and grading information
- The number and location of metastatic sites
- Previous treatment for the tumor, including any surgery, radiotherapy, and/or systemic therapy including start and stop dates and outcome.
- Any known genomic alterations such as but not limited to BRAF, KRAS, HER2, BRCA, and the immune markers status (i.e. microsatellite instability and/or DNA mismatch repair deficiency).
- The date of tumor progression after previous lines of treatment will be recorded if known, including start and end dates and outcome.

6.2.2 Treatment period(s)

If a patient is eligible for trial participation, the cycle 1 day 1 assessments will be performed as noted in the Flow Charts.

Treatment cycles are 14 days in duration.
Subsequent visits and assessments during the treatment period are performed as described in the Flowchart.
See Section 4.1.5.2 for criteria for receiving further treatment.
Patients may continue on treatment for unlimited cycles until criteria for stopping treatment are met (See Section 3.3.4.1).

PK, biomarkers, other speciality samples collected for reasons other than safety may be discontinued if the sponsor decides that sufficient information has been collected.

6.2.3 Follow-up period and trial completion

The post treatment period will consist of an End of Treatment (EoT) visit, a 30-day safety follow-up visit (EoR) as well as follow-up visits for disease progression (PD) and overall survival (OS).

6.2.3.1 End of treatment (EoT) visit

The EoT visit will be performed as soon as possible but not later than 14 days after permanent discontinuation of trial medication for any reason or e.g. when the investigator decided with the patient to permanently discontinue the trial medication or became aware that the trial medication had been terminated. The EoT assessments will be performed instead of the next planned visit as noted in the Flow Charts.

6.2.3.2 End of Residual Effect Period (EoR)

The End of Residual Effect Period (EoR) visit (FUP #1) should occur no earlier than 30 days (+ ≤ 5 days) after the last dose of treatment in order to evaluate safety. Assessments will be performed as noted in the Flow Charts

6.2.3.3 Follow-up for progressive disease

The end of study is defined as EOR. No further follow-up visits after EOR are required, unless follow-up is for S(AE) that occurred before EOR period.

If death date is known, this should be reported in the CRF.

6.2.3.4 Follow-up for overall survival status

Effective from CTP v4.0, this section is not applicable.

All patients will be followed-up for survival status at approximately 12 week (+/-7 days) intervals until;
- Death
- Withdrawal of consent

- Lost to follow-up or
- Completion of the whole trial

The follow-up visits for survival status will be performed in person, by telephone or via written correspondence. If a patient cannot be contacted for survival status, information may also be obtained by other means in accordance with informed consent language and local regulations (e.g. contact with patients' health care providers, public sources, e.g. death registry, obituary listing, etc.) when it is available and verifiable. The last follow-up visit will be considered the "end-of-trial" visit.
The following patient status information will be collected during the FUP timepoints for survival status:

- Date of contact
- Further anti-cancer treatment including surgery and radiotherapy: regimen and drug name, start and stop dates.
- For each reportable serious adverse event / AESI, the investigator should provide the information with regard to concomitant medication and the medication administered to treat the adverse events on the appropriate CRF pages and the SAE form including trade name, indication and dates of administration
- Outcome event (e.g. death: Record date of and reason for outcome event / death [if applicable])

6.2.3.5 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
• Refusal to be followed-up
• Death

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 NULL AND ALTERNATIVE HYPOTHESES

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

7.2 PLANNED ANALYSES

7.2.1 General considerations

No per protocol set will be used in the analysis. However, important protocol deviations (iPDs) will be summarised. Adherence to the protocol will be assessed by the trial team. iPDs categories will be specified in the iPD specification document. IPDs will be identified at trial oversight meetings and documented in the iPD log. The iPD categories will be updated as needed.

For determination of the MTD, only MTD evaluable patients with be considered. For analyses 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 used if not specified differently. Any other analysis set will be defined in the TSAP.

7.2.2 Handling of intercurrent events

The expected intercurrent events of interest are:
- treatment discontinuation during the MTD evaluation period
- progressive disease during the MTD evaluation period
- death during the MTD evaluation period
- dose reduction during the MTD evaluation period
- any events that cause missed visits during the MTD evaluation period

The strategy for handling intercurrent events in this trial is as follows:
If the intercurrent event follows criteria defined in section 3.3.4.1.1 then the patient will be considered not evaluable for MTD and will not be considered in the primary analysis, otherwise the patient should still be considered in the primary analysis. This corresponds to a principal stratum strategy.

7.2.3 Primary objective analyses

Phase Ia dose escalation:
This trial will be performed as an open label.
The primary objective in phase Ia is to determine the MTD and the recommended dose for expansion (RDE) of BI 905711 in combination with FOLFIRI plus bevacizumab. MTD is defined as the highest dose with less than 25% risk of the true DLT rate being equal or above 0.33 (EWOC criterion). Dose-escalation for each group will be guided by a two-parameter Bayesian Logistic Regression Model (BLRM), escalating with overdose control (EWOC)

(R13-4803; R13-4806).

The Bayesian logistic regression model (BLRM) is formulated as follows:

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

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

X_d denotes the random variable describing the observed number of DLTs in n_d patients at the dose d.

π_d represents the probability of having a DLT in the the MTD evaluation period at dose d, d* = 3.6 mg/kg is the reference dose, allowing for the interpretation of α as the odds of a DLT at dose d*, and $\theta = (\log(\alpha), \log(\beta))$ with $\alpha, \beta > 0$ is the parameter vector of the model.

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

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

The BLRM-recommended dose for the next dose cohort is the dose level with the highest posterior probability of the DLT rate falling in the target interval of [0.16, 0.33) among the doses fulfilling the EWOC principle. With the EWOC criterion, it should be unlikely (i.e. posterior probability <25%) that the DLT rate at the recommended dose will exceed 0.33. The maximum allowable dose increment for each escalation step shall not be more than 100%.

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

- the posterior probability of the true DLT rate in the target interval [0.16, 0.33) of the MTD is above 0.5
- OR at least 12 patients have been treated in phase Ia, of which at least 6 at the MTD.

The DRC may recommend stopping the dose escalation phase after the criterion for MTD is fulfilled.

Prior derivation:

By the time BLRM is analyzed, safety data for BI 905711 are expected to be available from BI Study 1412-0001. The information can be incorporated into the prior derivation meta-analytic predictive (MAP) approach. The safety data for BI 905711 in 1412-0001 dated April 15th 2021 can be found in Table 7.2.3:1, and is used in prior derivation.

Table 7.2.3: 1 Safety data for BI 905711 in 1412-0001 used in prior derivation

Dose level	Cohort	Number of evaluable patients	Number of evaluable patients with DLT during the first two cycles
0.02mg/kg	CRC	1	0
0.06mg/kg	CRC	1	0
0.2mg/kg	CRC Non-CRC	4 2	0 0
0.6mg/kg	CRC Non-CRC	4 4	0 0
1.2mg/kg	CRC	4	0

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

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

Mixture prior distributions have the advantage that they allow for specification of different logistic dose-toxicity curves, therefore making the prior more robust. The mixture prior includes the following two components:

- Component 1
  This informative prior is derived to reflect information from 1412-0001 trial using MAP approach in addition to the assumed mean DLT rates for FOLFIRI regimen plus bevacizumab being 10% in CRC cohort. The prior weight for the first component is set to be 0.9.
- Component 2
  A high-toxicity weakly informative prior is derived to reflect the case that the combination therapy would be much more toxic than expected. For this prior component, it was assumed that the median DLT rate at the starting dose of 0.6 mg/kg would equal 10%, and the median DLT rate at 4.8 mg/kg would equal 60%. The prior weight for the first component is 0.1.

