Clinical Trial Protocol

	Document Number:	**c36932219-03**
BI Trial No.	1502-0001	
BI Investigational Medicinal Product(s)	Ezabenlimab BI 765063	
Title	A Phase I open label study to assess safety, feasibility, efficacy, and biological activity of single administration of Ezabenlimab in combination with BI 765063 and Pembrolizumab in combination with BI 765063 as neoadjuvant treatments in patients with newly diagnosed surgically-resectable, locoregional colorectal cancer	
Lay Title	A study in people with colorectal cancer to test whether ezabenlimab or pembrolizumab in combination with BI 765063 lead to side effects or delays in surgery	
Clinical Phase	Phase I	
Clinical Trial Leader	[redacted] Phone: [redacted]	
[redacted] **Investigator**	[redacted]	
Current Version and Date	Version 3.0; 24 January 2022	
Original Protocol Date	2 November 2021	**Page 1 of 79**

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Original Protocol date	2 November 2021
Revision date	21 January 2022
BI trial number	1502-0001
Title of trial	A Phase I open label study to assess safety, feasibility, efficacy, and biological activity of single administration of Ezabenlimab in combination with BI 765063 and Pembrolizumab in combination with BI 765063 as neoadjuvant treatments in patients with newly diagnosed surgically-resectable, locoregional colorectal cancer
[redacted] **Investigator**	[redacted]
Trial site(s)	[redacted]
Clinical phase	Phase I
Trial rationale	Anti-SIRPα antibodies are a potential new tool for cancer immunotherapy. Preclinical data suggests that the combination of anti-SIRPα and anti-PD-1 antibodies may lead to better tumor control than either alone. There are preclinical and clinical data to suggest that neoadjuvant immunotherapy in early stages of disease may be more effective than later. A better understanding of the biological and clinical activity of combining PD-1 and SIRPα blockade in colorectal cancer (CRC), including the effect on infiltrating myeloid and lymphoid populations, is needed to inform more rational approaches to incorporating immunotherapy and other active agents in the treatment of CRC.
Trial objective(s)	**Primary objective** To investigate safety and feasibility of single administration of ezabenlimab in combination with BI 765063 and single administration of Pembrolizumab in combination with BI 765063 in patients with early stage resectable colorectal cancer in neoadjuvant setting. **Secondary objectives**

	• To investigate efficacy of the study treatments • To investigate biology activity of the study treatments **Further objectives** To define the immunodynamic effect of the combined immunotherapy regimens systemically and on the tumor immune microenvironment
Trial endpoints	**Primary endpoint(s)** The primary endpoint is a composite endpoint which estimates proportion of patients with at least one occurrence of safety or feasibility. The detailed definitions of safety and feasibility are as follows. **Safety** Safety is defined as any grade 3 or higher adverse events (according to NCI CTCAE v5.0) related to study treatments at any point within the follow up period following the administration of study treatments. **Feasibility** (delay in surgery) Feasibility or delay in surgery is defined as any treatment related adverse events (AE) leading to delays in surgery. Patients' surgery is scheduled to take place between 2 weeks and up to 6 weeks following the administration of study treatment. Any treatment related AE leading to a delay in surgery beyond the 6 weeks period following study treatment administration will be considered as a relevant AE for this endpoint. **Secondary endpoint(s)** • **Pathologic response** (PR) defined as at least 50% or more tumor regression classified as per Mandard tumor regression grading system (R21-1544), in viable adenocarcinoma cells in the surgical specimen, including lymph nodes. Pathological response includes complete pathology response (CR), near complete pathological response (near CR) and partial pathological response (R21-0915). • **Time from administration of trial treatment to surgery**, defined as the time in days that elapses between administration of neoadjuvant trial therapy and surgical resection. • **Radiographic response** on pre-surgical imaging, following receipt of the neoadjuvant therapy, as per RECIST v1.1.

Trial design	This is an open-label, two-arm, parallel group, single-center Phase 1 trial of Ezabenlimab in combination with BI 765063 (Cohort A) and Pembrolizumab in combination with BI 765063 (Cohort B) in patients with early stage resectable colorectal cancer in neoadjuvant setting.
Total number of patients	A total of approximately 50 patients will be treated in this trial
Number of patients per treatment group	25 patients per treatment group in 2 treatment groups. • 25 patients in Cohort A (Ezabenlimab/BI 754091) + BI 765063 • 25 patients in Cohort B (Pembrolizumab + BI 765063
Diagnosis	Resectable colorectal cancer (CRC)
Main inclusion and exclusion criteria	**Key inclusion criteria** Patients must satisfy all the following criteria for entry into the trial (protocol): 1. Signed and dated written informed consent in accordance with ICH-GCP and local legislation prior to admission to the trial. Ability to understand and the willingness to sign a written informed consent. 2. Male or female aged ≥ 18 years at the time of Informed Consent Form (ICF) signature. 3. Patients with histological diagnosis of resectable CRC, or radiographic/visual findings highly suggestive, with planned confirmatory biopsy. 4. CRC lesions must be at least 1 cm in largest diameter and amenable to endoscopic biopsy. 5. Patient must be willing and able to have endoscopic biopsy (Goal 3-6 core-needle or surgical/endoscopic biopsies, final number to be determined by the physician performing the procedure as safe) of tumor prior to initiation of therapy. 6. Eastern Cooperative Oncology Group (ECOG) performance status 0-1. The exception will be patients with long term disability (such as cerebral palsy) that is unlikely to significantly affect their response to therapy. 7. Patient is determined to be a surgical candidate for resection of their tumor.

8. Adequate organ and marrow function as defined below in Table 3.3.2:1.
9. Women of childbearing potential (WOCBP) 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, from signature of ICF until 6 months after administration of trial treatment. A list of contraception methods meeting these criteria is provided in the patient information. For further detail refer to Section 4.3.2.3.

Key exclusion criteria

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

1. Patients who are deemed to be at high risk for colonic obstruction and/or perforation per investigator assessment.
2. Patients eligible for neoadjuvant therapy (chemotherapy, radiotherapy, chemoradiotherapy) as standard of care.
3. Major surgery (major according to the investigator's assessment) performed within 4 weeks prior to administration of trial medication.
4. Patients who must or wish to continue the intake of restricted medications (see section 4.3.2.1) or any drug considered likely to interfere with the safe conduct of the trial.
5. Patients not expected to comply with the protocol requirements or not expected to complete the trial as scheduled (e.g. chronic alcohol or drug abuse or any other condition that, in the investigator's opinion, makes the patient an unreliable trial participant).
6. Previous enrolment in this trial.
7. Currently enrolled in another investigational device or drug trial, or less than 30 days since ending another investigational device or drug trial(s) or receiving other investigational treatment(s).
8. Patients who have had chemotherapy or radiotherapy within 6 months prior to entering the study for a different primary tumor, or those that have received locoregional therapy (radiation, chemoembolization, etc.) for the target lesion that will be biopsied and subsequently resected. Previous therapy for a different cancer (a different primary) is acceptable.
9. Prior immune checkpoint inhibitor therapy.

	10. Patients with metastatic or recurrent disease, for which the intent of surgery would not be curative. 11. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection requiring antibiotics (except antibiotics to be completed 4 weeks before initiation of treatment), symptomatic congestive heart failure, unstable angina pectoris, or psychiatric illness/social situations that would limit compliance with study requirements. 12. Patients who are pregnant or nursing or who plan to become pregnant while in the trial. 13. Has a diagnosis of primary immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the administration of trial treatment. Patients on chronic steroids (more than 4 weeks at stable dose) equivalent to ≤ 10mg prednisone will not be excluded. 14. Has active autoimmune disease that has required systemic treatment in the past 1 year (i.e. with use of disease modifying agents, corticosteroids, or immunosuppressive drugs). Replacement therapy (e.g. thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is acceptable. 15. Has any hematological malignancy. 16. Has a known additional somatic malignancy that is progressing and/or requires active treatment. Exceptions include basal cell carcinoma of the skin or squamous cell carcinoma of the skin that has undergone potentially curative therapy or in situ cervical or anal cancer, non-metastatic prostate cancer on stable dose of hormonal therapy without rising PSA, and breast cancer patients who have been treated with curative intent, who may be on hormonal therapy. 17. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the patient's participation for the full duration of the trial, or is not in the best interest of the patient to participate, in the opinion of the treating Investigator. 18. Patients with history of human immunodeficiency virus (HIV) infection who meet one or more of the following criteria; a. CD4+ count < 350 cells/µL b. Viral load > 200 copies/µL (local lab assessment) c. Not receiving antiretroviral therapy

	d. Receiving established antiretroviral therapy for less than four weeks prior to the start of study treatment e. History of AIDS-defining opportunistic infections within 12 months prior to start of study treatment Patients with a history of HIV who do not meet any of the criteria above are eligible to participate but the patient must be under the care of a HIV/Infectious Diseases specialist or a HIV/Infectious Diseases specialist must be consulted prior to inclusion. 19. Patients with a history of Hepatitis C (HCV) infection who meet one or both of the following criteria. a. Curative antiviral treatment is not complete b. HCV viral load is above the limit of quantification (HCV RNA positive) 20. Patients with chronic Hepatitis B (HBV) infection with active disease who meet the criteria for anti HBV therapy (according to local / institutional standard) who have not been adequately treated with suppressive antiviral therapy prior to initiation of study treatment. 21. History of allogeneic hematopoietic cell transplantation or solid organ transplantation. 22. Documented allergic or hypersensitivity response to any protein therapeutics (e.g., recombinant proteins, vaccines, intravenous immune globulins, monoclonal antibodies, receptor traps). 23. Neuropathy ≥ grade 2. 24. Principal Investigator believes that for one or multiple reasons the patient will be unable to comply with all study visits, or if they believe the trial is not clinically in the best interest of the patient.
Test product(s)	Ezabenlimab (BI 754091) BI 765063 Pembrolizumab
Dose	Ezabenlimab (BI 754091) 240 mg, IV, Day 1 BI 765063 [redacted] Pembrolizumab 200 mg, IV, Day 1
Mode of administration	Intravenous (i.v.) for all compounds
Duration of treatment	Single dose administration of the combination in both cohorts
Statistical methods	

	A Bayesian framework will be used to calculate the posterior probability that the Pathological Response (PR) rate is at least 15%. The 95% credible interval of the PR rate along with observed response rate and 95% confidence interval will be constructed.

FLOW CHART

		V01	V02	V03	EOS
	Screening Up to 21 days prior to D1	D1	[redacted]	[redacted]	End of Study Visit ≥91 days after D1
Informed Consent	X				
Medical history	X				
Physical exam, blood pressure, pulse rate	X	X	X	X	X
ECG	X				X
ECOG determination	X	X	X	X	X
Adverse Events	X	X	X	X	X
Concomitant Medications	X	X	X	X	X
Pregnancy Testing	X	X			
Imaging	X[1]			X[1]	
Standard Labs[2]	X[3]	X		X	
Biopsy[4]	X				
***Resected tumor collection and pathological response assessment [5]**				**X[5]**	
Research Blood		X	X	X	X
• SIRPα genotyping from blood[6]		X			
• Immune cell profiling from blood		X	X	X	X
• Soluble biomarker from plasma		X	X	X	X
• TCR sequencing from blood		X	X	X	X
• ctDNA analysis from plasma		X	X	X	X
Stool[7]	X[7]			X[7]	
Study treatment administration[8]		X			

1- Repeat imaging to be performed shortly prior to surgery. Tumor assessments must be performed according to RECIST 1.1 comparing screening and pre-surgery assessment. The same radiographic procedure(s) (e.g. CT scan, MRI) should be used throughout the trial. Tumor assessments performed prior to informed consent as part of routine clinical practice will be accepted if they meet the requirements of the protocol and are performed within the Screening visit window of 21 days prior to D1

2 - Standard labs include CBC w/differential, CMP, Magnesium, and TSH (with reflex free T4). (Refer to Section 5.2.3)

3 - All screening labs should be performed or repeated within 10 days prior to treatment initiation. (Refer to Section 5.2.3)
4 - Biopsies to include (target) 3-6 endoscopic biopsies of tumor, or as determined as safe by surgeon and/or gastroenterologist.
5 - *Resected tumor collection: Tumor tissue will be a sample from the tumor removed during the surgery. (*Note: "Resected tumor collection" is listed under V03 in the flow chart for practical reasons and should occur at the day of the surgery. All other activities will be performed prior to the surgery.)

6 - All eligible patients will be enrolled in the trial, genotyping will be performed retrospectively.
7 - Stool samples will be collected at Screening and V03 or on the day of before the surgery in a specified tube.
8 - Study treatment administration – *to be given to the patient after the study* required procedures for V01/D1have been completed.

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[redacted]

ABBREVIATIONS AND DEFINITIONS

AE	Adverse Event
AESI	Adverse Event of Special Interest
AIDS	Acquired Immuno Deficiency Syndrome
ALCOA	Attributable, Legible, Contemporaneous, Original, Accurate
ALT	Alanine Aminotransferase
AMP	Auxiliary Medicinal Products
AST	Aspartate Aminotransferase
BI	Boehringer Ingelheim
CA	Competent Authority
CBC	Complete Blood Count
CD172	SIRP Alpha monoclonal antibody
CI	Confidence Interval
CRA	Clinical Research Associate
CRC	Colorectal Cancer
CRF	Case Report Form, paper or electronic (sometimes referred to as “eCRF”)
CR	Complete response (complete pathological response)
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	Circulating Tumor DNA
CTLA - 4	Cytotoxic T-Lymphocyte associated protein 4
CTM	Clinical Trial Manager
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
CyTOF	Cytometry by Time of Flight
DBL	Database Lock
DILI	Drug Induced Liver Injury
DLT	Dose Limiting Toxicity
dMMR	deficient Mismatch Repair
DRC	Data Review Committee
EC	Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form

eDC	Electronic Data Capture
EGFR	Epidermal Growth Factor Receptor
EOS	End of Study (corresponds with End of Trial)
FC	Flow Chart
FIH	First In Human
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HA	Health Authority
HAART	Highly Active Antiretroviral Therapy
HBV	Hepatitis B
HCC	Hepato Cellular Carcinoma
HCV	Hepatitis C
HIV	Human Immunodeficiency Virus
IB	Investigator's Brochure
ICF	Informed Consent
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IgG4	Immunoglobulin G4
IMP	Investigational Medicinal Product
irAEs	Immune Related Adverse Events
IRB	Institutional Review Board
iRECIST	Guidelines for Response Criteria in Immunotherapies
IRR	Infusion Related Reactions
IRT	Interactive Response Technology
ISF	Investigator Site File
IUD	Intrauterine Device
IUS	Intrauterine Hormone-Releasing System
i.v.	Intravenous
IV	Intravenous
LPLT	Last patient last treatment
mAb	Monoclonal Antibody
MDSC	Myeloid Derived Suppressor Cell
MICSSS	Multipexed Immunohistochemical Cosecutive Staining on a Single Slide

MedDRA	Medical Dictionary for Drug Regulatory Activities
MoA	Mechanism of action
MSI-H	Microsatellite Instability - High
MSI-L	Microsatellite Instability – Low
MSS	Microsatellite Stable
OE	Outcome Events
ORR	Overall Response Rate
PCR	Polymerase Chain Reaction
PD-1	Programmed Cell Death 1
PI	Principal Investigator
pMMR	proficient Mismatch Repair
PK	Pharmacokinetics
PR	Pathological Response
q3W	Every 3 weeks
RA	Regulatory Authority
RMP	Risk Management Plan
RNASeq	RNA sequencing
SAE	Serious Adverse Event
scRNASeq	Single cell RNASeq
SIRPα	Signal Regulotory Protein Alpha
SMC	Safety Monitoring Committee
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reactions
TAM	Tumor associated macrophages
TCR	T-Cell Receptor
TMB	Tumor Mutational Burden
TME	Tumor Microenvironment
TSAP	Trial Statistical Analysis Plan
ULN	Upper limit of normal
VEGF	Vascular Endothelial Growth Factor
WES	Whole Exome Sequencing
WOCBP	Woman of childbearing potential

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

1.1.1 Colorectal Cancer (CRC)

Colorectal cancer is one of the most common and deadly cancers worldwide, with over 1.5 million new cases and over 800,000 deaths annually (R21_1422). In the US, 75% of patients are diagnosed with locoregional disease, while the remainder are diagnosed with advanced or metastatic disease (R21-1418). Five-year survival for locoregional disease is over 70%, while five-year survival of metastatic disease is just 14% (R21-1418).

Surgery is the indicated procedure for eligible patients with locoregional disease. Histological assessment of the resected specimen and regional lymph nodes aid in risk stratification. Stage II and Stage III disease are distinguished by the presence of involved lymph nodes. Adjuvant chemotherapy after surgery is generally recommended for those with Stage III disease and those with high-risk Stage II disease, as determined by clinical and histological factors. Nevertheless, a significant portion of patients relapse after surgery, and adjuvant chemotherapy only confers a modest absolute survival benefit of 5-10% (R21-1553).

Advanced and metastatic CRC is treated with systemic chemotherapy. Frontline chemotherapy typically consists of a fluoropyrimidine-based doublet with or without a targeted anti-VEGF or anti-EGFR agent. Anti-PD-1 antibodies are an option for patients with deficient mismatch repair or microsatellite instability-high (dMMR/ MSI-H) status. Clinical trials have demonstrated that dMMR/ MSI-H CRC has a response rate of 30-50% to anti-PD-1 monotherapy, while those with proficient mismatch repair or microsatellite instability-low (pMMR/MSI-L) do not respond to any immunotherapy monotherapy or combinatorial approaches (R16-1497, R18-1746). Combination therapy with an anti-PD-1 and anti-CTLA-4 agent is approved in the dMMR/MSI-H population (R18-1746, R21-1971).

1.2 DRUG PROFILE

BI 765063 (anti-SIRPα mAb)

BI 765063 is a humanized IgG4 monoclonal antibody that targets the human SIRPα (CD172) protein, thus antagonizing the CD47/SIRPα interaction.

SIRPα is a receptor protein expressed primarily on myeloid cells (including macrophages and dendritic cells). When activated by its ligand, the surface marker CD47 inhibits phagocytosis of the signaling cell. CD47 is expressed in normal tissue cell types and is often overexpressed by many types of tumor cells. The interaction of CD47 with SIRPα is considered a “do not eat” signal and induces tumorigenic environment, polarizing intratumoral myeloid cells towards a more regulatory/immunosuppressive phenotype.

BI 765063 is being investigated in the dose escalation/dose expansion trial 1443-0001 in patients with advanced cancer. The dose escalation part of the trial 1443-0001 has been fully enrolled. BI 765063 was well tolerated, both as a single agent up to [redacted] and in

combination with ezabenlimab up to [redacted], with no reported Dose Limiting Toxicities (DLTs) and a dose of [redacted] was identified for further study. BI 765063 was well tolerated as a monotherapy with the exception of IRR (infusion related reaction) occurring during the first infusion in approximately 47% of the patients. These IRR were mostly G1/G2 with the exception of a single Grade 3 event and were easily manageable with antihistamines and acetaminophen. Limited safety data from Phase I clinical development have not raised any safety concerns for BI 765063 monotherapy or the combination with ezabenlimab. The safety profile of the combination therapy has been consistent with what is expected based on the safety profiles of both monotherapies.

Preliminary anti-tumor activity was observed, with 1 patient with heavily pre-treated HCC experiencing a durable response (significant PR > 1 year) after monotherapy with [redacted] BI 765063. Two additional PRs in patients with microsatellite stable (MSS) endometrial cancer and a third iRECIST PR in a patient with MSS colorectal cancer were observed in the combination portion of the study. [redacted] dose forward for further study.

There are two major alleles of SIRPα, V1 and V2, and BI 765063 strongly binds to V1 alleles, while it only weakly binds to V2 alleles. In pre-clinical experiments, BI 765063 antagonizes CD47 binding to SIRPα on V1/V1 and, to much lower extent, V1/V2 on human monocytes; the magnitude of the effect was much greater for SIRPα V1/V1. No effect is expected on V2/V2 allele combination. SIRPα V1 and V2 allele frequencies can differ by geographic location. For the US population, the expected V2/V2 allele frequency is approximately 24%, The allele frequency for V1/V2 and V1/V1 is expected to be 36% and 40%, respectively.

For a more detailed description of the BI 765063 profile, please refer to the current Investigator's Brochure (c29693380).

Ezabenlimab (anti-PD-1 mAb)

Ezabenlimab is an IgG4 antibody which binds to PD-1 expressed on T cells. Ezabenlimab binding disrupts PD-1 interaction with the inhibitor ligand, PD-L1, which is expressed on a variety of cells including cancer cells.

As of July 2021, 117 patients with advanced/metastatic solid tumors have been treated with single agent Ezabenlimab. Of these, 108 patients were treated with the recommended Phase II dose of 240 mg every three weeks. Ezabenlimab demonstrated preliminary efficacy (ORR of approximately 15%) and was very well tolerated in this heterogeneous late stage patient population with a safety profile similar to other immune checkpoint inhibitors. Additionally, more than 800 patients have been treated with ezabenlimab in combination with other agents. The currently available ezabenlimab clinical data demonstrate that ezabenlimab is well tolerated. Recommended dose for further investigation was determined to be 240 mg once every 3 weeks

For a more detailed description of the ezabenlimab profile, please refer to the current Investigator's Brochure (c07895879).

Pembrolizumab (brand name Keytruda, anti-PD-1 mAb)

Pembrolizumab also binds to PD-1 expressed on T cells. It is approved for medical use in the United States and in other countries to treat several kinds of cancers.
For this trial, locally commercially available pembrolizumab will be used by the investigational site.
For a more detailed description for pembrolizumab, please refer to the US Package Insert.

Follow up period

The follow up period of ezabenlimab in combination with BI 765063 and pembrolizumab in combination with BI 765063 is 90 days. This is the period after the single dose administration that measurable drug levels and/or pharmacodynamic effects are still likely to be present.

1.3 RATIONALE FOR PERFORMING THE TRIAL

Anti-PD-1 checkpoint inhibitors have demonstrated efficacy in a variety of cancer types, including CRC. However, the role of anti-PD-1 agents in CRC is currently confined to a narrow subset of patients—namely, those with unresectable tumors with dMMR/MSI-H status. The prevalence of dMMR/MSI-H status among CRC patients is about 10 - 15% overall, while the prevalence is just 5% among those with Stage IV disease (R21-1420). In fact, the majority of CRC are pMMR/MSI-L, a category of tumors which have negligible response rates to anti-PD-1 monotherapy in the metastatic setting (R16-1497). However, data from patients with non-metastatic colon cancer (stage I, II, or III) indicate that patients with MMR-proficient tumors may benefit from a neoadjuvant treatment with ipilimumab and nivolumab (R21-0915). Additionally, though significant radiographic responses are not seen in clinical trials, it remains to be shown whether there are dynamic and/or beneficial changes to the tumor immune microenvironment in patients treated with PD-1 blocking antibodies. A better understanding of the activity of PD-1/PD-L1 blockade in CRC, and the effect on infiltrating myeloid and lymphoid populations, is needed to inform more rational approaches to incorporating immunotherapy and other active agents in the treatment of CRC.

The cancer-immune cycle provides a framework for conceptualizing how tumors evade the immune system, and where therapeutic interventions may restore effective anti-cancer immunity (R14-5099). It has been observed, for example, that dMMR/MSI-H CRCs are heavily infiltrated by cytotoxic T lymphocytes, but that they also overexpress inhibitory immune checkpoints such as PD-1 and PD-L1 (R21_1610). Thus, PD-1 blockade may be particularly effective for unleashing the pre-existing immune response against this tumor subtype, if immunosuppressive effects of the tumor can also be disrupted.

Tumor associated macrophages (TAMs) have come to light as an influential, heterogeneous, immune cell subclass within the tumor microenvironment (TME). Earlier studies identified conflicting associations between TAMs and prognosis in CRC (R21-1688, R21_1609). More recent work has recognized that macrophage subtypes matter; pro-inflammatory M1-like macrophages are associated with improved outcomes, while anti-inflammatory M2-like macrophages are associated with worse outcomes (R21-1607, R21-1608, R21-1616). The TME appears to promote polarization of macrophages towards pro-tumor phenotypes which contribute to several of the hallmarks of cancer, including angiogenesis (R21_1615), metastasis (R21-1614), and an immunosuppressive TME replete with inhibitory checkpoints (R21_1613, R21-1612), and regulatory T cells (R10-5119). Consequently, TAMs and pathways regulating their polarization between pro- and anti-tumor phenotypes have become targets of interest in cancer immunotherapy (R21-1611, R18_3350, R21-1601).