Summary of the prior distributions for CRC group is provided in Table 7.2.3:2. Additionally, the prior probabilities of DLTs at different doses, as well as the corresponding probability of under-, targeted and over-toxicity, are shown in Tables 7.2.3:3. It is worth noting that the uncertainty around the medians is large, showing the low amount of information these prior

distributions inform. A detailed evaluation of the model using hypothetical data scenarios is provided in the statistical Appendix 10.3.

Table 7.2.3: 2 Mixture of prior distributions for CRC group

Prior Component	Mixture Weight	Mean $\theta = (\log(\alpha), \log(\beta))$	SD $\theta = (\log(\alpha), \log(\beta))$	Correlation
1: Weakly inf.	0.9	-1.62, 0.39	1.75, 0.97	0.35
2: High Tox	0.1	0.045, 0.22	2, 1	0

Table 7.2.3: 3 Prior probabilities of DLT at selected doses – CRC group

Dose	Probability of true DLT rate in					Quantiles		
	[0–0.16)	[0.16–0.33)	[0.33–1]	Mean	SD	2.5%	50%	97.5%
0.6	0.895	0.058	0.047	0.06	0.133	0	0.01	0.496
1.2	0.823	0.094	0.084	0.095	0.164	0	0.027	0.639
2.4	0.652	0.168	0.18	0.175	0.214	0.002	0.084	0.803
3.6	0.456	0.2	0.344	0.283	0.266	0.007	0.19	0.909
4.8	0.354	0.174	0.471	0.38	0.313	0.009	0.298	0.979

The prior may be updated once the data in trial 1412-0001 has been updated. The prior used for each BLRM analysis for the DRC meetings will be documented in the DRC minutes, the prior used for the final analysis will be documented in the TSAP.

Phase Ib Dose Expansion:

A safety run-in will be performed for the first 6 patients in the PDAC expansion cohort. After the first 6 patients have been treated for at least two cycles, the DRC will assess the overall safety profile and confirm the RDE of BI 905711 plus FOLFIRI (or Liposomal Irinotecan plus 5-FU/Leucovorin) in PDAC cohort. If additional DLTs are observed during the safety run-in phase, a separate BLRM with overdose control will be used to re-estimate the recommended dose for PDAC expansion cohort. The available data from CRC cohorts can be incorporated into the model by a meta-analytic predictive (MAP) approach.

The primary endpoint in the dose-expansion part is objective response (OR) derived from the data of all cycles. Descriptive analyses will be conducted for this endpoint.

Details will be specified in the TSAP.

7.2.4 Secondary objective analyses

Secondary time-to-event endpoints will be analyzed by Kaplan-Meier estimates. Other secondary endpoints will be analyzed descriptively. Details of the secondary endpoint analyses will be specified in the trial statistical analysis plan (TSAP).

7.2.5 Further objective analyses

PK analyses are specified in Section 5.3.1 and will be calculated by means of noncompartmental analysis. Descriptive statistics will be used to evaluate plasma concentration data and PK parameters. Further details on analysis will be described in the TSAP.

Biomarker analysis are specified in Section 5.4. Exploratory analysis will be used to evaluate potential patient selection biomarkers and pharmacodynamic changes triggered by treatment intervention between baseline and on-treatment samples. All analysis will be further described in the TSAP.

The precise level of tumor markers could be expressed as median, mean, and range values including changes over time. Pearson correlation analysis could be used as acorrelation analysis of CEA and CA19-9. Further details and decisions on the analysis will be described in the TSAP.

PRO data collected using the PRO-CTCAE questionnaire will be analysed descriptively, including changes over time. Further details on analysis will be described in the TSAP.

7.2.6 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 REP will 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 REP. 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) at database lock.

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

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

7.2.7 Other analyses

Not applicable

7.2.8 Interim analyses

In the Phase Ia, interim safety evaluations will be performed as considered necessary. In particular safety evaluations, after each dose cohort, will be performed by the DRC. Based on this, the DRC will recommend the next dose level as well as the corresponding cohort size.

In the phase Ib, if any DLTs observed in patients enrolled in phase Ib, the BLRM will be run to confirm if the dose level still fulfills the overdose risk control.

No formal interim analysis of efficacy data is foreseen, although efficacy data, PK and biomarker data when available may be considered as part of the regular evaluation of trial data.

No formal interim analysis is planned for PK and immunogenicity.

Preliminary, exploratory analysis of PK and if applicable of immunogenicity may be performed prior to database lock during study conduct based on all evaluable data at the time of analysis. In contrast to the final calculations, the preliminary, exploratory analysis will be based on planned sampling times rather than on actual times, regardless of whether actual times were within the time windows or not. Therefore, minor deviations in preliminary and final results may occur. No formal preliminary PK and immunogenicity report will be written.

7.3 HANDLING OF MISSING DATA

Plasma concentration - time profiles
Concentration data identified with NOS (no sample), NOR (no valid result), NOA (not to the lag phase) will be ignored and not replaced by zero at any time point (including the lag phase). Descriptive statistics of concentrations at specific time points will be calculated only when at least 2/3 of the individuals have concentrations within the validated concentration range. The overall sample size to decide whether the “2/3 rule” is fulfilled will be based on

the total number of samples intended to be drawn for that time point (i.e., BLQ (below the limit of quantification), NOR, NOS, NOA are included).

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

Every effort will be made to include all concentration data in an analysis. If not possible, a case-to-case decision is required whether the value should only be excluded from half-life estimation or the complete analysis.

If a concentration is only excluded from half-life determination, it will be used for all other calculations (e.g., descriptive statistics) and for graphical presentation.

If a concentration value is excluded from all calculations, it will not be presented graphically or used for the calculation of descriptive statistics and parameter determination. However, the excluded concentration itself will be listed in the clinical trial report associated with an appropriate flag. If the actual sampling time is not recorded or is missing for a certain time point, the planned time will generally be used for this time point instead. Pharmacokinetic parameters which cannot be determined will be identified by "not calculated" (NC).

In general, no imputation will be performed on missing efficacy data. Missing baseline laboratory values will be imputed by the respective values from the screening visit. No other imputations will be performed on missing data although every effort will be made to obtain complete information on all AEs, with emphasis on potential DLTs.

7.4 RANDOMIZATION

Randomization will be performed in the CRC cohort of phase Ib part of this trial only.
The randomization list will be generated using a validated system. Randomization ratio is 2:1 for BI 905711 with FOLFIRI plus bevacizumab and FOLFIRI plus bevacizumab arms.

The randomization list will be generated using a validated system. Access to the randomization codes will be controlled and documented.

7.5 DETERMINATION OF SAMPLE SIZE

No formal statistical power calculations to determine sample size were performed for this trial. The sample size for dose escalation relies on the assumption of dose-toxicity correlation model. Up to 20 patients in dose escalation group are planned to be enrolled into the dose escalation phase based on the expected dose levels that are going to be investigated. However, the actual number of patients will depend on the number of dose cohorts tested.

In phase Ib 2nd line CRC cohort, 60 patients will be enrolled. Specifically, 40 patients will be treated with BI 905711 in combination with FOLFIRI + bevacizumab as treatment arm, and

20 patients will be treated with FOLFIRI + bevacizumab as control arm. The sample size is considered sufficient to limit the error probability of observing more than 15% difference in response rate to no more than around 6% if the true response rates are constant 30% in both arms. With this number of patients, the probability of observing a 15% increase in ORR from treatment arm to control arm will be at least around 75% under the scenario where ORR was assumed to be 20% higher in treatment arm than control arm.