Signal regulatory protein α (SIRPα) is a transmembrane protein expressed by macrophages which binds to CD47 expressed by target cells—the so-called “don’t eat me” signal—and inhibits phagocytosis. In preclinical models, anti-CD47 antibody induced phagocytosis of cancer cells by macrophages, led to increased priming of cytotoxic T lymphocytes and enhanced anti-cancer immunity (R18_3292, R21-1600). Clinical trials of an anti-CD47 antibody combined with rituximab and azacitidine have shown promising results in lymphoma (R20-0311) and myelodysplastic syndrome/acute myeloid leukemia (R21-1681), respectively. In a preclinical study of an anti-SIRPα antibody, investigators demonstrated that the antitumor effect of the antibody was mediated by macrophages, and that the effect of the antibody was to

increase the ratio of M1 to M2 macrophages (R18-2348). Furthermore, the combination of anti-SIRPα and anti-PD-1 antibodies led to better tumor control than either alone, lending further credence to potential synergy.

[redacted] Based on the safety and tolerability of the combination of ezabenlimab (anti-PD-1) and BI 765063 (anti-SIRPα) demonstrated in a first-in-human (FIH) dose escalation trial 1442-0001 (P21-08940), we propose advancing the combination to the neoadjuvant setting to assess safety, feasibility, efficacy and influence on biomarkers in an exploratory manner. Pembrolizumab in combination with BI 765063 is included in the design as an exploratory treatment arm for hypothesis generation. There are preclinical and clinical data to suggest that neoadjuvant immunotherapy may be more effective than adjuvant (R21-1599, R21-1682). The expansion of tumor-specific cytotoxic T cells associated with neoadjuvant therapy may confer protection from metastatic disease (R21-1682, R21-1683). In addition, survival benefit to immunotherapy has been shown to indirectly correlate with tumor burden, potentially related to decreased heterogeneity of clones in locoregional versus metastatic disease (R21-1684, R21-1681).

1.4 BENEFIT - RISK ASSESSMENT

1.4.1 Benefits

Anti-PD-1 checkpoint inhibitors have demonstrated efficacy in a variety of cancer types and at different stages of disease development, including as neoadjuvant treatment.

BI 765063 blocks SIRPα on the SIRPα/CD47 pathway, a receptor strongly expressed by myeloid cells, including macrophages. It restores effector functions of these cells, an activity that promotes the immune surveillance. It helps modify tumor associated macrophages (TAMs) and MDSC associated with a poor prognosis, possibly by transforming them into cells with "anti-tumor" (pro-inflammatory) properties.

As monotherapy, [redacted] (modifying the phenotype and function of myeloid derived suppressor cells [MDSCs], increasing myeloid chemokine secretion and T-cell infiltration in tumor core, decreasing exhausted T-cells).

As mentioned above, neoadjuvant immunotherapy may confer protection from metastatic disease. [redacted]

This trial is an opportunity to show that the benefits observed with checkpoint inhibitors and anti-SIRPα treatments in animal models will benefit CRC patients in the neoadjuvant setting. With this trial, we intend to show this by evaluating pathological response and safety of the

combinations. It is hoped that any efficacy from this treatment, [redacted].

1.4.2 Risks

Table 1.4.2: 1 displays the anticipated side effects of the study drugs, based on the mechanism of action, observed clinical data from ongoing studies, and published clinical data for drugs targeting SIRPα and PD-1 as well as the risk of trial procedures.

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 Products BI 765063 and ezabenlimab		
Unexpected adverse events and laboratory abnormalities	Due to limited clinical experience of the drugs.	Close monitoring of the data to ensure timely detection and reporting of any unexpected event. A Data Review Committee (DRC) will evaluate safety, feasibility, efficacy and biomarker results as available.
Immune-related adverse events (irAEs)	irAEs are associated with immune mediated mode of action and can be potentially severe.	Recommendations for the management of irAEs are provided according to international guidelines and product labels of approved PD-1 inhibitors [P19-00269]
Infusion related reactions (IRR)	As with any mAb, hypersensitivity reactions to study medication administration are possible and they are potentially severe.	Patients with history of severe hypersensitivity reactions to other mAbs are excluded. Recommendations for the management of infusion related reactions are given in Section 5.2.6.1.4
Drug Induced Liver Injury (DILI)	Rare but can be a potentially severe event, thus, under constant surveillance by sponsors for all drugs in development.	Timely detection, evaluation, and follow-up of laboratory alterations in selected liver laboratory parameters to ensure patients' safety.
Trial procedures		
Biopsies	Patients may experience biopsy related AEs such as pain or bleeding.	Site has to be selected based on ability and experience in performing all required trial procedures.

Possible or known risks of clinical relevance for this trial	Summary of data, rationale for the risk	Mitigation strategy
		The risks are clearly explained in the informed consent document.
Delay in surgery	Treatment related adverse events leading to delays in surgery	Patient will be monitored on an ongoing basis by the DRC for safety including treatment related events that may lead to a delay in surgery. The frequency of these events will be monitored, and enrolment will be adapted accordingly.

Potential risks related to BI 765063:

Based on its characteristic or mechanism of action, the primary safety concerns of SIRPα antagonism by BI 765063 are immune-related adverse events, infusion reactions and embryo-fetal toxicity. The 1443-0001 study is the FIH study to investigate BI 765063. Preliminary clinical safety information indicates that BI 765063 monotherapy in patients with advanced metastatic cancer is well tolerated with no reported DLTs or treatment related death.

Infusion-related reactions (IRRs) were reported by approximately half of the patients in the BI 765063 monotherapy dose escalation part of trial 1443-0001, when premedication prior to cycle 1 was not allowed. The majority of the IRRs were grade 1 to grade 2 and were well manageable. Pre-medication with an antihistamine and acetaminophen or paracetamol prior to cycle 1 resulted in a markedly reduction of IRR (as observed in the BI 765063 dose escalation in combination with fixed dose ezabenlimab part of trial 1442-0001).

Potential risks related to ezabenlimab:

Based on its mechanism of action, the primary safety concerns of PD-1 antagonism by ezabenlimab are immune-mediated adverse reactions, infusion reactions, and embryo fetal toxicity. Preliminary clinical safety information indicates that ezabenlimab monotherapy in patients with advanced metastatic cancer is well tolerated with no reported dose limiting toxicities (DLTs), treatment related SAE or treatment related deaths.

The available safety data from these patients suggests that treatment with ezabenlimab is anticipated to have a similar adverse events pattern to the currently marketed anti-PD-1 mAbs, with immune related adverse events (irAEs) as the most common AEs. These side effects are well manageable with validated guidelines.

Developmental and reproductive toxicology studies have not been conducted with ezabenlimab. Based on animal models, the PD-1/PD-L1 pathway is involved in the induction of maternal immune tolerance to allogenic fetal tissue, and therefore, is important in the maintenance of pregnancy. Administration of ezabenlimab is not expected to affect fertility

but may increase the risk of abortion and premature infant death if administered to pregnant women. Therefore, pregnant women are to be excluded from clinical trials and contraception measures as described in the informed consent have to be observed.

Potential risks related to pembrolizumab:

Potential risks related to pembrolizumab have been described. Please refer to the US Package Insert.

Potential risks related to the combination of BI 765063 and ezabenlimab / pembrolizumab:

Owing to the mechanism of action of each product and given that BI 765063 may potentiate the effect of ezabenlimab / pembrolizumab by increasing the adaptive immune effectors, special attention will be given to potential increase in irAEs in patients receiving the combination treatment.

Immune-related AE management guidance will be provided in the Section 5.2.6.1.4. Infusion-related reactions have been reported with checkpoint inhibitor treatment (as for all protein therapeutics). These reactions occur infrequently and are typically managed based on symptoms using treatments ranging from treatment with histamine antagonists, in mild cases, to administration of epinephrine, when symptoms of anaphylaxis are detected.

Potential risks related to COVID-19:

Based on their mode of action, the trial drugs are not expected to have a relevant impact on the susceptibility to or the course of an infection.

In case of a confirmed infection, trial treatment will not be provided and appropriate measures for monitoring, treatment and quarantine will be implemented. The patient may be treated following recovery from a SARS-CoV-2 infection if the patient is expected to derive clinical benefit, as agreed between the investigator and sponsor.

In case of an increased risk of SARS-CoV-2 infection due to the physical visits to the sites, the visits should be avoided where the investigator judges that this is the safest course of action. These measures ensure the safety of the patients throughout the trial, maintain the integrity of the trial and will not affect the benefit-risk ratio of BI 765063 given in combination with ezabenlimab or pembrolizumab.

1.4.3 Discussion

The risk-benefit relationship has been carefully considered in the planning of the trial. Based on the pre-clinical and clinical data available to date on the Investigational Medicinal Products (IMPs), the conduct of the trial is considered justifiable using the doses and dose regimens of the IMPs as specified in this CTP.

Patients will receive a single administration of trial medication (either a single dose ezabenlimab in combination with BI 765063 or a single dose pembrolizumab in combination

with BI 765063). Therefore, temporary or permanent discontinuation of trial treatment is not applicable in this trial. However, there is a remaining possibility that the administration of trial medication will be temporary or permanently discontinued during the infusion (administration) of trial medication or between the administration of the two combination drugs due to safety reasons or due to withdrawal of informed consent. It is expected that the safety risks associated with repeated exposure will not be a factor in this trial.

Respective risk mitigation measures, with regard to the expected potential adverse drug reactions to the IMPs and study procedures, have been implemented in the current clinical study. The measures taken during the trial to mitigate the risks are:

A Data Review Committee (DRC) will be established to oversee and assess the progress of the clinical trial, specifically for safety, feasibility, efficacy and biomarker results as available. Please see section 3.1

- The safety of the patients will be monitored continuously. All SAEs, irAEs, and adverse events of special interest (AESI) will be closely followed and reviewed with the DRC as necessary.
- Guidance in case of irAEs have been defined in the trial protocol.
- Regular clinical and biological monitoring of patients and their data will be performed during the study period by the investigators and the sponsor.
- In order to avoid a delay in surgery, study treatment will be provided as soon as possible. The results from the biomarker assessments will not be immediately available. Study treatment will be provided as soon as possible and will not be delayed by the availability of the biomarker assessment results (e.g. genotyping).

Considering the medical need for the development of a better tolerated and more effective treatment for patients with CRC, [redacted]

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

2.1.1 Main objectives

Primary objective:

The primary objective of the trial is to investigate safety and feasibility of single administration of ezabenlimab in combination with BI 765063 and single administration of pembrolizumab in combination with BI 765063 in patients with early stage resectable colorectal cancer in neoadjuvant setting.

The proportion of patients experiencing a safety and feasibility event at any time will be estimated for each arm. This is defined as a composite of whether treated patients experience one or more treatment-related events of the following types: grade 3 and higher adverse event

(according to NCI CTCAE v5.0) or treatment related adverse events leading to delays in surgery.

Secondary objectives:

- To investigate the efficacy of the study treatments.

Exploratory objectives:

- To investigate the biological activity of the study treatments.

2.1.2 Primary endpoint(s)

The primary endpoint is a composite endpoint which estimates proportion of patients with at least one occurrence of a safety or feasibility event. The detailed definitions of safety and feasibility are as follow.

Safety

Safety is defined as any grade 3 or higher adverse events (according to NCI CTCAE v5.0) related to study treatments at any point within the follow up period following the administration of study treatments.