In phase Ib 2nd line PDAC cohort, 20 patients will be enrolled. Historical control response rate for 2L PDAC is around 15% (chemotherapy only). The probability of observing 5 or more responders from 20 patients is no more than 17% assuming no additional benefit from investigational combination.

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

The trial will be carried out in compliance with the protocol, the ethical principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonized Guideline for Good Clinical Practice (GCP), relevant BI Standard Operating Procedures (SOPs), the EU directive 2001/20/EC / EU regulation 536/2014, the Japanese GCP regulations (Ministry of Health and Welfare Ordinance No. 28, March 27, 1997) and other relevant regulations. Investigators and site staff must adhere to these principles. Deviation from the protocol, the principles of ICH GCP or applicable regulations as will be treated as “protocol deviation”.

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

The investigator will inform the sponsor immediately of any urgent safety measures taken to protect the trial patients against any immediate hazard, as well as of any serious breaches of the protocol or of ICH GCP.
The Boehringer Ingelheim transparency and publication policy can be found on the following web page: trials.boehringer-ingelheim.com. The rights of the investigator and of the sponsor with regard to publication of the results of this trial are described in the investigator contract. As a rule, no trial results should be published prior to finalisation 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 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 or delegate 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 or delegate 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 or [redacted] delegate must sign (or place a seal on) and date the informed consent form. If a trial collaborator has given a supplementary explanation, the trial collaborator also signs (or places a seal on) and dates the informed consent.
Re-consenting may become necessary when new relevant information becomes available and should be conducted according to the sponsor's instructions.
The consent and re-consenting process should be properly documented in the source documentation.

8.2 DATA QUALITY ASSURANCE

A risk-based approach is used for trial quality management. It is initiated by the assessment of critical data and processes for trial subject protection and reliability of the results as well as identification and assessment of associated risks. An Integrated Quality and Risk Management Plan or alternative plan, in line with the guidance provided by ICH Q9 and ICH-GCP E6, for fully outsourced trials, documents the rationale and strategies for risk management during trial conduct including monitoring approaches, vendor management and other processes focusing on areas of greatest risk.
Continuous risk review and assessment may lead to adjustments in trial conduct, trial design or monitoring approaches.
A quality assurance audit / inspection of this trial may be conducted by the sponsor, sponsor's designees, or by IRB / IEC or by regulatory authorities. The quality assurance auditor will have access to all medical records, the investigator's trial-related files and correspondence, and the informed consent documentation of this clinical trial.

8.3 RECORDS

CRFs for individual patients will be provided by the sponsor. For drug accountability, refer to section 4.1.9.

8.3.1 Source documents

In accordance with regulatory requirements, the investigator should prepare and maintain adequate and accurate source documents and trial records that include all observations and other data pertinent to the investigation on each trial patient. Source data as well as reported data should follow the "ALCOA principles" and be **a**ttributable, **l**egible, **c**ontemporaneous, **o**riginal and **a**ccurate. Changes to the data should be traceable (audit trail).

Data reported on the CRF must be consistent with the source data or the discrepancies must be explained.
The current medical history of the patient may not be sufficient to confirm eligibility for the trial and the investigator may need to request previous medical histories and evidence of any diagnostic tests. In this case, the investigator must make at least three documented attempts to retrieve previous medical records. If this fails, a verbal history from the patient, documented in their medical records, would be acceptable.

Copies of source documents may be collected for safety review (i.e. CT/MRI, ECG). Before sending or uploading those copies, the investigator must ensure that all patient identifiers (e.g. patient's name, initials, address, phone number, social security number) have properly been removed or redacted from any copy of the patients' source documents.
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 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 or delegate will also monitor compliance with the protocol and GCP.

In the event of force majeure or other disrupting circumstances (e.g. pandemic, war, please see section 6). Site access may be restricted thus limiting the ability to perform standard site monitoring activities on site such as on-site source data review and source data verification.

Therefore, some of these activities may be performed remotely or replaced by centralized monitoring to the extent possible, based on a documented risk assessment and in alignment with local regulations

8.3.3 Storage period of records

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

8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

BI is responsible to fulfil their legal and regulatory reporting obligation in accordance with regulatory requirements.
Exemptions from expedited reporting are described in section 5.2.6.2.4.

8.5 STATEMENT OF CONFIDENTIALITY AND PATIENT PRIVACY

Data protection and data security measures are implemented for the collection, storage and processing of patient data in accordance with the principles 7 and 12 of the WHO GCP handbook.
To ensure confidentiality of records and personal data, only pseudonymised data will be transferred to the sponsor by using a patient identification number instead of the patient's name. The code is only available at the site and must not be forwarded to the sponsor. In case patient's records will be forwarded e.g. for SAE processing or adjudication committees, personal data that can identify the patient will be redacted by the site prior to forwarding.
Access to the patient files and clinical data is strictly limited: personalised 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 at the site 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.

A potential data security breach will be assessed regarding the implications for rights and privacy of the affected person(s). Immediate actions as well as corrective and preventive actions will be implemented. Respective regulatory authorities, IRBs / IECs and patients will be informed as appropriate.

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, 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, incl. audit trail for clinical data and samples to identify and destroy such samples according to ICF is in place
- A fit for the purpose documentation (biomarker proposal, analysis plan and report) ensures compliant usage
- A fit for purpose approach will be used for assay / equipment validation depending on the intended use of the biomarker data
- Samples and / or data may be transferred to third parties and other countries as specified in the biobanking ICF

8.6 TRIAL MILESTONES

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

The end of the trial is defined as the date of last patient in the whole trial (end of Phase Ib) ("Last Patient Completed"), or when all patients have been discontinued from study treatment and have been followed up for overall survival for at least 12 weeks after treatment discontinuation.

The "**Last Patient Last Treatment"** (LPLT) date is defined as the date on which the last patient in the whole trial is administered the last dose of trial treatment (as scheduled per protocol or prematurely). Individual investigators will be notified of SUSARs occurring with the trial medication until 30 days after LPLT 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 DRC composed of participating investigators and members of the BI trial team will be established to review individual and aggregated safety data at regular intervals to determine the safety profile and risk/benefit ratio and make decisions on next dose level, dose escalation, dose de-escalation, dose modification and next cohort size. Further details are contained in the DRC charter.

Relevant documentation on the participating (Principal) Investigators (e.g. their curricula vitae) will be filed in the ISF.
The investigators will have access to the BI web portal Clinergize to access documents provided by the sponsor.

BI has appointed a Clinical Trial Leader 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 Clinical Trial Managers, Clinical Research Associates (CRAs), and investigators of participating countries.

In the participating countries the trial 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) based on a contract outlining the responsibilities.

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, a central imaging 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.

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9.2 UNPUBLISHED REFERENCES

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10. APPENDICES

10.1 PHARMACOKINETIC ANALYSES

If feasible, the following PK parameters of BI 905711 will be evaluated using non compartmental analysis methods.

After the first doses:
• Cmax (maximum measured concentration)
• AUC0-∞ (area under the concentration-time curve over the time interval from zero extrapolated to infinity)
• AUC0-tz (area under the concentration-time curve over the time interval from 0 up to the last quantifiable data point)
• tz (time point of the last quantifiable plasma concentration)
• %AUCtz-∞ (the percentage of the AUC0-∞ that is obtained by extrapolation)
• AUCt1-t2 (area under the concentration time curve over the time interval t1 to t2)
• tmax (time from dosing to the maximum measured concentration)
• Cpre,N (the pre-dose concentration of the analyte in plasma immediately before administration of the Nth dose after N-1 doses were administered)
• t1/2 (terminal half-life)
• CL (total clearance of the analyte)
• Vz (apparent volume of distribution during the terminal phase)
• Vss (volume of distribution after intravenous infusion)

If feasible, the following additional PK parameters may be determined after repeated doses [If steady state can reasonably be assumed, the parameters will be denoted with ss as shown; otherwise, they will be denoted with the dose number of the last dose]:

• Cmax,ss (maximum measured concentration at steady state)
• Cmin,ss (minimum concentration at steady state)
• tmin,ss (time to reach minimum concentration at steady state)
• Cavg (average concentration at steady state)
• Cpre, N,ss (pre-dose concentration at steady state immediately before administration of the next dose)
• AUCτ,ss (area under the concentration-time curve at steady state over a uniform dosing interval τ)
• AUCt1-t2,ss (area under the concentration time curve over the time interval t1 to t2 at steady state)
• tmax,ss (time from last dosing to maximum concentration at steady state)
• tz,ss (time of last measurable concentration within the dosing interval τ at steady state)
• λz,ss (terminal rate constant at steady state)
• t1/2,ss (terminal half-life at steady state)
• MRTinf,ss (mean residence time in the body after intravenous infusion at steady state)
• CLss (total clearance at steady state)
• Vz,ss (volume of distribution during the terminal phase after multiple intravascular administrations at steady)

- Vss,ss (volume of distribution after multiple intravascular administrations at steady state)
- RA,Cmax (accumulation ratio based on Cmax)
- RA,AUC (accumulation ratio based on AUC0-τ)
- RA,Cpre,N (accumulation ratio based on Cpre,N)
- LI (linearity index, AUCτ,ss/AUC0-∞)
- PTF (Peak-Trough Fluctuation)

If deemed necessary, further appropriate pharmacokinetic parameters might be calculated.

10.2 TIME SCHEDULE FOR PHARMACOKINETIC (PK) BLOOD SAMPLING NO LONGER APPLICABLE PER CTP V4.0

Table 10.2: 1 Time schedule for PK and biomarker blood sampling for Phase Ia -No longer applicable per CTP v4.0

Treatment Course (each cycle is 14 days)	Visit	Visit No.	Day	Time Point[a] [hh:min]	CRF Time /PTM	Event	PK	ADA	Nab	Plasma for cell death biomarker	Plasma for cfDNA[c]	Blood gDNA[c]
Pre-Cycle 1	SCR	001	-28 to -5	0:00	0:00	Blood sampling				X		
Cycle 1	C01_D1	101	1	Just before Start of Bevacizumab and/ or FOLFIRI infusion	-48:05	Blood sampling				X	X	X
				Start of Bevacizumab and/or FOLFIRI infusion	-48:00	Bevacizumab and/or FOLFIRI infusion	---					
	C01_D3	103	3	Just before Start of BI 905711 infusion (SOI)	-0:05	Blood sampling	X	X	X	X		
				SOI	0:00	infusion	---					
				Immediately before end of BI 905711 infusion (EOI)[b]	0:30	Blood sampling	X					
				7 hours post SOI	7:00	Blood sampling	X			X		
	C01_D4	104	4	24 hours post SOI[f]	24:00	Blood sampling	X			X		
	C01_D5	105	5	48 hours post SOI	48:00	Blood sampling	X			X		
	C01_D10	110	10	168 hours post SOI	168:00	Blood sampling	X			X	X	
Cycle 2	C02_D1	201	1	Start of Bevacizumab and/or FOLFIRI infusion	-48:00	Bevacizumab and/or FOLFIRI infusion	---					
	C02_ D3	203	3	Just before (SOI)	-0:05	Blood sampling	X	X	X	X		
				0:00	0:00	SOI	---					
				Immediately before EOI	0:30	Blood sampling	X					
	C02_D4	204	4	24 hours post SOI [f]	24:00	Blood sampling	X			X		

Table 10.2: 1 Time schedule for PK and biomarker blood sampling for Phase Ia (cont) -No longer applicable per CTP v4.0

Treatment Course (each cycle is 14 days)	Visit	Visit No.	Day	Time Point[a] [hh:min]	CRF Time /PTM	Event	PK	ADA	Nab	Plasma for cell death biomarker	Plasma for cfDNA[c]	Blood for gDNA[c]
Cycle 3	C03_D1	301	1	Start of Bevacizumab and/or FOLFIRI infusion	-48:00	Bevacizumab and/or FOLFIRI infusion	---				X	
	C03_D3	303	3	Just before Start of BI 905711 infusion (SOI)	-0:05	Blood sampling	X	X	X	X		
				SOI	0:00	infusion	---					
				Immediately before EOI	0:30	Blood sampling	X					
				7 hours post SOI	7:00	Blood sampling	X			X		
	C03_D4	304	4	24 hours post SOI [f]	24:00	Blood sampling	X			X		
	C03_D5	305	5	48 hours post SOI	48:00	Blood sampling	X			X		
	C03_D10	310	10	168 hours post SOI	168:00	Blood sampling	X			X		
Cycle 4	C04_D1	401	1	Start of Bevacizumab and/or FOLFIRI infusion	-48:00	Bevacizumab and/or FOLFIRI infusion	---				X	
	C04_D3	403	3	Just before start of BI 905711 infusion (SOI)	-0:05	Blood sampling	X			X		
				0:00	0:00	SOI	---					
				Immediately before EOI	0:30	Blood sampling	X					
	C04_D4	404	4	24 hours post SOI [f]	24:00	Blood sampling	X			X		
Cycle 5	C05_D1	501	1	Start of Bevacizumab and/or FOLFIRI infusion	-48:00	Bevacizumab and/or FOLFIRI infusion	---				X	
Cycle 6	C06_D3	603	3	Just before start of BI 905711 infusion (SOI)	-0:05	Blood sampling	X	X	X			
Cycle 8	C08_D3	803	3	Just before SOI	-0:05	Blood sampling	X	X	X			
Cycle 10	C10_D3	1003	3	Just before SOI	-0:05	Blood sampling	X	X	X			
Cycle 12	C12_D3	1203	3	Just before SOI	-0:05	Blood sampling	X	X	X			
Cycle 14[d]	C14_D3	1403	3	Just before SOI	-0:05	Blood sampling	X [d]	X [d]	X [d]			
Cycle 20, 26	C20_D3, C26_D3	2003, 2603	3	Just before SOI	-0:05	Blood sampling	X [d]	X [d]	X [d]			

Table 10.2: 1 Time schedule for PK and biomarker blood sampling for Phase Ia (cont) -No longer applicable per CTP v4.0

Treatment Course (each cycle is 14 days)	Visit	Visit No.	Day	Time Point[a] [hh:min]	CRF Time /PTM	Event	PK	ADA	Nab	Plasma for cell death biomarker	Plasma for cfDNA[c]	Blood for gDNA[c]
EOT[e]	EOT	9960				Blood sampling	X	X	X		X	
30-Day Safety Follow-up	EOR	9970				Blood sampling	X	X	X			

PTM = Planned Time; SOI=Start of [BI 905711] Infusion; EOI= End of [BI 905711] Infusion

[a]The following windows of time are allowed for PK sampling:

1. Pre-dose (PTM -0:05): within 1 hour before next drug infusion/drug administration.
2. 7h: within ± 15 min of designated time
3. 24- 48h: within ±60 min of designated time.
4. 168h ±24 hour

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

[b]In the event that infusion duration is >60 minutes longer than planned, the subsequent time points for PK blood collection on the day of drug infusion should be adjusted accordingly.