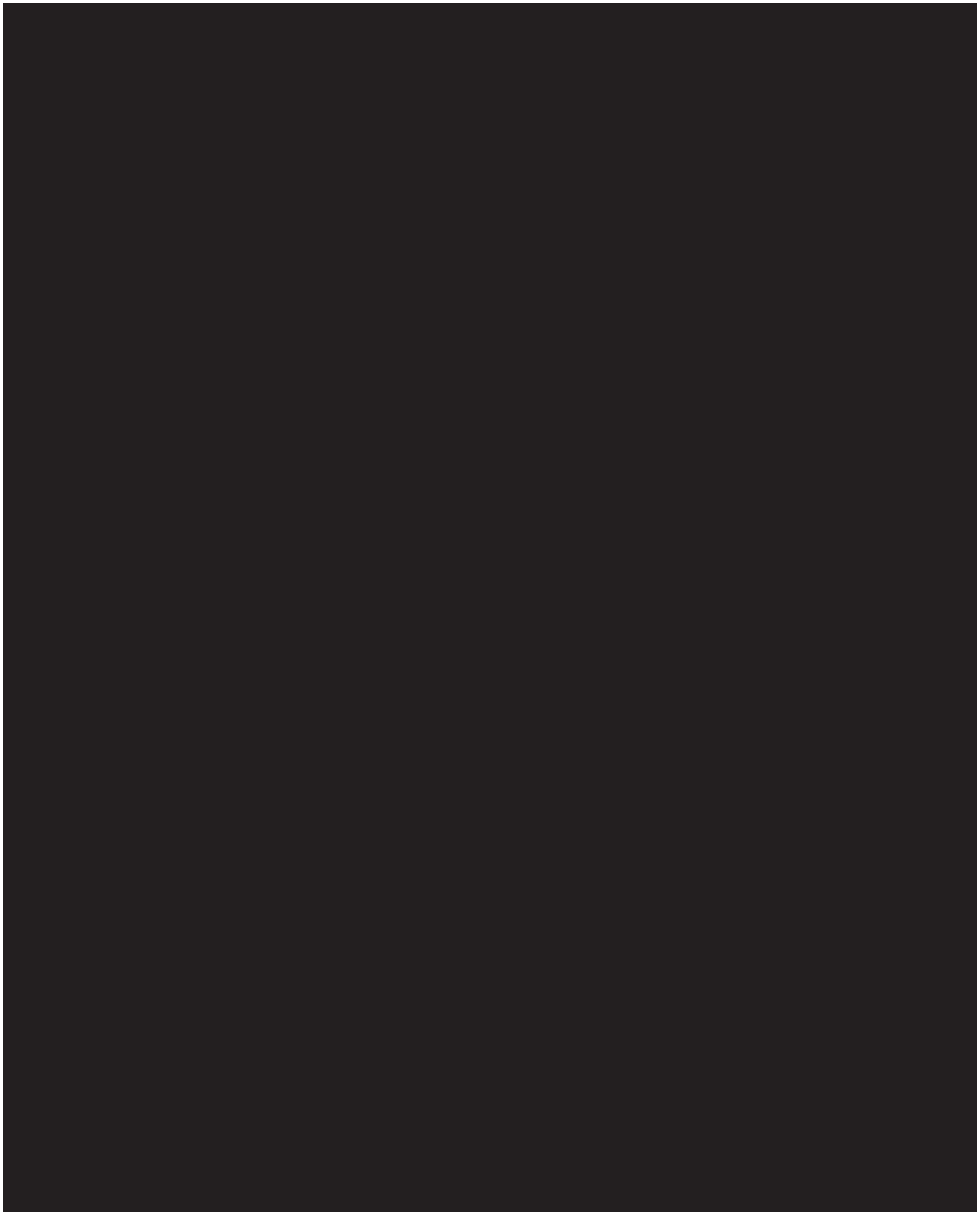
Feasibility (delay in surgery)

Feasibility or [redacted]

Patient's surgery is scheduled to take [redacted] following the administration of study treatment. [redacted]

2.1.3 Secondary endpoint(s)

- **Pathologic response** (PR) defined as at least 50% or more tumor regression classified as per Mandard tumor regression grading system (R21-1544), in viable adenocarcinoma cells in the surgical specimen, including lymph nodes. Pathological response includes complete pathology response (CR), near complete pathological response (near CR) and partial pathological response (R21-0915).
- **Time from administration of trial treatment to surgery**, defined as the time in days that elapses between administration of neoadjuvant trial therapy and surgical resection.
- **Radiographic response** on pre-surgical imaging, following receipt of the neoadjuvant therapy, as per RECIST v1.1.



3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN

This is an open-label, two-arm, parallel group, single-center Phase 1 trial of Ezabenlimab in combination with BI 765063 (Cohort A) and Pembrolizumab in combination with BI 765063 (Cohort B) in patients with early stage resectable colorectal cancer in the neoadjuvant setting. Patients will be assigned alternatingly (sequentially one by one) to either of the cohorts and will receive one-time either of the combination treatments.

This trial is exploratory by design. Both treatment cohorts are considered exploratory. Analyses performed are intended to be descriptive, and supportive of further investigation. Pembrolizumab in combination with BI 765063 is included in the design as an exploratory treatment arm for hypothesis generation. The study is planned to treat 25 patients in each arm. For details of sample size calculation please see section 7.5.

An overview of the trial procedures is shown in Figure 3.1: 1.

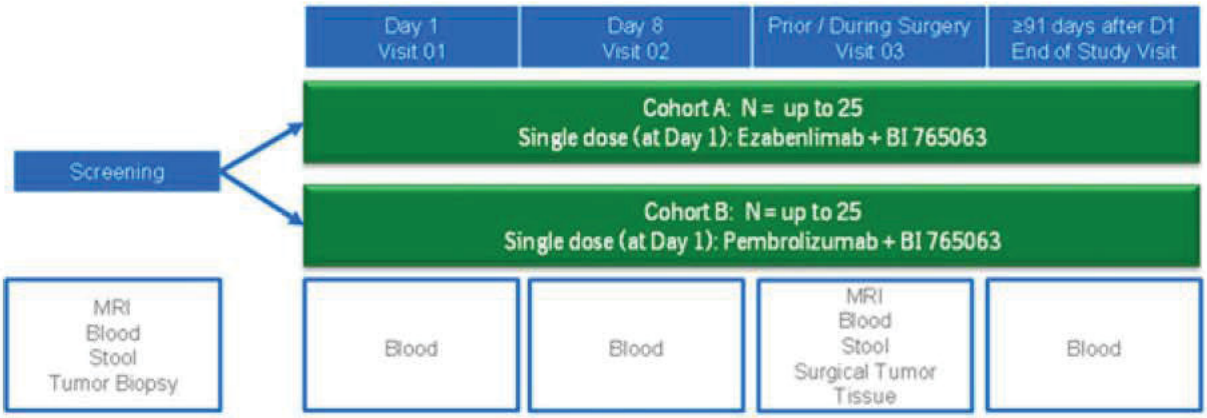


Figure 3.1: 1 Overview of trial procedures (Visits, Cohorts, Imaging and Biomarker sampling)

Patients will be enrolled (screened) in the trial once they have signed the informed consent form. In addition to the medical assessment, tumor tissue (via biopsy), blood and stool will be collected during the screening visit.

Patients who meet all eligibility criteria will be treated with one dose of ezabenlimab in combination with BI 765063 or pembrolizumab in combination with BI 765063.

After the patient completes the treatment, safety assessment will be conducted and blood and stool will be collected as indicated in the flow chart.

[redacted]

After the end of the 90 days follow-up period, an end of study (EOS) visit will be conducted in order to perform safety assessments and to collect blood for research assessment.

For more details please refer to the flow chart and section 6.2.

Table 3.1:1 Study treatments and schedules

Study Treatments				
Agent	**Cohort**	**Dose**	**Route**	**Schedule**
Ezabenlimab	Cohort A	240 mg	IV	Day 1 only
Pembrolizumab	Cohort B	200 mg	IV	Day 1 only
BI 765063	Cohort A and B	[redacted]	IV	Day 1 only

3.1.1 Data review committee (DRC)

A total of approximately 50 patients will be treated in this trial, i.e. approximately 25 patients in each arm. A Data Review Committee (DRC) will be established to oversee and assess the progress of the clinical trial, specifically for safety, feasibility, efficacy and biomarker results as available. The DRC will operate according to specifications defined in a separate DRC charter.

The DRC will consist of the following members:
- Principal Investigator (PI), decision maker
- BI Safety physician (pharmacovigilance officer), decision maker
- BI Clinical Program Leader (CPL), decision maker,
- BI Statistician (Stat), participates if needed
- BI Clinical Trial Leader (CTL), participates if needed

All members can be represented by a deputy.

The first scheduled DRC meeting to review data will take place after approximately 5 patients in each arm have been treated, and while recruitment continues. A second meeting of the DRC will be scheduled to review the data after approximately 15 patients have been treated in each arm. After each of these meetings the DRC will recommend to continue, to modify, or to stop the trial due to any safety concern. The DRC may meet to review data any other time if deemed necessary.

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

The above described trial design is appropriate for a trial with exploratory intent.
In order to avoid a delay in surgery, study treatment will be provided as soon as possible. Since biomarker assessment needs time for processing, study treatment will be provided without having the results of biomarker assessment (e.g. SIRPα genotype status) available. SIRPα genotype status will be assessed retrospectely. For details please see section 7.2.5

3.3 SELECTION OF TRIAL POPULATION

This trial is planned as a single center trial at Icahn School of Medicine at Mount Sinai, US. Further investigational sites may be added as appropriate. Screening for the trial will stop at the site/all sites at the same time once a sufficient number of patients have been screened. The investigator/s will be notified about screening completion and will then not be allowed to screen additional patients for this trial. Patients already in screening at the time that screening has stopped will be allowed to continue 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 with investigational drug or not.

If retrospectively it is found that a patient has been treated with study drug in error (e.g. did not meet all inclusion criteria or met one or more exclusion criteria), the sponsor or delegate should be contacted immediately to assess the safety of the patient.

3.3.1 Main diagnosis for trial entry

Patients with diagnosis of resectable CRC will be included. 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

Patients must satisfy all the following criteria for entry into the trial (protocol):

1. Signed and dated written informed consent in accordance with ICH-GCP and local legislation prior to admission to the trial. Ability to understand and the willingness to sign a written informed consent.
2. Male or female aged ≥ 18 years at the time of ICF signature.
3. Patients with histological diagnosis of resectable CRC, or radiographic/visual findings highly suggestive, with planned confirmatory biopsy.
4. CRC lesions must be at least 1 cm in largest dimeter and amenable to endoscopic biopsy.
5. Patient must be willing and able to have endoscopic biopsy (Goal 3-6 core-needle or surgical/endoscopic biopsies, final number to be determined by the physician performing the procedure as safe) of tumor prior to initiation of therapy.

6. Eastern Cooperative Oncology Group (ECOG) performance status 0-1. The exception will be patients with long term disability (such as cerebral palsy) that is unlikely to significantly affect their response to therapy.
7. Patient is determined to be a surgical candidate for resection of their tumor.
8. Adequate organ and marrow function as defined below in Table 3.3.2:1.

9. Women of childbearing potential (WOCBP)[1] 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, from signature of ICF until 6 months after administration of trial treatment. A list of contraception methods meeting these criteria is provided in the patient information. For further detail refer to Section 4.3.2.3.

[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.

Table 3.3.2: 1 Adequate organ and marrow function for inclusion

System	**Laboratory Value**
Hematologic	
Absolute neutrophil count (ANC)	≥1,500 /mcL (1,000 /mcl for African American patients)
Platelets	≥100,000 /mcL
Hemoglobin	≥10 g/dL
Renal*	
Serum creatinine **OR** Measured or calculated[a] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 X upper limit of normal (ULN) **OR** ≥60 mL/min for patient with creatinine levels > 1.5 X institutional ULN
Hepatic*	
Serum total bilirubin	≤ 1.5 X ULN **OR** Direct bilirubin ≤ ULN for patients with total bilirubin levels > 1.5 ULN
AST and ALT	≤ 2.5 X ULN
Albumin	≥2.5 mg/dL
Coagulation*	
International Normalized Ratio (INR) or Prothrombin Time (PT) Activated Partial Thromboplastin Time (aPTT)	≤1.5 X ULN unless patient is receiving anticoagulant therapy as long as PT is within therapeutic range of intended use of anticoagulants ≤1.5 X ULN unless patient is receiving anticoagulant therapy as long as PTT is within therapeutic range of intended use of anticoagulants
[a] Creatinine clearance should be calculated per institutional standard. * If laboratory criteria are not met due to what the investigator determines to be a biologic cause (e.g. Gilbert's syndrome causing elevated bilirubin or excessive muscle mass affecting creatinine) or drug-related cause (e.g. elevating in transaminases due to HAART therapy, elevated INR due to anticoagulation) then the lab values will not be used to exclude patient from this trial. Similarly, for patients with elevated bilirubin due to biliary obstruction from tumor, this will not serve as an exclusion criterion. This determination will be made by PI.	