[c] One blood sample to isolate genomic DNA will be obtained at C1V1 before treatment. 6 plasma samples will be collected to isolate circulating nucleic acids (e.g. cfDNA) from plasma: at C1V1 before treatment, C1D10, C3D1, C4D1, C5D1 and EOT after treatment.

[d]PK, ADA and NAB sampling is to be collected pre-dose (-0:05) at Day 3 of Cycle 14 and every 3 months thereafter (Cycle 20, Cycle 26, etc.)..

[e]If the patient will not continue treatment in the next scheduled cycle, pre-dose sampling scheduled for Day 3 of the next cycle needs to be performed at the EOT visit.

[f]Per section 4.2.4.1, if less than 50% of the planned dose of BI 905711 was administered due to an infusion-related reaction, a further dose of 50% of the intended total dose may be administered on the following day and after recovery to baseline for at least 24 hours. If this scenario occurs, the PK sample should be collected just before the start of the further infusion. A second PK sample should also be collected before the end of the further infusion.

Table 10.2: 2 Time schedule for PK and biomarker blood sampling for Phase Ib-No longer applicable per CTP v4.0

Treatment Course (each cycle is 14 days)	Visit	Visit No.	Day	Time Point[a] [hh:min]	CRF Time /PTM	Event	PK[b]	ADA	Nab	Plasma for cell death biomarker	Plasma for cfDNA[e]
Pre-Cycle 1	SCR	001	-28 to -5	0:00	0:00	Blood sampling				X[d]	
Cycle 1	C01_D1	101	1	Just before Start of standard of care treatment	-48:05	Blood sampling				X	X
				Start of standard of care treatment	-48:00	Bevacizumab and/or FOLFIRI infusion	---				
	C01_D3	103	3	Just before Start of BI 905711 infusion (SOI)	-0:05	Blood sampling	X	X	X	X	
				SOI	0:00	infusion	---				
				Immediately before end of BI 905711 infusion (EOI)[c]	0:30	Blood sampling	X				
				7 hours post SOI	7:00	Blood sampling	X			X	
	C01_D4	104	4	24 hours post SOI[h]	24:00	Blood sampling	X			X	
	C01_D5	105	5	48 hours post SOI	48:00	Blood sampling	X			X	
	C01_D10	110	10	168 hours post SOI	168:00	Blood sampling	X			X	
Cycle 2	C02_D1	201	1	Start of standard of care treatment	-48:00	Bevacizumab and/or FOLFIRI infusion	---				X
	C02_D3	203	3	Just before (SOI)	-0:05	Blood sampling	X	X	X	X	
				0:00	0:00	SOI	---				
				Immediately before EOI	0:30	Blood sampling	X				
	C02_D5	205	5	48 hours post SOI[h]	48:00	Blood sampling	X			X	

Table 10.2: 2 Time schedule for PK and biomarker blood sampling for Phase 1b (cont) -No longer applicable per CTP v4.0

Treatment Course (each cycle is 14 days)	Visit	Visit No.	Day	Time Point[a] [hh:min]	CRF Time /PTM	Event	PK[b]	ADA	Nab	Plasma for cell death biomarker	Plasma for cfDNA[e]
Cycle 3	C03_D1	301	1	Start of standard of care treatment	-48:00	SOC infusion	---				
	C03_D3	303	3	Just before Start of BI 905711 infusion (SOI)	-0:05	Blood sampling	X	X	X	X	
				SOI	0:00	infusion	---				
				Immediately before EOI	0:30	Blood sampling	X				
				7 hours post SOI	7:00	Blood sampling	X			X	
	C03_D4	304	4	24 hours post SOI [h]	24:00	Blood sampling	X			X	
	C03_D5	305	5	48 hours post SOI	48:00	Blood sampling	X			X	
	C03_D10	310	10	168 hours post SOI	168:00	Blood sampling	X			X	
Cycle 4	C04_D1	401	1	Start of standard of care treatment	-48:00	SOC infusion	---				
	C04_D3	403	3	Just before start of BI 905711 infusion (SOI)	-0:05	Blood sampling	X			X	
				0:00	0:00	SOI	---				
				Immediately before EOI	0:30	Blood sampling	X				
	C04_D4	404	4	24 hours post SOI [h]	24:00	Blood sampling	X			X	
Cycle 6	C06_D3	603	3	Just before start of BI 905711 infusion (SOI)	-0:05	Blood sampling	X	X	X		
Cycle 8	C08_D1	801	1	Start of standard of care treatment	-48:00	SOC infusion	---				X
	C08_D3	803	3	Just before SOI	-0:05	Blood sampling	X	X	X		
Cycle 10	C10_D3	1003	3	Just before SOI	-0:05	Blood sampling	X	X	X		
Cycle 12	C12_D3	1203	3	Just before SOI	-0:05	Blood sampling	X	X	X		
Cycle 14 [d,f]	C14_D1	1401	1	Start of standard of care treatment	-48:00	SOC infusion	---				X
	C14_D3	1403	3	Just before SOI	-0:05	Blood sampling	X [f]	X [f]	X [f]		
Cycle 20, 26	C20_D1, C26_D1	2001, 2601	1	Start of standard of care treatment	-48:00	SOC infusion	---				X
	C20_D3, C26_D3	2003, 2603	3	Just before SOI	-0:05	Blood sampling	X [f]	X [f]	X [f]		

Table 10.2: 2 Time schedule for PK and biomarker blood sampling for Phase 1b (cont) -No longer applicable per CTP v4.0

Treatment Course (each cycle is 14 days)	**Visit**	**Visit No.**	**Day**	**Time Point[a] [hh:min]**	**CRF Time /PTM**	**Event**	**PK[b]**	**ADA**	**Nab**	**Plasma for cell death biomarker**	**Plasma for cfDNA[e]**
EOT[g]	EOT	9960				Blood sampling	X	X	X		X
30-Day Safety Follow-up	EOR	9970				Blood sampling	X	X	X		

PTM = Planned Time; SOI=Start of [BI 905711] Infusion; EOI= End of [BI 905711] Infusion

[a]The following windows of time are allowed for PK sampling:

1. Pre-dose (PTM -0:05): within 1 hour before next drug infusion/drug administration.
2. 7h: within ± 15 min of designated time
3. 24- 48h: within ±60 min of designated time.
4. 168h ±24 hour

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

[b]PK sample will not be collected from CRC cohort Arm B patient

[c]In the event that infusion duration is >60 minutes longer than planned, the subsequent time points for PK blood collection on the day of drug infusion should be adjusted accordingly.

[d]At least one pre-dose plasma sample for cell death biomarker analysis of caspase activity needs to be collected.

[e] Plasma samples will be collected to isolate circulating nucleic acids (e.g., cfDNA) from plasma: at C1D1 before treatment, C2D1, C8D1, C14D1, C20D1, C26D1 (every 6 cycle thereafter) and EOT after treatment.

[f]PK, ADA and NAB sampling is to be collected pre-dose (-0:05) at Day 3 of Cycle 14 and every 3 months thereafter (Cycle 20, Cycle 26, etc.).

[g]If the patient will not continue treatment in the next scheduled cycle, pre-dose sampling scheduled for Day 3 of the next cycle needs to be performed at the EOT visit.