3.3.3 Exclusion criteria

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

1. Patients who are deemed to be at high risk for colonic obstruction and/or perforation per investigator assessment.
2. Patients eligible for neoadjuvant therapy (chemotherapy, radiotherapy, chemoradiotherapy) as standard of care.
3. Major surgery (major according to the investigator's assessment) performed within 4 weeks prior to administration of trial medication.
4. Patients who must or wish to continue the intake of restricted medications (see section 4.3.2.1) or any drug considered likely to interfere with the safe conduct of the trial.
5. Patients not expected to comply with the protocol requirements or not expected to complete the trial as scheduled (e.g. chronic alcohol or drug abuse or any other

condition that, in the investigator's opinion, makes the patient an unreliable trial participant).

6. Previous enrolment in this trial.
7. Currently enrolled in another investigational device or drug trial, or less than 30 days since ending another investigational device or drug trial(s) or receiving other investigational treatment(s).
8. Patients who have had [redacted] prior to entering the study for a different primary tumor, or those that have received locoregional therapy (radiation, chemoembolization, etc.) for the target lesion that will be biopsied and subsequently resected. Previous therapy for a different cancer (a different primary) is acceptable.
9. Prior immune checkpoint inhibitor therapy.
10. Patients with metastatic or recurrent disease, for which the intent of surgery would not be curative.
11. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection requiring antibiotics (except antibiotics to be completed 4 weeks before initiation of treatment), symptomatic congestive heart failure, unstable angina pectoris, or psychiatric illness/social situations that would limit compliance with study requirements.
12. Patients who are pregnant or nursing or who plan to become pregnant while in the trial.
13. Has a diagnosis of primary immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the administration of trial treatment. Patients on chronic steroids (more than 4 weeks at stable dose) equivalent to ≤ 10mg prednisone will not be excluded.
14. Has active autoimmune disease that has required systemic treatment in the past 1 year (i.e. with use of disease modifying agents, corticosteroids, or immunosuppressive drugs). Replacement therapy (e.g. thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is acceptable.
15. Has any hematological malignancy.
16. Has a known additional somatic malignancy that is progressing and/or requires active treatment. Exceptions include basal cell carcinoma of the skin or squamous cell carcinoma of the skin that has undergone potentially curative therapy or in situ cervical or anal cancer, non-metastatic prostate cancer on stable dose of hormonal therapy without rising PSA, and breast cancer patients who have been treated with curative intent, who may be on hormonal therapy.
17. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the patient's participation for the full duration of the trial, or is not in the best interest of the patient to participate, in the opinion of the treating Investigator.
18. Patients with history of human immunodeficiency virus (HIV) infection who meet one or more of the following criteria:

- CD4+ count < 350 cells/µL
- Viral load > 200 copies/µL (local lab assessment)
- Not receiving antiretroviral therapy
- Receiving established antiretroviral therapy for less than four weeks prior to the start of study treatment
- History of AIDS-defining opportunistic infections within 12 months prior to start of study treatment

Patients with a history of HIV who do not meet any of the criteria above are eligible to participate but the patient must be under the care of a HIV/Infectious Diseases specialist or a HIV/Infectious Diseases specialist must be consulted prior to inclusion.

19. Patients with a history of Hepatitis C (HCV) infection who meet one or both of the following criteria:
    - Curative antiviral treatment is not complete
    - HCV viral load is above the limit of quantification (HCV RNA positive)
20. Patients with chronic Hepatitis B (HBV) infection with active disease who meet the criteria for anti HBV therapy (according to local / institutional standard) who have not been adequately treated with suppressive antiviral therapy prior to initiation of study treatment.
21. History of allogeneic hematopoietic cell transplantation or solid organ transplantation.
22. Documented allergic or hypersensitivity response to any protein therapeutics (e.g., recombinant proteins, vaccines, intravenous immune globulins, monoclonal antibodies, receptor traps).
23. Neuropathy ≥ grade 2.
24. Principal Investigator believes that for one or multiple reasons the patient will be unable to comply with all study visits, or if they believe the trial is not clinically in the best interest of the patient.

3.3.4 Discontinuation of patients from treatment or assessments

Patients will receive a single administration of trial medication (either single dose ezabenlimab in combination with BI 765063 or single dose pembrolizumab in combination with BI 765063).

If a patient is considered eligible for trial participation, but cannot be treated with trial medication for any reason, this patient will be replaced by another patient.

Patients which have received treatment will not be replaced (regardless whether the treatment is administered completely or not).

Please refer to section 3.3.4.2 regarding withdrawal of consent to trial participation.
Please refer to section 6.1 regarding situations where a patient is unable or unwilling to attend a clinic visit.

3.3.4.1 Discontinuation of trial treatment

This is a single dose trial. Trial medication will be given one time on Day 1 of the study and will not be given any more throughout the study. Patients will continue to be followed as described in the flowchart and in section 6.

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 discontinuation of administration of the single trial treatment (e.g. after one infusion dose), and withdrawal of consent to trial participation, as well as explain the options for continued follow-up safety assessments.

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 administration of the 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 5.2.6.2).

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.
2. New efficacy or safety information invalidating the earlier positive benefit-risk-assessment.
3. Deviations from GCP, the trial protocol, or the contract impairing the appropriate conduct of the trial.

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

4. TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

On Day 1 (treatment day)

Patients in Cohort A will receive [redacted].

Patients in Cohort B will receive [redacted].

[redacted]

The expected infusion time is about 30 minutes for ezabenlimab and 90 minutes for BI 765063. The duration of infusion should not be prolonged to more than 6 hours for BI 765063, nor to more than 3 hours for ezabenlimab. Pembrolizumab will be administered according to its label.

Regarding management of IRR please see section 5.2.6.1.4

Regarding premedication please see section 4.1.3.

Patients should be scheduled for surgery to take place at least 2 weeks following the administration of study treatment.

4.1.1 Identity of the Investigational Medicinal Products

Ezabenlimab (BI 754091)

Table 4.1.1:1 Ezabenlimab (BI 754091)

Substance:	Ezabenlimab
Pharmaceutical formulation:	Solution for infusion
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	20 mg /mL (15 mL vial)
Posology:	Rate controlled infusion on Day 1
Route of administration:	i.v.
Duration of use:	One time

BI 765063

Table 4.1.1:2 BI 765063

Substance:	BI 765063
Pharmaceutical formulation:	[redacted]
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG

Unit strength:	[redacted]
Posology:	Rate controlled infusion on Day 1
Route of administration:	[redacted]
Duration of use:	One time

Pembrolizumab

Table 4.1.1:3 Pembrolizumab

Substance:	Pembrolizumab
Pharmaceutical formulation:	Concentrate for solution for infusion
Source:	To be taken from the market by the investigator
Unit strength:	Pembrolizumab 200 mg, IV, Day 1
Posology:	Rate controlled infusion on Day 1
Route of administration:	i.v.
Duration of use:	One time

4.1.2 Selection of doses in the trial and dose modifications

Cohort A: Ezabenlimab in combination with BI 765063:
On Day 1 only, patients assigned to the Cohort A will all receive the recommended Phase II dose (RP2D) of ezabenlimab i.e. a flat dose of 240 mg [redacted].

Cohort B: Pembrolizumab in combination with BI 765063:
On Day 1 only, patients assigned to the Cohort B will receive pembrolizumab flat dose of 200 mg [redacted].

4.1.3 Method of assigning patients to treatment groups

Patients will be assigned alternatingly (sequentially one by one) to either of the cohorts and will receive one-time either of the combination treatments with the first patient allocated to Cohort A and the second patient allocated to Cohort B. All eligible patients will be enrolled in the trial and genotyping will be performed retrospectively. Assignments will be conducted at the site and recorded in the eCRF.

4.1.4 Drug assignment and administration of doses for each patient

Each patient will receive the appropriate dose for their assigned cohort. The trial drug will be prepared and handled according to the 'Medication Handling Instruction' which will be filed in the ISF. Upon notification of the treatment cohort of the patient, the pharmacy will prepare the trial drugs for administration to the patient.

Pembrolizumab, Ezabenlimab (BI 754091), and BI 765063 will be given as an intravenous infusion by authorised site staff in a specialised unit where emergency care can be provided (e.g. intensive care unit available, medical personnel trained in advanced life support). The maximum infusion duration including the interruption time, the infusion rate and storage conditions are indicated in the ISF.

The pembrolizumab will be administered per the US package insert information.

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

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

4.1.5.2 Unblinding and breaking the code

Not applicable.

4.1.6 Packaging, labelling, and re-supply

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

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

4.1.7 Storage conditions

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 Research Associate (CRA, as provided in the list of contacts) must be contacted immediately.

4.1.8 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 (RA), e.g. competent authority,
- Availability of the curriculum vitae of the Principal Investigator,
- Availability of a signed and dated clinical trial protocol,
- Availability of the proof of a medical license for the Principal Investigator,
- Availability of FDA Form 1572 (if applicable).

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

The investigator 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 and/or appointed CRO, the investigator or designee must verify that all unused or partially used drug supplies have been returned by the clinical trial patient and that no remaining supplies are in the investigator's possession.

4.2 CONCOMITANT MEDICATIONS

Medications specifically prohibited (see section 4.2.2) are not allowed during the ongoing trial. If there is a clinical indication for one of these or other medications or vaccinations specifically prohibited during the trial, discontinuation from the trial may be required. The Investigator should discuss any questions regarding this with the Study PI and Sponsor. The final decision on any supportive therapy or vaccination rests with the Investigator and/or the patient's primary physician.

4.2.1 Acceptable Concomitant Medications

All treatments that the Investigator considers necessary for a patient's welfare may be administered at the discretion of the Investigator in keeping with the community standards of medical care. Regarding pre-medication please refer to section 4.2.3. All concomitant medication will be recorded on the case report form (CRF) including all prescription, over-the-

counter (OTC), herbal supplements, and intravenous medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included on the CRF.

4.2.2 Prohibited Concomitant Medications

Patients are prohibited from receiving the following therapies during the Screening and Neoadjuvant Treatment Phase of this trial:

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Radio-therapy
- Systemic glucocorticoids for any purpose other than those used to modulate symptoms from an AE of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the PI, and patients on long-term steroids equivalent to 10mg or less of prednisone daily may be enrolled.
- Live attenuated vaccines are prohibited during the trial and for 90 days after the administration of trial treatment.

Any standard of care therapy is allowed in the adjuvant (post-operative setting) that is deemed clinically indicated by the treating physician.

Patients may receive other medications that the Investigator deems to be medically necessary.

4.2.3 Pre-medication

Infusion-related reactions (IRRs) were reported by approximately half of the patients when premedication prior was not allowed. Pre-medication with an antihistamine and acetaminophen or paracetamol resulted in a markedly reduction of IRR (for details please refer to section 1.4.2, subsection “Potential risks related to BI 765063”).
Therefore, pre-medication with an antihistamine and acetaminophen or paracetamol to reduce the risk of IRRs is recommended prior to drug administration of BI 765063. Pre-medication should be administered at sufficient time prior to initiation of infusion to allow the agents to exert their effect. Corticosteroids will not be allowed in pre-medication regimens.

4.3 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

4.3.1 Other treatments and emergency procedures

There are no special emergency procedures to be followed.

4.3.2 Restrictions

4.3.2.1 Restrictions regarding concomitant treatment

Please see section 4.2.2 “Prohibited Concomitant Medications”

4.3.2.2 Restrictions on diet and lifestyle

The usual restrictions on diet and lifestyle that were already applicable for a given patient before entry into the trial, according to his/her medical condition, have to be continued.

4.3.2.3 Contraception requirements

WOCBP (for the definition please refer to section 3.3) must use medically approved methods of birth control as described below.

WOCBP 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.

Highly effective methods of contraception:

- Combined (estrogen and progestogen containing) hormonal birth control that prevents ovulation (oral, intravaginal, transdermal).
- Progestogen-only hormonal birth control that prevents ovulation (oral, injectable, implantable).
- Intrauterine device (IUD) or intrauterine hormone-releasing system (IUS).
- Bilateral tubal occlusion.
- Vasectomised partner (provided that this partner is your sole sexual partner and that your vasectomised partner has received medical assessment of the surgical success).
- Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period (stated above) of risk associated with the study treatments. This is defined as being in line with the only 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.

Although use of a contraceptive pill and Intrauterine device (IUD) are considered a highly-effective method of birth control, women of childbearing potential taking a contraceptive pill must use an additional barrier method from signature of ICF until 6 months after the administration of trial treatment.

4.4 TREATMENT COMPLIANCE

The trial drug products should only be used as directed in this protocol. The treatments will be taken at the investigational site under the supervision of the investigator and/or authorized and trained designee. Therefore, actual dosing is expected to precisely follow the assigned dose which will be administered as an intravenous infusion at the clinical site under the supervision of trained site personnel. The dose 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

Pathological response (PR), will be assessed as per Mandard tumor regression grading system (R21-1544). Please see also section (please see section 2.1.2)

Tumor assessments must be performed according to RECIST 1.1 comparing screening and pre-surgery assessments. The same radiographic procedure(s) (e.g. CT scan, MRI) should be used throughout the trial. Tumor assessments performed prior to informed consent as part of routine clinical practice will be accepted if they meet the requirements of the protocol and are performed within the Screening visit window (within 21 days prior toof Day 1).

Clinical imaging data acquired in this trial might also be analysed further to build diagnostic, prognostic and predictive models using radiomics. This exploratory analysis might be performed in collaboration with an independent third party nominated by the Sponsor.

5.2 ASSESSMENT OF SAFETY

5.2.1 Physical examination

A complete physical examination will be performed at the time points specified in the flowchart. It includes at a minimum general appearance, neck, lungs, cardiovascular system, abdomen, extremities, and skin.

Measurement of height (in cm, only at screening), body weight (in kg), and the evaluation of the ECOG performance score (see Appendix 10.4) will be performed at the time points specified in the flow chart.

The results must be included in the source documents available at the site.

5.2.2 Vital signs

Vital signs will be evaluated at the time points specified in the flow chart, prior to blood sampling. This includes systolic and diastolic blood pressure and pulse rate (electronically or by palpation count for 1 minute) in a seated position after 5 minutes of rest. The results must be included in the source documents available at the site.

5.2.3 Safety laboratory parameters

Safety laboratory parameters will be analysed at a local laboratory. Safety laboratory examinations will include tests as listed in Table 5.2.3:1 and should be obtained at the time points specified in the flow chart.

All analyses will be performed by the site's local laboratory, the respective reference ranges will be provided in the ISF.

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

Instructions regarding sample collection, sample handling / processing and sample shipping are provided in the Laboratory Manual (to be filed ISF).

The local laboratory will send reports to the investigator. 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 the criteria for hepatic injury are fulfilled, a number of additional measures will be performed (please see section 5.2.6.1) and the DILI Checklist provided in the ISF system. The amount of blood taken from the patient concerned will be increased due to this additional sampling.

The laboratory will transfer the results of the analysis to the sponsor or delegate.

Table 5.2.3:1 Safety laboratory tests

Category	Parameters
Haematology	Haemoglobin, haematocrit, platelet count, reticulocytes, red blood cell count, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, erythrocytes distribution width, white blood cell count with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils) preferably expressed in absolute values.
Biochemistry	Glucose, sodium, potassium, chloride, calcium, magnesium, phosphate, venous bicarbonate HCO_3, total protein, albumin, uric acid and creatinine kinase (CK; if CK is elevated, then CK-MB [cardiac], Troponin I or T, and myoglobin should be reactively tested). A thyroid panel (TSH, free T4, and free T3) will be done at the time of each standard biochemistry panel. If symptoms of pancreatitis are observed, amylase and lipase should be tested at the discretion of the Investigator.
Liver function	AST, ALT, alkaline phosphatase, lactate dehydrogenase, bilirubin (direct and indirect bilirubin in case of elevated total bilirubin values)
Renal function	Blood urea or blood urea nitrogen, and creatinine. 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).
Coagulation	Activated partial thromboplastin time (aPTT) and prothrombin time (PT) (expressed either in seconds or as percentage) or International Normalised Ratio (INR)
Urinalysis	pH, glucose, erythrocytes, leukocytes, protein, and nitrite analysed by dipstick (semi-quantitative measurements). The result will be kept in source document, but not entered in the CRF/database and will not be reported in the CTR. Clinically relevant abnormal findings will be reported either as baseline condition (if identified at the Screening visit) or otherwise as adverse event.
Pregnancy	Beta human chorionic gonadotropin (β-HCG) pregnancy test in serum performed for women of childbearing potential at Screening. Urine or serum test performed within 72 hours before study treatment on Day 1.
For patients with history of HIV or HCV infection only:	For patients with history of HIV infection: CD4+ count, Viral load, according to local standard.

	For patients with a history of HCV infection: HCV viral load according to local standard as needed. Additional testing for infectious diseases can be added as required. The result will be kept in source document, but not entered in the CRF/database and will not be reported in the CTR. Clinically relevant abnormal findings will be reported either as baseline condition (if identified at the Screening visit) or otherwise as adverse event. Tests performed no more than 4 weeks prior to screening (day of blood collection) can be used and do not need to be repeated for screening.

All screening labs should be performed or repeated within 10 days prior to treatment initiation with the exception of the urine pregnancy test which should be conducted within 72 hours of initiating treatment; all other screening assessments are performed within 21 days of initiation of study treatment (Day 1).

5.2.4 Electrocardiogram

The 12-lead ECGs must be administered by a qualified technologist as scheduled in the flowchart. 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.

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

None

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 5.2.6.2.3

- 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 (except planned hospitalization for tumor resection),
- 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 medial 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.

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 administration of the trial medication and must be reported as described in section 5.2.6.2, subsections “AE Collection” and “**AE reporting to sponsor and timelines**”.

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 5.2.6.2.1.

The following are considered as AESIs:

Infusion related reactions

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

The following terms describe those events that are to be considered potential infusion-related AEs. Regardless of grade, these events are considered as AESIs and must be reported to the Sponsor Drug Safety Department within 24 hours of the knowledge of the event (refer to Section 5.2.6.2):

- Allergic reaction
- Anaphylaxis
- Cytokine-release syndrome
- Serum sickness
- Infusion reactions
- Infusion-like reactions

If the Investigator determines that another event (not on the list) may be a potential infusion-related AE, the Investigator may also report that event as an AESI.

Management of infusion related reactions (IRR):

As a routine precaution, patients enrolled in this trial must be observed for at least 4 hours post-infusion of study drugs, with immediate access to emergency resuscitation teams and equipment in addition to the ability to admit patients to an intensive care unit if necessary.

Monitoring will include measurement of body temperature, heart rate, and blood pressure at regular intervals. Patients will be assessed for signs or symptoms of IRR, e.g. hypotension, hypoxia, tachycardia, fever, nausea, fatigue, headache, myalgias, and malaise.

Patients will be informed about possible signs and symptoms of IRR during, or after, administration of study drugs.

The following recommendations for the management of IRR regarding administration of study drugs should be considered by the Investigator as guidance:

- Regarding premedication please see section 4.1.3.
- Grade ≤ 2: In the event of an infusion-related reaction ≤ Grade 2, the infusion rate of study drug(s) may be decreased by 50%, or interrupted, until resolution of the event and resumed at 50% of the initial rate until completion of the infusion. In case infusion must be stopped due to infusion related reactions (IRR) or similar situation, the duration of infusion can be prolonged up to 6 hours for BI 765063, or to 3 hours for ezabenlimab. Infusion duration for BI 765063 beyond 6 hours may be possible on a case-by-case bases after discussion with the sponsor. The details of dose preparation as well as the infusion duration are specified in "Instruction for Pharmacists".
- Grade 3 or higher in severity at any time point during the infusion of study drug, the infusion has to be permanently discontinued.

Immune-related adverse event (irAE)

Immune-related AEs are AEs associated with immunotherapy treatments that appear to be associated with the immune therapy's mechanism of action. These adverse reactions, which can be severe, may involve the gastrointestinal, skin, liver, endocrine, respiratory, renal, or other organ systems. The sponsor has defined a list of potential irAEs which need to be reported as irAEs in Section 10.3. If an investigator determines another event (not on the list) should be a potential irAE, the investigator may also report that event as an AESI.

Hepatic injury

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

- For patients with abnormal liver function at baseline (AST and/or ALT>ULN)
  - an elevation of AST and/or ALT ≥ 5 fold ULN combined with an elevation of total bilirubin ≥2 fold ULN measured in the same blood draw sample, with the exclusion of the causes due to underlying diseases, and/or
  - Marked peak aminotransferase (ALT, and/or AST) elevations ≥ 10 fold ULN
- For patients with normal liver function at baseline (ALT, AST, and bilirubin within normal limits at baseline):
  - an elevation of AST and/or ALT ≥3 fold ULN combined with an elevation of total bilirubin ≥2 fold ULN measured in the same blood draw sample, and/or
  - Marked peak aminotransferase (ALT, and/or AST) elevations ≥ 10 fold ULN

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

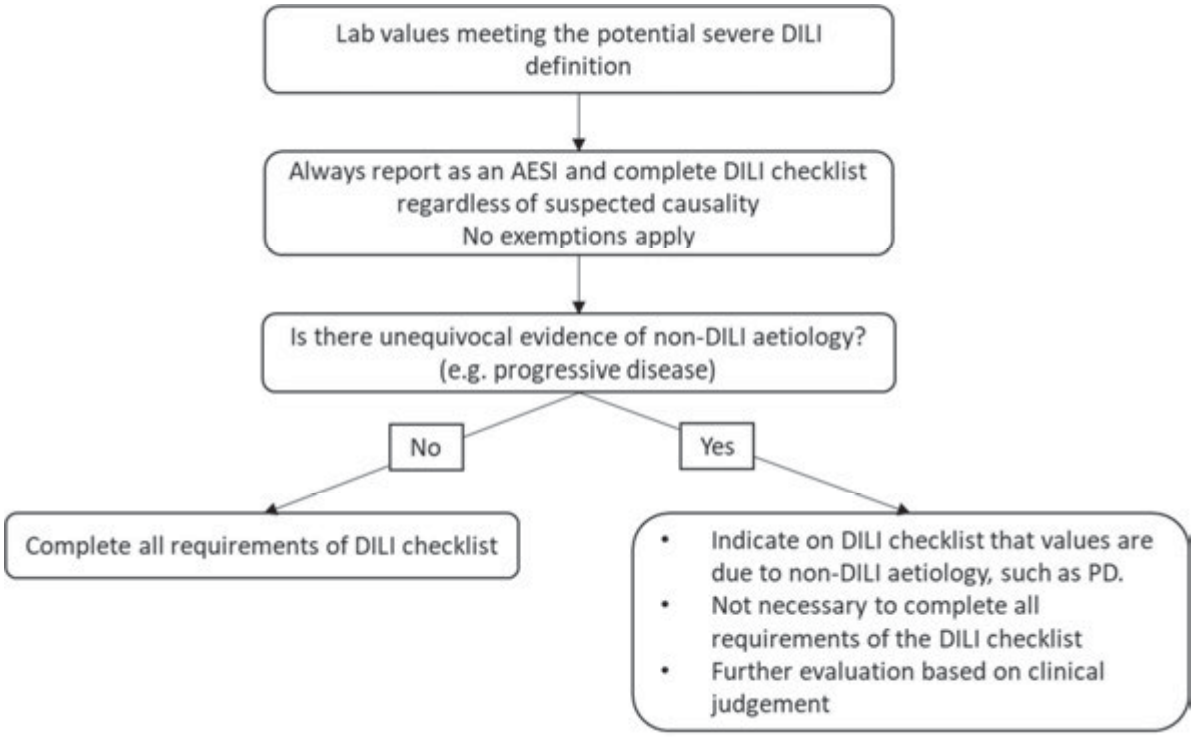


Figure 5.2.6.1.4:1 Potential severe DILI reporting –in case of a DILI please follow the above procedure on how to report the DILI as an AESI.

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

5.2.6.1.5 Intensity (severity) of AEs

The intensity (severity) of adverse events should be classified and recorded in the CRF according to the Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0.

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).

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, considering 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

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 end of trial (including the Follow up Period):
  all AEs (serious and non-serious) and all AESIs.

- After the individual patient's end of trial:
  the investigator does not need to actively monitor the patient for new AEs but should only 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 (see section 5.2.6.2.1), but not on the CRF.

The rules for Adverse Event Reporting exemptions still apply, please see section 5.2.6.2.3.

5.2.6.2.1 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.

5.2.6.2.2 Pregnancy

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

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

5.2.6.2.3 Exemptions to SAE reporting

The outcome "disease progression" is used to assess trial endpoints for the analysis of efficacy and as such is exempted from AE/SAE reporting. Signs and symptoms of disease progression which can exclusively be determined to be due to the progression of the underlying malignancy and meet the expected pattern of disease progression for the disease under study are also exempted from AE/SAE reporting.