[h]Per section 4.2.4.1, if less than 50% of the planned dose of BI 905711 was administered due to an infusion-related reaction, a further dose of 50% of the intended total dose may be administered on the following day and after recovery to baseline for at least 24 hours. If this scenario occurs, the PK sample should be collected just before the start of the further infusion. A second PK sample should also be collected before the end of the further infusion.

10.3 STATISTICAL APPENDIX INCLUDING MODEL PERFORMANCE AND DATA SCENARIOS

A BLRM with overdose control will be used to guide dose escalation. The model is introduced in Section 7 including prior specifications for the model. After patients in each cohort have completed at least the MTD evaluation period, the prior distribution will be updated with the accumulated DLT data from the MTD evaluation period. Posterior probabilities for the rate of DLTs will be summarised from the BLRM. Selection of the next dose level will be based on these probabilities as well as on other safety and laboratory data.

The purpose of this statistical appendix is to present performance metrics (operating characteristics) that illustrate the precision of the design in estimating the MTD under various dose-toxicity relationships through computer simulation. These results are summarised in Table 10.3:3. In addition, recommendations of the next dose level by the BLRM with overdose control principle are also provided under various hypothetical outcome scenarios to show how it facilitates on-trial dose-escalation decisions (see Table 10.3: 1). For simplicity reasons, a cohort size of 3 patients who are all evaluable is assumed.

The simulations for scenarios and operating characteristics were produced using ***R version 4.0.2 and Jags version 4.3.0.***

Hypothetical data scenarios for dose escalation
Hypothetical data scenarios are shown in Table 10.3: 1. These scenarios reflect potential on-trial data scenarios and related escalation as allowed by the model, the probability of overdose for the current dose level, as well as the next potential dose level and related probabilities of DLT rate falling into the under toxicity, target toxicity and over toxicity intervals.

For example, Scenario 1 represents the case where 3 patients were treated in 1412-0003 trial with no DLTs and the current dose level in 1412-0003 trial is 0.6 mg/kg. Given this information, the posterior probability of over-dose for the current dose level in 1412-0003 trial is 0.008, which is under the EWOC threshold. In this case, the BLRM recommendation is to escalate to 1.2 mg/kg.

Scenario 2 shows to stay at the current dose level and enroll more patients when the first DLT occurs out of 3 patients in the first dose level cohort.

Similarly, in scenario 3 when no DLT occurs out of 3 patients in the first two cohorts, the BLRM recommends escalating to the next dose level.

Scenarios 4, 8 and 9 show examples of staying at the current dose level with 1 DLT out of 3 patients and continue to observe more patients. The probability of over-dose for the current dose level in scenario 4 trial is 0.104, which is under the EWOC threshold.

Scenarios 6, 7 show that with 0 DLT up to the current dose level, the model's recommendation is to escalate to the next dose level which over-dose is under control.

Scenario 10 shows to deescalate to the previous dose and continue the trial when 2 out of 3 patients had DLT at the current dose level.

Scenario 11 illustrates potentially observed data adding on to Scenario 10 can conclude the MTD reached at dose level 3.6 mg/kg.

Table 10.3: 1 Hypothetical data scenario for dose escalation

Scenario	Dose (mg/kg)	# Pat	# DLT	Current Dose: P(OD)	Next recommended dose based on EWOC and escalation rule	Next recommended dose		
						P(UD)	P(TD)	P(OD)
1	0.6	3	0	0.008	1.2	0.888	0.079	0.032
2	0.6	3	1	0.183	0.6	0.553	0.264	0.183
3	0.6 1.2	3 3	0 0	0.008	2.4	0.779	0.146	0.075
4	0.6 1.2	3 3	0 1	0.104	1.2	0.629	0.267	0.104
5	0.6 1.2	3 6	0 1	0.035	2.4	0.428	0.334	0.238
6	0.6 1.2 2.4	3 3 3	0 0 0	0.015	3.6	0.675	0.185	0.140
7	0.6 1.2 2.4 3.6	3 3 3 3	0 0 0 0	0.031	4.8	0.684	0.180	0.136
8	0.6 1.2 2.4 3.6	3 3 3 3	0 0 0 1	0.212	3.6	0.458	0.330	0.212
9	0.6 1.2 2.4 3.6 4.8	3 3 3 3 3	0 0 0 0 1	0.208	4.8	0.463	0.330	0.208
10	0.6 1.2 2.4 3.6 4.8	3 3 3 3 3	0 0 0 0 2	0.588	3.6	0.443	0.414	0.143
11	0.6 1.2 2.4 3.6 4.8	3 3 3 6 3	0 0 0 1 2	0.171	3.6	0.308	0.522	0.171

Operating characteristics

Operating characteristics are a way to assess the long-run behaviour of a model. Under an assumed true dose-toxicity curve, metrics such as the probability of recommending a dose with true DLT rate in the target interval can be approximated via simulation. Table 10.3:2 describes 5 assumed true dose-toxicity scenarios which were used to assess the operating characteristics of the model. These scenarios reflect a wide range of possible cases as follows:

- Scenario 1: aligned with prior means
- Scenario 2: high-toxicity scenario
- Scenario 3: low-toxicity scenario
- Scenario 4: non-logistic dose-toxicity scenario
- Scenario 5: low-toxicity followed by high-toxicity
- Scenario 6: high toxicity followed by extremely toxic scenario

Table 10.3: 2 Probability of having a DLT under the assumed dose-toxicity scenarios

Scenario/Dose	0.6	1.2	2.4	3.6	4.8
1: Prior information (mean)	0.06	0.1	0.18	**0.28**	0.38
2: High toxicity	0.1	**0.2**	**0.25**	0.39	0.45
3: Low toxicity	0.01	0.02	0.04	0.1	**0.18**
4: Non-logistic	0.05	0.12	**0.2**	**0.3**	0.4
5: Low-high	0.02	0.07	**0.3**	0.36	0.45
6: Extremely toxic	**0.32**	0.36	0.40	0.45	0.50

Note: Probabilities in bold indicate the true DLT rates which fall into the targeted toxicity interval [0.16, 0.33).

For each of the five scenarios, 1000 trials were simulated. Each cohort consisted of 3 patients and dose escalation complied with the following rules: escalate to the dose which maximises the probability of the targeted toxicity region and satisfies the overdose criterion if it is ≤ 100% increase from the current dose.

The MTD was considered reached when the rules in Section 7.1 are fulfilled. If the MTD could not be reached, because already the first specified dose level was too toxic, or none of the dose levels revealed any DLTs, the simulated trial was stopped.

The simulation assessed how often a dose was declared as MTD with true DLT rate in the under-, targeted- or over-dose range. 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 10.3: 3.

Table 10.3: 3 Simulated operating characteristics

Scenario	% of trials declaring MTD with true DLT rate in			% of stopped trials	# Patients	# DLTs
	Under dose	Target dose	Over dose		Mean (Min-Max)	Mean (Min-Max)
1.Prior	27.6	62.1	8.4	1.9	15.8 (3 – 39)	2.5 (1 - 8)
2. High	13.1	71.9	8	7	14.8 (3 – 39)	3.1 (1 – 9)
3. Low	43.3	56.7	0	0	19 (12 – 45)	1.5 (1 – 6)
4. Non-logistic	33.9	58.7	6.4	1	15.6 (3 - 39)	2.6 (1 - 7)
5. Low-high	40.6	49.6	9.7	0.1	15 (3 – 33)	2.6 (1 – 8)
6. Extremely toxic	0	16.3	23.1	60.6	9.2 (3 – 27)	3.2 (1 – 8)

In Scenario 1, which reflects the case that the true dose-toxicity is aligned with the prior expectations regarding toxicity probabilities, 62.1% of the simulated trials choose the correct dose as MTD, that is a dose as MTD with the assumed true DLT rate in the target dose range.