Disease progression of the patient's underlying malignancy will be recorded on the appropriate pages of the eCRF as part of efficacy data collection only. It will not be recorded on the AE page in the eCRF and will not be reported on the SAE Form even when it meets standard seriousness criteria.

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

When there is evidence suggesting a causal relationship between the trial 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.
Exempted events are monitored at appropriate intervals

5.3 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

Not applicable

5.4 ASSESSMENT OF BIOMARKER(S)

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

Exploratory biomarkers will be analysed to provide clinical evidence of the biological mode of action of the combination of BI 765063 and ezabenlimab or BI 765063 and Pembrolizumab (i.e., pharmacodynamic biomarkers), to molecularly characterize an individual patient's cancer in neoadjuvant setting. Biomarker maybe useful to retrospectively correlate patient subgroups with differential responses to treatment and/or to prognosis. These analyses are hypothesis generating and will be used to expand the current understanding of the trial drugs and the disease. Participation in the biomarker testing is mandatory and is a prerequisite for participating in the study.

Should other tissues or blood-based biomarkers beyond those exploratory biomarkers in the Flowchart become relevant, these may also be explored. The list of biomarkers planned to be studied during the trial may change based on new information in the scientific literature or early trial analysis.

Any remaining samples or derived material from pre-specified analyses (RNA, DNA) will be destroyed no later than 5 years after the final trial report is archived.

The following biomarkers are planned to be examined in this trial (for detailed sampling times, refer to the Flowchart).

5.4.1 Biomarkers planned to be assessed in this trial

- Assessment of biomarkers of potential predictive value
    - SIRPα genotype (V1/V1, V1/V2, V2/V2), through WES/PCR
    - Baseline SIRPα and CD47 expression in tumor, through bulk RNAseq and scRNAseq
    - Baseline MMR/MSI status, TMB status, PD-L1 expression, T cell and macrophage infiltration in tumor through WES, bulk RNAseq, and MICSSS

- Pharmacological modulations of key MoA biomarkers upon Ezabenlimab/BI 765063 combination

- Macrophage reprograming in tumor (changes in macrophage phenotype from baseline) through bulk RNAseq and scRNAseq
- CD8 T cell infiltration in tumor, through MICSSS, bulk RNAseq and scRNAseq
- Changes of lymphoid/myeloid populations in tumor and in blood through CyTOF
- TCR clonality for clonal expansion/enrichment analysis in tumor and in blood through TCR sequencing on tissue and blood
- Longitudinal mutation analysis, baseline TMB from ctDNA analysis in blood
- MoA-related cytokine modulation
- Changes of microbiome in stool through 16s sequencing

5.4.2 Methods of Sample Collection, Handling of Samples and Biomarker Results

Detailed instructions for handling, storage, and shipment of the biomarker samples will be provided in the laboratory manual. All tumor and blood samples will be obtained at time points as defined in the Flow Chart. Biomarker data performed by the laboratory could be reported to investigators upon request.

5.5 BIOBANKING

5.5.1 Methods and timing of sample collection

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

The following biomarker samples specified in section 5.4, Assessment of Biomarkers, will be banked: pre-treatment and surgery tumor tissue, fixed in formalin and embedded in paraffin.

5.6 OTHER ASSESSMENTS

Not applicable

5.7 APPROPRIATENESS OF MEASUREMENTS

All measurements performed during this trial are standard measurements and will be performed in order to monitor patients' safety and to determine biological activity and efficacy in an appropriate way. The scheduled measurements will allow monitoring of changes in vital signs, standard laboratory values, and ECG parameters that might occur as a result of administration of trial medication. The safety assessments are standard, are accepted for evaluation of safety and tolerability of an intravenously administered drug, and are widely used in clinical trials.

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

Patients meeting the inclusion and exclusion criteria who have signed a written ICF are eligible for participation in the trial. Patients will visit the clinical site at the time points specified in the Flowchart. All patients should adhere to the visit schedule as specified in the Flowchart. The allowed windows for each visit and assessment are specified in the Flowcharts. Additional flexibility (e.g. to allow for public holidays and patient unavailability) may be allowed if agreed between the investigator and the sponsor.

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 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 situations where a patient is unable or unwilling to attend a clinic visit, the investigator must assess the risk-benefit for the individual patient and may decide to perform a visit remotely if this is in the best interests of the patient and if agreed with the sponsor. Patient safety must be ensured when determining if a visit may be remote.

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

The investigations as outlined in the flowchart will be performed at the respective visits. Specific details to conduct of physical examination, collection of vital signs, including blood pressure measurement, laboratory investigations, assessment of ECG, and other safety parameters can be found in the subsections of section 5.2.2.

6.2.1 Screening and run-in period(s)

Screening Period
Patients may be consented to the clinical trial if they have imaging or other findings highly suggestive of a diagnosis of CRC. Such patients should subsequently undergo diagnostic and research biopsies in parallel, during screening, in order to avoid repeating procedures. Consented patients found to have a diagnosis other than CRC will be considered as screen-fail. Such patients will be replaced.

Following informed consent, the patient will undergo screening assessments as indicated in the flowchart. The assessments must fall within the acceptable Screening visit window but do not need to be performed on the same day. Screening assessments may be repeated as long as they fall within the Screening visit window of 21 days. If more than one screening assessment is available, the latest assessment prior to the start of treatment must be used to assess eligibility.

Tumor assessments performed prior to informed consent as part of routine clinical practice will be accepted if they meet the requirements of the protocol and are performed within the Screening visit window of 21 days.

There is no mandatory order of assessments, but the biopsy must only be performed on patients who are expected to be eligible. Where applicable, the pre-treatment/baseline biopsy must be obtained prior to the dose.

If the patient meets the eligibility criteria during screening, the treatment visit should be scheduled. Any baseline conditions which are present at the Screening visit should be reported in the eCRF.

Re-screening of patients who have previously failed screening will be permitted. In this situation patients will be allocated a new patient number.

- 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
- Pregnancy testing - serum
- Ethnicity and race in order to sufficiently characterize the patient population, to support possible subgroup analyses if needed unless not acceptable according to local regulations.
- Information on tobacco use

Baseline Conditions

Any baseline conditions which are present at the screening visit should be reported in the eCRF.

Demographics
Demographics (sex, birth year, race, and ethnicity [where allowed]), and baseline medical conditions will be collected during the screening visit.

Medical History of Cancer:

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

Other Medical History
Past diseases and/or concomitant diagnoses relevant to the patient's safety during the trial, assessment of biomarker such as PD-L1 expression, microsatellite instability (MSI), TMB information, and efficacy, as judged by the Investigator, will be recorded in eCRF.

Concomitant Medication
Past medications relevant to the patient's safety during the trial, as judged by the Investigator, will be recorded in the eCRF. From the date of signature of the main ICF, all concomitant medications will be recorded.

Please refer to the Flowchart for a detailed presentation of the Screening visit.

6.2.2 Treatment period(s)

In this trial the investigational combination treatment will be provided as single administration. Eligible patients will be administered study medication on Day 1.

Visit 1 (V01) – Day 1 (treatment day)

Patients in Cohort A will receive [redacted].

Patients in Cohort B will receive [redacted]. Refer to Table 3.1:1 for more details on treatments.

Patients will be allocated to Cohorts A and B alternatingly, with the first patient allocated to Cohort A and the second patient allocated to Cohort B. All eligible patients will be enrolled in the trial and genotyping will be performed retrospectively.

Patients must be observed for at least 4 hours post-infusion of study drugs, with immediate access to emergency resuscitation teams and equipment in addition to the ability to admit patients to an intensive care unit if necessary.

The following procedures are required at visit 1/Day 1

- Physical exam
- ECOG determination
- Adverse Events assessment
- Pregnancy testing (urine or serum)
- Standard labs (hematology/chemistry)
- Research blood samples

Visit 2 (V02) - [redacted]

The following procedures are required at visit 2/[redacted]

- Physical exam
- ECOG determination
- Adverse Events assessments
- Research blood samples

Visit 3 (V03) – [redacted]

The patient will have a day of surgery scheduled per the patient's treatment. Within five (5) days and as close as possible prior to this surgery, the following procedures will be performed:

- Physical exam
- ECOG determination
- Adverse Events assessments
- Imaging
- Standard labs (hematology/chemistry)
- Research blood samples
- Stool sample (Note: on the day of before the surgery)

- ***Resected tumor collection**: Tumor tissue will be a sample from the tumor removed during the surgery. (*Note: "Resected tumor collection" is listed under visit 3 in the flow chart for practical reasons and should occur at the **day of the surgery**. All other activities will be performed prior to the surgery.)

Please refer to the Flow Chart for a detailed presentation of each visit during Visits 1 through Visit 3.

6.2.3 Follow-up period and trial completion, End of Study (EOS) Visit

After the patient completes visit 1 through visit 3, there is a single visit to be conducted at ≥ 91 days and no later than 120 days from Day 1. The following procedures need to be performed at the End of Study (EOS) Visit:

- Physical exam
- ECG
- ECOG determination
- Adverse Events assessments
- Research blood samples

After EOS visit, the patient has completed the trial and no further data collection is required.

If needed in the opinion of the investigator, after EOS visit, additional visits may be scheduled for continued safety monitoring. For information on follow-up period, see section 7.2.6.

Abnormal assessments or lab values judged clinically relevant by the investigator will be monitored until they returned to a medically acceptable level.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

This is an open-label, two-arm, parallel group, single-center Phase 1 trial of ezabenlimab in combination with BI 765063 and Pembrolizumab in combination with BI 765063 in patients with early stage resectable colorectal cancer in neoadjuvant setting. Patients will be assigned alternatingly (sequentially one by one) to either of the cohorts and will receive one-time either of the combination treatments.

This is an exploratory study where the primary objective is to assess safety of patients treated with both the treatments in the neoadjuvant setting and also to ensure that the neoadjuvant treatment does not delay the recommended surgery. In addition, this trial will investigate efficacy as secondary objective and biological activity (including immunodynamic effect of the combined immunotherapy regimens systemically and on the tumor immune microenvironment) as further objectives.

7.1 NULL AND ALTERNATIVE HYPOTHESES

No formal hypothesis testing is planned in this trial. All the analyses in this trial are descriptive and exploratory. Results collected will be used for potential hypothesis generation. A Bayesian framework will be used to assess safety and feasibility. Any other analyses will be described in the Trial Statistical Analysis Plan (TSAP).

7.2 PLANNED ANALYSES

7.2.1 General considerations

For analyses of primary and secondary endpoints, all patients in the treated set (i.e., patients treated with one dose of trial medication) will be used if not specified differently. No per protocol set will be used in the analysis. However, important protocol violations will be identified and listed. Any other analysis set will be defined in the TSAP.

7.2.2 Handling of Intercurrent Events

Considering that patients will be treated with one-time treatment in both cohorts, no major intercurrent event is anticipated in this trial.

7.2.3 Primary objective analyses

The primary endpoint of the trial is a composite endpoint, safety and feasibility. Primary evaluation of safety and feasibility will be reported for all treated patients and will be measured as proportion of patients (along with 95% CI) who will meet the criterion of safety or feasibility (or both) defined in section 2.1.2. Safety and feasibility will be summarized separately for each arm.

In addition, safety and feasibility will be monitored, at interim and at final, using a Bayesian method. The incidence of complications after surgery for colorectal cancer is assumed approximately 20%. We consider that a neoadjuvant therapy with one of the regimens is not feasible if at least 20% of the patients with 85% or higher probability experience treatment related grade 3 or higher adverse events or have delay in surgery due to treatment related adverse events. Interim and final assessments for safety and feasibility will be conducted, separately, approximately after 5, 15 and 25 (final) patients being treated in each arm.

With a conservative prior probability of unfavorable “safety/feasibility” as Beta (0.1,0.4), the stopping boundaries are defined as seeing unfavorable “safety/feasibility” in ≥ 3 of first 5 patients, ≥ 5 of first 15, 8 or more out of 25 patients (Table 7.2.3:1). In case one arm needs to be closed due to unfavorable “safety/feasibility”, accrual to the remaining arm will continue. The calculation was performed using the Shiny Application: Bayesian Toxicity Monitoring version 2.2.1.0.

Table 7.2.3: 1 Early stopping boundary for unfavorable "safety/feasibility

# of patients (inclusive) per cohort	# of patients with related grade ≥ 3 AE or surgery delay	Decisions
5	3-5	Stopping
15	5-15	Stopping
25	8-25	Reached to final sample size

7.2.3.1 Sensitivity Analyses

Currently no sensitivity analysis is planned for the primary endpoint. Any additional sensitivity analysis will be described in the TSAP.

7.2.3.2 Subgroup Analyses

No subgroup analysis is planned for the primary endpoint.

7.2.3.3 Supplementary Analyses

No supplementary analysis is planned for the primary endpoint.

7.2.4 Secondary objective analyses

Pathological response (PR) will be assessed as per Mandard tumor regression grading system (R21-1544). The study will apply a Bayesian framework to calculate the posterior probability of PR rate for each arm separately. The 95% credible interval of the PR rate will be constructed along with observed PR (naïve estimate) and corresponding 95% confidence interval. In addition, at the final analysis, posterior probability, for each arm, that the PR rate is at least 15% will be calculated (i.e., suggesting that drug is efficacious) under the beta-binomial model with a weakly informative prior: Beta (0.15, 0.85).
Any additional analysis (including sensitivity analysis) to assess pathological responses will be separately described in the Trial Statistical Analysis Plan (TSAP).

Time from administration of trial treatment to surgery will be calculated as [Date of surgery – Date of first treatment administered + 1]. Time from administration of trial therapy to surgery will be summarized descriptively.

Radiographic response will be summarized descriptively along with 95% confidence interval.

7.2.5 Further objective analyses

The study will employ exploratory biomarker analyses to address modulation of key MoA and prognostic biomarkers as supportive evidence for pharmacodynamic response to the treatment. Refer to section 2.2.2 for all the proposed further endpoints.

In addition, retrospective and exploratory subgroup analyses for safety and efficacy would be done for [redacted] All the subgroup analysis will be summarized descriptively.

By nature, the biomarker analysis would be rather descriptive than quantitative. Thus, the biomarker analysis focuses on detection of significant modulation of those MoA biomarkers from baseline upon one cycle of ezabenlimab/BI 765063 combination treatment. More details on the analyses of further endpoints will be specified in 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 follow-up period, a period of 90 days after the administration of trial medication, 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 follow up period. Adverse events that start before first drug intake and deteriorate under treatment will also be considered as 'treatment-emergent'.

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

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 or other safety-relevant data observed at screening, 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

Two interim analyses are planned to assess safety and feasibility of the treatments. A Bayesian framework will be used to assess safety and feasibility after, approximately, 5 and 15 patients are treated in each arm. A Data Review Committee (DRC) will review the overall data along with the results from Bayesian calculation at interim.

7.3 HANDLING OF MISSING DATA

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. For partial or missing AE onset and/or end dates, BI internal rules will be followed (see Reference Document 001-MCG-156_RD01 "Handling of missing and incomplete AE dates")

7.4 RANDOMIZATION

No randomization will be performed. Patients will be assigned alternatingly (sequentially one by one) to either of the cohorts and will receive one-time either of the combination treatments.

7.5 DETERMINATION OF SAMPLE SIZE

No formal statistical assumption is used for the sample size calculation. A total sample size of 50 (25 in each arm) evaluable patients is planned to enroll in this trial. With a sample size of 25 patients in each arm, the study will have a very low probability (0.01) to wrongly declare that the study shows unfavorable "safety/feasibility" when the true rate is 10%, while it will have a high probability of 89% to identify a high true unfavorable "safety/feasibility" rate of 40% (Table 7.5:1).

The simulation was performed using the Shiny Application: Bayesian Toxicity Monitoring version 2.2.1.0.

Table 7.5:1 Operating characteristic, based on 10000 simulated trials, for Bayesian monitoring for unfavorable "safety/feasibility"

Scenario	True Rate of unfavorable "safety/feasibility"	Probability of Early Stop	Probability of Declaring unfavorable "safety/feasibility"	Average No of patients	Average No of unfavorable "safety/feasibility"	Observed rate of unfavorable "safety/feasibility"
1	0.1	0.01	0.02	24.72	2.47	0.10
2	0.2	0.18	0.21	22.57	4.51	0.22
3	0.3	0.50	0.60	18.31	5.49	0.35
4	0.4	0.79	0.89	13.88	5.55	0.47
5	0.5	0.94	0.98	10.55	5.27	0.57

For pathological response (PR), a weakly informative prior for PR as Beta (0.15, 0.85) along with an observed PR of 5 out of 25 patients will provide a posterior probability of 70% that PR rate is more than 15%.

Table 7.5:2 Posterior probability of true pathological response

# of observed PR out of 25	Posterior probability that (PR > 0.05)	Posterior probability that (PR > 0.10)	Posterior probability that (PR > 0.15)
4	0.97	0.78	0.49
5	0.99	0.91	0.70
6	0.99	0.97	0.85

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

The investigator will inform the sponsor or delegate 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 (CTR).

The certificate of insurance cover is made available to the investigator and the patients and is stored in the ISF.

8.1 TRIAL APPROVAL, PATIENT INFORMATION, INFORMED CONSENT

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

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

The investigator 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 (RMP) 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 4.2.1.

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 one documented attempt to retrieve previous medical records. If this fails, a verbal history from the patient, documented in their medical records, would be acceptable.

Certified copies of source documents necessary for data review and monitoring are accepted. 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 (OE) (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 always be available 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.

8.3.3 Storage period of records

Trial site:
The trial site 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.

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

8.6 TRIAL MILESTONES

The start of the trial is defined as the date when the first patient in the whole trial signs informed consent.
The end of the trial is defined as the date of the last visit of the last patient in the whole trial ("Last Patient Completed"). The "**Last Patient Last Treatment"** (LPLT) date is defined as the date on which the last patient in the whole trial is administered trial treatment (as scheduled per protocol). Individual investigators will be notified of SUSARs occurring with the trial medication until 90 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 (HA) request.

8.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL

The trial is sponsored by Boehringer Ingelheim (BI).

A DRC will be established as described in section 3.1.1. and section 7.2.8.

Relevant documentation on the participating (Principal) Investigator (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 (if applicable).

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 (CT Managers), and Clinical Research Associates (CRAs).

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.

An IRT vendor will be used in this trial. Details will be provided in the IRT Manual available in the ISF.

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c29693380	Investigator's Brochure BI 765063 version 1.0 dated 28 May 2021.
c07895879	Investigator's Brochure BI 754091 version 5.0 dated 08 Feb 2021
001-MCG-156_RD01	“Handling of missing and incomplete AE dates”)

10. APPENDICES

10.1 TIME SCHEDULE FOR PHARMACOKINETIC (PK) BLOOD SAMPLING

Not Applicable

10.2 TIME SCHEDULE FOR PHARMACODYNAMIC AND BIOMARKER SAMPLING

Please see the **Flowchart**

10.3 IMMUNE-RELATED ADVERSE EVENTS OF SPECIAL INTEREST

This table defines immune-related AEs that must be reported as AESIs if they occur after exposure to the trial treatment. For each category examples are provided, but these are not exhaustive.

Table 10.3: 1 Immune-related adverse events of special interest

Immune-related adverse events of special interest
Pneumonitis (report as AESI if an irAE is ≥ Grade 2)
• Acute interstitial pneumonitis • Interstitial lung disease • Pneumonitis
Colitis (report as AESI if an irAE is ≥ Grade 2 or any grade resulting in dose modification or use of systemic steroids to treat the AE)
• Intestinal obstruction • Colitis • Colitis microscopic • Enterocolitis • Enterocolitis haemorrhagic • Gastrointestinal perforation • Necrotising colitis • Diarrhea
Endocrine (report as AESI if an irAE is ≥ Grade 3 or ≥ Grade 2 and resulting in dose modification or use of systemic steroids to treat the AE)

Immune-related adverse events of special interest
• Adrenal insufficiency • Hyperthyroidism • Hypophysitis • Hypopituitarism • Hypothyroidism • Thyroid disorder • Thyroiditis • Hyperglycaemia, if ≥ Grade 3 and associated with ketosis or metabolic acidosis
Endocrine (report as AESI for any grade)
• Type 1 diabetes mellitus (if new onset)
Haematologic (report as AESI if an irAE is ≥ Grade 3 or any grade resulting in dose modification or use of systemic steroids to treat the AE)
• Autoimmune haemolytic anaemia • Aplastic anaemia • Thrombotic thrombocytopenic purpura • Idiopathic (or immune) thrombocytopenia purpura • Disseminated intravascular coagulation • Haemolytic-uraemic syndrome • Any Grade 4 anaemia regardless of underlying mechanism
Hepatic (report as AESI if an irAE is ≥ Grade 2, or any grade resulting in dose modification or use of systemic steroids to treat the AE)
• Hepatitis • Autoimmune hepatitis • Transaminase elevations (ALT and/or AST)
Infusion Reactions (report as AESI for any grade)
• Allergic reaction • Anaphylaxis • Cytokine release syndrome • Serum sickness • Infusion reactions • Infusion-like reactions
Neurologic (report as AESI for any grade)
• Autoimmune neuropathy • Guillain-Barre syndrome • Demyelinating polyneuropathy • Myasthenic syndrome

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

10.4 ECOG PERFORMANCE STATUS

ECOG PERFORMANCE STATUS	
Grade	**ECOG**
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

Date of amendment		21 January 2022
EudraCT number **EU number**		Not applicable
BI Trial number		1502-0001
BI Investigational Medicinal Product(s)		Ezabenlimab BI 765063
Title of protocol		A Phase I open label study to assess safety, feasibility, efficacy, and biological activity of single administration of Ezabenlimab in combination with BI 765063 and Pembrolizumab in combination with BI 765063 as neoadjuvant treatments in patients with newly diagnosed surgically-resectable, locoregional colorectal cancer
Global Amendment		X
Section to be changed		Lay Title

Description of change		Old Lay Title – A study to test the safety and activity of one dose of ezabenlimab or pembrolizumab in combination with BI 765063 in people with newly diagnosed colorectal cancer who are scheduled for surgery. New Lay Title – A study in people with colorectal cancer to test whether ezabenlimab or pembrolizumab in combination with BI 765063 lead to side effects or delays in surgery.
Rationale for change		The lay title was updated
Section to be changed		Flowchart
Description of change		Line “Optional BioBanking from blood” removed Reference deleted from bottom of flowchart:
Rationale for change		The study will not collect blood for Biobanking
Section to be changed		Grammar, typographical errors, and grammar was corrected throughout the document.
Description of change		Grammar, typographical errors, and grammar was corrected throughout the document.
Rationale for change		The corrections were made throughout the document to ensure that grammar and all errors in tense were corrected.
Section to be changed		Section 3.3.3.- Exclusion Criteria
Description of change		The following exclusion criteria was added: 1. Patients who are deemed to be high risk for colonic obstruction and/or perforation per investigator assessment 2. Patients eligible for neoadjuvant therapy (chemotherapy, radiotherapy, chemoradiotherapy) as standard of care.

Rationale for change		Clarification of eligibility criteria following FDA comments from 15th and 16th of December 2021
Section to be changed		Section 4.1.1:1 Ezabenlimab (BI 754091)
Description of change		Language “concentrate for solution” was changed to read “solution for infusion”
Rationale for change		The previous language was incorrect per our Clinical Trial Supply Unit (CTSU). It has been corrected to read properly
Section to be changed		4.2.2 Prohibited Concomitat Medications
Description of change		The following information was added: Any standard of care therapy is allowed in the adjuvant (post-operative setting) that is deemed clinically indicated by the treating physician.
Rationale for change		Clarification of the description of other therapies to be allowed in the study by the treating physician.
Section to be changed		5.5 Biobanking
Description of change		Additional language added to section 5.5: Also, Option for blood biobanking has been removed from the protocol.
Rationale for change		Due to the low number of patients to be enrolled in the study the decision was made to delete the option for blood biobanking
Section to be changed		6.2.2 Treatment period(s); Visit 1 (V01)
Description of change		Pregnancy testing - (urine or serum) was added
Rationale for change		Urine or serum was added to give the site a choice for either test to capture pregnancy testing at Visit 1
Section to be changed		Section 10.2 – 10.2

Description of change		Table was deleted. The time schedule is found on the flowchart on page 9
Rationale for change		The table was redundant and did not provide any additional information.