In Scenario 2 (high-toxicity scenario), the starting dose level has 10% probability of observing DLTs in the first cohort. This would result in 7% of the simulated trials stopping due to too high toxicity.

Scenario 3 (low-toxicity scenario) shows that only the highest dose level falls in the target dose range. In this case, 43.3% of the simulated trials choose a dose as MTD, which the assumed true DLT rate is within the under-dose range. 56.7% of the simulated trials result in an MTD with the assumed true DLT rate in the target-dose range. And the probability of declaring an over toxic dose as MTD is 0%.

When the true dose toxicity curve does not follow logistic function, as shown in Scenario 4, the percentage of declaring a dose as MTD with the assumed true DLT rate in the target dose range is 58.7%.

In scenario 5, the probability of declaring MTD with the assumed true DLT rate in the target dose range is 49.6%.

In scenario 6, due to extremely high toxicity, the probability of stopping the trial is 60.6%.

The mean patient numbers range from 9.2 patients (Scenario 6) to 19 patients (Scenario 3) and the maximum number of patients was 45. Therefore, the patient numbers are as expected and increase when moving away from the high-toxicity scenario.
Overall, by reviewing the OC presented in Table 10.3: 3, it can be seen that the model is robust to different scenarios of true dose-toxicity curves. In general, the model is conservative due to the overdose control criteria. In all scenarios, the probabilities of recommending a dose with true P(DLT) ≥ 33% as MTD are much smaller than probabilities of recommending a dose with true P(DLT) between 16% and 33% as MTD.

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 BI clinical trial team and trial investigators in deciding the dose levels to be tested in order to determine the MTD estimate.

R version 4.0.2 and RStudio 1.3.959 version were used for the simulations.

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

11.1 GLOBAL AMENDMENT 1

Date of amendment		11 OCT 2021
EudraCT number **EU number**		2021-003041-37
BI Trial number		1412-0003
BI Investigational Medicinal Product(s)		BI 905711
Title of protocol		A phase Ia/b, open label, multicentre, dose escalation study of BI 905711 in combination with chemo-therapy followed by expansion cohorts in patients with advanced gastrointestinal cancers
Global Amendment due to urgent safety reasons		
Global Amendment		x
Section to be changed		Clinical Trial Synopsis, Section 3.3.2
Description of change		Inclusion criteria 13 was revised for better clarification. For CRC cohort, both Phase 1a and 1b patient need to have PD after prior oxaliplatin-based first line therapy or within 6 months after the end of oxaliplatin-based adjuvant therapy. Oredering of other inclusion criteria were also revised for better clarification.
Rationale for change		Typo correction, better clarification
Section to be changed		Flowchart
Description of change		Footnote 16 added to make it clear about EF measument during Screening.
Rationale for change		For better understanding of procedure.
Section to be changed		Flowchart
Description of change		Safety lab testing, “x” added on C1D10 and EOT.
Rationale for change		Typo correction.
Section to be changed		Flowchart footnote 6
Description of change		Revised to clearly mention that pregnancy test is needed every 2 cycles.
Rationale for change		Typo correction.
Section to be changed		Flowchart, footnote 13, Section 5.4.2.6
Description of change		Required timing to conduct [^{18}F]FDG-PET/CT during Screening was revised to 14 days (±7 days) prior to treatment start.

		Deleted requirement to complete imaging with "contrast".
Rationale for change		Typo correction.
Section to be changed		Section 1.2
Description of change		Detailed PK information from 1412-0001 added,
Rationale for change		Based on requirement from authority.
Section to be changed		Section 1.3, Section 1.4.2 and 1.4.3
Description of change		Detailed Safety information from 1412-0001 added.
Rationale for change		Based on requirement from authority.
Section to be changed		Section 3.3.2
Description of change		Inclusion criteria 6 was revised to correct typo as below. 6. Availability and willingness to provide tumor tissue (fresh biopsy <u>or</u> ~~and~~ archival)
Rationale for change		Typo correction
Section to be changed		Section 4.1.5.2
Description of change		Below point was revised for better clarification · Absence of worsening <u>(any CTCAE grade)</u> or new neurological signs/symptoms CTCAE grade <u>≥1</u> ~~≥ 2~~.
Rationale for change		Based on requirement from authority.
Section to be changed		Section 5.2.3
Description of change		Amylase added to safety lab parameter
Rationale for change		Based on authority request.
Section to be changed		Section 5.2.6.1.1
Description of change		Revised to describe more clearly, that worsening of pre-existing conditions other than the underlying disease should be reported as AE.
Rationale for change		For better clarification.
Section to be changed		Section 5.4 and 5.5
Description of change		Add explanation that China will not participate to Cell death biomarkers, gDNA, circulating free DNA and biobanking.
Rationale for change		Due to local requirement.
Section to be changed		Section 6.2.3.1
Description of change		Revised to correct typo abut rqquired timeframe

		for EOT.
Rationale for change		Typo correction.
Section to be changed		Section 10.2
Description of change		Table 10.2 footnote "c" and "e" revised to correct typo. Footnote c; …C1D~~8~~10, C2D1, C3D1, C4D1, C5D1 and EOT after treatment. Footnote e; …pre-dose sampling scheduled for Day ~~1~~3 of the next cycle needs to be performed at the EOT visit.
Rationale for change		Typo correction.

11.2 GLOBAL AMENDMENT 2

Date of amendment		22 JUL 2022
EudraCT number **EU number**		2021-003041-37
BI Trial number		1412-0003
BI Investigational Medicinal Product(s)		BI 905711
Title of protocol		A phase Ia/b, open label, multicentre, dose escalation study of BI 905711 in combination with chemo-therapy followed by expansion cohorts in patients with advanced gastrointestinal cancers
Global Amendment due to urgent safety reasons		
Global Amendment		x
Section to be changed		Clinical Trial Synopsis, Section 1.3, Section 1.4.3
Description of change		Latest information from 1412-0001 updated.
Rationale for change		Information update
Section to be changed		Clinical Trial Synopsis and relevant section.
Description of change		Liposomal Irinotecan plus 5-FU/Leucovorin added as background therapy for PDAC cohort.
Rationale for change		Based on feedback from PIs
Section to be changed		Clinical Trial Synopsis
Description of change		Below sentences added in Primary endpoint for Phase 1b. · In PDAC cohort safety run-in part: number of patients with DLTs during the MTD evaluation period assessed in the first 6 patients.
Rationale for change		To make consistent with Section 2.1.

Section to be changed		Clinical Trial Synopsis and Section 3.3.2
Description of change		Inclusion criteria 8, requirement for serum lipase updated. Specific requirement for PDAC cohort added considering patient background.
Rationale for change		Based on BI internal discussion and decision.
Section to be changed		Flowchart Phase 1a
Description of change		- Minor correction for better clarification. - Tumor marker measurement frequency has changed to every 2 cycles.
Rationale for change		For better clarification and understanding of efficacy.
Section to be changed		Flowchart Phase 1b and footnote 17
Description of change		- Minor correction for better clarification. - Tumor marker measurement frequency has changed to every 2 cycles. - PRO-CTCAE added.
Rationale for change		For better clarification, understanding of efficacy and clinical utility of a medical intervention.
Section to be changed		Flowchart Phase 1b, footnote 12,
Description of change		Visit of Cycle 2 Day 4 has changed to Cycle 2 Day 5.
Rationale for change		Based on BI internal discussion and decision.
Section to be changed		Flowchart Phase 1b, footnote 11 and 12, Section 5.4.3.1
Description of change		Requirement for provision of biopsy samples has relaxed. - Archival tissue collected within 6 months can be accepted, instead of 3 months. - Fresh biopsy are not mandatory anymore if archival tissue collected within 6 months can be provided. - An on-treatment biopsy are not mandatory anymore and switched to optional requirement. - Other minor change for better flexibility and clarification
Rationale for change		Based on feedback from PIs
Section to be changed		Section 1.2
Description of change		PK characteristic description has updated based on recent information from 1412-0001.

Rationale for change		Information updated
Section to be changed		[redacted]
Description of change		
Rationale for change		
Section to be changed		
Description of change		
Rationale for change		
Section to be changed		Section 4.1.5, Table 4.1.5.3.1
Description of change		Dose for liposaml irinotecan added. 5-FU (infusion) dose corrected.
Rationale for change		Due to additional background therapy option and typo correction
Section to be changed		Section 4.1.5, Table 4.1.5.3.2
Description of change		Dose modification instruction for interstitial lung disease and anaphylactic reaction added.
Rationale for change		Based on BI internal discussion and decision for patient safety.
Section to be changed		Section 4.2.1.1
Description of change		Regimen information of Liposomal Irinotecan plus 5-FU/Leucovorin) added.
Rationale for change		Due to additional background therapy option
Section to be changed		Section 5.1
Description of change		Tumor marker measurement frequency has changed to every 2 cycles.
Rationale for change		For better understanding of efficacy.
Section to be changed		Section 5.3.2
Description of change		Description added for analysis with leftovers sample.
Rationale for change		Based on BI internal discussion and decision for better understanding of product.
Section to be changed		Section 5.4
Description of change		Plan for biomarker analysis updated. Description which stated no sample collection for cell death biomarker, gDNA and cicurating DNA in China deleted.
Rationale for change		Based on BI internal discussion and decision for

		better understanding of product.
Section to be changed		Section 5.4.2.1
Description of change		Description added for analysis with leftovers sample.
Rationale for change		Based on BI internal discussion and decision for better understanding of product.
Section to be changed		Section 5.4.2.4
Description of change		Description added for better clarification.
Rationale for change		For better clarification,
Section to be changed		Section 5.4.2.5
Description of change		Description added for better clarification.
Rationale for change		For better clarification,
Section to be changed		Section 5.4.2.6
Description of change		Description of allowance for assessment added for better clarification.
Rationale for change		For better clarification,
Section to be changed		Section 5.4.3.2
Description of change		Description added about optional collection of pre-dose plasma samples.
Rationale for change		Based on BI internal discussion and decision for better understanding of product.
Section to be changed		Section 5.6 and Section 5.7
Description of change		Explanation of PRO-CTCAE added.
Rationale for change		For better understanding of clinical utility of a medical intervention.
Section to be changed		Section 7.2.5
Description of change		Description of further objective analyses added for PRO-CTCAE.
Rationale for change		For better understanding of clinical utility of a medical intervention.
Section to be changed		Section 7.1.8
Description of change		Safety evaluation during Phase 1b part added. Preliminary, exploratory analysis of PK and immunogenicity added.
Rationale for change		For better patient safety. Based on BI internal discussion and decision for

		better understanding of product.
Section to be changed		Section 7.2.1
Description of change		Description of iPD added.
Rationale for change		For better clarification.
Section to be changed		Appendix 10.2 Table 10.2: 1, footnote d
Description of change		Table 10.2: 1 split into two tables, Table 10.2: 1 for Phase 1a part and Table 10.2: 2 for Phase 1b part. Collection of ADA and NAB sample has changed to continue after cycle 26, instead of stop collection from cycle 26.
Rationale for change		For better clarification. Based on BI internal discussion and decision for better understanding of product.
Section to be changed		Appendix 10.2, Table 10.2: 2
Description of change		New table created specific for Phase 1b.
Rationale for change		For better clarification.

11.3 GLOBAL AMENDMENT 3

Date of amendment		27 Apr 2023
EudraCT number **EU number**		2021-003041-37
BI Trial number		1412-0003
BI Investigational Medicinal Product(s)		BI 905711
Title of protocol		A phase Ia/b, open label, multicentre, dose escalation study of BI 905711 in combination with chemo-therapy followed by expansion cohorts in patients with advanced gastrointestinal cancers
Global Amendment due to urgent safety reasons		
Global Amendment		**x**
Section to be changed		Flowcharts
Description of change		Section amended to clarify visits, assessments and procedures that are mandatory/not mandatory for ongoing patients.
Rationale for change		Recruitment in this trial was discontinued

		prematurely during the Phase I expansion cohort. Reduced procedures and assessments for ongoing patients to those needed for safety monitoring.
Section to be changed		1.3
Description of change		Added text "Based on available preliminary data from phase I clinical studies (1412.1 and 1412.3), the decision was made to terminate BI 905711 (TRAILR2/CDH17) development program. This decision is not related to any safety concerns or unfavorable benefit/risk balance, but to the lack of predictive biomarkers and the limited efficacy particularly in the context of the evolving treatment landscape for advanced CRC and other GI cancers. The purpose of CTP v4.0 is to reduce the study related activities to the minimum required to monitor patient safety and to avoid undue burden on patients."
Rationale for change		Explain rationale for CTP v4.0
Section to be changed		3.1
Description of change		Added text "Recruitment in Phase Ia is complete" Added text "Recruitment in this trial was discontinued during Phase I expansion, and no PDAC patients were enrolled in this expansion cohort."
Rationale for change		Recruitment in Phase Ia is complete. Recruitment in Phase Ib discontinued prematurely.
Section to be changed		5.1
Description of change		Updated to reflect that tumor assessments will be assessed per institutional practice, and only overall response and disease progression will be collected in the eCRF.
Rationale for change		To be consistent with flowchart revision.
Section to be changed		5.2.1, 5.2.2, 5.2.3, 5.2.4
Description of change		Physical examination, vital signs, safety labs, and ECGs will be done as per institutional practice.
Rationale for change		To be consistent with flowchart revision.
Section to be changed		5.3.2, 5.4
Description of change		Effective from CTP v4.0, PK, ADA/Nab, Biomarker, Tumor Biopsy samples and FDG-PET

		scans are no longer collected for ongoing patients.
Rationale for change		Blood, tissue samples and FDG-PET are no longer collected.
Section to be changed		6.2.3.1
Description of change		Deleted “If the patient finishes study treatment without having progressive disease, tumor assessment/imaging must be performed at the time of treatment discontinuation, unless it has been done within the past 4 weeks.”
Rationale for change		To be consistent with flowchart revision.
Section to be changed		6.2.3.3, 6.2.3.4
Description of change		Sections amended to define EOR as end of study. No further follow-up visits after EOR are required, unless follow-up is for S(AE) that occurred before EOR period.
Rationale for change		To be consistent with flowchart revision.
Section to be changed		10.2
Description of change		Sampling tables for PK and Biomarkers no longer applicable per CTP v4.0
Rationale for change		To be consistent with flowchart revision.

APPROVAL / SIGNATURE PAGE

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Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval-Biostatistics	[redacted]	27 Apr 2023 14:29 CEST
Approval-Team Member Medicine		28 Apr 2023 13:11 CEST
Approval-Clinical Trial Leader		02 May 2023 12:28 CEST
Verification-Paper Signature Completion		02 May 2023 12:32 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed