Document Type:	Study Protocol
Official Title:	An Open-Label Study of Regorafenib in Combination with Pembrolizumab in Patients with Advanced or Metastatic Hepatocellular Carcinoma (HCC) after PD-1/PD-L1 Immune Checkpoint Inhibitors
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Title Page

Protocol Title: An Open-Label Study of Regorafenib in Combination with Pembrolizumab in Patients with Advanced or Metastatic Hepatocellular Carcinoma (HCC) after PD-1/PD-L1 Immune Checkpoint Inhibitors

Protocol Number: 21469 Global Amendment 1

Compound: BAY 73-4506

Study Phase: 2

Short Title: Pilot study of regorafenib plus pembrolizumab in advanced HCC patients who have been previously treated with PD-1/PD-L1 Immune Checkpoint Inhibitors

Sponsor Name and Legal Registered Address:

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Medical Monitor Name and Contact Information: Will be provided separately

This is an electronically generated document that does not bear any sponsor signatures. The signature of the sponsor's medically responsible person is filed in the Trial Master File (TMF) and is available on request.

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Global Amendment 1	08 JUN 2021
Original Protocol	20 AUG 2020

Amendment 1 (08 JUN 2021)

This amendment is considered substantial based on the relevant criteria of the European Union (EU) clinical trial legislation.

Overall Rationale for the Amendment:

The changes implemented in this protocol amendment are primarily due to health authority requests.

Section Number and Name	Description of Change	Brief Rationale
Health Authority requests		
2.1 Study Rationale	Modified text regarding recent approval for atezolizumab/bevacizumab and nivolumab/ipilimumab	Clarification of meaning
2.3.2 Benefit Assessment; and 11 References	Updated DOR information from the phase IB/II trial of lenvatinib plus pembrolizumab, and new reference cited	Correction of information cited
5.1 Inclusion Criteria; and 10.4.2 Contraception	Clarified duration of contraception use	Align with wording of Investigator's Brochure (IB)
5.2 Exclusion criteria	Changed the definition of uncontrolled hypertension to systolic blood pressure of ≥140 mmHg, diastolic blood pressure of ≥90 mmHg	Updated definition of uncontrolled hypertension
5.2 Exclusion criteria	Added gastrointestinal perforation or fistula	Align with wording of regorafenib Summary of product characteristics (SmPC)
5.2 Exclusion criteria; and 6.5.3 Prohibited Prior and Concomitant Therapies	Excluded patients using strong UGT1A9 inhibitors within 2 weeks prior to starting study intervention, and added a recommendation to avoid co-administration of strong UGT1A9 inhibitors during regorafenib treatment	
6.6 Dose Modification (Table 6–3)	Added guidance for regorafenib for Grade 3 and Grade 4 non-hematologic toxicities for current evidence of gastrointestinal perforation or fistula, and cardiac ischemia and/or infarction	
6.6.2 Dose Modification and Management of Liver Toxicity (Table 6–5)	Added guidance for monitoring liver toxicities for regorafenib for ALT/AST elevations; aligned AST/ALT values in text and table	Align with wording of regorafenib SmPC

Section Number and Name	Description of Change	Brief Rationale
10.2 Appendix 2: Clinical Laboratory Tests (Table 10–2)	Updated to mandate an amylase assessment in Panel A laboratory tests	
6.6.3 Dose Modification and Toxicity Management for Immune-related AEs Associated with Pembrolizumab (Table 6–7)	Added guidance for Grade 3 irAEs that require discontinuation from pembrolizumab. Added guidance for neurological toxicities and exfoliative dermatologic conditions. Updated guidance for all other irAEs as well as myocarditis. Added footnote for T1DM, G3/4 hypophysitis, G3/4 and hyperthyroidism. Added grading guidance for nephritis and renal function. Specified that discontinuation is permanent.	Align with wording of pembrolizumab SmPC and due to an update of pembrolizumab IB; dose modification guidelines for irAEs associated with pembrolizumab were updated
6.6.2.1 Hepatic Events of Clinical Interest (Table 6–6); and 10.2 Appendix 2: Clinical Laboratory Tests (Table 10–3)	Added HCV serotyping if genotyping is not available for HCV infection and recurrence/flare	Increase flexibility in HCV assessments
Other changes (unrelated to health authority requests)		
1.1 Synopsis; 4.1 Overall Design; and 5.1 Inclusion Criteria	Added that Cohort 1 includes participants treated with atezolizumab plus bevacizumab **only**, and specified that all participants must have had **only one** prior line of systemic immunotherapy treatment with a PD-1/PD-L1 mAb	Clarification of meaning
1.3.1 Schedule of Activities (Table 1–1); and 10.2 Appendix 2: Clinical Laboratory Tests (Table 10–1)	Added optional Panel A laboratory assessment on W1D1	Panel A tests are to be performed within 7 days of the first study intervention (W1D1). If the tests were performed in screening but >7 days before W1D1, the tests would need to be performed again on W1D1 to have updated tests and ensure patient eligibility
1.3.1 Schedule of Activities (Table 1–1); and 8.2.2 Vital Signs	Added flexibility to the relative timing of collection of vital signs and ECG; removed vital signs assessment in screening within 28 days prior to the first dose	To support best practices at hospitals and facilities; not necessary to collect vital signs twice during screening
1.3.3 Pharmacokinetic and Immunogenicity Sampling (Table 1–3)	Replaced “extension” with “expansion” in the table footnotes	Consistency throughout the protocol

Section Number and Name	Description of Change	Brief Rationale
2.1 Study Rationale; 2.2.1 Hepatocellular Carcinoma; 2.2.4 Combination of Regorafenib and Anti-PD-1 Antibody; 2.3.2 Benefit Assessment; 4.3 Justification for Dose; and 11 References	Updated results for Phase 1b study 19497; updated overall survival results data and reference for IMbrave study	New results and additional follow-up data available
4.1.1.2 Intervention Period; 4.3 Justification for Dose; 6 Study Intervention; and 6.1 Study Intervention(s) Administered (Table 6–1)	Modified the timing of regorafenib dose escalation, so it is allowed any time after the first cycle of regorafenib; removed the consultation with the sponsor in case of a decision not to escalate the dose	To allow more flexibility in the timing of dose escalation and to align with the regorafenib clinical oncology development program.
5.1 Inclusion Criteria	Updated Criterion #4 for duration of prior PD-1/PD-L1 treatment Re-worded Criterion #4 to be more precise Specified a time window for Criteria #7 and #8	To exclude hyper-progressors from the study Clarification of eligibility after disease progression Alignment with the SoA
5.2 Exclusion Criteria; 6.5 Concomitant Therapy; and 6.5.3 Prohibited Prior and Concomitant Therapies	Modified the vaccination criteria to exclude patients receiving recent live attenuated replication competent vaccines and to allow vaccines in a pandemic-related context	Clarification of vaccination criteria
6.6.1 Dose Modification and Management of Lower Gastro-intestinal Toxicity (Table 6–4)	Updated dose modification guidance for Grade 2 diarrhea	Align with wording of pembrolizumab SmPC
6.6.2.1 Hepatic Events of Clinical Interest	Updated ALT criteria for hepatic events of clinical interest	Align with available regulatory guidance
8.1 Efficacy Assessments	Updated the timing of tumor assessments after participants discontinue study treatment without confirmed radiological disease progression Updated the review of centrally collected imaging data	Consistency throughout the protocol Alignment of language with the central analysis plan

Section Number and Name	Description of Change	Brief Rationale
8.2.6 Baseline Characteristics	Specified that TMB, MSI, and PD-L1 expression are to be collected only if results are available Corrected the time window of collection of medications taken prior to study intervention	Clarification of data collection Consistency throughout the protocol
8.8 Biomarkers	Modified sentence on biomarker reporting	Clarification of meaning
9.2. Sample size determination	Updated the number of responders required to rule out an ORR of ≤ 20% in scenario 2: 34 responders are sufficient to rule out an ORR ≤ 20% using an exact binomial test	Correction of error
9.4.2 Safety Analyses	Specified that in the pilot phase, safety analyses will be done by first line treatment only and not overall Updated details regarding analysis of laboratory abnormalities	The analyses are planned to identify the respective safety profile of the drug combination in each of the two populations In clinical trials using CTCAE v.5.0, values of laboratory parameters are no longer graded
10.5.2 mRECIST for HCC	Described that non-enhancing atypical liver lesions can be selected as target lesions if needed but typical liver lesions should be prioritized; updated the criteria for complete response related to porta hepatis lymph nodes	Clarification of measurable disease within the liver parenchyma
10.5.3 iRECIST (Table 10–11)	Removed tumor imaging timing details, instead refer to the SoA	Consistency throughout the protocol
Throughout	Made several minor editorial and document formatting revisions, which are not summarized	Consistency, readability

A tracked changes version of the document will be provided separately.

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1. Protocol Summary

1.1 Synopsis

Protocol Title: An Open-Label Study of Regorafenib in Combination with Pembrolizumab in Patients with Advanced or Metastatic Hepatocellular Carcinoma (HCC) after PD-1/PD-L1 Immune Checkpoint Inhibitors

Short Title: Pilot study of regorafenib plus pembrolizumab in advanced HCC patients who have been previously treated with PD-1/PD-L1 Immune Checkpoint Inhibitors

Rationale: Recent clinical data support immunotherapy with checkpoint inhibitors as treatment options in first line (1L) for patients with advanced HCC, including nivolumab and pembrolizumab in monotherapy regimens and the recently approved combinations of atezolizumab and bevacizumab, and nivolumab in association with ipilimumab. In addition, other combination treatments with PD-1/PD-L1 inhibitors, such as durvalumab in association with tremelimumab, atezolizumab in association with cabozantinib, and pembrolizumab in association with levantinib, among others, are being assessed in Phase 3 trials.

The approved regimens in 1L have demonstrated superior survival benefits in the HCC patient population when compared to the current standard of care with oral multi-kinase inhibitors, such as sorafenib. However, a high unmet clinical need remains for patients with advanced HCC who have progressed on 1L treatment options with immunotherapy agents.

The rationale for combining immunotherapy with anti-angiogenic treatments in second line (2L) is supported by promising clinical activity observed in early phase trials for treatment-refractory cancers, such as metastatic renal cell carcinoma (RCC), after progression with a PD-1/PD-L1 immune checkpoint inhibitor (Lee et al. 2020).

Regorafenib is an oral small molecule that potently blocks multiple protein kinases and is approved for the treatment of HCC in patients who progressed after 1L therapy with sorafenib. Pembrolizumab is a highly selective and potent humanized immunoglobulin G4 (IgG4) monoclonal antibody that binds to the PD-1 receptor, blocking interaction with PD--L1 and PD-L2, thereby enhancing the functional activity of the target lymphocytes to facilitate tumor regression. Pembrolizumab has also demonstrated a survival benefit in patients who have progressed on initial treatment with sorafenib. Based on complementary modes of action between multi-kinase inhibitors (MKIs) and PD-1 inhibitors and their potentially synergistic effects on the cancer-immunity pathway, the combination of regorafenib and pembrolizumab might provide a greater clinical benefit in HCC patients.

Objectives and Endpoints (Primary and Secondary):

Objectives	Endpoints
Primary	Pilot and Expansion phases
To demonstrate the objective anti-tumor activity of regorafenib in combination with pembrolizumab as a 2L treatment for advanced HCC	Objective response rate (ORR) per Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST 1.1) by central assessment
Secondary	Pilot and Expansion phases
To evaluate other measures of anti-tumor activity of regorafenib in combination with pembrolizumab as a 2L treatment for advanced HCC	• Duration of response (DOR) per RECIST 1.1 by central assessment • Objective response rate (ORR) per RECIST 1.1 by investigator assessment • Duration of response (DOR) per RECIST 1.1 by investigator assessment
To evaluate safety and tolerability of regorafenib in combination with pembrolizumab	• Number of participants with adverse events (AEs) • Number of participants with serious adverse events (SAEs) • Number of participants with safety-relevant changes in clinical parameters • Number of participants with dose modification (dose interruption, dose reduction, dose discontinuation)

2L = second line; AE = adverse event; DOR = duration of response; HCC = hepatocellular carcinoma; ORR= objective response rate; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors 1.1; SAE = serious adverse event

Overall Design: This is a multicenter, open-label, single arm, Phase 2 trial of regorafenib in combination with pembrolizumab.

Patients with advanced or metastatic HCC who have received only one line of systemic therapy with PD-1/PD-L1 immune checkpoint inhibitors will be enrolled. All participants will be assigned to receive a starting dose of regorafenib of 90 mg every day (QD) for 3 weeks of every 4 weeks (i.e., 3 weeks on, 1 week off). If the starting dose of 90 mg QD is well tolerated after the first 4-week cycle of regorafenib, the dose should be escalated to the established MTD for regorafenib for this treatment combination (120 mg, QD) on the 3 weeks on/ 1 week off schedule. Participants will be treated with 400 mg pembrolizumab intravenously (IV) every 6 weeks (Q6W).

The study is divided into an initial pilot phase and an expansion phase. Results from the pilot phase will inform the selection of the appropriate population for further study in the expansion phase.

a) **Pilot phase:** Approximately 52 participants will be enrolled to receive regorafenib in combination with pembrolizumab
   - **Cohort 1:** 26 participants after one systemic line of therapy consisting of atezolizumab plus bevacizumab treatment combination only
   - **Cohort 2:** 26 participants after one systemic line of therapy consisting of any IO containing first line treatment (excluding atezolizumab with or without bevacizumab) in monotherapy or combination regimens

b) **Expansion phase:** If the target ORR is achieved in the pilot phase (i.e. at least 8 responders out of 26 treated in cohort 1 or at least 8 responders in each cohort), the study can enroll approximately 67 new additional participants. These additional participants can be from cohort 1 (i.e. patients progressing on atezolizumab plus bevacizumab combination) or the combined population from cohort 1 plus cohort 2 (i.e., patients progressing on any immune checkpoint inhibitor), depending on which cohorts meet the response rate criteria for expansion.

Disclosure Statement: This is an open-label sequential treatment study with a single arm, consisting of a pilot phase and an expansion phase.

Number of Participants: Approximately 170 participants will be screened to achieve a target of approximately 119 treated participants in total, including the pilot and expansion phases.

Note: "Enrolled" means a participant's, or their legally acceptable representative's (if acceptable by local law), agreement to participate in a clinical study following completion of the informed consent process.

Intervention Groups and Duration: In the pilot phase, participants will be enrolled in two cohorts based on the treatment received in first line. The participant population for the expansion phase will be determined based on the pilot phase.

The start of the screening period is defined by signing of the informed consent form (ICF). Participants will be screened for eligibility up to 28 days prior to Week 1 Day 1 (W1D1)

The start of the intervention period is defined by the first administration of the study intervention combination. Participants will be treated in 6-week cycles for pembrolizumab (400 mg IV, Q6W) and in 4-week cycles for regorafenib. Regorafenib will be administered orally (90 mg, QD starting dose) on a 3 weeks on / 1 week off schedule. If the starting dose of 90 mg QD is well tolerated after the first 4-week cycle of regorafenib, the dose should be escalated to the established MTD for regorafenib for this treatment combination (120 mg, QD) on the 3 weeks on/ 1 week off schedule. Participants will receive study intervention until disease progression (as defined by RECIST 1.1), unacceptable toxicity, consent withdrawal, withdrawal from the study at the discretion of the investigator or his/her designated associate(s), or until any other withdrawal criteria are met. Treatment beyond radiological progression is possible if the participant is still benefiting from treatment.

Participants who complete 18 infusions of pembrolizumab (after approximately 2 years of treatment) need to discontinue treatment with pembrolizumab. Regorafenib treatment can be continued beyond 2 years until withdrawal criteria are met.

After permanent discontinuation from study intervention, the active follow-up period begins, including safety and efficacy follow-up visits. An end of treatment (EoT) visit will be

performed first, within 14 days (window of +7 days) after the last dose of study intervention or decision to discontinue intervention. A safety follow-up visit will take place 30 days (window of +7 days) after the last administration of study intervention, and additionally, 90 days (window of +7 days) after the last administration of pembrolizumab. Efficacy follow-up visits will take place for participants who discontinued study intervention for reasons other than radiologically confirmed progressive disease (PD), death, withdrawal of consent, or lost to follow-up. These visits include tumor assessments, study intervention-related toxicity/AEs, and information about subsequent anti-cancer therapy. Active follow-up will be terminated by radiological PD, the start of a new anti-cancer treatment, death, withdrawal of consent for further participation, or lost to follow-up.

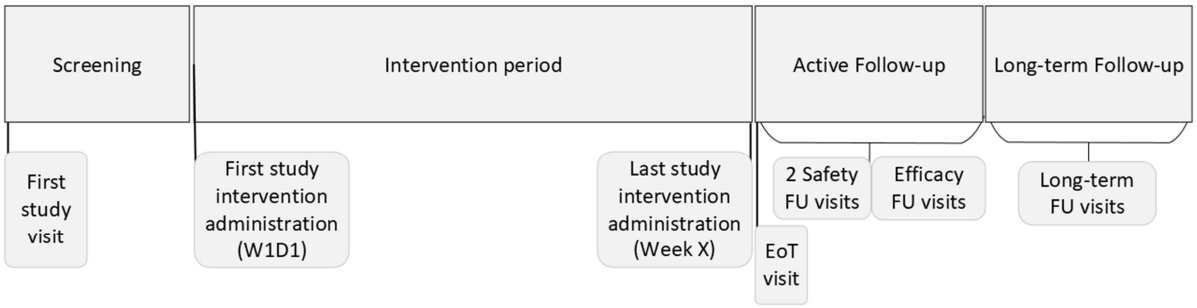
After completion of the active follow-up period, participants will enter the long-term follow-up period. Participants will be followed for survival status and subsequent anti-cancer therapy by a telephone call at 3-month intervals (± 14 days) until the end of the study, withdrawal of consent, lost to follow-up, or death, whichever comes first.

Data Monitoring Committee: Not applicable

1.2 Schema

An overview of the study schema is presented in Figure 1–1.

Figure 1–1: Study Schema



EoT = End of treatment; FU = follow-up; W1D1 = Week 1 Day 1

The overall study design (see Figure 4–1) is described in Section 4.1.

1.3 Schedule of Activities (SoA)

1.3.1 Schedule of Activities

Table 1–1: Schedule of Activities

Procedure	Screening		Intervention Period (weeks)													End of treatment (DC)	Active follow-up			Long-term follow-up visits after DC	Notes
																	Safety follow-up visits		Efficacy follow-up visits until PD		
	Within 28 days prior to the first dose	Within 7 days prior to the first dose	**W 1 D1**	**W 2 D1**	**W 3 D1**	**W 4 D1**	**W 5 D1**	**W 6 D1**	**W 7 D1**	**W 8 D1**	**W 9 D1**	**W 13 D1**	**W 17 D1**	**W 19 D1**	**Subseq pembro infusion visit Q6W**	**Subseq rego admin. visit Q4W**	Within 14 days after last dose or DC decision (both rego and pembro)	30 days after last study dose	90 days after last pembro infusion[g]	Every 6 weeks / Every 9 weeks[h]	Every 3 months	
Visit window			± 3 days														+7 days	+7 days	+7 days	±7days	±14 days	
Informed consent	X																					
IxRS[a]	X		←----------														----------→					Contact the IxRS as described in [a]
General																						
Demography	X																					See Section 8.2.6
Medical history (including substance usage: drugs, alcohol, tobacco, and caffeine)	X																					Prior disease histology, diagnosis, disease classification, treatments, co-existing diseases, prior surgery, and allergy history
Inclusion and exclusion criteria	X	X	X																			Re-check status before 1st dose of study medication

Table 1–1: Schedule of Activities

Procedure	Screening		Intervention Period (weeks)													End of treatment (DC)	Active follow-up			Long-term follow-up visits after DC	Notes
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	Within 28 days prior to the first dose	Within 7 days prior to the first dose	**W 1 D1**	**W 2 D1**	**W 3 D1**	**W 4 D1**	**W 5 D1**	**W 6 D1**	**W 7 D1**	**W 8 D1**	**W 9 D1**	**W 13 D1**	**W 17 D1**	**W 19 D1**	**Subseq pembro infusion visit Q6W**	**Subseq rego admin. visit Q4W**	Within 14 days after last dose or DC decision (both rego and pembro)	30 days after last study dose	90 days after last pembro infusion[g]	Every 6 weeks / Every 9 weeks[h]	Every 3 months	
Visit window			± 3 days														+7 days	+7 days	+7 days	±7days	±14 days	
BCLC staging		X																				See Appendix 8, Section 10.8
AFP		X															X					
Child-Pugh score		X																				See Appendix 9, Section 10.9
History of prior anti-cancer treatment	X																					Systemic therapy, surgery, loco-regional therapy and radiotherapy

Table 1–1: Schedule of Activities

Procedure	Screening		Intervention Period (weeks)												End of treatment (DC)	Active follow-up			Long-term follow-up visits after DC	Notes
																Safety follow-up visits		Efficacy follow-up visits until PD		
	Within 28 days prior to the first dose	Within 7 days prior to the first dose	**W 1 D1**	**W 2 D1**	**W 3 D1**	**W 4 D1**	**W 5 D1**	**W 6 D1**	**W 7 D1**	**W 8 D1**	**W 9 D1**	**W 13 D1**	**W 17 D1**	**W 19 D1**	**Subseq pembro infusion visit Q6W**	**Subseq rego admin. visit Q4W**	Within 14 days after last dose or DC decision (both rego and pembro)	30 days after last study dose	90 days after last pembro infusion[g]	Every 6 weeks / Every 9 weeks[h]	Every 3 months	
Visit window			± 3 days														+7 days	+7 days	+7 days	±7days	±14 days	
Blood or urine pregnancy test if applicable (women of childbearing potential only)[b]		X[f]	Monthly															X	X			Monthly testing should be conducted as per local regulations where applicable, up to and including whichever is latest: the safety FU visit or 4 months after the last pembrolizumab infusion
Hepatitis B and C screening, Hepatitis virus panel	X		If clinically indicated																			See Table 10–3
Safety																						See Section 8.2

Table 1–1: Schedule of Activities

Procedure	Screening		Intervention Period (weeks)													End of treatment (DC)	Active follow-up			Long-term follow-up visits after DC	Notes
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	Within 28 days prior to the first dose	Within 7 days prior to the first dose	**W 1 D1**	**W 2 D1**	**W 3 D1**	**W 4 D1**	**W 5 D1**	**W 6 D1**	**W 7 D1**	**W 8 D1**	**W 9 D1**	**W 13 D1**	**W 17 D1**	**W 19 D1**	**Subseq pembro infusion visit Q6W**	**Subseq rego admin. visit Q4W**	Within 14 days after last dose or DC decision (both rego and pembro)	30 days after last study dose	90 days after last pembro infusion[g]	Every 6 weeks / Every 9 weeks[h]	Every 3 months	
Visit window			± 3 days														+7 days	+7 days	±7days	±14 days	
12-lead ECG	X		X													X					See Section 8.2.3; must be preceded by 5 minutes of rest
Vital signs		X	X	X	X		X	X	X		X	X	X	X	X	X	X	X			See Section 8.2.2; must be preceded by 5 minutes of rest
ECOG PS		X	X				X		X		X	X	X	X	X	X	X	X	X		See Section 8.2.5
AE/SAE review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[i]		After EoT: Up to 30 (+7) days after last regorafenib or pembrolizumab dose; up to 90 (+7) days for SAE related to pembrolizumab unless a new anticancer therapy has been initiated See Section 8.3

Table 1–1: Schedule of Activities

Procedure	Screening		Intervention Period (weeks)													End of treatment (DC)	Active follow-up			Long-term follow-up visits after DC	Notes
																	Safety follow-up visits		Efficacy follow-up visits until PD		
	Within 28 days prior to the first dose	Within 7 days prior to the first dose	W 1 D1	W 2 D1	W 3 D1	W 4 D1	W 5 D1	W 6 D1	W 7 D1	W 8 D1	W 9 D1	W 13 D1	W 17 D1	W 19 D1	Subseq pembro infusion visit Q6W	Subseq rego admin. visit Q4W	Within 14 days after last dose or DC decision (both rego and pembro)	30 days after last study dose	90 days after last pembro infusion[g]	Every 6 weeks / Every 9 weeks[h]	Every 3 months	
Visit window			± 3 days														+7 days	+7 days	+7 days	±7days	±14 days	
Concomitant medication review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			After EoT: Up to 30 (+7) days after last regorafenib or pembrolizumab dose; up to 90 (+7) days for concomitant medication for SAE related to pembrolizumab unless a new anticancer therapy has been initiated
Full physical examination	X		X														X					See Section 8.2.1
Directed physical examination		X		X	X	X	X	X	X	X	X	X	X	X	X	X						See Section 8.2.1
Laboratory assessments																						See Section 8.2.4
Panel A		X	X[j]						X			X		X	X	X		X				See Section 10.2
Panel B				X	X	X	X	X		X	X		X			X	X					See Section 10.2

Table 1–1: Schedule of Activities

Procedure	Screening		Intervention Period (weeks)													End of treatment (DC)	Active follow-up			Long-term follow-up visits after DC	Notes
																	Safety follow-up visits		Efficacy follow-up visits until PD		
	Within 28 days prior to the first dose	Within 7 days prior to the first dose	**W 1 D1**	**W 2 D1**	**W 3 D1**	**W 4 D1**	**W 5 D1**	**W 6 D1**	**W 7 D1**	**W 8 D1**	**W 9 D1**	**W 13 D1**	**W 17 D1**	**W 19 D1**	**Subseq pembro infusion visit Q6W**	**Subseq rego admin. visit Q4W**	Within 14 days after last dose or DC decision (both rego and pembro)	30 days after last study dose	90 days after last pembro infusion[g]	Every 6 weeks / Every 9 weeks[h]	Every 3 months	
Visit window			± 3 days														+7 days	+7 days	+7 days	±7days	±14 days	
Treatment intervention																						
Pembrolizumab infusion			X						X			X		X	X							Every 6 weeks until a maximum of 18 infusions are completed
Regorafenib and diary dispensing			X				X				X	X	X			X						
Regorafenib administration[c]			X	X	X		X	X	X		X*	X*	X*	X*	X*	X*						The regorafenib break must not be shorter than 7 days and should not be longer than 10 days. * 3 weeks on, 1 week off, QD.

Table 1–1: Schedule of Activities

Procedure	Screening		Intervention Period (weeks)													End of treatment (DC)	Active follow-up			Long-term follow-up visits after DC	Notes
																	Safety follow-up visits		Efficacy follow-up visits until PD		
	Within 28 days prior to the first dose	Within 7 days prior to the first dose	**W 1 D1**	**W 2 D1**	**W 3 D1**	**W 4 D1**	**W 5 D1**	**W 6 D1**	**W 7 D1**	**W 8 D1**	**W 9 D1**	**W 13 D1**	**W 17 D1**	**W 19 D1**	**Subseq pembro infusion visit Q6W**	**Subseq rego admin. visit Q4W**	Within 14 days after last dose or DC decision (both rego and pembro)	30 days after last study dose	90 days after last pembro infusion[g]	Every 6 weeks / Every 9 weeks[h]	Every 3 months	
Visit window			± 3 days														+7 days	+7 days	+7 days	±7days	±14 days	
Drug accountability, collect unused study intervention and check participant diary			X				X				X	X	X			X						
Efficacy																						
Tumor assessment	X		Every 6 weeks (±7days) until PD during the first 54 weeks of treatment; Every 9 weeks (±7days) until PD afterwards																			Schedule for tumor assessments to be followed regardless of potential dose delays for either drug. See Section 8.1 for details
Survival status																					X	

Table 1–1: Schedule of Activities

Procedure	Screening		Intervention Period (weeks)													End of treatment (DC)	Active follow-up			Long-term follow-up visits after DC	Notes
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	Within 28 days prior to the first dose	Within 7 days prior to the first dose	**W 1 D1**	**W 2 D1**	**W 3 D1**	**W 4 D1**	**W 5 D1**	**W 6 D1**	**W 7 D1**	**W 8 D1**	**W 9 D1**	**W 13 D1**	**W 17 D1**	**W 19 D1**	**Subseq pembro infusion visit Q6W**	**Subseq rego admin. visit Q4W**	Within 14 days after last dose or DC decision (both rego and pembro)	30 days after last study dose	90 days after last pembro infusion[g]	Every 6 weeks / Every 9 weeks[h]	Every 3 months	
Visit window			± 3 days														+7 days	+7 days	+7 days	±7days	±14 days	
Review of subsequent anti-cancer therapy																				X	X	
Research sample collection																						
Regorafenib PK sampling			X	X	X		X		X													See Table 1–3 for details, and see Section 8.5
Pembro PK sampling			See Table 1–3 for sampling time points																			
IM sampling			See Table 1–3 for sampling time points																			
Biomarker blood sampling		See Table 1–2 for sampling time points																				
Biomarker baseline tumor tissues[d]	X																					See Section 8.8

Table 1–1: Schedule of Activities

Procedure	Screening		Intervention Period (weeks)													End of treatment (DC)	Active follow-up			Long-term follow-up visits after DC	Notes
																	Safety follow-up visits		Efficacy follow-up visits until PD		
	Within 28 days prior to the first dose	Within 7 days prior to the first dose	**W 1 D1**	**W 2 D1**	**W 3 D1**	**W 4 D1**	**W 5 D1**	**W 6 D1**	**W 7 D1**	**W 8 D1**	**W 9 D1**	**W 13 D1**	**W 17 D1**	**W 19 D1**	**Subseq pembro infusion visit Q6W**	**Subseq rego admin. visit Q4W**	Within 14 days after last dose or DC decision (both rego and pembro)	30 days after last study dose	90 days after last pembro infusion[g]	Every 6 weeks / Every 9 weeks[h]	Every 3 months	
Visit window			± 3 days														+7 days	+7 days	+7 days	±7days	±14 days	
Biomarker on-treatment / EoT tumor tissue[e]								X*								X**					*Mandatory if medically feasible on W6D1 (+/- 3 days) **Optional biopsy at EoT (+7 days) for BM collection after progression See Section 8.8

admin. = administration; AE = adverse event; AFP = alpha-fetoprotein; BCLC = Barcelona Clinic Liver Cancer staging; BM = biomarker; D = day; DC = discontinuation of study intervention; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group Performance status; eCRF = electronic case report form; EoT = end of treatment; FU = follow-up; hCG = human chorionic gonadotropin; IM = immunogenicity; IxRS = Interactive Voice/Web Response System; PD = progressive disease; pembro = pembrolizumab; PI/ICF = patient information/Informed consent form; PK = pharmacokinetic(s); Q4W = every 4 weeks; Q6W = every 6 weeks; QD = once daily; rego = regorafenib; SAE = serious adverse event; subseq = subsequent; W = week(s)

a. Contact the IxRS to record the following: 1. To register the participant who has signed the PI/ICF (a unique participant identifier will be assigned), 2. In case the participant is a screening failure, 3. On the week of every pembrolizumab infusion so that the specific participant drug vial(s) can be provided for dispensing purposes, 4. On every 4th week so that the specific participant drug bottle(s) of regorafenib can be provided for dispensing purposes, 5. In case the participant has discontinued study intervention (EoT) for any reason.

b. Highly sensitive (serum or urine) hCG pregnancy test (as needed for women of childbearing potential). Postmenopausal women who have not had periods for more than 1 year or surgically sterilized women will not be required to undergo a pregnancy test (this information should be recorded under medical history on the eCRF).

c. Site personnel are asked to call participants for at least the first 3 cycles to remind them of omitting regorafenib during the 4th week of a cycle.

d. Provision of recent tumor tissue (i.e. tumor tissue obtained within 180 days of enrollment and after the last dose of most recent anti-cancer therapy OR a new biopsy) is mandatory for all participants at screening. Exceptions will be accepted for participants with no recent baseline tumor tissues after documented discussion and approval by the sponsor. Archival tumor tissue is mandatory if available.

e. On treatment: W6D1 (± 3 days), mandatory if medically feasible. At progression: EoT (+7 days), optional. The lesion accessible for biopsy may not be the only target lesion and should not be located in a previously irradiated field. Ideally, the same lesion should be biopsied before treatment and on treatment whenever possible.

f. Pregnancy testing should be done within 24 hours before the first dose for urine and within 72 hours before the first dose for serum.

Table 1–1: Schedule of Activities

Procedure	Screening		Intervention Period (weeks)												End of treatment (DC)	Active follow-up			Long-term follow-up visits after DC	Notes
																Safety follow-up visits		Efficacy follow-up visits until PD		
	Within 28 days prior to the first dose	Within 7 days prior to the first dose	**W 1 D1**	**W 2 D1**	**W 3 D1**	**W 4 D1**	**W 5 D1**	**W 6 D1**	**W 7 D1**	**W 8 D1**	**W 9 D1**	**W 13 D1**	**W 17 D1**	**W 19 D1**	**Subseq pembro infusion visit Q6W**	**Subseq rego admin. visit Q4W**	Within 14 days after last dose or DC decision (both rego and pembro)	30 days after last study dose	90 days after last pembro infusion[g]	Every 6 weeks / Every 9 weeks[h]	Every 3 months	
Visit window			± 3 days														+7 days	+7 days	+7 days	±7days	±14 days	

g. If pembrolizumab is permanently discontinued first and the day 90 safety follow-up visit after the last dose of pembrolizumab falls into the regorafenib treatment period or regorafenib day 30 safety follow-up period, no separate pembrolizumab day 90 safety follow-up visit is necessary as the information gathering and examinations will occur with regorafenib treatment cycle visit, EoT visit, or day 30 safety follow-up visit (required for either regorafenib, pembrolizumab, or combination). All pregnancies and exposure during breastfeeding should be collected from the start of study intervention through 120 days following discontinuation of study intervention, or 30 days following discontinuation of study intervention if the participant initiates new anti-cancer therapy.

h. Every 6 weeks (±7 days) until PD during the first 54 weeks of treatment; every 9 weeks (±7days) until PD afterwards

i. Study intervention-related AEs only

j. Optional; however, Panel A is required on W1D1 if screening tests were not completed within 7 days of first study intervention.

1.3.2 Biomarker Sampling

Table 1–2: Schedule of Biomarker Blood Sampling

Procedure	Screening		Intervention Period (weeks)[a]												End of treatment (DC)
	Within 28 days prior to the first dose	Within 7 days prior to the first dose	W1 D1	W2 D1	W3 D1	W4 D1	W5 D1	W6 D1	W7 D1	W8 D1	W9 D1	W13 D1	W19 D1	W25 D1	Within 14 days after last dose or DC decision (DC of both rego and pembro)
			± 3 days												+ 7 days
Whole blood for pharmacogenetics			X												
Biomarker blood for flow cytometry 1[b]		X	X	X			X		X		X	X	X	X	X
Biomarker blood for flow cytometry 2[b]		X	X	X			X		X		X	X	X	X	X
Biomarker serum		X	X	X			X		X		X	X	X	X	X
Biomarker plasma		X	X	X			X		X		X	X	X	X	X
Biomarker plasma for ctDNA		X	X				X		X			X	X	X	X

ctDNA = circulating tumor deoxyribonucleic acid; D = day; DC = discontinuation of study intervention; pembro = pembrolizumab; W = week(s)

a: All samples are to be collected pre-dose.

b. Blood will be collected for flow cytometry from participants enrolled in the expansion phase only, and may only be collected in a subset of participants.

1.3.3 Pharmacokinetic and Immunogenicity Sampling

Table 1–3: Pharmacokinetic and Immunogenicity Sample Collection Plan

Sampling time	Regorafenib, M-2 and M-5 PK	Pembrolizumab PK[b,c]	Pembrolizumab immunogenicity[c]	Exploratory immunogenicity[d]
W1 D1	pre-dose and at 0.5 h[a] and 3-4 h[a] after oral intake	pre-infusion	pre-infusion	pre-infusion
W2 D1	pre-dose			
W3 D1	pre-dose and 2-4 h[a] after oral intake			
W5 D1	pre-dose and at 0.5 h[a] and 3-4 h[a] after oral intake			
W7 D1	pre-dose and 2-4 h[a] after oral intake	pre-infusion	pre-infusion	pre-infusion
W13 D1		pre-infusion	pre-infusion	
W19 D1		pre-infusion	pre-infusion	
W25 D1		pre-infusion	pre-infusion	
W37 D1		pre-infusion	pre-infusion	
W49 D1		pre-infusion	pre-infusion	
W73 D1		pre-infusion	pre-infusion	
W97 D1		pre-infusion	pre-infusion	

ADA = anti-drug antibodies; D = day; h = hour(s); M-2 / M-5 = metabolites of regorafenib; PK = pharmacokinetics; W = week
Note: Also refer to Section 8.5.

a. If regorafenib is not administered on the day of PK sampling, the pre-dose samples will be collected and the post-dose samples will not be collected.
b. Pembrolizumab pre-dose samples should be taken just prior to start of infusion (within 24 hours before infusion of pembrolizumab). If the infusion is delayed and a pre-dose sample is already collected, there is no need to collect an additional pre-dose sample. If pembrolizumab is not administered on the scheduled day, PK pre-dose samples should still be collected. Otherwise PK sampling should always be linked to the pembrolizumab administration.
c. Pembrolizumab PK and ADA samples will be collected while the participant is receiving pembrolizumab treatment. Samples will be collected during the pilot phase of the study and may be collected during the expansion phase based on emerging data.
d. Additional exploratory ADA samples will be collected during the pilot phase of the study and may be collected during the expansion phase based on emerging data.

2. Introduction

2.1 Study Rationale

This clinical study aims to evaluate the efficacy and safety of regorafenib in combination with pembrolizumab for the treatment of advanced hepatocellular carcinoma (HCC) in adult participants who have been previously treated with PD-1/PD-L1 immune checkpoint inhibitor in monotherapy or combinations regimens.

The rationale for evaluating regorafenib in combination with pembrolizumab in patients with unresectable advanced HCC is as follows:

- **Treatment of advanced HCC remains an area of high unmet need in 2L**. Patients with tumors in the advanced stage (Barcelona Clinic Liver Cancer [BCLC] stage C) have a dismal prognosis if untreated, with a median overall survival (OS) of 8 months (Llovet et al. 2008).

  Until 2020, only two oral MKIs, sorafenib and levantinib, were the approved first line systemic treatments for advanced HCC. However, the landscape is rapidly changing for patients with unresectable HCC. Recently, the Food and Drug Administration (FDA) approved the combination of atezolizumab, a PD-L1 checkpoint inhibitor, and bevacizumab, a monoclonal antibody that inhibits vascular endothelial growth factor (VEGF), as first line treatment. In 2020, the FDA approved the combination of nivolumab, a PD-L1 checkpoint inhibitor, and ipilimumab, an anti-CTLA-4 antibody in patients with HCC previously treated with sorafenib. There are additional ongoing Phase 2 and 3 clinical trials with immune checkpoint inhibitors in monotherapy and combination regimens also targeting the first line setting.

  The best regimen in second line is not well established and all the current options were approved for the patients who were previously treated with MKI. Therefore, an ongoing high unmet medical need remains for patients with unresectable HCC who progressed or did not tolerate these novel immunotherapy agents.

- **Regorafenib has established clinical activity as a single agent in advanced HCC.** Regorafenib is an MKI and is the first systemic treatment shown to provide a survival benefit in HCC patients progressing on sorafenib treatment (Bruix et al. 2017). Regorafenib is approved for second line HCC treatment, and has shown a comparable level of clinical benefit in the second line setting as observed with sorafenib as first line therapy. Pembrolizumab, an anti-PD-1 antibody, is approved for the treatment of patients with HCC previously treated with sorafenib (Zhu et al. 2018).

- **Preliminary results from the ongoing Phase 1b study of regorafenib in combination with pembrolizumab in patients with advanced HCC with no prior systemic therapy have shown promising efficacy and an acceptable safety profile**. Regorafenib is approved for the treatment of patients with HCC who progressed after first line therapy with sorafenib. Pembrolizumab is a highly selective and potent humanized IgG4 monoclonal antibody that binds to the PD-1 receptor, blocking interaction with PD-L1 and PD-L2, thereby enhancing the functional activity of the target lymphocytes to facilitate tumor regression. Of the 35 participants treated with 120 mg regorafenib QD (3 weeks on, 1 week off), 31 were evaluable for efficacy and 9 (29%) achieved a partial response (PR) per RECIST 1.1, with a disease control rate (DCR) of 94%. At the MTD of regorafenib (120 mg/day), approximately three-

quarters of the participants had a regorafenib dose reduction or interruption. An additional exploratory cohort was established to evaluate regorafenib 80 mg QD (3 weeks on, 1 week off). As of NOV 2020, 22 participants had been treated with regorafenib at the 80 mg/day dose level. Of the 21 participants who were evaluable for efficacy, 3 (14%) had a PR with a DCR of 86%. The efficacy data were immature at the NOV 2020 cut-off, as treatment was ongoing in 13 of 22 participants (59%). The 80 mg regorafenib dose level demonstrated a more favorable safety profile, with 50% of the participants requiring a regorafenib dose modification (dose reduction or interruption).

- **Targeting both the anti-angiogenic and immune checkpoint pathways may provide synergistic anti-tumor activity.** The rationale for combining immunotherapy with anti-angiogenic treatments has been outlined by Khan and Kerbel (Khan and Kerbel 2018) and is supported by both preclinical and clinical results in various indications including HCC (Ikeda et al. 2018, Kato et al. 2019). Immune checkpoint inhibitors appear to affect the tumor vasculature as well, which may synergize with the inhibition of VEGF signaling by regorafenib. Therefore, therapies combining regorafenib with a PD-1 antibody, such as pembrolizumab, present an opportunity to improve the effectiveness of second line therapy in patients with unresectable advanced or metastatic HCC.
- **Combination of MKI and ICI may provide mechanisms to overcome resistance to immunotherapy.** Despite promising efficacy in different tumor indications, some patients fail to respond to immune checkpoint inhibitors (ICI), and others who demonstrate encouraging results can acquire resistance during treatment. Resistance to ICIs has been linked to local immunosuppression effects (O'Donnell et al. 2017). MKIs are associated with modifications in the tumor microenvironment, including the alteration of immune cell infiltration, which can lead to a decreased function of immune suppressor cells (Kwilas et al. 2015). Based on the current approved treatments in 1L for HCC, fewer than one-third of patients respond to immunotherapy, therefore, there is also an opportunity to explore whether a different combination of treatment including a MKI can overcome ICI resistance and improve response among HCC patients.

2.2 Background

2.2.1 Hepatocellular Carcinoma

HCC is an aggressive tumor that frequently occurs in the setting of chronic liver disease and cirrhosis and accounts for up to 85% of all primary liver cancers worldwide (Bray et al. 2018). Liver cancer was reported to be the fourth most common cause of cancer death in the world and to be responsible for nearly 782,000 deaths in 2018 (accounting for 8.2% of total cancer deaths) (Bray et al. 2018). Although there are a number of treatment options available for HCC, mortality is still high.

For 1L, sorafenib and lenvatinib (oral multi-kinase inhibitors) are indicated based on proven benefit in Phase 3 studies. In the SHARP trial, sorafenib was shown to improve OS from 7.9 to 10.7 months compared to placebo in patients with advanced HCC (Llovet et al. 2008). Lenvatinib has been shown to be non-inferior to sorafenib as first line treatment in terms of OS in the REFLECT trial in patients with unresectable HCC (Kudo et al. 2018).

There are recent data supporting immunotherapy with checkpoint inhibitors, in monotherapy or combination regimens, as treatment options in 1L.

Recently, the combination of atezolizumab, a PD-L1 checkpoint inhibitor, and bevacizumab, a monoclonal antibody that inhibits VEGF, and also the combination of nivolumab, a PD-L1 checkpoint inhibitor, and ipilimumab, an anti-CTLA-4 antibody, were approved as front line treatments for treatment for patients with advanced HCC previously treated with sorafenib.

The regulatory approval of the atezolizumab and bevacizumab combination was based on results of the Phase 3 IMbrave 150 trial, which demonstrated a significant improvement in median OS and progression-free survival (PFS) in the atezolizumab plus bevacizumab treatment arm when compared to patients under sorafenib treatment. The results based on additional follow-up data showed a hazard ratio (HR) of 0.66 (95% CI [0.52; 0.85], $p \leq 0.0009$) for OS after a median follow-up of 15.6 months (Finn et al. 2021).

The efficacy of the nivolumab and ipilimumab for patients with advanced HCC was determined in the Phase I/II CheckMate040 trial, a multicenter, multiple cohort, open-label trial conducted in patients with HCC who progressed on or were intolerant to sorafenib. After a follow-up of 28 months, 33% (95% CI [20; 48]) of the patients responded to this treatment combination, with 8% achieving complete response (CR) and 24% PR. The DOR ranged from 4.6 to 30.5 months (Yau et al. 2019a).

Multiple studies to assess combination treatments for 1L are ongoing and the landscape for 1L therapy in patients with advanced HCC is rapidly changing.

Although the primary endpoint of OS did not achieve statistical significance, preliminary results of the Phase 3 CheckMate 459 trial showed clinically meaningful improvement in OS (median 16.4 versus 14.7 months) of nivolumab when compared to sorafenib in patients with advanced HCC (Yau et al. 2019b). The interim results of the Phase 1b KEYNOTE-524 study also showed promising anti-tumor activity (ORR of 44.8% per mRECIST evaluation) for the combination of lenvatinib and pembrolizumab in patients with advanced HCC not eligible for loco-regional treatment (Llovet et al. 2019).

In addition combinations such as durvalumab, an anti-PD-L1, with tremelimumab, an anti-CTLA-4 antibody, cabozantinib, a multi-receptor tyrosine kinase inhibitor, plus atezolizumab, among others, are being assessed in 1L in large Phase 3 trials for patients with advanced HCC.

For 2L, regorafenib, ramucirumab and cabozantinib have been approved based on Phase 3 studies that showed survival benefits compared to placebo in patients treated with sorafenib. Clinical data also support pembrolizumab and nivolumab in monotherapy as treatment options for patients previously treated with sorafenib.

Cabozantinib is a potent inhibitor of several receptor tyrosine kinases, which demonstrated superior efficacy in OS (10.2 versus 8 months), in the patient population after second or third line therapy (Abou-Alfa et al. 2018).

Ramucirumab is a recombinant human IgG1 monoclonal antibody that binds to VEGF receptor 2 (VEGFR2), which also demonstrated superior OS (8.5 versus 7.3 months; 95% CI [0.53; 0.95]) over placebo in Child-Pugh A HCC patients with alpha-fetoprotein (AFP) ≥400 who had progressed after first line sorafenib treatment (Zhu et al. 2019).

Results from the Phase 2 KEYNOTE-224 study support the benefits of pembrolizumab (anti-PD-1 monoclonal antibody) as an alternative PD-1 inhibitor for the patients previously treated with sorafenib. The median duration of treatment was of 4.2 months, with an ORR of 17%

and with 44% stable disease (SD). These results were confirmed in the Phase 3 KEYNOTE-240 trial of best supportive care (BSC) plus either pembrolizumab or placebo for second line therapy of advanced HCC, which also demonstrated survival benefit in second line HCC. After a median follow-up of 13.8 months, both PFS (3 versus 2.8 months) and OS (13.9 versus 10.6 months, HR 0.78, 95% CI [0.61; 0.998]) were improved. The ORR was higher for pembrolizumab (18.3% versus 4.4%), there were more complete responders with pembrolizumab (6 versus none), and responses were durable (median DOR 13.8 months, range 1.5 to 23.6+ months) (Finn et al. 2020).

Nivolumab monotherapy also showed superior efficacy in patients with HCC and Child-Pugh A cirrhosis who have progressed on or were intolerant to sorafenib based on the results of the multicohort Phase 1/2 CheckMate 040 trial. The ORR by RECIST 1.1, was 15% (95% CI [6; 28]) in the dose escalation phase, with 3 CR and 4 PR. The median DOR was 17 months (95% CI [6; 24]) and the 6-month and 9-month OS rates were both 66% (95% CI [51; 78]) (El-Khoueiry et al. 2017).

Regorafenib is approved for the treatment of patients with HCC who progressed during sorafenib treatment based on the RESORCE study, a randomized, double-blind, placebo-controlled, Phase 3 study (Bruix et al. 2017). There, the addition of regorafenib to BSC resulted in significantly better OS compared to placebo plus BSC, with a HR of 0.63 (95% CI [0.50; 0.79]; one-sided $p<0.0001$) and a median OS of 10.6 months vs. 7.8 months; this represents a 37% reduced risk of death in the regorafenib group compared to the placebo group. In addition, the study showed similar clinical benefit for regorafenib in the second line setting as observed with sorafenib in the first line.

Although these drugs are available for patients previously treated with tyrosine kinase inhibitors, a high unmet clinical need remains in this patient population for the patients who have progressed on first line treatment options with immunotherapy agents.

2.2.2 Regorafenib

Regorafenib (BAY 73-4506) is an oral small molecule tyrosine kinase inhibitor that potently blocks multiple protein kinases, including kinases involved in tumor angiogenesis (VEGFR1, -2, -3, TIE2), oncogenesis (KIT, RET, RAF-1, BRAF, $BRAF^{V600E}$), metastasis (VEGFR3, PDGFR, FGFR) and tumor immunity (CSF1R). In preclinical studies, regorafenib has demonstrated potent anti-tumor activity as a single agent in a broad spectrum of tumor models including hepatocellular tumor models, which is likely mediated by its anti-angiogenic and anti-proliferative effects.

2.2.2.1 Pharmaceutical and Therapeutic Background

The recommended dose of regorafenib as monotherapy is 160 mg (4 tablets, each containing 40 mg regorafenib), taken orally once daily for 3 weeks on therapy followed by 1 week off therapy to comprise a cycle of 4 weeks.

Based on the dose escalation study (study 11650), the 160 mg QD dose given for 3 weeks followed by 1 week off treatment in repeated 4 weeks cycles was selected for future Phase 2 and 3 studies in adults. Three large randomized Phase 3 company-sponsored studies in metastatic colorectal cancer (mCRC), gastrointestinal stromal tumor (GIST), and HCC have reported positive outcomes with this dosing regimen.

Regorafenib undergoes extensive and complex metabolism, including oxidation and glucuronidation leading to metabolites that can be reduced and / or cleaved in the intestinal milieu, resulting in enterohepatic cycling *in vivo*. Regorafenib is metabolized primarily in the

liver by oxidative metabolism mediated by cytochrome P450 3A4 (CYP3A4), as well as by glucuronidation mediated by UGT1A9. The main circulating metabolites of regorafenib in human plasma are M-2 (N-oxide) and M-5 (N-oxide and N-desmethyl), which are pharmacologically active. Whereas plasma concentrations of M-2 and M-5 after a single dose of regorafenib are lower than those of the parent compound, steady state plasma concentrations of M-2 and M-5 are comparable to those of regorafenib.

Metabolites may be reduced or hydrolyzed in the gastrointestinal tract by microbial flora, allowing reabsorption of the unconjugated drug and metabolites (enterohepatic circulation). Co-administration of a single dose of regorafenib after pre-treatment with neomycin (a poorly absorbed antimicrobial agent that eradicates the gastrointestinal microflora) had no significant effect on the exposure of regorafenib. There was a decrease in the exposure of M-2 and M-5 by 76% and 86%, respectively.

The concentrations of regorafenib and its major pharmacologically active metabolites M-2 and M-5 were highest when given after a low fat (light) breakfast as compared to either a high fat breakfast or fasting condition. The exposure for regorafenib was increased by 48% when administered with high fat breakfast, and 36% when administered with a low fat breakfast, compared to fasting.

Plasma concentration-time profiles for regorafenib as well as for the major circulating metabolites showed multiple peaks across the 24 hour dosing interval, which are attributed to enterohepatic circulation. Protein binding of regorafenib to human plasma proteins *in vitro* is high (99.5%). Following oral administration, mean elimination half-life for regorafenib and its metabolite M-2 in plasma ranges from 20 to 30 hours in different studies. The mean elimination half-life for the metabolite M-5 is approximately 60 hours (range from 40 to 100 hours).

Accumulation of regorafenib at steady state results in about a 2-fold increase in plasma concentrations, which is consistent with the elimination half-life and dosing frequency. At steady state, regorafenib reaches mean maximum observed plasma concentrations of about 3.9 mg/L (8.1 micromolar) after oral administration of 160 mg regorafenib, with a peak to trough ratio of mean plasma concentrations of less than 2.

The pharmacokinetics of regorafenib in Child-Pugh A and B (mild to moderate) hepatic impaired patients were similar to the pharmacokinetics in patients with normal hepatic function. There are no data for patients with Child-Pugh C (severe) hepatic impairment, since regorafenib is mainly eliminated via the liver, and exposure might be increased in this patient population.

Age did not affect the regorafenib pharmacokinetics over the studied age range (29-85 years).

The exposure of regorafenib in various Asian populations (Chinese, Japanese, Korean) is within the same range as seen in Caucasians.

2.2.2.2 Pre-clinical and Clinical Trials

In pre-clinical studies regorafenib has demonstrated potent anti-tumor activity in a broad spectrum of tumor models including colorectal, breast, pancreatic, non-small cell lung cancer, gastrointestinal stromal tumor, gastric cancer, head and neck squamous cell carcinoma/esophageal squamous cell carcinoma, liver cancer, glioma, and pediatric medulloblastoma, which is likely mediated by its anti-angiogenic and anti-proliferative effects (Abou-Elkacem et al. 2013, Schmieder et al. 2014, Takigawa et al. 2016, Wilhelm et al. 2011, Zopf et al. 2011); see the Investigator's Brochure (IB) for more information.

In addition, regorafenib has shown anti-metastatic effects *in vivo*. Major human metabolites (M-2 and M-5) exhibited similar efficacies, compared to regorafenib in *in vitro* and *in vivo* models.

As of 26 SEP 2018, more than 8,300 subjects with advanced solid-organ malignancies have been treated with regorafenib cumulatively in clinical studies and access programs, and approximately 141,722 patients have been exposed to regorafenib (post-marketing patients).

Currently, regorafenib is approved in more than 90 countries (including the United States of America [USA], the European Union [EU], and Japan). Approved indications include pretreated advanced colorectal cancer (CRC), pre-treated advanced gastrointestinal stromal tumor (GIST) and pre-treated advanced HCC.

2.2.3 Pembrolizumab

Pembrolizumab is a potent humanized IgG4 monoclonal antibody (mAb) with high specificity of binding to the PD-1 receptor, thus inhibiting its interaction with PD-L1 and PD-L2. Based on preclinical *in vitro* data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an IV immunotherapy for advanced malignancies. Pembrolizumab is indicated for the treatment of patients across a number of indications. For more details on specific indications and background information refer to the current IB / approved labeling.

2.2.3.1 Pharmaceutical and Therapeutic Background

The importance of intact immune surveillance function in controlling outgrowth of neoplastic transformations has been known for decades (Disis 2010). Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8+ T cells and the ratio of CD8+ effector T cells/FoxP3+ regulatory T cells (T-regs) correlates with improved prognosis and long-term survival in solid malignancies, such as ovarian, colorectal, and pancreatic cancer; hepatocellular carcinoma; malignant melanoma; and renal cell carcinoma. Tumor-infiltrating lymphocytes can be expanded *ex vivo* and reinfused, inducing durable objective tumor responses in cancers such as melanoma (Dudley et al. 2005, Hunder et al. 2008).

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an immunoglobulin (Ig) superfamily member related to cluster of differentiation 28 (CD28) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) that has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2) (Greenwald et al. 2005, Okazaki et al. 2001).

The structure of murine PD-1 has been resolved (Zhang et al. 2004). PD-1 and its family members are type I transmembrane glycoproteins containing an Ig-variable–type (IgV type) domain responsible for ligand binding and a cytoplasmic tail responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif, and an immunoreceptor tyrosine-based switch motif. Following T cell stimulation, PD-1 recruits the tyrosine phosphatases, SHP-1 and SHP-2, to the immunoreceptor tyrosine-based switch motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3 zeta (CD3ζ), protein kinase C-theta (PKCθ), and zeta-chain-associated protein kinase (ZAP70), which are

involved in the CD3 T cell signaling cascade (Chemnitz et al. 2004, Okazaki et al. 2001, Riley 2009, Sheppard et al. 2004). The mechanism by which PD-1 down-modulates T cell responses is similar to, but distinct from, that of CTLA-4, because both molecules regulate an overlapping set of signaling proteins (Francisco et al. 2010, Parry et al. 2005). As a consequence, the PD-1/PD-L1 pathway is an attractive target for therapeutic intervention in patients with HCC.

2.2.3.2 Pre-clinical Data

Therapeutic studies in mouse models have shown that administration of antibodies blocking PD-1/PD-L1 interaction enhances infiltration of tumor-specific CD8+ T cells and ultimately leads to tumor rejection, either as a monotherapy or in combination with other treatment modalities (Blank et al. 2004, Curran et al. 2010, Hirano et al. 2005, Pilon-Thomas et al. 2010, Spranger et al. 2014, Strome et al. 2003, Weber 2010). Anti-mouse PD-1 or anti-mouse PD-L1 antibodies have demonstrated anti-tumor responses in models of squamous cell carcinoma, pancreatic carcinoma, melanoma, acute myeloid leukemia and colorectal carcinoma (Curran et al. 2010, Nomi et al. 2007, Pilon-Thomas et al. 2010, Strome et al. 2003, Zhang et al. 2004). In such studies, tumor infiltration by CD8+ T cells and increased IFN-γ, granzyme B and perforin expression were observed, indicating that the mechanism underlying the anti-tumor activity of PD-1 checkpoint inhibition involved local infiltration and activation of effector T cell function *in vivo* (Curran et al. 2010). Experiments have confirmed the *in vivo* efficacy of anti-mouse PD-1 antibody as a monotherapy, as well as in combination with chemotherapy, in syngeneic mouse tumor models (see the IB).

2.2.4 Combination of Regorafenib and Anti-PD-1 Antibody

The rationale for combining immunotherapy with anti-angiogenic treatments has been outlined by Khan and Kerbel (Khan and Kerbel 2018) and is supported by both pre-clinical and clinical results in various indications including HCC (Ikeda et al. 2018, Kato et al. 2019).

Pre-clinically, the combination of regorafenib with anti-PD-1 demonstrated beneficial anti-tumor activity versus single agents in mouse models of colorectal cancer (CRC) (Hoff et al. 2017), melanoma (Wu et al. 2019), and HCC (data on file).

Mechanistically, this effect may be mediated by

1. a reduction/reprogramming of tumor associated macrophages by the inhibition of the CSF1R by regorafenib (Hoff et al. 2017).
2. suppression of interferon gamma induced PD-L1 and indolamine-2,3-dioxygenase (IDO1) expression, with minor effects on major histocompatibility complex 1 (MHC1) expression due to inhibition of RET and RAF (Wu et al. 2019).
3. increased infiltration of cytotoxic T cells in HCC tumors, mediated by elevated expression of CXCL10 (the ligand for CXCR3), which occurs on T cells (data on file).

Furthermore, VEGF signaling is known to suppress immune activity either directly on immune cells or indirectly by affecting the tumor vasculature (Khan and Kerbel 2018). Regorafenib as a potent VEGFR kinase inhibitor may thereby attenuate the immunosuppressive effects of VEGF. Inhibition of VEGFR and its signaling pathway may normalize tumor blood vessels and improve cytotoxic T cell infiltration (Zopf et al. 2016). Immune checkpoint inhibitors appear to affect the tumor vasculature as well, which may synergize with the inhibition of VEGF signaling by regorafenib (Tian et al. 2017).

Additional clinical evidence of the potential synergistic effects of combining immune checkpoint inhibitors with VEGF inhibitors is also derived from REGONIVO, an open-label, dose-finding, and dose-expansion Phase 1b study of regorafenib and nivolumab in patients with advanced microsatellite-stable CRC and gastric cancer (Fukuoka et al. 2019). The combination was tolerable and an encouraging 38% ORR was observed across tumor types.

A multicenter, non-randomized, open-label dose escalation Phase 1b study of regorafenib in combination with pembrolizumab in patients with advanced HCC with no prior systemic therapy (study 19497) is currently being conducted to determine the safety and tolerability of regorafenib in combination with pembrolizumab. Preliminary data from this trial (NOV 2020) did not result in any new safety signals considering the safety profile of either drug alone, and also showed promising anti-tumor activity (ORR 29%, DCR 94%, for patients treated at the 120mg MTD).

2.3 Benefit/Risk Assessment

2.3.1 Risk Assessment

Both regorafenib and pembrolizumab have manageable and well-understood safety profiles, and no new safety signals have been seen with the combination to date in HCC.

Pembrolizumab is generally well-tolerated but can induce immune-related adverse events (irAEs). Study participants will be closely monitored for development of irAEs and will receive treatment such as administration of corticosteroids, anti-inflammatory therapies, and other appropriate supportive care measures. Overlapping side effects such as liver toxicity, diarrhea, and skin reactions are possible. More detailed information about the known and expected benefits and risks, and expected AEs of regorafenib and pembrolizumab can be found in the most recent IB of each drug.

Additional considerations on safety monitoring: every effort will be made to minimize AEs of this drug combination during the study, through participant selection (e.g., only Child-Pugh A patients will be enrolled) and extensive safety monitoring. Special importance will be given to liver toxicity, as fatal cases of liver failure following toxic hepatitis have been reported in adult patients on regorafenib, and as there is a potential overlapping toxicity with pembrolizumab. Liver function tests will be closely monitored in all participants (weekly for the first 8 weeks and then monthly with mandatory assessments before each regorafenib treatment cycle).

No drug-drug interaction between regorafenib and pembrolizumab is expected because pembrolizumab is a therapeutic monoclonal antibody that is not metabolized and is also not a cytokine modulator. This is supported by preliminary pharmacokinetics (PK) data from the ongoing Phase 1b study 19497 indicating that regorafenib exposure, when administered in combination with pembrolizumab, is similar to regorafenib monotherapy. Since pembrolizumab is cleared by nonspecific proteases, similar to endogenous proteins, no effect of regorafenib on pembrolizumab PK is expected.

2.3.2 Benefit Assessment

Regorafenib is a potent MKI with an extensive kinase-inhibition profile, exhibiting robust efficacy data in pre-treated HCC patients. The RESORCE study showed similar clinical benefit for regorafenib for the second line setting as observed with sorafenib in the first line. This observed level of clinical benefit in a pre-treated population suggests that regorafenib

has the potential to offer benefit in a patient population previously treated with other 1L systemic therapy, justifying studying it in the 2L setting.

Recently published data support the combination of an MKI with an anti-PD-L1 as an option for treatment-refractory cancer such as metastatic RCC after progression with a PD-1/PD-L1 immune checkpoint inhibitor. In the Phase 2 trial of lenvatinib in combination with pembrolizumab for disease progression after PD-1/PD-L1 immune checkpoint inhibitor in metastatic RCC, 65% of patients had prior PD-1/VEGF combination therapy and 37% had prior ipilimumab/nivolumab during a median prior duration of immunotherapy of 7 months. The objective response of the study treatment combination was of 51%, with a median PFS of 11.7 months and median DOR of 9.9 months (Lee et al. 2020).

Immune checkpoint inhibitors have shown promising clinical activity and durable responses in patients with HCC. Based on complementary modes of action between MKIs and PD-1 inhibitors and their potentially synergistic effects on the cancer-immunity pathway, the combination of regorafenib and pembrolizumab might provide a greater clinical benefit in HCC patients.

Preliminary data from the Phase 1b study 19497 of regorafenib in combination with pembrolizumab in patients with advanced HCC with no prior systemic therapy have demonstrated a potential efficacy signal in 1L and a tolerable safety profile. As of NOV 2020, 9 out of the 31 participants who started 120 mg regorafenib QD (3 weeks on / 1 week off) and pembrolizumab 200mg Q3W and were evaluable for efficacy achieved PR per RECIST 1.1, with a DCR of 94%. Of the 21 patients who started 80 mg regorafenib QD (3 weeks on / 1 week off) and pembrolizumab 200mg Q3W and were evaluable for efficacy, 3 achieved PR per RECIST 1.1, with a DCR of 86%. Efficacy data for the 80 mg cohort were immature as of the cut-off date for this analysis.

2.3.3 Overall Benefit / Risk Assessment

In preclinical and clinical studies, regorafenib has demonstrated potent anti-tumor activity as a single agent in a broad spectrum of tumor models including hepatocellular tumor models, which is likely mediated by its anti-angiogenic and anti- proliferative effects. A positive benefit to risk profile is expected and combining regorafenib with an anti-PD-1 such as pembrolizumab is a potential and promising second line therapeutic option in advanced liver cancer.

Based on the data available to date, the conduct of the clinical trial is regarded as justified.

3. Objectives and Endpoints

The purpose of this study is to evaluate the efficacy and safety of regorafenib in combination with pembrolizumab for the treatment of advanced HCC in adult participants who have been previously treated with a PD-1/PD-L1 immune checkpoint inhibitor. The objectives and endpoints for the study are summarized in Table 3–1.

Table 3–1: Objectives and Endpoints

Objectives	Endpoints
Primary	
To demonstrate the objective anti-tumor activity of regorafenib in combination with pembrolizumab as 2L treatment for advanced HCC	• ORR per RECIST 1.1[a] by central assessment

Table 3–1: Objectives and Endpoints

Objectives	Endpoints
Secondary	
To evaluate other measures of anti-tumor activity of regorafenib in combination with pembrolizumab as 2L treatment for advanced HCC	• DOR per RECIST 1.1 by central assessment • ORR per RECIST 1.1 by investigator assessment • DOR per RECIST 1.1 by investigator assessment
To evaluate safety and tolerability of regorafenib in combination with pembrolizumab	• Number of participants with AEs • Number of participants with SAEs • Number of participants with safety-relevant changes in clinical parameters • Number of participants with dose modification (dose interruption, dose reduction, dose discontinuation)
Tertiary/Exploratory	
• To establish further exploratory indicators of efficacy of regorafenib in combination with pembrolizumab	• DCR per RECIST 1.1 by central assessment and investigator assessment • PFS as per RECIST 1.1 by central assessment and investigator assessment • Overall survival (OS) • ORR per HCC mRECIST and iRECIST by investigator assessment • DOR per HCC mRECIST and iRECIST by investigator assessment
• To evaluate the PK of regorafenib when concomitantly administered with pembrolizumab • To evaluate PK and immunogenicity of pembrolizumab when concomitantly administered with regorafenib	• Exposure of regorafenib and pembrolizumab, and incidence of anti-drug antibody (ADA) for pembrolizumab
• To identify biomarkers in baseline tumor materials and/or blood that may associate with response • To explore pharmacodynamic effects of regorafenib and pembrolizumab combination • To evaluate the PK/pharmacodynamic relationship for correlative biomarkers in blood such as peripheral lymphocytes, circulating proteins or nucleic acids (DNA or RNA), and/or tissues as well as measures of safety and/or efficacy • To further investigate the study intervention and similar drugs (i.e., mode-of-action-related effects and/or safety) and to further investigate pathomechanisms deemed relevant to cancer and associated health problems	• Correlation of biomarkers before treatment with other study endpoints • Change from baseline in levels of biomarkers in blood or tumor • Retrospective exploratory analysis of the relationship between regorafenib exposure and biomarker, safety and/or efficacy measures • Various biomarkers (e.g., diagnostic, safety, pharmacodynamic, monitoring, or potentially predictive biomarkers)

2L = second line; ADA = anti-drug antibodies; AE = adverse event; DCR = disease control rate; DNA = deoxyribonucleic acid; DOR = duration of response; HCC = hepatocellular carcinoma; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetics; RECIST = Response Evaluation Criteria in Solid Tumors; RNA = ribonucleic acid; SAE = serious adverse event

a. See Appendix 5 (Section 10.5) for tumor response criteria RECIST 1.1, HCC mRECIST, and iRECIST

4. Study Design

4.1 Overall Design

This is an open-label, Phase 2 trial to evaluate efficacy and safety of regorafenib in combination with pembrolizumab in patients with advanced HCC post PD-1/PD-L1 immune checkpoint inhibitors, in monotherapy or combination regimens.

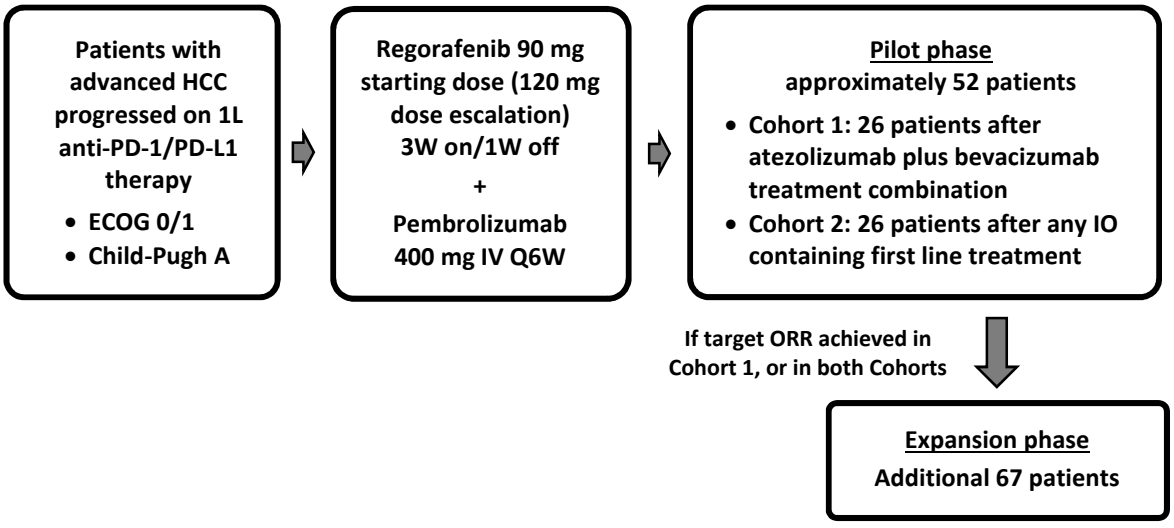
This study will investigate if the combination of regorafenib with PD-1 inhibitor pembrolizumab can improve the clinical outcome for patients with advanced HCC in the second line setting and follows a two phase design, consisting of an initial pilot phase and an expansion phase (see Figure 4–1):

a) **Pilot phase:** Approximately 52 participants will be enrolled to receive regorafenib in combination with pembrolizumab
   - **Cohort 1:** 26 participants after one systemic line of therapy consisting of atezolizumab plus bevacizumab treatment combination only
   - **Cohort 2:** 26 participants after one systemic line of therapy consisting of any IO containing first line treatment (excluding atezolizumab with or without bevacizumab) in monotherapy or combination regimens

b) **Expansion phase:** If the target ORR is achieved in the pilot phase (i.e. at least 8 responders out of 26 treated in cohort 1 or at least 8 responders in each cohort), the study can enroll approximately 67 new additional participants. These additional participants can be from cohort 1 (i.e. patients progressing on atezolizumab plus bevacizumab combination) or the combined population from cohort 1 plus cohort 2 (i.e., patients progressing on any immune checkpoint inhibitor), depending on which cohorts meet the response rate criteria for expansion (see Section 9.2).

Results from the pilot phase will inform the selection of the appropriate population for further study in the expansion phase.

Figure 4–1: Study Design



ECOG = Eastern Cooperative Oncology Group performance status; HCC = hepatocellular carcinoma; IV = intravenous; IO = immune oncology; ORR = objective response rate; PD-1 = Programmed cell death 1; PD-L1 = Programmed death-ligand 1; Q6W = every 6 weeks; W = week

4.1.1 Study Periods

4.1.1.1 Screening Period

The start of the screening phase is defined by signing of the ICF. Participants will be screened for eligibility up to 28 days immediately prior to W1D1.

During this time, the inclusion and exclusion criteria will be assessed and all screening procedures will be performed. Results of all screening/baseline evaluations must be reviewed by the investigator or his/her designee prior to assignment to treatment of each participant into the study to ensure that all inclusion and exclusion criteria have been satisfied. See the schedule of activities (SoA) in Section 1.3.1 for the procedures during the screening period.

4.1.1.2 Intervention Period

The start of the intervention period is defined by the first administration of the combination study intervention.

Participants will be treated with 400 mg pembrolizumab IV Q6W.

Regorafenib will be given orally (p.o.) at a starting dose of 90 mg QD for 3 weeks of every 4 weeks (i.e., 3 weeks on, 1 week off). If the starting dose of 90 mg daily is well tolerated (absence of any grade rash/hand-foot skin reaction [HFSR] or other Grade 2 or higher clinically significant toxicity), the dose can be escalated to 120 mg daily any time after the first cycle of regorafenib, starting with W5D1. Dose modification guidelines for dose reduction in case of toxicity are detailed in Section 6.6.

To support participants in establishing the drug intake rhythm (i.e. 6-week cycle for pembrolizumab, 4-week cycle for regorafenib), the site personnel are asked to call participants regularly for at least the first 3 regorafenib treatment cycles to remind them of omitting regorafenib during the 4th week of a cycle.

Participants will continue to receive study intervention until disease progression as defined by RECIST 1.1, unacceptable toxicity, consent withdrawal, withdrawal from the study at the discretion of the investigator or his/her designated associate(s), or until any other withdrawal criteria are met. Treatment beyond radiological progression is possible if the participant is still benefiting from treatment (see Section 6).

Participants who complete 18 infusions of pembrolizumab need to discontinue treatment with pembrolizumab. Regorafenib treatment can be continued beyond 2 years until withdrawal criteria are met. Treatment with individual drugs (regorafenib or pembrolizumab) may continue on schedule even if the other drug is interrupted or permanently discontinued due to toxicity.

During the study, participants will undergo evaluations for safety, efficacy, PK, and tissue and blood/plasma for biomarker will be collected. See the SoA in Section 1.3 for the assessments during the intervention period.

4.1.1.3 Active Follow-up

A mandatory safety follow-up visit will take place 30 days (window of +7 days) after the last administration of the last study intervention (regorafenib and/or pembrolizumab).

If applicable, an additional safety follow-up must occur 90 days (window of +7 days) after the last pembrolizumab administration. Longer safety follow-up for pembrolizumab is required due to the long half-life of the antibody. Note: If pembrolizumab is permanently discontinued first and the day 30 or the day 90 safety follow-up visit after the last infusion of

pembrolizumab falls into the regorafenib treatment period or regorafenib day 30 safety follow-up visit, no separate pembrolizumab day 30 or day 90 safety follow-up visit is necessary as the information gathering and examinations will occur with regorafenib treatment cycle visit, EoT visit, or day 30 safety follow-up visit. If regorafenib is discontinued first and the day 30 safety follow-up visit falls into pembrolizumab treatment or pembrolizumab day 30 follow-up visit, no separate regorafenib safety follow-up visit is necessary.

All pregnancies and exposure during breastfeeding should be collected from the start of study intervention through 120 days following discontinuation of study intervention, or 30 days following discontinuation of study intervention if the participant initiates new anti-cancer therapy.

Participants who discontinue study intervention due to radiologically confirmed PD will complete the mandatory safety follow-up visits.

Participants who discontinue from the study for any reason other than PD (or death, withdrawal of consent, or lost to follow-up) will be followed for progression during the active follow-up period. During the active follow-up period, computed tomography (CT) / magnetic resonance imaging (MRI) evaluations will be performed at efficacy follow-up visits (see the SoA in Section 1.3.1). In addition, study intervention-related toxicity/AE, information about survival status, and subsequent anti-cancer therapy will be followed up until completion of the active follow-up.

Active follow-up will be terminated by radiological PD, or the start of a new anti-cancer treatment, or death, or withdrawal of consent for further participation, or lost to follow-up.

4.1.1.4 Long-term Follow-up

All surviving participants will enter the long-term follow-up period after discontinuing from the active follow-up period except for participants who explicitly withdraw consent or are lost to follow-up.

Participants will be followed for OS and subsequent anti-cancer therapy at 3-month intervals (± 14 days) until the end of the study, withdrawal of consent, lost to follow-up, or death, whichever comes first (telephone contact is sufficient). Participants may be contacted at additional times throughout the course of the study in order to collect survival data to ensure that long-term follow-up data is current.

4.2 Scientific Rationale for Study Design

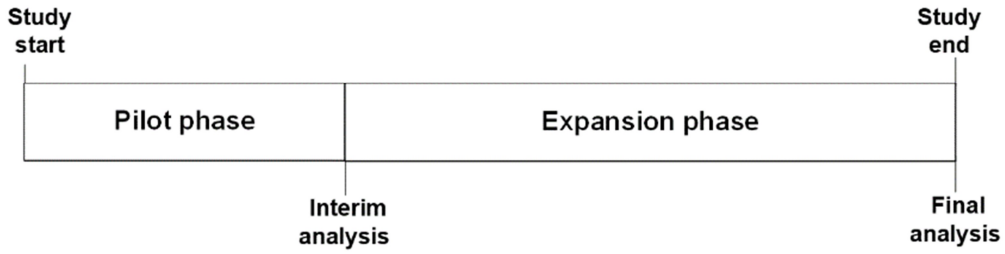
Recent clinical data support immunotherapy with checkpoint inhibitors as treatment options in first line for patients with advanced HCC. Although these drugs are available, a high unmet clinical need remains for the patients with advanced HCC who have progressed in first line treatment options with immunotherapy agents.

Regorafenib has established activity as a single agent and has been shown to provide survival benefit in HCC patients progressing on sorafenib treatment (Bruix et al. 2017).
Pembrolizumab has been granted accelerated FDA approval for the treatment of HCC patients who have been previously treated with sorafenib (Zhu et al. 2018).

This study follows a two-phase design, consisting of an initial pilot phase and an expansion phase (Figure 4–2).

An interim analysis is planned when the last participant enrolled in each of the cohorts is assessed for ORR (as defined by RECIST 1.1) during at least two post-baseline scans, or has been followed for approximately 14 weeks from the first dose, unless they have discontinued before due to progression or any other reason. Both cohorts will be analyzed separately and no pause of recruitment is expected between the study phases until the results of the interim analysis become available.

Figure 4–2: Study Design and Planned Analyses



Participants recruited in the pilot phase to one or both cohorts that achieve the response rate criterion for expansion will also be analyzed as part of the expansion phase.

The expansion phase will continue until the achievement of the study primary completion parameters outlined in Section 4.4.

4.3 Justification for Dose

Regorafenib dose

Regorafenib PK has been well characterized in patients with various solid tumors including HCC patients. In the dose-finding study 11650, regorafenib PK was investigated for dose levels of 10 mg, 30 mg, 60 mg, 120 mg, 160 mg up to 220 mg QD with a schedule of 3 weeks on / 1 week off. The regorafenib dose of 160 mg QD for the first 3 weeks of each 4-week cycle was declared as the MTD/RP2D based on exposure and a positive benefit-risk profile. This dosing regimen was further evaluated in several pivotal Phase 3 studies and approved worldwide, as monotherapy, in several indications including 2L HCC.

Recently, clinical evidence has been generated suggesting an increased benefit with the combination of regorafenib and anti-PD-1 agents such as pembrolizumab or nivolumab. The REGONIVO study is an open-label, dose-finding, and dose-expansion Phase 1b trial of regorafenib and nivolumab in patients with advanced microsatellite-stable CRC and gastric cancer (Fukuoka et al. 2019). In this study, the combination was shown to be tolerable and an encouraging 40% objective response rate was observed as compared to the historical response rate of regorafenib monotherapy in this population of 1-2% (Grothey et al. 2013). The MTD for regorafenib in this combination, based on pre-defined dose-limiting toxicity (DLT) criteria, was deemed to be 120 mg. However, in the first 18 participants treated at the 120 mg dose of regorafenib in the dose expansion cohort, all but one required dose reduction to 80 mg for AEs mostly related to Grade 3 skin toxicities. All remaining participants (N=18) were treated with a regorafenib starting dose of 80 mg and tolerated treatment well. Regorafenib exposure is similar across tumor types (CRC vs. HCC) and has shown comparable tolerability, so the results from the Phase 1 study mentioned above were considered for dose selection of the planned Phase 3 study in HCC.

The ongoing Phase 1b study, 19497, designed to investigate regorafenib in combination with pembrolizumab as 1L treatment in patients with HCC, has declared regorafenib 120 mg QD at a schedule of 3 weeks on / 1 week off as the MTD. Out of 18 evaluable participants for DLT, four had DLT events including Grade 3 HFSR, Grade 3 liver function test (LFT) increase accompanied with Grade 2 bilirubin increase (2 each). Based on the modified toxicity probability interval (mTPI) study design, regorafenib 120 mg daily 3 weeks on / 1 week off in combination with pembrolizumab was defined as the MTD for this combination however, the dose of 120 mg is associated with a relatively high incidence of dose reduction and discontinuation and a new expansion cohort has been opened for recruitment to evaluate 80 mg QD (3 weeks on / 1 week off) in NOV 2019. The combination indicated a preliminary efficacy signal. As of NOV 2020, preliminary efficacy data show PR by RECIST 1.1 in 9 out of the 31 participants who started 120 mg regorafenib QD (3 weeks on / 1 week off) and were evaluable for efficacy.

As a result of the high discontinuation rate associated with the 120 mg dose as well as the results from the REGONIVO study, the planned Phase 2 study will use a regorafenib starting dose level of 90 mg QD in cycle 1, if tolerated, escalating to 120 mg any time after the first cycle of regorafenib in a 3 weeks on / 1 week off schedule (for details on dose modification, see Section 6.6).

The rationale for changing from an 80 mg starting dose to a 90 mg starting dose is based on emerging data from ongoing clinical studies (Fukuoka et al. 2019) of regorafenib in combination with IO (e.g. nivolumab or pembrolizumab), where 80 mg is the currently recommended starting dose with the option to escalate to 120 mg in patients who can tolerate it. However, a number of patients who start at a dose of 80 mg still require dose reductions due to safety/tolerability. With the currently available 40 mg tablet, the only options are to reduce to 40 mg QD which is a 50% dose reduction or to 80 mg every other day (QOD) which is more difficult for patient compliance and still a 50% dose reduction. Therefore, the sponsor is proposing a new tablet strength of 30 mg for regorafenib in combination with IO. A 30 mg tablet would allow for a starting dose of 90 mg QD for the first 3 weeks of each 4-week cycle. Due to the high inter-subject PK variability, a dose of 90 mg is expected to provide very similar exposure to the currently recommended combination starting dose of 80 mg. A 30 mg tablet also will allow for a dose modification step to 60 mg which is a more conventional 33% dose reduction as compared to 50% with the 40 mg tablet.

Pembrolizumab dose

The planned dose of pembrolizumab for this study is 400 mg Q6W.

A 400 mg Q6W dosing regimen of pembrolizumab is approved by the US FDA for use in both monotherapy and combination therapy settings. This dosing regimen is expected to have a similar benefit-risk profile as 200 mg Q3W, in all indications in which 200 mg Q3W pembrolizumab is currently appropriate (Lala et al. 2018). Specifically, the dosing regimen of 400 mg Q6W for pembrolizumab is considered adequate based on modeling and simulation (M&S) analyses, given the following rationale:

- PK simulations demonstrating that in terms of pembrolizumab exposures –
    - Average concentration over the dosing interval (C_{avg}) (or area under the curve [AUC]) at 400 mg Q6W is similar to that at the approved 200 mg Q3W dose, thus bridging efficacy between dosing regimens.

- Trough concentrations (C_{min}) at 400 mg Q6W are generally within the range of those achieved with 2 mg/kg or 200 mg Q3W in the majority (>99%) of patients.
- Peak concentrations (C_{max}) at 400 mg Q6W are well below the C_{max} for the highest clinically tested dose of 10 mg/kg every 2 weeks (Q2W), supporting that the safety profile for 400 mg Q6W should be comparable to the established safety profile of pembrolizumab.
- Exposure-response (E-R) for pembrolizumab has been demonstrated to be flat across indications, and OS predictions in melanoma and non-small cell lung cancer (NSCLC) demonstrate that efficacy at 400 mg Q6W is expected to be similar to that observed at 200 mg Q3W.

4.4 End of Study Definition

The end of the study (EoS) as a whole will be reached when the last visit of the last patient (LPLV) has been achieved in all participating centers.

LPLV of a participant is reached if he/she has completed the last scheduled procedure shown in the SoA (see Section 1.3; this also includes telephone contacts during long-term follow-up) unless the participant died or withdrew consent or is lost to follow-up.

Furthermore, to reach EoS, either the following criteria or both need to be satisfied in this study:

- All participants have disease progression or are no longer on study intervention (regorafenib and/or pembrolizumab).
- The last included participant has been followed for at least 2 years since the first study treatment administration or is deceased.

Decisions on trial termination, protocol amendment, or cessation of patient recruitment can be made by the sponsor at any point in the study, guided by the monitoring boundaries at the interim analysis of the pilot phase, cumulative safety review, or strategic expectations for the study compounds after primary completion has been reached.

If the study is stopped by the sponsor but benefits are observed for ongoing participants, further treatment options may be discussed and agreed between the investigator, sponsor, and the participant (for further information refer to Section 6.5.5). Therefore, the LPLV date may also be reached based on the last participant switching to a roll-over study, post-trial access program or being switched to commercial drug supply with no cost to the participant.

Primary completion

The primary completion date according to FDA Amendment Act is defined as date that the final participant was examined or received an intervention for the purposes of final collection of data for the primary outcome. In this trial, the primary completion is defined as when all evaluable participants in the expansion phase have been assessed for objective response rate as defined by RECIST 1.1.

Participants are considered evaluable for efficacy once they have completed at least two post-baseline scans or have been followed for approximately 14 weeks from the first study treatment dose, unless they have discontinued before due to progression or any other reason.

5. Study Population

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

Inclusion criteria must be met at the time of screening unless otherwise specified.

Participants are eligible to be included in the study only if all of the following criteria apply:

Age

1. ≥18 years of age on the day of signing informed consent.

Type of Participant and Disease Characteristics

2. Histological or cytological confirmation of HCC or non-invasive diagnosis of HCC as per American Association for the Study of Liver Diseases (AASLD) criteria (see Appendix 11, Section 10.11) in cirrhotic participants.
3. Unresectable advanced HCC eligible for systemic therapy.
4. Participants must have progressed after only one prior line of systemic immunotherapy treatment with an anti-PD-1/PD-L1 mAb administered either as monotherapy or in combination with other checkpoint inhibitors or other therapies (for prior therapy in the cohorts in the pilot phase see Section 4.1). A wash out period of at least 28 days or 5 half-lives, whichever is shorter, must be completed for eligibility in this trial. PD-1/PD-L1 treatment progression is defined by meeting all of the following criteria:
   a. Has received at least 2 doses of an approved anti-PD-1/PD-L1 mAb or received PD-1/PD-L1 treatment for 8 weeks, whichever is longer.
   b. Has demonstrated disease progression after PD-1/PD-L1 treatment as defined by RECIST 1.1 (see Appendix 5, Section 10.5.1). In the absence of rapid clinical progression, the initial evidence of RECIST 1.1 disease progression is to be confirmed using iRECIST (see Appendix 5, Section 10.5.3) by a second assessment no less than four weeks from the date of the first documented progressive disease.
      i. This determination is made by the investigator. Once progressive disease is confirmed, the initial date of RECIST 1.1 progressive disease documentation will be considered that date of disease progression.
      ii. In cases of unequivocal clinical or radiological progression, disease progression confirmation may not be required after documented discussion and approval by the sponsor.
   c. Progressive disease has been documented within 12 weeks from the last dose of anti-PD-1/PD-L1 mAb.
5. Participants who receive anti-PD-1 therapy as adjuvant treatment following complete resection of liver cancer and have disease recurrence (unresectable loco-regional disease or distant metastases) are eligible if they progressed while on active treatment or within 6 months of stopping anti-PD-1 therapy. This will be considered the first line of systemic therapy.

For these participants, the following applies:

1) a second assessment to confirm disease progression beyond recurrence is not required; and
2) they must have received at least 2 prior doses of anti-PD-1/PD-L1 mAb.

6. Barcelona Clinic Liver Cancer (BCLC) stage B or C (see Appendix 8, Section 10.8).
7. Liver function status should be Child-Pugh (CP) Class A (see Appendix 9, Section 10.9) within 7 days prior to the first dose of study intervention. CP status should be calculated based on clinical findings and laboratory results during the screening period.
8. Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of 0 or 1 within 7 days prior to prior to the first dose of study intervention.
9. At least one measurable lesion by CT scan or MRI according to RECIST 1.1. Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, may be considered measurable if there has been demonstrated progression in the lesion.
10. Have adequate organ function as defined in the following table (Table 5–1). Specimens must be collected within 7 days prior to the start of study intervention.

Table 5–1: Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1000/mm^3
Platelets	≥60 000/mm^3
Hemoglobin	≥8.5 g/dL[a]
Renal	
Creatinine OR Measured or calculated[b] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 × ULN OR ≥30 mL/min for participant with creatinine levels >1.5 × institutional ULN
Hepatic/Pancreatic	
Total bilirubin	≤2 mg/dL. Mildly elevated total bilirubin (<6 mg/dL) is allowed if Gilbert's syndrome is documented.
AST and ALT	≤5.0 × ULN
Lipase	≤ 3 x ULN without symptoms
Coagulation	
International normalized ratio (INR) OR prothrombin time (PT) Activated partial thromboplastin time (aPTT)	PT-INR <2.3 and aPTT <1.5 x ULN unless receiving treatment with therapeutic anticoagulation

Table 5–1: Adequate Organ Function Laboratory Values

ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; INR = international normalized ratio; CrCl = creatinine clearance; GFR = glomerular filtration rate; PT = prothrombin time; ULN = upper limit of normal.
a. Criteria must be met without packed red blood cell (pRBC) transfusion within the prior 2 weeks. Participants can be on stable dose of erythropoietin (≥ approximately 3 months).
b. Creatinine clearance (CrCl) should be calculated per institutional standard.
Note: This table includes eligibility-defining laboratory value requirements for treatment; laboratory value requirements should be adapted according to local regulations and guidelines for the administration of specific chemotherapies.

11. Participants with controlled (treated) hepatitis B virus (HBV) infection will be allowed if they meet the following criteria:
    - Antiviral therapy for HBV must be given for at least 4 weeks and HBV viral load must be less than 500 IU/mL prior to first dose of study intervention.
    - Participants on active HBV therapy with viral loads under 500 IU/ml should stay on the same therapy throughout study treatment.
    - Participants who are anti-HBc (+), negative for HBsAg, negative for anti-HBs, and have an HBV viral load under 500 IU/mL that do not require HBV antiviral prophylaxis.
12. Participants may have a past or ongoing hepatitis C virus (HCV) infection. Participants must have completed their treatment at least 1 month prior to W1D1 or have received at least 1 month of direct acting antiviral (DAA) HCV therapy with no DAA related safety events and stable LFTs. For participants not on anti-HCV therapy at the time of study enrollment, DAAs for treatment of HCV infection can be initiated per the investigator's discretion, if LFTs are stable after 3-6 months of study intervention upon sponsor consultation.
13. Provision of recent tumor tissue (as defined below) is mandatory at screening. Exceptions will be accepted for participants with no recent baseline tumor tissues after documented discussion and approval by the sponsor.
    - Tumor tissue obtained within 180 days of enrollment and after the last dose of most recent anti-cancer therapy.
    - Or a new biopsy.

Sex

14. Male and/or female who meet the requirements for contraception and breastfeeding as follows (additional contraception guidance is provided in Appendix 4, Section 10.4.2):
    - A male participant must agree to use highly effective contraception (see Appendix 4, Section 10.4.2) during the intervention period and for 120 days after the last dose of regorafenib and refrain from donating sperm during this period.
    - A female participant is eligible to participate if she is not pregnant (see Appendix 4, Section 10.4.3), not breastfeeding, and at least one of the following conditions applies:
      a) Not a woman of childbearing potential (WOCBP) as defined in Appendix 4, Section 10.4.1.

b) A WOCBP who agrees to follow the contraceptive guidance in Appendix 4, Section 10.4.2 during the study intervention period and for at least 120 days after the last dose of pembrolizumab, and 210 days after the last dose of regorafenib.

Informed Consent

15. Capable of giving signed informed consent as described in Appendix 1 (Section 10.1), which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

    Participants must provide a signed informed consent before any screening procedures.

5.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply at the time of screening:

Medical Conditions

1. Pregnant or breastfeeding patients or expecting to conceive or father children within the projected duration of the study, starting with the screening visit through at least 120 days after the last dose of pembrolizumab, and 210 days after the last dose of regorafenib.

   Note: A WOCBP who has a positive urine pregnancy test (e.g. within 72 hours) prior to treatment. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
2. Fibrolamellar and mixed hepatocellular/cholangiocarcinoma subtypes.
3. Patients unable to swallow and retain oral medications.
4. Patients with disease that is suitable for local therapy administered with curative intent.
5. Patients who experienced any CTCAE $\geq$ 3 or any other immune-related toxicities that led to permanent discontinuation of treatment with immune checkpoint inhibitors in 1 L.
6. Persistent proteinuria of CTCAE Grade 3 or higher. Urine dipstick result of 3+ or abnormal, based on type of urine test strip used, is allowed if protein excretion (estimated by urine protein/creatinine ratio on a random urine sample) is <3.5 g / 24 hours.
7. Diagnosis of immunodeficiency or patient is receiving chronic systemic steroid therapy (in doses exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior to the first dose of study interventions. The use of physiologic doses of corticosteroids may be approved after consultation with the sponsor.
8. Active autoimmune disease that has required systemic treatment in past 2 years (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) is not considered a form of systemic treatment and is allowed.

9. History of (non-infectious) pneumonitis that required steroids or current pneumonitis.
10. History of interstitial lung disease.
11. Major surgical procedure or significant traumatic injury within 28 days before start of study medication.

    Note: If the participant received major surgery, he/she must have recovered adequately from the toxicity and/or complications from the intervention prior to starting study treatment.
12. Non-healing wound, non-healing ulcer, or non-healing bone fracture.
13. Patients with evidence or history of any bleeding diathesis, irrespective of severity.
14. Any hemorrhage or bleeding event CTCAE Grade ≥ 3 within 28 days prior to the start of study medication.
15. Patients with large esophageal varices at risk of bleeding that are not being treated with conventional medical intervention: beta-blockers or endoscopic treatment. Assessment of esophageal varices (see Appendix 10, Section 10.10) should be performed by endoscopy within 6 months of the start of study intervention. For patients in whom conventional medical intervention for known esophageal varices is already in place, assessment should be performed by endoscopy as per local standard of care.
16. Arterial or venous thrombotic or embolic events such as cerebrovascular accident (including transient ischemic attacks), deep vein thrombosis or pulmonary embolism within 6 months before the start of study medication (except for portal vein thrombosis and adequately treated catheter-related venous thrombosis occurring more than one month before the start of study medication).
17. History of organ allograft.
18. Known history of human immunodeficiency virus (HIV) infection (HIV 1/2 antibodies).
19. Ongoing infection CTCAE Grade > 2 requiring systemic therapy.
20. Dual active HBV infection (HBsAg (+) and / or detectable HBV DNA) and HCV infection (anti-HCV Ab (+) and detectable HCV RNA) at study entry.
21. Uncontrolled hypertension (systolic blood pressure ≥ 140 millimeter of mercury [mmHg] or diastolic pressure ≥ 90 mmHg) on more than 2 separate measurements despite optimal medical management.
22. Congestive heart failure of New York Heart Association (NYHA) class ≥2 (see Appendix 7, Section 10.7).
23. Unstable angina (angina symptoms at rest), new-onset angina (begun within the last 3 months).
24. Myocardial infarction less than 6 months before start of study intervention.
25. Uncontrolled cardiac arrhythmias despite optimal medical management.
26. Pleural effusion or ascites that causes respiratory compromise (CTCAE Grade ≥2 dyspnea). Note: Participants treated with thoracentesis/paracentesis within 14 days

prior to signing informed consent are eligible if clinically stable and have recovered to dyspnea Grade ≤1 or baseline after the procedure.

27. Patients with previous malignancies (except non-melanoma skin cancers, and the following in situ cancers: bladder, gastric, colon, cervical/dysplasia, melanoma, or breast) are excluded unless a complete remission was achieved at least 3 years prior to study entry and no additional therapy is required or anticipated to be required during the study period.
28. Known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Participants with previously treated brain metastases may participate provided they are radiologically stable, i.e., without evidence of progression for at least 4 weeks by repeat imaging (note that the repeat imaging should be performed during study screening), clinically stable and without requirement of steroid treatment for at least 14 days prior to first dose of study treatment.
29. Seizure disorder requiring medication.
30. Significant acute gastrointestinal disorders with diarrhea as a major symptom e.g., Crohn's disease, malabsorption, or CTCAE Grade ≥2 diarrhea of any etiology.
31. Current evidence or suspicion of gastrointestinal perforation or fistula.
32. Known hypersensitivity (Grade ≥3) to any of the study interventions, study intervention classes, or excipients in the formulation.

Prior/Concomitant Therapy

33. Prior monotherapy treatment with any tyrosine kinase inhibitor in 1L.
34. Prior treatment with regorafenib, in combination regimens with immune checkpoint inhibitors.
35. Patients who received prior radiotherapy within 2 weeks of start of study treatment. Participants must have recovered from all radiation-related toxicities, not require corticosteroids, and not have had radiation pneumonitis. A 1-week washout is permitted for palliative radiation (≤2 weeks of radiotherapy) to non-CNS disease.
36. Patients who have received a live vaccine or live attenuated replication competent vaccine within 30 days prior to the first dose of study intervention. Seasonal injectable influenza vaccines and vaccines administered in a pandemic context are allowed.
37. Prior transplantation of human cells, tissues and organs (e.g. liver transplant) or candidates for any type of transplantation.
38. Transfusion of blood products (including platelets or red blood cells) within 7 days prior to signing informed consent, or administration of colony stimulating factors (including G-CSF, GM-CSF or recombinant erythropoietin) within 4 weeks prior to signing informed consent.
39. Patients on concomitant use of CYP3A4 inducers, strong CYP3A4 inhibitors (see Appendix 6 in Section 10.6) and strong UGT1A9 inhibitors (e.g. mefenamic acid, diflunisal, and niflumic acid) within 2 weeks prior to start of study intervention.

Prior/Concurrent Clinical Study Experience

40. Previous assignment to treatment during this study. Participants permanently withdrawn from study intervention will not be allowed to re-enter screening.

41. Previous (at least a minimum of 28 days, or 5 half-lives of an investigational drug before the start of study treatment, whichever is shorter) or concomitant participation in another clinical study with investigational medicinal product(s).
42. Participants must have recovered from all AEs due to previous therapies to Grade ≤1 or baseline. Participants with treatment-related alopecia and Grade ≤2 neuropathy may be eligible.

Other Exclusions

43. 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.
44. Known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.

5.3 Lifestyle Considerations

Meals and Dietary Restrictions

Regorafenib should be administered with a low fat meal. There is no dietary restriction for pembrolizumab administration, participants should maintain a normal diet unless modifications are required to manage an AE such as diarrhea, nausea, or vomiting.

For details, refer to Section 6.

5.4 Screen Failures

Screen failures are defined as patients who consent to participate in the clinical study but do not start administration of either study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. The following data are to be recorded for all screen failure patients:

- Confirmation of informed consent
- Demographic information
- The reason for premature discontinuation (if the participant leaves the study for any reason during the screening period)

For participants who experience an SAE, or an AE related to a study procedure:

- AE CRF
- All information related to the SAE such as:
  - Concomitant medications
  - Medical history
  - Complementary SAE CRF and other relevant information (e.g. lab data, death (if applicable))

To assess any potential impact on participant eligibility with regards to safety, the investigator must refer to the current IBs for detailed information regarding warnings, precautions,

contraindications, AEs, and other significant data pertaining to the investigational product being used in this study.

If one or more screening laboratory tests do not support eligibility, laboratory re-test is permitted only once without the need of re-consent. Only the laboratory tests that are out of range need to be repeated. Re-testing must be performed within 14 days of the initial test and with approval from the sponsor. The investigator has to ensure that the re-testing procedures do not expose the participant to an unjustifiable health risk and that results are available within the 28-day screening period. Participants may not begin study intervention until the results of re-testing are available and documented to be within protocol required range.

In the event that the laboratory test(s) cannot be performed within the 28-day screening period, or the re-test(s) do not meet the entrance criteria, or other eligibility criteria have changed and are not met anymore, the participant is considered a screen failure, and must be discontinued from the study.

Re-screening of patients who have failed screening may only be allowed once after discussion with the sponsor's designated medical representative and after approval by the sponsor. Sponsor approval of re-screening for a patient who has failed screening must be documented. The screen failure will be registered manually in the Interactive Voice/Web Response System (IxRS) to close the original patient identification number (PID), and re-screening will start again by the participant signing a new informed consent form and being assigned a new PID via IxRS.

All required screening activities must be performed when the participant is re-screened for participation in the study.

Note: The investigator must be informed as soon as possible about any medications taken from the time of screening until the participant is discharged from the study.

6. Study Intervention

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

The following interventions are to be administered during the study:

Regorafenib

Refer to the Summary of Product Characteristics (SmPC) / most recent IB for regorafenib for more details regarding drug properties and formulation.

Regorafenib will be given orally (p.o.) at a starting dose of 90 mg QD for 3 weeks of every 4 weeks (i.e., 3 weeks on, 1 week off). If the starting dose of 90 mg daily is well tolerated (absence of any grade rash/HFSR or other Grade 2 or higher clinically significant toxicity), the dose can be escalated to 120 mg any time after the first cycle of regorafenib, starting with W5D1. Dose modification guidelines for dose reduction in case of toxicity are detailed in Section 6.6.

Regorafenib should be taken within 2 hours after a light meal with approximately 240 mL (8 fluid ounces) of water, preferably in the morning. If necessary, regorafenib may be taken at different times of the day, but there should be consistency with respect to dosing intervals (the recommendation is to have at least a 20-hour interval between doses).

If a dose of regorafenib will be missed, the missed dose should be skipped (vomited tablets cannot be made up), and the next dose should be taken at the regular time. The subsequent dose of regorafenib should not be doubled. The investigator should be informed if the dose of regorafenib taken has exceeded the scheduled dose.

Regorafenib may start up to 3 days after the scheduled day after a 7-day break due to administrative reasons. Participants who halt regorafenib therapy for more than 28 consecutive days - including the 1-week drug holiday - should be withdrawn from regorafenib. However, continuation of regorafenib may be considered if, in the investigator's opinion, the participant may continue to benefit from the regorafenib treatment, and after consultation with sponsor.

On days when pre-dose PK blood samples will be collected, participants will take the morning dose of regorafenib at the clinic after all required samples are collected. On days when PK samples are not required, regorafenib can be taken at home or in the clinic. On days when biomarker blood samples will be collected, the biomarker blood samples shall be collected up to 1 hour before the morning dose if feasible.

Pembrolizumab

Refer to the SmPC / most recent IB for pembrolizumab for more details regarding drug properties and formulation.

Pembrolizumab will be administered as a dose of 400 mg using a 30-minute IV infusion Q6W. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window between -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes, -5 min/+10 min). Pembrolizumab must be infused before regorafenib when study interventions are given on the same day. The Pharmacy Manual contains specific instructions for the preparation of the pembrolizumab infusion and administration of infusion solution.

Pembrolizumab may be administered up to 3 days before or after the scheduled day of dosing due to administrative reasons. Note: dosing interruptions are permitted in the case of medical / surgical events or logistical reasons (i.e. elective surgery, unrelated medical events, participant vacation, holidays) not related to pembrolizumab. Participants should be placed back on pembrolizumab therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the sponsor. The reason for interruption should be documented in the participant’s study record. See Section 6.6 for the maximum infusion delay time permitted due to treatment-related reasons. Pembrolizumab treatment should be stopped after a participant has received 18 infusions.

Participants will receive study intervention until tumor progression, unacceptable toxicity, withdrawal of consent, investigator’s decision to stop therapy for the participant, sponsor’s decision to terminate the study, or death. If in the opinion of the investigator, the participant may still derive clinical benefit despite disease progression, continuation of study intervention is permitted after discussion with the sponsor.

At the investigator’s discretion, a participant may continue on study intervention beyond radiological progression as defined by RECIST 1.1 if the clinical condition of the participant is stable or the participant is improving symptomatically, and the investigator expects continued clinical benefit for the participant until subsequent progression determined by iRECIST criteria (see Section 7.1).

6.1 Study Intervention(s) Administered

Table 6–1: Administration of Study Intervention

Intervention Name	Regorafenib	Pembrolizumab
Type	Small molecule drug (MKI)	Monoclonal antibody, biologic
Dose Formulation	Tablet	Solution for infusion
Unit Dose Strength	30 mg / tablet	100 mg / 4 mL vial (25 mg/mL)
Dosage Level(s)	3 x 30 mg tablets every day for 21 days (QD) of every 28 days cycle (i.e. 3 weeks on, 1 week off) as a starting dose of 90 mg. If the starting dose of 90 mg QD is well tolerated (absence of any grade rash/HFSR or other ≥ regorafenib related Grade 2 toxicity, except asymptomatic lab abnormalities that resolve to Grade ≤1 within 72 hours), the dose can be escalated to 120 mg orally QD (4x30 mg tablets) any time starting with W5D1.	400 mg (4 x 100 mg / 4 mL vials) are to be administered as an IV infusion Q6W (see Pharmacy Manual for details)
Route of Administration	Oral	IV infusion
Use	Experimental	Experimental
IMP and NIMP	IMP	IMP
Sourcing	Regorafenib will be provided centrally by the sponsor.	Pembrolizumab will be provided centrally by the sponsor.
Packaging and Labeling	Regorafenib is available in high density polyethylene bottles with a white child-resistant closure and induction seal. The packaging configuration is 21 tablets regorafenib 30 mg and a 3 g desiccant per bottle of regorafenib 30 mg. The bottles will be labeled as required per country requirement.	Pembrolizumab will be provided in glass injection vials. Each glass injection vial will be labeled as required per country requirement.
Current/Former Name(s) or Alias(es)	Stivarga / BAY 73-4506	Keytruda / MK-3475

D = day; HFSR = hand-foot skin reaction; IMP = investigational medicinal product; IV = intravenous; MKI = multi-kinase inhibitor; NIMP = non-investigational medicinal product; Q6W = every 6 weeks; W = week

6.2 Preparation/Handling/Storage/Accountability

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.

Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused study interventions are provided in the site file.

Handling/Storage/Accountability at the participant's home

Participants will follow the instructions provided by authorized site staff for storage and administration of study intervention at home, as well as for return of unused study intervention to the site.

6.3 Measures to Minimize Bias: Randomization and Blinding

This is an open-label study. Randomization is not applicable for the study. All participants will be centrally assigned to the study intervention using an IxRS and will be given a unique PID prior to the start of study intervention.

6.4 Study Intervention Compliance

6.4.1 Pembrolizumab

Participants are dosed at the site, and they will receive pembrolizumab directly from the investigator or designee. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the electronic case report form (eCRF). The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention. Reasons for dose delay or infusion interruption will also be recorded in the source data and in the eCRF. The number of vials used will be recorded on the appropriate treatment dispensing form.

6.4.2 Regorafenib

When participants self-administer study intervention(s) at home, compliance with study intervention will be assessed at each visit. Participants will be instructed to take study intervention as scheduled, and to return all of the study intervention packaging including unused study intervention and empty packaging. Participants should fill in the paper-based patient drug diary after each intake of study intervention. To monitor compliance, drug accountability information will be documented for each participant. Compliance will be assessed by counting returned tablets during the site visits and documented in the source documents and eCRF. To support participants in establishing the drug intake rhythm (i.e. 6-week cycle for pembrolizumab, 4-week cycle for regorafenib), the site personnel are asked to call participants regularly for at least the first 3 regorafenib treatment cycles to remind them of omitting regorafenib during the 4th week of a cycle. Deviation(s) from the prescribed dosage regimen should be recorded in the eCRF. A record of the number of tablets dispensed to and returned by each participant must be maintained and reconciled with intervention start and stop dates, including dates for dose delays and/or dose reductions which will also be recorded in the eCRF. Any discrepancies between actual and expected amount of returned study intervention must be discussed with the participant at the time of the visit, and any explanation must be documented in the source records. An adequate record of receipt, distribution, and return/destruction of all study intervention must be kept.

A record of the number of study intervention(s) tablets dispensed to and taken by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays and/or dose reductions will also be recorded in the eCRF.

When participants are dosed at the site, they will receive regorafenib directly from the investigator or designee.

6.5 Concomitant Therapy

Medication other than the investigational products should not be taken during the study without consulting the investigator.

Any medication that is considered necessary for the participant's welfare, and which is not expected to interfere with the evaluation of the study medications, may be given at the discretion of the investigator.

All concomitant medications that may affect efficacy or toxicity or are taken for any concurrent medical conditions at the time of enrollment or during the study (including start/stop dates, dose frequency, route of administration and indication) must be recorded in the participant's source documentation, as well as in the appropriate pages of the eCRF.

In general, participants should be closely monitored for side effects of all concomitant medications regardless of elimination pathway, especially those with narrow therapeutic index, such as warfarin, quinidine and cyclosporine.

Administration of contrast media for protocol-specified radiological procedures does not need to be reported, unless there is an AE related to the contrast medium injection (e.g. allergic reaction).

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for any medication or vaccination specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The investigator should discuss any questions regarding this with the sponsor. The final decision on any supportive therapy or vaccination rests with the investigator and/or the participant's primary physician. However, the decision to continue the participant on study treatment requires the mutual agreement of the investigator, the sponsor and the participant.

Listed below are specific prohibited medications for concomitant therapy or vaccination during the course of the study:

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than regorafenib and pembrolizumab
- Radiation therapy

  Note: Palliative radiotherapy during the study for local pain control or to the brain may be allowed at the investigator's discretion.
- Live or live attenuated replication competent vaccines within 30 days prior to the first dose of study treatment and while participating in the study. Note: killed vaccines are allowed.
- Systemic glucocorticoids are permitted only for the following purposes:

- To modulate symptoms of an AE that are suspected to have an immunologic etiology
- As needed for the prevention of emesis
- Premedication for IV contrast allergies
- Short-term oral or IV use in doses >10mg/day prednisone equivalent for chronic obstructive pulmonary disease (COPD) exacerbations
- For chronic systemic replacement, not to exceed 10 mg/day prednisone equivalent
- In addition, the following glucocorticoid use is allowed:
  - For topical use or ocular use
  - Intra-articular joint use
  - For inhalation in the management of asthma or COPD

Note: Inhaled steroids are allowed for management of asthma.

All concomitant medications received within 28 days prior to the first dose of study treatment and up to 30 days after the last dose of study treatment should be recorded. Concomitant medications administered 30 days after the last dose of study treatment should be recorded for SAEs and events of clinical interest (ECIs) as defined in Section 8.3.6.

6.5.1 Drug-drug Interactions Relevant for Regorafenib

6.5.1.1 Inhibitors / Inducers of CYP3A4

Administration of ketoconazole (400 mg for 18 days), a strong CYP3A4 inhibitor, with a single dose of regorafenib (160 mg on Day 5) resulted in an increase in mean exposure (AUC) of regorafenib of approximately 33%, and a decrease in mean exposure of the active metabolites, M-2 (N-oxide) and M-5 (N-oxide and N-desmethyl), of approximately 90%. It is recommended to avoid concomitant use of strong inhibitors of CYP3A4 activity as their influence on the steady-state exposure of regorafenib and its metabolites has not been studied.

Administration of rifampicin (600 mg for 9 days), a strong CYP3A4 inducer, with a single dose of regorafenib (160 mg on Day 7) resulted in a reduction in AUC of regorafenib of approximately 50%, a 3- to 4-fold increase in mean exposure of the active metabolite M-5, and no change in exposure of active metabolite M-2. Other CYP3A4 inducers may also increase metabolism of regorafenib. Inducers of CYP3A4 should be avoided, or selection of an alternate concomitant medicinal product, with no or minimal potential to induce CYP3A4 should be considered.

Appendix 6 (Section 10.6) provides an overview of the most commonly used strong CYP3A4 inhibitors and CYP3A4 inducers that should be avoided during the study.

6.5.1.2 UGT1A1 and UGT1A9 Substrates

In vitro data indicate that regorafenib as well as its active metabolites M-2 inhibit glucuronidation mediated by UGT1A1 and UGT1A9 whereas M-5 only inhibits UGT1A1 at concentrations which are achieved *in vivo* at steady state.

Administration of regorafenib with a 5-day break prior to administration of irinotecan resulted in an increase of approximately 44% in mean exposure (AUC) of SN-38, a substrate of UGT1A1 and an active metabolite of irinotecan. An increase in mean exposure (AUC) of irinotecan of approximately 28% was also observed. This indicates that co-administration of

regorafenib may increase systemic exposure to UGT1A1 and UGT1A9 substrates. The clinical significance is unknown and is dependent on the substrate.

6.5.1.3 Breast Cancer Resistance Protein and P-glycoprotein Substrates

Administration of regorafenib (160 mg for 14 days) prior to administration of a single dose of rosuvastatin (5 mg), a breast cancer resistance protein (BCRP) substrate, resulted in a 3.9-fold increase in mean exposure (AUC) of rosuvastatin and a 4.6-fold increase in C_{max}. This indicates that co-administration of regorafenib may increase the plasma concentrations of other concomitant BCRP substrates (e.g. methotrexate, fluvastatin, atorvastatin). Therefore, it is recommended to monitor participants closely for signs and symptoms of increased exposure to BCRP substrates.

6.5.1.4 CYP Isoform-selective Substrates

A cytochrome P450 enzyme probe substrate study in cancer patients was conducted to evaluate the effect of regorafenib on the pharmacokinetics of CYP2C9 substrate warfarin (10 mg), CYP2C19 substrate omeprazole (40 mg), CYP3A4 substrate midazolam (2 mg) and CYP2C8 substrate rosiglitazone (4 mg) and to provide information about potential changes in exposure of these substrates when administered with regorafenib.

Overall, PK data suggest that regorafenib may be given concomitantly with substrates of CYP3A4, CYP2C8, CYP2C9, and CYP2C19 without the expectation of a clinically meaningful drug interaction.

6.5.1.5 Antibiotics

The concentration-time profile indicates that regorafenib and its metabolites may undergo enterohepatic circulation. Co-administration with neomycin, a poorly absorbed antimicrobial agent used for eradicating the gastrointestinal microflora (which may interfere with the enterohepatic circulation of regorafenib) had no effect on the regorafenib exposure. There was an approximately 80% decrease in the exposure of the active metabolites M-2 and M-5. Effects of other antibiotics have not been studied. The clinical significance of the neomycin effect and potential interactions with other antibiotics is unknown, but may result in a decreased efficacy of regorafenib.

6.5.1.6 Bile Salt-sequestering Agents

Bile salt-sequestering agents may interact with regorafenib by forming insoluble complexes which may impact absorption (or reabsorption), thus resulting in potentially decreased exposure. The clinical significance of these potential interactions is unknown, but may result in a decreased efficacy of regorafenib.

6.5.2 Drug-drug Interactions Relevant for Pembrolizumab

No formal PK drug interaction studies have been conducted with pembrolizumab. Since pembrolizumab is cleared from the circulation through catabolism, no metabolic drug-drug interactions are expected.

6.5.3 Prohibited Prior and Concomitant Therapies

Participants are prohibited from receiving the following therapies during the screening and intervention periods of this trial:

- The use of systemic corticosteroids or immunosuppressants before starting pembrolizumab should be avoided because of their potential interference with the

pharmacodynamic activity and efficacy of pembrolizumab. Note: replacement therapy such as physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency (in dosing not exceeding 10 mg daily of prednisone equivalent) is not considered a form of systemic treatment, and inhaled steroids are allowed for management of asthma. Moreover, systemic corticosteroids or other immunosuppressants can be used after starting pembrolizumab to treat immune-related adverse reactions.

- Disease-specific anti-neoplastic therapies, including kinase inhibitors, immunotherapy, chemotherapy, or experimental therapies other than regorafenib and pembrolizumab.
- Surgery for symptom management or tumor control.
- Strong CYP3A4 inhibitors or CYP3A4 inducers (See Section 6.5.1.1, and Appendix 6 in Section 10.6).
- Co-administration of strong UGT1A9 inhibitors (e.g. mefenamic acid, diflunisal, and niflumic acid) during regorafenib treatment should be avoided, as their influence on the steady-state exposure of regorafenib and its metabolites has not been studied.
- Live vaccines or live attenuated replication competent vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Seasonal injectable influenza vaccines and vaccines administered in a pandemic context are allowed.

The exclusion criteria describe other medications that are prohibited in this trial (Section 5.2). Participants who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the study.

6.5.4 Permitted Concomitant Therapies

All concomitant medications (including start / stop dates, total daily dose, and indication) must be recorded in the participant's source documentation and in the eCRF.

- Treatment with non-conventional therapies (e.g. herbs or acupuncture) and vitamin/mineral supplements is acceptable provided that they do not interfere with the study endpoints, in the opinion of the investigator. However, St John's Wort (herbal preparation based on the plant species hypericum) is not permitted.
- Participants who are therapeutically treated with an agent such as warfarin or heparin or novel oral anticoagulants (NOACs) such as dabigatran or rivaroxaban will be allowed to participate provided that no prior evidence of underlying abnormality in coagulation parameters exists. Close monitoring of at least weekly evaluations for participants on warfarin will be performed until the INR is stable based on a measurement that is pre-dose as defined by the local standard of care.
- P-glycoprotein substrates: clinical data indicate that regorafenib has no effect on digoxin pharmacokinetics, therefore can be given concomitantly with p-glycoprotein substrates, such as digoxin, without a clinically meaningful drug interaction (see Section 6.5.1.3).
- Participants may receive palliative or supportive care for any underlying illness.
- Palliative and supportive care for other disease-related symptoms and for toxicity associated with treatment will be offered to all participants on this trial. The use of anti-diarrheal or anti-emetics according to standard practice is strongly encouraged.

- Bisphosphonates and/or RANKL (receptor activator of nuclear factor kappa-B ligand) inhibitor therapies (such as denosumab) for bone metastases may be continued if treatment with an agent from one of these two classes was initiated prior to signing informed consent. Bisphosphonates and/or RANKL inhibitor therapies cannot be initiated after informed consent has been signed, unless in the opinion of the investigator, the participant does not have PD.
- Radiotherapy:
  - Palliative radiotherapy during the study is allowed for local pain control after individual benefit-risk assessment provided that:
    - In the opinion of the investigator, the participant does not have PD,
    - No more than 25% of the participant's bone marrow is irradiated,
    - The radiation field does not encompass a target lesion, and
    - The radiation field does not encompass a lung field (to reduce the risk for interstitial lung disease [ILD] caused by irradiation pneumonitis).
  - Regorafenib may only be continued during palliative radiotherapy after an individual benefit-risk assessment. The investigator should consult the sponsor.
  - Pembrolizumab must be held during radiation treatment and should be resumed no earlier than the next scheduled administration of study intervention.

  Note: administration of palliative radiation therapy to a symptomatic solitary lesion or to the brain will be considered clinical progression for the purposes of determining PFS.
- Analgesics.
- Nutritional support.
- Major surgery for any reason different than symptom management or tumor control should only be performed during the study period if, in the opinion of the investigator and after careful individual benefit / risk assessment (taking into account the potential wound healing complications that have been described with all anti-VEGF drugs), the surgery will be beneficial for the participant. It is recommended to stop regorafenib treatment two weeks before surgery. The decision to resume regorafenib after surgery should be based on clinical judgment of adequate wound healing. Participants should be placed back on study therapy within 4 weeks of the scheduled interruption of regorafenib.

  Note: if treatment interruption of regorafenib will be >28 consecutive days - including the 1 week drug holiday – the participant must be discontinued from regorafenib. However, continuation of regorafenib may be considered if, in the investigator's opinion, the participant may continue to benefit from the regorafenib treatment, and after consultation with the sponsor.

  Participants who experience a delay of more than 12 weeks before the subsequent pembrolizumab infusion must be discontinued from pembrolizumab.
- Participants may receive other medications that the investigator deems to be medically necessary.

6.5.5 Post-study Therapy

There are no prohibited therapies during the post-intervention active and long-term follow-up periods. Further new anti-cancer treatment after the end of the study combination treatment will be at the discretion of the investigator. Information on at least the first new anti-cancer regimen must be recorded in the participant's source documentation, as well as in the appropriate pages of the eCRF.

At the conclusion of the study, participants who demonstrate clinical benefit may be eligible to continue to receive study treatment. They may receive further treatment, assessments and/or be followed either via a post-trial access program, a roll-over study - subject to approval by the competent health authority and ethics committee - or through any other mechanism in accordance with local legal and compliance rules. This applies to participants on study treatment and in follow-up.

Until the transition to other supportive programs, participants will continue to follow all the procedures and visits required in the current version of the protocol.

6.6 Dose Modification

Based on the known toxicity profiles of regorafenib and pembrolizumab, certain AEs are likely to be associated with one drug versus the other. For example, treatment-emergent hypertension and HFSR are likely to be associated with regorafenib rather than pembrolizumab; similarly, immune-related AEs are likely to be associated with pembrolizumab rather than regorafenib. However, some drug-related AEs such as rash, diarrhea, abnormal thyroid function, and fatigue are overlapping. Therefore, it is important to evaluate each AE and consider time of onset, perform the appropriate work-up for etiology or exclude other causes in order to determine proper management of the adverse reaction and action regarding study treatment. A careful decision should be made by investigators based on all clinical information, e.g., relatedness to study medications.

Dose modifications of regorafenib and pembrolizumab will be based on the highest grade of AE that occurred since the last contact. If a participant experiences multiple toxicities, dose modification will be based on the toxicity with the highest grade. In case of multiple toxicities of the same grade, the investigator may modify the dose based on the toxicity that appears most likely related to study interventions.

In case of dose delays, assessments should be performed on Day 1, according to the SoA (see Section 1.3).

Regorafenib dose modifications should be done according to Table 6–2.

The recommendations regarding dose adjustments and treatment interruptions from Table 6–3 to Table 6–8 can be used as support for the clinical decision and respective monitoring/ treatment guidance. A careful decision will be made by investigators based on all clinical information, e.g. relatedness to study medications.

Once a dose reduction of regorafenib has been performed, there will be no intra-participant re-escalation.

Where it is indicated to reduce regorafenib one dose level, Table 6–2 should be followed:

Table 6–2: Regorafenib Dose Reduction Scheme

Dose Level	Daily Regorafenib (3 weeks on, 1 week off)	Daily Regorafenib (3 weeks on, 1 week off)
Current Dose	90 mg	120 mg
Dose Level -1	60 mg	90 mg
Dose Level -2	Not applicable	60 mg

Table 6–3: Dose Modification Guidance, Non-immune Toxicities

Event	Regorafenib	Pembrolizumab
Hematologic toxicities		
G3/4 Neutropenia G3/4 Anemia G3/4 Thrombocytopenia	• Hold until recovery to ≤ G2 and reduce 1 dose level[a] • 1st re-appearance: Hold until recovery to ≤ G2 and reduce 1 additional dose level[a] • 2nd re-appearance: discontinue	• G3 (excluding G3 neutropenia): - Hold and restart at same dose if resolution to ≤ G1 or baseline ≤ 12 weeks of last infusion - Hold and consider discontinuation if NO resolution ≤ 12 weeks of last infusion • G4: discontinue[b]
Non-hematologic toxicities		
General guidance for G2 events	• No modifications	• Consider withholding for persistent symptoms • Restart at same dose if resolution to ≤ G1 or baseline ≤ 12 weeks of last infusion • Consider discontinuation if NO resolution ≤ 12 weeks of last infusion[b]
General guidance for G3 events	• Hold until recovery to ≤ G2 and restart at same dose level or reduce 1 dose level[a] (at the investigator's discretion) • 1st + 2nd re-appearance: Hold until recovery to ≤ G2 and reduce 1 dose level[a] (at the investigator's discretion) • 3rd re-appearance: Discontinue • Discontinuation is required for gastrointestinal perforation or fistula • Hold until recovery in case of cardiac ischemia and/or infarction. At the investigator's discretion restart at same dose level or reduce 1 dose level[a]. Permanently discontinue if there is no resolution.	• Hold and restart at same dose if resolution to ≤ G1 or baseline ≤ 12 weeks of last infusion • Hold and discontinue if NO resolution ≤ 12 weeks of last infusion[b]
General guidance for G4 events	• Hold until recovery to ≤ G2 and reduce 1 dose level • 1st re-appearance: Hold until recovery to ≤ G2 and reduce 1 additional dose level[a] • 2nd re-appearance: Discontinue • Discontinuation is required for gastrointestinal perforation or fistula • Hold until recovery in case of cardiac ischemia and/or	• Discontinue[b]

Table 6–3: Dose Modification Guidance, Non-immune Toxicities

Event	Regorafenib	Pembrolizumab
	infarction. At the investigator's discretion restart at same dose level or reduce 1 dose level[a]. Permanently discontinue if there is no resolution.	
Specific guidance for hand-foot skin reaction (HFSR)		
G1	• Maintain dose level and institute supportive measures immediately for symptomatic relief	• No modification
G2	• 1st occurrence: Consider decrease by 1 dose level and institute supportive measures immediately[a]. If no improvement, interrupt for ≥ 7 days, until toxicity resolves or improves to G1 • No improvement ≤ 7 days or 2nd occurrence: Interrupt until toxicity resolves or improves to G1. When resuming treatment, treat at reduced dose level[a]. • 3rd occurrence: Discontinue	• No modification
G3	• 1st occurrence: Institute supportive measures immediately. Interrupt therapy for ≥ 7 days until toxicity resolves or improves to G1. When resuming treatment, decrease by 1 dose level[a]. • 2nd occurrence: Institute supportive measures immediately. Interrupt therapy for ≥ 7 days until toxicity resolves or improves to G1. When resuming treatment, decrease by 1 additional dose level[a]. • 3rd occurrence: Discontinue	• No modification
Specific guidance for skin and subcutaneous disorders other than HFSR (includes rash, rash erythematous, rash follicular, rash generalized, rash macular, rash maculopapular, rash papular, rash pruritic, exfoliative rash, pruritus, eczema, dermatitis)		
G2	• No modifications	• Consider withholding for persistent symptoms • Restart at same dose if resolution to ≤ G1 or baseline ≤ 12 weeks of last infusion • Consider discontinuation if NO resolution ≤ 12 weeks of last infusion[b]

Table 6–3: Dose Modification Guidance, Non-immune Toxicities

Event	Regorafenib	Pembrolizumab
G3	• Hold until recovery to ≤ G2 and restart at same dose level or reduce 1 dose level[a] (at the investigator's discretion) • 1st + 2nd re-appearance: Hold until recovery to ≤ G2 and reduce 1 dose level[a] (at the investigator's discretion) • 3rd re-appearance: Discontinue	• Hold and restart at same dose if resolution to ≤ G1 or baseline ≤ 12 weeks of last infusion • Hold and discontinue if NO resolution ≤ 12 weeks of last infusion[b]
G4 (when applicable)	• Hold until recovery to ≤ G2 and reduce 1 dose level[a] • 1st re-appearance: Hold until recovery to ≤ G2 and reduce 1 additional dose level[a] • 2nd re-appearance: Discontinue	• Discontinue[b]
Specific guidance for HYPERTENSION		
G1	• No change. Consider increased BP monitoring	• No modification
G2	• If symptomatic, hold until symptoms resolve AND diastolic BP ≤ 90 mmHg. At restart, continue at the same dose level	• No modification
G3	• Hold until diastolic BP ≤ 90 mm Hg, and if symptomatic, until symptoms resolve. At restart, continue at the same dose level • If BP is not controlled with the addition of new or more intensive therapy, reduce by 1 dose level[a] • If G3 hypertension recurs despite dose reduction and antihypertensive therapy, reduce another dose level[a]	• No modification
G4	• Discontinue	• Discontinue[b]

BP = blood pressure; G1/2/3/4 = Grade 1/2/3/4; HFSR = hand-foot skin reaction; QD = every day

a: If reductions are required resulting in a dose of less than 60 mg QD of regorafenib, then regorafenib will be permanently discontinued. For Grade 3 neutropenia, the participant could stay on regorafenib for the first appearance, or hold until resolved to Grade 2 or less, restart at the same dose level or lower after discussion between the investigator and the sponsor.

b: After consultation with the sponsor, if toxicity is considered at least possibly related to pembrolizumab.

6.6.1 Dose Modification and Management of Lower Gastrointestinal Toxicity

Gastrointestinal (GI) toxicity in the form of diarrhea could be very common and a potentially serious event caused by regorafenib and pembrolizumab combination therapy, as both regorafenib and pembrolizumab may cause gastrointestinal adverse reactions. Diarrhea could be either the only presenting symptom of GI toxicity, potentially self-limiting, or part of immune checkpoint inhibitor-induced colitis that could require hospitalization and intensive treatment. Immune-related colitis (any grade) has been reported in 1.8% of patients receiving pembrolizumab. The median time to onset of immune-related colitis was 3.5 months whereas the median duration was 1.4 months, leading to discontinuation of pembrolizumab in 0.5% of patients. No predictive marker for the occurrence of gastrointestinal toxicity related to immune checkpoint inhibitors has been validated yet. As such, it is important to distinguish among different types of diarrhea and exclude alternative etiology (e.g. disease progression, other medications, infections).

Table 6–4: Dose Modification Guidance, Lower Gastrointestinal Toxicity

General instructions for management of lower gastrointestinal toxicity:

- Monitor all participants for signs and symptoms of enterocolitis (i.e. diarrhea, abdominal pain, blood or mucus in stool with or without fever) and bowel perforation (i.e. peritoneal signs and ileus)
- For diarrhea G1 and G2:
  - Oral fluids, loperamide, avoid high fiber/lactose diet
- For diarrhea G2 (> 7 days) or higher, consider per local institutional guidelines:
  - Blood tests (e.g. hematology and general chemistry including liver function tests (AST, ALT, Bilirubin))
  - Stool (e.g. culture, *Clostridium difficile*, cytomegalovirus (CMV) or other viral etiology, ova, and parasite)
  - GI consultation and imaging (e.g., CT scan of abdomen and pelvis and GI endoscopy with biopsy)
  - Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper upon AE improving to ≤ G1 and continue to taper over at least 4 weeks
- For severe and life-threatening diarrhea and/or immune-related colitis:
  - Consider hospitalization or outpatient facility for participants with dehydration or electrolyte imbalance
  - Fluid and electrolytes should be administered via IV infusion
  - Urgent GI consultation and imaging (e.g., CT scan of abdomen and pelvis and GI endoscopy with biopsy)
  - IV corticosteroid should be initiated first followed by oral steroid. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids

Event	Regorafenib	Pembrolizumab
Diarrhea G1; <4 stools/day over baseline	No modifications	No modifications
Diarrhea G2; 4-6 stools/day over baseline	No modifications, BUT if diarrhea G2 persistent (not back to ≤ G1 in 7 days), hold regorafenib until	• G2: Withhold; restart at same dose if resolution to ≤ G1 or baseline ≤ 12 weeks of

Table 6–4: Dose Modification Guidance, Lower Gastrointestinal Toxicity

	back to ≤ G1. Restart at same dose level or reduce 1 dose level[a] (at the investigator's discretion).	last infusion and corticosteroid has been tapered
Diarrhea G3; ≥7 stools/day over baseline	• G3: Hold regorafenib until back to ≤ G1. Restart at same dose level or reduce 1 dose level[a] (at the investigator's discretion)	• G3: Withhold; restart at same dose if resolution to ≤ G1 or baseline ≤ 12 weeks of last infusion and corticosteroid has been tapered • Recurrent G3: permanently discontinue
Diarrhea G4; Life-threatening consequences	• G4: Interrupt until ≤ G1. Restart at one dose level below[a]	• G4: Permanently discontinue

AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CMV = cytomegalovirus; CT = computed tomography; G1/2/3/4 = Grade 1/2/3/4; GI = gastrointestinal; IV = intravenous; irAE = immune-related adverse event; QD = every day

a: If reductions are required resulting in a dose of less than 60 mg QD of regorafenib, then regorafenib will be permanently discontinued.

6.6.2 Dose Modification and Management of Liver Toxicity

Elevation of liver enzymes could be a very common finding during the course of regorafenib and pembrolizumab combination therapy. In the ongoing 19497 study of regorafenib and pembrolizumab in HCC patients in first line, as of 06 JAN 2020, 31% of the patients experienced Grade 3 treatment-emergent AE (TEAE) of AST or ALT increase and 6% of them experienced Grade 4 occurrences.

A careful assessment should be done to define the proper etiology of any hepatic alteration found in the course of the study in order to exclude the underlying disease and an immune-mediated hepatic events as possible causes, before defining a liver toxicity as related to the study interventions.

Participants with a history of HBV or HCV with elevated transaminases who meet the criteria below should be evaluated for viral exacerbation/reactivation and viral load and hepatitis serologies (as needed) should be performed for evaluation of viral exacerbation/reactivation:

- Among participants with baseline AST/ALT ≤2×ULN: AST/ALT >5×ULN
- Among participants with baseline AST/ALT >2×ULN: AST/ALT >3×the baseline level
- AST/ALT >500 U/L regardless of baseline level

Table 6–5: Dose Modification Guidance; Specific Guidance for Liver Toxicity

Event	Regorafenib	Pembrolizumab
General instructions: • If any of below outlined events will occur: Monitor liver function tests weekly or more frequently until recovery to baseline or stabilization • The recommendations regarding dose adjustments and treatment interruptions can be used as support for the clinical decision. A careful decision will be made by investigators based on all clinical information, e.g. relatedness to study medications • Follow the guidance provided in Table 6–6 with respect to Hepatitis B flare, Hepatitis C recurrence or flare and immune-related hepatitis • For any G3/4 increases in ALT/AST or bilirubin: o If the increases are primarily seen under ongoing regorafenib treatment (e.g. last pembrolizumab infusion was given one week before): ▪ Closely monitor for potential de-challenge, i.e. whether a decrease in ALT/AST and/or bilirubin values is seen within 3 days of regorafenib interruption ▪ In case no such decrease is seen and/or a further deterioration in liver function is seen: Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper If immune-related hepatitis is suspected: Directly follow guidance provided in Table 6–6.		
ALT/AST > 5 x ULN if ALT/AST ≤ 2 x ULN at baseline OR ALT/AST 3-fold increase from D1 level but not exceeding 8 x ULN if ALT/AST > 2 x ULN at baseline	• Assess according to guidance given in Table 6–6 • Hold until recovery to ≤ G1 or baseline, then reduce 1 dose level[a] • At restart monitor liver function tests weekly for at least 4 weeks • 1st re-appearance: Discontinue	• Hold and assess + decide on potential restart according to guidance given in Table 6–6
ALT or AST > 5 x ULN accompanied by a t-hyperbilirubinemia ≥ 3 x ULN	• Assess according to guidance given in Table 6–6 • At restart monitor liver function tests weekly for at least 4 weeks • Hold until recovery to ≤ G1 or baseline, then reduce 1 dose level[a] • A participant with Gilbert's syndrome should be managed according to observed elevation of ALT and/or AST if the observed bilirubin increase is below actual increased baseline bilirubin value	• Hold and assess + decide on potential restart according to guidance given in Table 6–6
Any t-bilirubin > 3.0 mg/dL irrespective of ALT/AST values	• Assess according to guidance given in Table 6–6 • Hold until recovery to ≤ G1 or baseline, then reduce 1 dose level[a] • 1st re-appearance: Discontinue • For a participant with Gilbert's syndrome a continuation of regorafenib might be considered at the discretion of	• Hold and assess + decide on potential restart according to guidance given in Table 6–6

Table 6–5: Dose Modification Guidance; Specific Guidance for Liver Toxicity

Event	Regorafenib	Pembrolizumab
	the investigator if the observed bilirubin increase is below actual increased baseline bilirubin value	
AST and / or ALT > 20 x ULN	• Discontinue and assess according to guidance given in Table 6–6	• Discontinue and assess according to guidance given in Table 6–6
Hepatic Encephalopathy	• Discontinue unless hepatic encephalopathy is manageable and reversible[b] and assess according to guidance given in Table 6–6	• Discontinue unless hepatic encephalopathy is manageable and reversible[b] and assess according to guidance given in Table 6–6
Child-Pugh score of > 9 points	• Discontinue and assess according to guidance given in Table 6–6	• Discontinue and assess according to guidance given in Table 6–6
New onset of clinically detectable ascites requiring intervention for >3 days	• No modifications	• Discontinue and assess according to guidance given in Table 6–6
Gastrointestinal bleeding suggestive of portal hypertension (e.g., esophageal or gastric varices)	• Discontinue and assess according to guidance given in Table 6–6	• Hold and assess + decide on potential restart according to guidance given in Table 6–6
Recurrence of a severe or life-threatening event, or of any of the laboratory abnormalities listed above	• Discontinue and assess according to guidance given in Table 6–6	• Discontinue and assess according to guidance given in Table 6–6
If the participant is off study treatment therapy for infection, obstruction, or drug/alcohol-related toxicity for more than 3 weeks, or if they have esophageal bleeding, or become CP C at any point	• Discontinue and assess according to guidance given in Table 6–6	• Discontinue and assess according to guidance given in Table 6–6

ALT = alanine aminotransferase; AST = aspartate aminotransferase; G1/2/3/4 = Grade 1/2/3/4; QD = every day; ULN = upper limit of normal

a: If reductions are required resulting in a dose of less than 60 mg QD of regorafenib, then regorafenib will be permanently discontinued. For Grade 3 neutropenia, the participant could stay on regorafenib for the first appearance, or hold until resolved to Grade 2 or less, restart at the same dose level or lower after discussion between the investigator and the sponsor.

b: Hold until recovery to Grade ≤ 1 and restart at the same dose level or reduce 1 dose level [a] (at the investigator's discretion) if hepatic encephalopathy is manageable and reversible, after discussion with the sponsor.

6.6.2.1 Hepatic Events of Clinical Interest

The following events and laboratory abnormalities, if not associated with disease progression under study per investigator's judgement, are considered as hepatic events of clinical interest (HECI) and must be reported as SAEs (within 24 hours of the investigator's awareness):

- ALT:
  - ALT ≥5 × ULN if baseline ALT <2 x ULN
  - ALT >3 × baseline level if baseline ALT ≥2 x ULN
  - Any ALT >500U/L
- Any t-bilirubin >3.0 mg/dL
- Regardless of laboratory values, hepatic decompensation diagnosed clinically, including:
  - New onset of clinically detectable ascites requiring intervention for >3 days
  - Hepatic encephalopathy

Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The trial site guidance for assessment and follow up of these criteria can be made available. It may also be appropriate to conduct an additional evaluation for an underlying etiology in the setting of abnormalities of liver blood tests including ALT and bilirubin that do not meet the criteria noted above. In these cases, the decision to proceed with additional evaluation will be made through consultation between the study investigators and the Sponsor Clinical Director. However, abnormalities of liver blood tests that do not meet the criteria noted above are not ECIs for this trial.

Table 6–6: Guidance on Assessment and Further Dosing Following Occurrence of Hepatic Events of Clinical Interest

Assessment procedure to be applied
• Notification of the sponsor within 24 hours via SAE report if applicable (see also Section 8.3). Refer to Section 8.3.6 for AEs of special safety interest that must be reported as SAEs • Consider a consultation with a hepatologist. • Consider a work-up for hepatitis if there is no underlying hepatitis, including hepatitis A, B, C, D, E, Epstein-Barr virus (EBV), cytomegalovirus (CMV). • Assess for ingestion of drugs/supplements with hepatotoxic potential. • Assess for alcohol ingestion. • Assess for potential bacterial infection, biliary obstruction, or occult gastrointestinal bleeding • Repeat ALT, AST, t-bilirubin, direct bilirubin, ALP, GGT, INR, and CBC (complete blood count) with differential. • Other laboratories or imaging studies as clinically indicated. • Consider liver biopsy if indicated by hepatologist. • Infection needs to be ruled out with cultures of blood, urine, and ascites (if possible), as well as chest X-ray and abdominal imaging if relevant. If an infection is found, antibiotics should be started. • If t-bilirubin is elevated above baseline, magnetic resonance cholangio-pancreatography or ultrasound with Doppler should be obtained to rule out vascular compromise, biliary obstruction, and/or tumor progression. • If biliary obstruction is present, consultation with a gastroenterologist and/or an interventional radiologist should be obtained to see if the obstruction may be relieved. • A careful review of drugs, including herbal and alternative medications, should be obtained, and alcohol use should be ruled out. • Hepatitis C-infected participants (including participants who previously achieved sustained

Table 6–6: Guidance on Assessment and Further Dosing Following Occurrence of Hepatic Events of Clinical Interest

virological response [SVR] for 12 consecutive weeks after the cessation of antiviral treatment [SVR 12]): Measure HCV RNA viral load.

- Hepatitis B-infected participants: HBV DNA, HBsAg, HBeAg, anti-HBc (total and IgM), anti-HBe, and anti-HBs; participants should be questioned about compliance with the use of antiviral agents

Further information concerning Hepatitis B Flare

Hepatitis B flares are characterized by rapid elevations of ALT and AST to >5 × ULN and/or >3 × baseline. ALT elevation to ≥10 × ULN is common. In the absence of hepatic decompensation, ALT/AST elevations are typically isolated (i.e., limited/no elevations of bilirubin/ALP). Participants who are compliant with antiviral therapy should have continued suppression of HBV DNA at the time of flare; thus, detection of HBV DNA should prompt questioning of participants for compliance. Laboratory abnormalities secondary to flare are typically observed for 3-5 weeks.

Among participants with HBV, a flare should be considered if this pattern is observed and there is no evidence of an alternative etiology. Guidelines for participants with a diagnosis of HBV flare are as follows:

- Care should be instituted in consultation with a hepatologist.
- For participants who have detectable HBV DNA, re-institute antiviral therapy.
- If the participant is clinically stable, pembrolizumab dosing may be interrupted for up to 12 weeks. Participants should undergo weekly laboratory tests including: AST, ALT, ALP, Tbil, Dbil, INR, HBsAg, HBV DNA (if detected at the onset of the flare). Obtain anti-HBe, anti-HBs, and HBV DNA levels (if not detected at the onset of the flare) every 2-3 weeks.
- Restart pembrolizumab intervention only if ALT returns to normal or Grade 1 (if normal at baseline), or to baseline grade (if Grade 2 at baseline) within 12 weeks, and the participant is clinically stable, otherwise the participant should be permanently discontinued.

Further information concerning Hepatitis C Recurrence or Flare

Participants who achieved SVR 12 and participants with ongoing HCV infection are eligible for enrollment. In rare circumstances, HCV participants who achieve SVR 12 may relapse at later time points. Relapse is characterized by detection of HCV RNA, often accompanied by ALT elevations to >5 × ULN. In the absence of hepatic decompensation, ALT/AST elevations are typically isolated (i.e., limited/no elevations of bilirubin/ALP).

Among participants with uncontrolled hepatitis C, virologic flares are possible. Hepatitis C flares are characterized by rapid elevations of ALT and AST to >5 × ULN and/or >3 × baseline along with a rise in HCV RNA. ALT elevation to ≥10 × ULN and a 1 log elevation in HCV RNA level are common. In the absence of hepatic decompensation, ALT/AST elevations are typically isolated (i.e., limited/no elevations of bilirubin/ALP). Laboratory abnormalities secondary to flare or recurrence are typically observed for 3-5 weeks.

Guidelines for participants with recurrent HCV infection or an HCV flare are described below:

- Interrupt pembrolizumab intervention for **up to 12 weeks**
- Restart pembrolizumab intervention only if ALT returns to normal or G1 (if normal at baseline), or to baseline grade (if G2 at baseline) within 12 weeks, and the participant is clinically stable, otherwise, the participant should be permanently discontinued

Recurrent HCV infection (relapse of HCV infection for participants successfully treated or with new HCV infection):

If the participant entered the study with an HCV RNA test of “Target not Detected” and has confirmed detectable HCV RNA (2 specimens, 1 week apart), then the participant has experienced a late HCV relapse or a recurrent infection.

- Question the participant about use of injection or inhalation drugs
- At the time of first detection of HCV RNA, send a specimen for HCV genotyping or serotyping (if genotyping is not available) (local laboratory)
- Measure AST, ALT, ALP, Tbil, Dbil, and INR weekly
- Measure HCV RNA levels every 2 weeks
- Therapy with HCV antiviral treatments should be strongly considered.

HCV Flare (hepatitis C exacerbation in participants with HCV RNA positive):

- At the time of first detection of HCV RNA, send a specimen for HCV genotyping or serotyping (if genotyping is not available) (local laboratory)

Table 6–6: Guidance on Assessment and Further Dosing Following Occurrence of Hepatic Events of Clinical Interest

• Measure AST, ALT, ALP, Tbil, Dbil, INR weekly • Measure HCV RNA levels every 2 weeks • Therapy with HCV antiviral treatments should be strongly considered

Further information concerning Immune-related hepatitis
Description: Immune-related hepatitis due to study treatment should be suspected if any of the following is seen:
• ALT baseline values are less than 2 × ULN, and AST or ALT laboratory values increase to ≥5 × ULN
• Among participants with baseline ALT ≥2 × ULN, levels increase to >3× the baseline level
• ALT >500 U/L regardless of baseline level
• Total bilirubin >3.0 mg/dL regardless of baseline level
Immune-related hepatitis is a diagnosis made after excluding other possible etiologies for the change. Viral flare (if applicable), biliary or vascular obstruction, infection, medications, and alcohol use must be ruled out (see below).
Management:
• Interrupt pembrolizumab intervention for up to 12 weeks
• Start IV corticosteroid (60 mg/day of prednisone or equivalent) followed by oral corticosteroid
  • Monitor with biweekly laboratory tests including AST, ALT, Tbil, Dbil, ALP, and INR
  • **Restart pembrolizumab intervention only if:**
  o Abnormal laboratory values resolve to Grade ≤1 or baseline (if abnormal at baseline)
  o Taper steroid over 28 days
  o Steroid treatment is tapered to prednisone <10 mg/day or equivalent
  • **Permanently Discontinue pembrolizumab intervention if:**
  o Laboratory abnormalities do not resolve within 3 weeks
  o Steroids cannot be lowered to ≤10 mg/day (or prednisone equivalent) within 12 weeks
  o Evidence of decompensation to CP C status

Further information concerning other causes: • Rule out infection with blood, urine and ascites culture – antibiotics should be started if infection is found • If total bilirubin is elevated, imaging should be obtained to rule out vascular compromise, biliary obstruction, and/or tumor progression by imaging. If biliary obstruction is present, consultation with a gastroenterologist and/or an interventional radiologist should be obtained to see if the obstruction may be relieved. • Ruled out alcohol use and hepatotoxic drugs including herbal and alternative medications • Interrupt pembrolizumab intervention for up to 12 weeks • Restart pembrolizumab only if laboratory values have returned to Grade 1 or baseline (if normal or Grade 1 at start) or to baseline grade **within 3 weeks**

AE = adverse event; ALP = alkaline phosphatase; ALT = alanine aminotransferase; anti-HBc = Hepatitis B core antibody; anti-HBe = hepatitis B e-antigen; anti-HBs = hepatitis B surface antibody; AST = aspartate aminotransferase; CP = Child-Pugh (score); Dbil = direct bilirubin; dL = deciliter; DNA = deoxyribonucleic acid; G1/2/3/4 = Grade 1/2/3/4; GGT = gamma-glutamyl transferase; HBeAg = Hepatitis B e-antigen; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; IV = intravenous; IgM = Immunoglobulin M; INR = international normalized ratio; mg = milligram; RNA = ribonucleic acid; SAE = serious adverse event; SVR = sustained viral response; Tbil = total bilirubin; ULN = upper limit of normal

6.6.3 Dose Modification and Toxicity Management for Immune-related AEs Associated with Pembrolizumab

AEs associated with pembrolizumab exposure may represent an immunologic etiology. These irAEs may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than one body system simultaneously. The irAEs may be fatal and may occur after discontinuation of pembrolizumab. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical trial data, most irAEs were reversible and could be managed with interruptions of pembrolizumab, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue pembrolizumab and administer corticosteroids.

Table 6–7: Dose Modification Guidance, Other Immune-related Adverse Events

Event	Regorafenib	Pembrolizumab
Specific guidance for IMMUNE-RELATED ADVERSE EVENTS		
General instructions concerning pembrolizumab: 1. Severe and life-threatening irAEs should be treated with IV corticosteroids followed by oral steroids. Other immunosuppressive treatment should begin if the irAEs are not controlled by corticosteroids. 2. Pembrolizumab must be permanently discontinued if the irAE does not resolve or the corticosteroid dose is not ≤10 mg/day within 12 weeks of the last pembrolizumab treatment. 3. The corticosteroid taper should begin when the irAE is ≤ Grade 1 and continue at least 4 weeks. 4. If pembrolizumab has been withheld, pembrolizumab may resume after the irAE decreased to ≤ Grade 1 after corticosteroid taper.		
Pneumonitis • Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment	• G2 or higher: Interrupt until ≤ G1 • Restart at same dose level for G2 and decrease by 1 dose level for G3/4[a]	• G2: Withhold • Recurrent G2, G3, or G4: Permanently discontinue • Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper: add prophylactic antibiotics for opportunistic infections

Table 6–7: Dose Modification Guidance, Other Immune-related Adverse Events

Event	Regorafenib	Pembrolizumab
Specific guidance for IMMUNE-RELATED ADVERSE EVENTS		
New onset Type 1 Diabetes Mellitus (T1DM) or G3 or G4 hyperglycemia associated with evidence of β-cell failure • Monitor participants for hyperglycemia or other signs and symptoms of diabetes	• Interrupt until ≤ G1. Restart at same dose level.	• Withhold[b] • Initiate insulin replacement therapy for participants with T1DM • Administer anti-hyperglycemic in participants with hyperglycemia
Hypophysitis • Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)	• Interrupt until ≤ G1. Restart at same dose level.	• G2: Withhold • G3/4: Withhold or discontinue (at the investigator's discretion)[b] • Administer corticosteroids and initiate hormonal replacements as clinically indicated
Hyperthyroidism • Monitor for signs and symptoms of thyroid disorders	• G2: No modifications • G3/4: Interrupt until ≤ G2. Restart at same dose level.	• G2: Continue • G3/4: Withhold or discontinue (at the investigator's discretion)[b] • Treat with non-selective beta-blockers (e.g. propranolol) or thionamides as appropriate
Hypothyroidism • Monitor for signs and symptoms of thyroid disorders	• No modification • Initiate thyroid replacement hormones (e.g. levothyroxine or liothyronine) per standard of care	• Continue • Initiate thyroid replacement hormones (e.g. levothyroxine or liothyronine) per standard of care
Nephritis and renal dysfunction • Monitor changes of renal function; grading according to increased creatinine or acute kidney injury	• G2: Continue • G3/4: Interrupt until ≤ G2. Restart at same dose level.	• G2: Withhold • G3/4: Permanently discontinue • Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper
Neurological toxicities	• G2 or higher: Interrupt until ≤ G1 • Restart at same dose level for G2 and decrease by 1 dose level for G3/4[a]	• G2: Withhold • G3/4: Permanently discontinue • Based on severity of AE administer corticosteroids

Table 6–7: Dose Modification Guidance, Other Immune-related Adverse Events

Event	Regorafenib	Pembrolizumab
Specific guidance for IMMUNE-RELATED ADVERSE EVENTS		
Myocarditis • Ensure adequate evaluation to confirm etiology and/or exclude other causes	• G2 or higher: Interrupt until ≤ G1 • Restart at same dose level for G2 and decrease by 1 dose level for G3/4[a]	• Grade 1: Withhold • Grade 2/3/4: Permanently discontinue • Based on severity of AE administer corticosteroids
Exfoliative dermatologic conditions	• Suspected Steven-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), or drug rash with eosinophilia and systemic symptoms (DRESS): Withhold • Confirmed SJS, TEN, or DRESS: Permanently discontinue • Based on severity of AE administer corticosteroids • Ensure adequate evaluation to confirm etiology or exclude other causes	• Suspected SJS, TEN, or DRESS: Withhold • Confirmed SJS, TEN, or DRESS: Permanently discontinue • Based on severity of AE administer corticosteroids
All other immune-related AEs (e.g. immune-mediated arthritis, pancreatitis, uveitis, etc.) • Ensure adequate evaluation to confirm etiology or exclude other causes	• G2 or higher: Interrupt until ≤ G1 • Restart at same dose level for G2 and decrease by 1 dose level for G3/4[a]	• Persistent G2: Withhold • G3: Withhold or discontinue based on the event[c] • Recurrent G3 or G4: Permanently discontinue • Based on severity of AE administer corticosteroids

AE = adverse event; DRESS = drug rash with eosinophilia and systemic symptoms; G1/2/3/4 = Grade 1/2/3/4; irAEs = immune-related adverse event; IV = intravenous; QD = every day; SJS = Steven-Johnson Syndrome; T1DM = type 1 diabetes mellitus; TEN = toxic epidermal necrolysis

a: If reductions are required resulting in a dose of less than 60 mg QD of regorafenib, then regorafenib will be permanently discontinued.

b: The decision to withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician. If control achieved or ≤ Grade 2, pembrolizumab may be resumed.

c: Events that require discontinuation include, but are not limited to: Guillain-Barre Syndrome, encephalitis, myelitis, and other clinically important irAEs (eg, vasculitis and sclerosing cholangitis).

6.6.4 Dose Modification and Toxicity Management of Infusion Reactions Related to Pembrolizumab

Pembrolizumab may cause severe or life-threatening infusion reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab-associated infusion reaction are provided in Table 6–8.

Table 6–8: Dose Modification Guidance, Pembrolizumab-associated Infusion Reactions

Event	Regorafenib	Pembrolizumab	Premedication at Subsequent Dosing of Pembrolizumab
Specific guidance for PEMBROLIZUMAB-ASSOCIATED INFUSION REACTIONS			
• Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration • For further information, refer to CTCAE v 5.0			
G1 Mild reaction; infusion interruption not indicated; intervention not indicated	No modification	• Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator.	None

G2
Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hours
	No modification	• **Stop Infusion**
		• Additional appropriate medical therapy may include but is not limited to:
		  ○ IV fluids
		  ○ Antihistamines
		  ○ NSAIDs
		  ○ Acetaminophen
		  ○ Narcotics
		• Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator.
		• If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g. from 100 mL/hour to 50 mL/hour). Otherwise dosing will be held until symptoms resolve and the **participant should be premedicated for the next scheduled dose**.
		• Participants who develop G2 toxicity despite adequate premedication, pembrolizumab
			Participant may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab with: Diphenhydramine 50 mg p.o. (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg p.o. (or equivalent dose of analgesic).

Table 6–8: Dose Modification Guidance, Pembrolizumab-associated Infusion Reactions

Event	Regorafenib	Pembrolizumab	Premedication at Subsequent Dosing of Pembrolizumab
Specific guidance for PEMBROLIZUMAB-ASSOCIATED INFUSION REACTIONS			
		should be permanently discontinued.	
G3 Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) G4 Life-threatening; pressor or ventilator support indicated	No modification	• **Stop Infusion** • Additional appropriate medical therapy may include but is not limited to: o Epinephrine (In cases of anaphylaxis, epinephrine should be used immediately) o IV fluids o Antihistamines o NSAIDs o Acetaminophen o Narcotics o Oxygen o Pressors o Corticosteroids • Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. • Hospitalization may be indicated. • Pembrolizumab should be permanently discontinued. **In cases of anaphylaxis, epinephrine should be used immediately. Participant is permanently discontinued from further study drug treatment	No subsequent dosing
Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, refer to the Common Terminology Criteria for Adverse Events v5.0 (CTCAE) at http://ctep.cancer.gov			

CTCAE = Common Terminology Criteria for Adverse Events; G1/2/3/4 = Grade 1/2/3/4; IV = intravenous; NSAID = nonsteroidal anti-inflammatory drug; p.o. = per os (oral)

6.6.5 Rescue Medication and Supportive Care

Participants should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined along with the dose modification guidelines in Section 6.6.3 (Table 6–7). Where appropriate, these guidelines include the use of oral or IV treatment with corticosteroids, as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to pembrolizumab.

Note: If after the evaluation of the event it is determined not to be related to pembrolizumab, the investigator does not need to follow the treatment guidance. Refer to Section 6.6 for guidelines regarding dose modification and supportive care.

It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event.

6.7 Intervention after the End of the Study

Continued Access: Participants who are still on study intervention at the time of study completion/termination may continue to receive study intervention if they are experiencing clinical benefit. Continued access to study intervention will end when a criterion for discontinuation is met or 18 administrations of pembrolizumab had been administered. However, continuation of treatment with regorafenib can be individually discussed with the investigator for participants who do not experience disease progression after 2 years based on clinical benefit.

7. Discontinuation of Study Intervention and Participant Discontinuation / Withdrawal

All participants who enter the study should complete all applicable study periods, including the EoT visit. Participants can be withdrawn from any study period at any time.

Discontinuation from the intervention period alone does not constitute withdrawal from the study.

Participants who withdraw from the intervention period for any reason should come to the site for the safety follow-up visits and are to be encouraged to remain on the study for follow-up of primary, secondary and other objectives (i.e. continue in the active follow-up and long-term follow-up periods). Participants are expected to participate in follow-up unless they explicitly object. Withdrawal of consent to the intervention period should be documented in the participant's medical record. If the participant does not wish to be followed up further, this additional consent withdrawal for follow-up must also be documented.

For a full list of withdrawal criteria, refer to Section 7.2.

In all cases, the reason for withdrawal must be recorded in the participant's medical records and in the eCRF. For participants who withdraw consent, no further study-related procedures will be allowed. The participant will not suffer any disadvantage as a result.

All participants who discontinue due to AEs should be followed up until they recover or stabilize, and the subsequent outcome recorded. If any participant dies during treatment, or within 30 days after the last dose of regorafenib if a participant was on regorafenib monotherapy, or within 90 days after the last dose of regorafenib/pembrolizumab treatment or pembrolizumab monotherapy administration, the investigator or his/her designated associate(s) will inform the sponsor and the cause of death should be recorded in detail within 24 hours of awareness on a SAE form and transmitted to the sponsor.

7.1 Discontinuation of Study Intervention

In some circumstances, it may be necessary for a participant to permanently discontinue (definitive discontinuation) study intervention. If study intervention is definitively discontinued, the participant will remain in the study to be evaluated for disease progression and/or OS. See the SoA (Section 1.3.1) for data to be collected at the time of withdrawal of study intervention, in follow-up, and for any further evaluations that need to be completed.

The study interventions may be interrupted for situations other than treatment-related AEs such as medical / surgical events or logistical reasons not related to study therapy. Participants should be placed back on study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the sponsor. The reason for interruption should be documented in the participant's study record

7.1.1 Withdrawal Criteria

7.1.1.1 Withdrawal from Study Intervention Period

Participants MUST be withdrawn from the study intervention if any of the following occurs:

- At their own request or at the request of their legally acceptable representative (if acceptable by local law). At any time during the study and without giving reasons, a participant may decline to participate further. The participant will not suffer any disadvantage as a result.
- If, in the investigator's opinion, continuation of the study intervention would be harmful to the participant's well-being.
- Progressive disease as per RECIST 1.1; however, treatment beyond radiological progression per iRECIST is possible if the participant is still benefiting from treatment.
- Clinical progression (every effort should be made to obtain radiological confirmation of disease progression [PD] during active follow-up). Note: In cases where radiographic evaluation is not possible, clinical progression may be used. Clinical progression is based on the judgment of the investigator (e.g., defined as worsening of the ECOG PS ≥3 or symptomatic deterioration including increase in liver function tests).
- The development of a second primary malignancy that requires a different treatment.
- Development of any intercurrent illness or situation which may, in the judgment of the investigator, affect assessments of clinical status and study endpoints to a relevant degree.
- Severe allergic reactions, such as exfoliate erythroderma, anaphylaxis, or vascular collapse.
- Start of a new anti-cancer therapy.

- Use of illicit drugs or other substances that may, in the opinion of the investigator or their designated associate(s), have a reasonable chance of contributing to toxicity or otherwise confound the results.
- Pregnancy.
- Participant lost to follow-up.
- Death.

Participants MAY be withdrawn from the study intervention for the following reasons:

- At the specific request of the sponsor and in liaison with the investigator (e.g. obvious non-compliance, safety concerns).
- Participants should be taken off study intervention for disease progression. However, if a participant has radiographic progression but is achieving a clinically meaningful benefit, an exception to continue study intervention may be considered following consultation with the sponsor.
    - If the investigator considers radiographic changes secondary to drug-induced inflammation and not to tumor progression (i.e. in case of suspected pseudo-progression), the investigator may postpone a diagnosis of progressive disease until the next radiographic evaluation in the study, as per the criteria outlined in Appendix 10.5 in Section 10.5.3.
- Withdrawal of study intervention for abnormal liver function should be considered by the investigator when a participant meets one of the conditions outlined in Table 6–3 or if the investigator believes that it is in best interest of the participant.
- If a clinically significant electrocardiogram (ECG) finding is identified (including, but not limited to changes from baseline in QT interval corrected using Fridericia's formula [QTcF]) after enrollment, the investigator or qualified designee will determine if the participant can continue in the study and if any change in participant management is needed. This review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding should be reported as an AE.

See the SoA (Section 1.3.1) for data to be collected at the time of intervention permanent discontinuation and follow-up and for any further evaluations that need to be completed.

7.1.1.2 Withdrawal of Regorafenib only

Participants must be withdrawn from regorafenib for the following reasons:

- Participants who halt therapy for more than 28 consecutive days - including the 1-week drug holiday. However, continuation of regorafenib may be considered if, in the investigator's opinion, the participant may continue to benefit from the regorafenib treatment, and after consultation with sponsor.
- Unacceptable toxicity, i.e. an event requiring permanent discontinuation of regorafenib according to dose modification guidance in Section 6.6.

7.1.1.3 Withdrawal of Pembrolizumab only

Participants MAY be withdrawn from pembrolizumab for the following reasons:

- Participants who experience a delay of more than 12 weeks to receive the subsequent pembrolizumab infusion due to treatment-related toxicity or corticosteroids cannot be

reduced to ≤10 mg prednisone or equivalent per day within 12 weeks, according to dose modification guidance in Section 6.6.

- Unacceptable toxicity, i.e. event requiring permanent discontinuation of pembrolizumab according to dose modification guidance in Section 6.6.
- Discontinuation of pembrolizumab may be considered for participants who have attained a confirmed CR that have been received at least 8 infusions (24 weeks) of pembrolizumab and had at least 2 infusions with pembrolizumab beyond the date when the initial CR was declared.

7.2 Participant Discontinuation/Withdrawal from the Study

A participant must be withdrawn from the study at any time at his/her own request or at the request of their legally acceptable representative (if acceptable by local law).

A participant may be withdrawn from the study at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon.

If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a participant withdraws from the study, and additionally requests destruction of her/his samples taken but not yet tested, the investigator must document this (either destruction by site or request to central lab, as applicable) in the site study records.

Withdrawal from active follow-up

Participants MUST be withdrawn from active follow-up if any of the following occurs:

- At their own request or at the request of their legally acceptable representative (if acceptable by local law). At any time during the study and without giving reasons, a participant may decline to participate further. The participant will not suffer any disadvantage as a result.
- Radiologically confirmed PD is observed and/or clinical progression (for participants who discontinued study intervention before PD due to any other reason).
- Start of subsequent systemic anti-cancer treatment.
- Development of a second primary malignancy that requires a different treatment.
- Substantial non-compliance with the requirements of the study.
- If, in the investigator's opinion, continuation of the active visits would be harmful to the participant’s well-being.
- Participants lost to follow-up.
- Death.

Participants MAY be withdrawn from active follow-up if any of the following occurs:

- At the specific request of the sponsor and in liaison with the investigator (e.g. obvious non-compliance).

Withdrawal from long-term follow-up

Participants MUST be withdrawn from long-term follow-up if any of the following occurs:

- Withdrawal of consent to long-term follow-up.

- Participants lost to follow-up.
- Death.

Participants MAY be withdrawn from long-term follow-up if any of the following occurs:

- At the specific request of the sponsor and in liaison with the investigator (e.g. obvious non-compliance).

7.3 Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered lost to follow-up.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 1 (Section 10.1.9).

8. Study Assessments and Procedures

Study procedures and their timing are summarized in Section 1.3. Protocol waivers or exemptions are not allowed.

Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in Section 1.3, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

Changes in study visit schedules, missed visits, or participant discontinuations may lead to missing information (e.g. for protocol-specified procedures). The specific information (e.g.

explanation of the basis of the missing data) will be captured in the CRF and the information will be summarized in the clinical study report. In all cases, existing regulatory requirements for maintaining investigational product accountability remain and should be addressed and documented.

8.1 Efficacy Assessments

Tumor Response Assessments

Assessment of disease

Tumor response evaluated using RECIST 1.1 (Eisenhauer et al. 2009) (see Appendix 5, Section 10.5.1) will be applied to determine the anti-tumor activity and efficacy variables of this study (see Section 9.4.1).

mRECIST guidelines (Lencioni and Llovet 2010) (see Appendix 5, Section 10.5.2) were developed in order to evaluate the treatment response accounted for the induction of intra-tumoral necrotic areas in estimating the decrease in tumor load, and not just a reduction in overall tumor size.

iRECIST (Seymour et al. 2017) (see Appendix 5, Section 10.5.3) is based on RECIST 1.1, but adapted to account for the unique tumor response seen with immunotherapeutic drugs. iRECIST may be used by the investigator to assess tumor response and progression and support treatment-related decisions in this study.

Both mRECIST and iRECIST will be used in exploratory analyses.

Imaging modalities:

The preferred and recommended imaging modality for tumor response assessment is multi-detector CT with both oral and IV contrast. Anatomic coverage should be chest, abdomen and pelvis at all timepoints along with any other anatomic areas of known or suspected disease (e.g., neck, limbs). CT scans of the abdomen should be done in three phases (arterial, portal venous and late venous) for proper liver lesion detection followed by CT of the pelvis and chest in the late venous/delayed phase. The slice thickness for CT and MRI (see below) is strongly recommended to be ≤ 5mm.

MRI with IV gadolinium chelate-based contrast may be performed in lieu of contrast-enhanced CT for the abdomen and pelvis when institutional policy does not recommend the use of CT or there is a contraindication to IV iodinated CT contrast. The chest should be evaluated by CT without contrast in case of allergy. Following a pre-contrast T1-weighted acquisition, contrast-enhanced MRI of the abdomen including the liver should be performed during the late arterial, the portal venous, and the delayed phases, followed by pelvic MRI during the delayed phase. The scan parameters for postcontrast imaging should be the same as those of the pre-contrast T1-weighted acquisition. If a participant develops a contraindication to CT contrast media during the course of the study after the baseline imaging, contrast-enhanced MRI is recommended over non-contrast CT for the abdomen and pelvis. Even if IV contrast cannot be administered (for example, in the situation of allergy to contrast), a non-contrast CT of the chest is still preferred over MRI or chest X-ray.

Ultrasound is not an acceptable modality to assess tumor response in this study. Chest X-rays should not be used at baseline in lieu of chest CT assessments. However, if an unequivocal new tumor lesion(s) is identified on at a chest X-ray during the study and that lesion was not present on the most recent prior CT chest assessment, this chest X-ray is acceptable as imaging evidence for progressive disease.

For participants with known or suspected brain metastases and/or carcinomatous meningitis, brain MRI (with gadolinium-based contrast agent; preferred) or CT with iodinated contrast should be performed at screening. Participants with previously treated brain metastases may be included in the study provided they are radiologically stable, i.e., without evidence of progression for at least 4 weeks by repeat imaging (note that the repeat imaging should be performed during study screening), clinically stable and without requirement of steroid treatment for at least 14 days prior to first dose of study treatment. Participants diagnosed with active CNS metastases and/or carcinomatous meningitis at baseline will not be allowed to enter the study. The MRI/CT scans should be repeated when clinically indicated.

If bone metastases are known or suspected, a whole-body bone scan with both anterior and posterior projection using a technetium-99m-labeled phosphonate tracer (methylene diphosphonate (MDP), hydroxymethylene diphosphonate (HMDP), hydroxyethylene diphosphonate (HDP), or 2,3-dicarboxypropane-1,1-diphosphonate (DPD)) should be performed at screening. Bone scans should be repeated when CR or PR is identified in the CT/MRI assessments to confirm the absence of new bone lesion(s) disease or when progression in bone is suspected. A newly-detected bone lesion on bone scan should be confirmed by radiologic assessment (X-ray, CT, MRI if not already evident on the CT/MRI tumor assessment scans).

For consistency, the same imaging modality and equivalent technique (e.g. contrast agent, slice thickness, field of view, protocol, sequence, phosphonate tracer) should be used for all scans and tumor assessments across all time points performed on an individual participant, including screening/baseline scans.

Initial tumor imaging:

The time points for CT/MRI scans are described in the SoA (Section 1.3.1). A baseline radiological tumor assessment will be conducted within 28 days before the start of study treatment. Scans performed as standard of care that were obtained prior to the participant signing the informed consent may be used for the baseline tumor assessment, provided that they were performed within 42 days of starting study intervention and meet this protocol's imaging requirements. The investigator must review screening images to confirm the participant has measurable disease per RECIST 1.1 and to determine this participant's eligibility.

Tumor imaging on study:

Following treatment initiation, regardless of potential dose delays for either drug, subsequent tumor assessments will occur every 6 weeks with a maximum window of ± 7 days during the first 54 weeks and every 9 weeks ± 7 days thereafter.

For participants who discontinue study treatment without confirmed radiological disease progression, the investigator should perform a complete physical, laboratory, and radiological assessment as soon as possible. Every effort should then be made to continue to perform tumor assessments every 6 weeks ± 7 days during the first 54 weeks and every 9 weeks ± 7 days thereafter. Imaging assessments will continue to be performed until whichever of the following occurs first:

- Investigator-assessed disease progression is confirmed
- The start of new anti-cancer treatment
- Withdrawal of consent
- Death
- The end of the study

Response assessment:

RECIST 1.1 (see Appendix 5, Section 10.5.1) and mRECIST criteria for HCC (see Appendix 5, Section 10.5.2) will be used for radiological tumor evaluation in this study. iRECIST (see Appendix 5, Section 10.5.3, Table 10–11 and Figure 10–1) can be used by the investigator to assess tumor response and progression and support treatment-related decisions in this study.

By inclusion criteria, participants must have at least one evaluable and measurable lesion per RECIST 1.1 on the baseline scan. Tumor measurements and assessments are to be performed at the local sites and are to be entered in the eCRF. All scans should be interpreted by the same radiologist/investigator during the study, where at all possible. Any lesion that has been previously treated with radiotherapy should be considered as a non-target lesion. However, if a lesion previously treated with radiotherapy has clearly progressed on the baseline/screening scan, it can be considered as a measurable lesion.

The minimum time interval required between two tumor assessments for determination of SD is 6 weeks. Objective response should be confirmed by a repeat imaging assessment. CT/MRI scans for confirmation of response should be performed no sooner than 4 weeks after the initial scan demonstrating PR or CR. Participants will then return to regular scheduled imaging, starting with the next scheduled imaging time point. Participants who receive additional imaging for confirmation do not need to undergo the next scheduled tumor imaging if it is less than 4 weeks later. For these participants, tumor imaging may resume at the subsequent scheduled imaging time point.

Imaging data:

All image files (coded with study participant number and in Digital Imaging and Communications in Medicine (DICOM) format for CT/MRIs and bone scans) as well as imaging-related adjunctive data (e.g. dose of contrast agent) must be stored locally. In this study, image files and imaging-related adjunctive data will also be collected centrally by an imaging core laboratory designated by Bayer starting at the beginning of the study for a centralized independent imaging review of tumor response9. Further guidance on the acquisition of CT/MRIs and bone scans as well as information on how to transmit image files to the imaging core laboratory will be provided in the Imaging Guidance for this study.

8.2 Safety Assessments

Standard safety monitoring and grading will be performed using CTCAE v. 5.0.

Investigators should refer to the Safety Information sections of the current IBs of regorafenib and pembrolizumab for the expected side effects including unexpected AEs and hypersensitivity reactions. The IB will be updated if any new relevant safety data are obtained.

Safety will be assessed by monitoring and recording all AEs and SAEs, cardiac, hematologic and blood chemistry parameters, vital signs, ECG, ECOG PS, and any abnormal findings observed during the performance of physical examinations.

Planned time points for all safety assessments are provided in the SoA (Section 1.3.1).

Therapeutic monitoring should be performed following dose modification of study intervention in a manner consistent with the local clinical standard of care. In general, participants should be closely monitored for adverse drug reactions of all concomitant medications regardless of the path of drug elimination.

In the event of implausible results, the laboratory may measure additional parameters to assess the quality of the sample (e.g., clotted or hemolyzed) and to verify the results. The results from such additional analyses may neither be included in the clinical database of this study nor evaluated further. If the results are relevant, the investigator will be informed to determine follow-up activities outside of this protocol.

Abnormal physical examination findings are recorded either as medical history or as AEs (see Section 8.3). Additional assessments may be indicated at any time during the course of the study at the discretion of the investigator. In addition, lab tests may be repeated at the discretion of the investigator, if clinically indicated.

8.2.1 Physical Examinations

A full physical examination will be performed by the investigator or qualified designee as outlined in the SoA (Section 1.3.1). Full physical examination includes, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, and neurological systems, and of skin status. Height and weight will also be measured and recorded. Height will be measured at screening only.

The investigator or qualified designee will perform a symptom-directed physical exam as clinically indicated, according to the SoA (Section 1.3.1). New clinically significant abnormal findings should be recorded as AEs. Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.2.2 Vital Signs

Body temperature, heart rate, oxygen saturation, and blood pressure will be assessed.

ECG, blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (e.g., television, cell phones).

When blood pressure measurement and PK sample collection are scheduled at the same time point, the participant’s blood pressure must be measured before collection of the PK sample.

8.2.3 Electrocardiograms

A 12-lead ECG will be locally obtained as outlined in the SoA (Section 1.3.1) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals.

12-lead ECGs will be evaluated by a physician. He / She will document the diagnosis(-ses) including an overall assessment of the findings and their clinical relevance. The overall interpretation of the ECG (normal/abnormal, clinical relevance) and the ECG diagnosis will be documented in the source documents and on the eCRF.

8.2.4 Clinical Safety Laboratory Assessments

See Appendix 2 (Section 10.2) for the list of clinical laboratory tests to be performed and to the SoA (Section 1.3.1) for the timing and frequency.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

All clinically significant abnormal laboratory tests during participation in the study or within 30 days after the last dose of study intervention (and within 90 days after the last dose of pembrolizumab for the laboratory values assessed as/related to SAEs) should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator, unless a new anti-cancer therapy has been initiated.

- If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.
- All protocol-required laboratory assessments, as defined in Appendix 2 (Section 10.2), must be conducted in accordance with the SoA (Section 1.3.1).

  If laboratory values from non-protocol-specified laboratory assessments performed at the institution’s local laboratory require a change in participant management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification), then the results must be recorded in the CRF.

8.2.5 ECOG Performance Status

A participant’s ability to manage activities of daily living will be appraised using ECOG PS. Grading definitions for ECOG PS are given in Table 8–1. The participant’s ECOG PS will be estimated according to the SoA (Section 1.3.1). Change of ECOG PS will be measured for safety reasons.

Table 8–1: Definitions for ECOG PS Grading

Grade	Description
0	Fully active, able to carry on all pre-diseases 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 housework, 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.

ECOG PS = Eastern Cooperative Oncology Group performance status

8.2.6 Baseline Characteristics

Demographic

Baseline participant data pertaining to demographic information should be documented accordingly in the appropriate eCRFs include the following:

- Date of birth (year, age) if allowed according to local law
- Gender
- Race, if legally allowed
- Ethnicity, if legally allowed
- Weight
- Height
- Childbearing status (if applicable)

Medical history

Medical history findings (i.e. previous diagnoses, diseases or surgeries) meeting all criteria listed below will be collected as available to the investigator:

- Start before signing of the informed consent
- Considered relevant for the participant's study eligibility

Other baseline characteristics

Other baseline characteristics will be collected, including but not limited to:

- Baseline cancer characteristics, including cancer type, location of the primary tumor, histology, tumor stage at study entry, date of diagnosis of first metastasis, presence of metastases (e.g. liver, lung, brain or bone), date of most recent progression, prior cancer therapies and procedures. In addition, if results are available: tumor mutational burden (TMB), microsatellite instability (MSI) status, and PD-L1 expression.
- All medications (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by the participant within 28 days prior to the study intervention

All the population characteristic data should be recorded in the eCRF. Detailed instructions on baseline characteristics can be found in the eCRF completion guidelines.

8.3 Adverse Events and Serious Adverse Events

Progression per se should not be regarded as AE. Instead, the associated signs and symptoms should be recorded as AEs.

The intensity of AEs should be documented using the CTCAE v. 5.0.

The study intervention action should be recorded separately for each study intervention as detailed in the eCRF.

- Drug withdrawn
- Drug interrupted
- Drug delayed
- Dose reduced
- Dose not changed
- Dose increased
- Not applicable
- Unknown

The definitions of an AE or SAE can be found in Section 10.3.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative (if acceptable by local law) or health care professional not involved in the study).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE. They remain responsible for following up SAEs, or AEs, considered related to the study intervention or study procedures, or those that caused the participant to discontinue the study intervention (see Section 7). AEs of Special Interest (AESI) have to be followed up regardless of causality or relationship to study intervention.

Investigators should refer to the Safety Information section of the current IB of regorafenib and the current IB of pembrolizumab for the expected side effects. As with any agent, there is always the potential for unexpected AEs, including hypersensitivity reactions. The IB will be updated if any new relevant safety data are obtained.

8.3.1 Time Period and Frequency for Collecting AE and SAE Information

All AEs and SAEs will be collected from the signing of the ICF until 30 days after last dose of study intervention as specified in the SoA (Section 1.3.1). In addition, SAEs will be collected for 90 days after the last dose of pembrolizumab, unless a new anti-cancer therapy has been initiated. See Section 8.3.5 for reporting of pregnancy and exposure during breastfeeding.

An AE (irrespective of causal relationship) not completely resolved at the end of the pre-defined collection period must be followed up until resolution or until the investigator considers the event will not improve further.

Medical occurrences that begin before obtaining informed consent will be recorded on the medical history section of the eCRF. Medical occurrences that begin before the start of study

intervention but after obtaining informed consent will be recorded on the AE section of the eCRF. Medical occurrences that started before but deteriorated after obtaining informed consent will be recorded as AEs.

All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3, Section 10.3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.3.2 Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided Appendix 3, Section 10.3.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, and AESI (as defined in Section 8.3.6), will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Appendix 3, Section 10.3.

8.3.4 Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5 Pregnancy

If a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4, Section 10.4.

If a participant inadvertently becomes pregnant while on study intervention, the participant will be immediately discontinued from study treatment. The site will contact the participant at least monthly and document the participant's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the sponsor without delay and within 24 hours if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the sponsor.

It is unknown whether pembrolizumab or regorafenib is excreted in human milk. Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, participants who are breastfeeding are not eligible for enrollment.

All pregnancies and exposure during breastfeeding must be reported by the investigator, from the start of study intervention through 120 days following withdrawal of study intervention, or 30 days following withdrawal of study intervention if the participant initiates new anti-cancer therapy. Details of all pregnancies in female participants and, if indicated, female partners of male participants will be collected after the start of study intervention and until outcome.

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

For a pregnancy in the partner of a male study participant, all efforts will be made to obtain similar information on course and outcome, subject to the partner's consent.

For all reports, the forms provided are to be used. The investigator should submit them within the same timelines as an SAE.

8.3.6 Adverse Events of Special Interest

Selected non-serious and serious AEs are also known as Events of Clinical Interest (ECI) and must be reported to the sponsor.

ECI for this trial include:

1. Pembrolizumab overdose, as defined in Section 8.4, that is not associated with clinical symptoms or abnormal laboratory results
2. HECIs as defined in Section 6.6.2.1

8.4 Treatment of Overdose

Overdose of regorafenib

For this study, any dose of regorafenib greater than **160 mg** within one day will be considered an overdose.

In the event of an overdose, the investigator/treating physician should:

- Closely monitor the participant for any AE/SAE and laboratory abnormalities until study intervention can no longer be detected systemically.

- Obtain a plasma sample for PK analysis within 3 days from the date of detection of overdose if requested by the sponsor (determined on a case-by-case basis).
- Any overdose or incorrect administration of study intervention should be noted on the Study Drug Administration eCRF.
- AEs associated with an overdose or incorrect administration of study intervention should be recorded on the AE eCRF.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the sponsor based on the clinical evaluation of the participant.

For detailed guidance on overdosing, refer to the most current version of the IB for regorafenib.

There is no specific treatment for regorafenib overdose. The highest dose of regorafenib studied clinically is 220 mg QD. The AEs observed at this dose were primarily dermatological events, hoarseness, diarrhea, mucositis, and nausea. In the event of suspected overdose, regorafenib should be immediately withheld and supportive care instituted under the supervision of a qualified health care professional.

Overdose of pembrolizumab

For this study, an overdose of pembrolizumab will be defined as any dose of 1000 mg or greater (≥2.5 times the study dose).

No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

8.5 Pharmacokinetics

For all participants enrolled, sparse pharmacokinetic samples will be collected for determination of regorafenib and its metabolites M-2 and M-5 (in plasma) and pembrolizumab (in serum) as specified in Table 1–3.

Sampling times outside the suggested sampling time intervals will not be considered as protocol deviations. However, omission of samples specified in the PK sampling (Table 1–3) will be considered a protocol deviation. The date and clock time of each sample as well as dates and times of the regorafenib administration and start and stop times of pembrolizumab infusion will be recorded in the eCRF as PK estimates will be based on the sampling times relative to dosing times. If regorafenib is not administered on the day of PK sampling, the pre-dose samples will be collected and the post-dose samples will not be collected.

Samples may be collected irrespective of any dose modifications during the treatment cycle. No detailed dosing history is required before the pre-dose sample, but the regorafenib dose that separates the pre- and post-dose sample needs to be taken under supervision and the time of dosing should be recorded. In addition, the time of meal intake prior to regorafenib administration on PK sampling days needs to be reported in the patient diary and together with the dosing time is recorded in the eCRF.

Regorafenib data from this study may be pooled with data from other clinical studies for pharmacometric analysis.

Model-determined exposures of regorafenib may be used for exposure-response analyses of selected measures of efficacy, safety or biomarker changes. The results of population PK and exposure-response analyses will be reported separately from the overall study results.

The PK analyses will be performed using validated analytical methods. Exploratory measurements of other moieties may be performed, if needed.

PK samples for pembrolizumab will be held until the end of the study by the central lab. At that time, the determination will be made if analysis will be done on the samples, however, samples may be analyzed prior to the end of the study if safety or efficacy concerns arise.

Instructions for the collection, processing, storage and shipment of PK samples will be provided separately by the sponsor (e.g., sample handling sheets or laboratory manual).

8.6 Pharmacodynamics

Pharmacodynamics biomarkers are described in Section 8.8.1.

8.7 Genetics

Pharmacogenetic analyses except whole genome sequencing will be part of the biomarker investigations in this study. See Section 8.8 for details.

8.8 Biomarkers

Biomarker investigations in the current study will include pharmacodynamic biomarker assessments and assessments of biomarkers that may associate with efficacy and/or safety.

Both genetic as well as non-genetic biomarkers will be investigated. Genetic investigations may be of any kind (including whole exome sequencing), except for whole genome sequencing.

Timing: See the SoA (Table 1–1) and the schedule of biomarker blood sampling (Table 1–2) for planned time points of sample collection.

Additional samples may be collected at additional time points during the study if warranted and agreed upon between the investigator and the sponsor. Sampling time points might also be moved or removed.

For details regarding tumor tissue collection, refer to the below specification:

Tumor tissue requirement: Formalin-fixed paraffin-embedded block (preferred) or minimum of 20 slides, obtained from core biopsy or surgical specimen.

At screening:

- Archival tumor tissue sample is mandatory if available.
- Recent tumor tissue as defined below is mandatory for all participants. Exceptions will be accepted for participants with no recent baseline tumor tissues after documented discussion and approval by the sponsor.
    - an archival biopsy no older than 6 months and after the last anti-tumor treatment
    - or a new biopsy.

On treatment / at EoT

- New tumor biopsies at W6D1 (+/-3 days) is mandatory if medically feasible, in consultation with the sponsor.
- Collection of a new biopsy at EoT (+ 7 days) is optional.

Sample handling and storage: Details on the collection, processing, shipment, and storage of samples will be provided in separate documents (e.g., sample handling sheets or lab manual). Samples may be stored for a maximum of 15 years (or according to local regulations) following the end of the study at a facility selected by the sponsor to enable further analyses.

Reporting: Results of biomarker investigations may be reported separately (e.g., in a biomarker evaluation report).

8.8.1 Pharmacodynamics Biomarkers

Pharmacodynamics biomarkers will be evaluated in biomarker samples collected before and during treatment to investigate the impact of regorafenib and pembrolizumab on these biomarkers, and may be correlated with safety and/or efficacy. Tissue-based pharmacodynamics biomarker evaluations will be conducted in available paired tumor tissues (recent tumor tissues and on-treatment/EoT tumor biopsy).

Candidate pharmacodynamics biomarkers may include (but are not limited to):

- Intra-tumor pharmacodynamics biomarkers such as immune cell infiltrations (e.g. Teff, Treg, macrophages), expression of immune genes/signatures (e.g. myeloid expression signature, Treg signature), and/or parameters in the regorafenib targeted pathways (e.g. VEGFR2) in paired tumor biopsies (pre- and on-treatment)
- Quantification and characterization of immune cell populations in blood (e.g. Teff, Treg, macrophages, myeloid-derived suppressor cells [MDSC], etc.), analyzed e.g., by flow-cytometry
- Systemic levels of immune mediators (e.g., cytokines, chemokines) from serum or plasma and tumor markers from circulating tumor deoxyribonucleic acid (ctDNA)
- Plasma proteins of interest for regorafenib (e.g., sVEGFR2, angiopoietin 1 [Ang1])
- Circulating miRNA

8.8.2 Biomarkers that May Associate with Response

Baseline candidate biomarkers from tumor and blood samples will be evaluated for correlation with response to treatment (to identify possible “predictive biomarkers”). Samples from tumor materials and blood will retrospectively be analyzed.

Candidate biomarkers from baseline samples that may associate with response may include (but are not limited to):

- Tumor immune status (e.g., myeloid expression signature, Treg signature, PD-L1 expression) at baseline
- Expression of parameters of interest for regorafenib (e.g. VEGFR2) in baseline tumor materials
- Baseline TMB/tumor mutations (e.g. mutations in Wnt pathway) as detected in tumor and/or ctDNA
- Baseline immune cell populations in blood and baseline systemic levels of immune mediators (e.g., cytokines/chemokines)
- Germline genetic variants in genes of interest (e.g., cc-chemokine ligands CCL4 and CCL3, cc-chemokine receptor 5 [CCR5])
- Baseline circulating miRNA markers

8.8.3 Other Biomarkers

In addition to the biomarkers described above, further biomarkers related to the mode of action or the safety of regorafenib and pembrolizumab and similar drugs may be examined. The same applies to further biomarkers deemed relevant to cancer and associated health problems. These investigations may include e.g., diagnostic testing, potentially predictive, safety, pharmacodynamics or monitoring biomarkers.

8.9 Immunogenicity Assessments

Blood (serum) samples will be collected from all participants treated with pembrolizumab for analysis of anti-drug antibodies (ADAs) as specified in Table 1–3. Additional exploratory ADA samples will be collected as specified in Table 1–3, which may be used for exploratory analyses including assessing the potential impact of ADAs formed against previous PD-1/PD-L1 treatment.

A decision to analyze the immunogenicity samples described above will be made during the course of the study. Until that time, samples will be stored at a central laboratory.

Instructions for the collection, processing, storage and shipment of immunogenicity samples will be provided separately by the sponsor (e.g., sample handling sheets or laboratory manual).

8.10 Medical Resource Utilization and Health Economics

Not applicable.

9. Statistical Considerations

This is a single arm, Phase 2 study with ORR per RECIST1.1 by central review as the primary endpoint.

In the pilot phase of the study, the participant population for the expansion phase is determined. Participants from the pilot phase who match the population of the expansion phase (atezolizumab plus bevacizumab vs. atezolizumab plus bevacizumab and other first line treatments) will be included in the analysis of the expansion phase.

Historical (background) response rate is assumed to be 20% (per RECIST 1.1, an ORR of 7% was observed in the regorafenib arm of the HCC trial RESORCE (Bruix et al. 2017), and an ORR of 18% was observed in the pembrolizumab arm of the HCC trial KEYNOTE-240 (Finn et al. 2020); as the sum of the ORR was about 25%, in order to show a synergistic effect this study is designed to rule out an ORR of 20%). Target response rate (i.e. true underlying response rate for which there is 95% power conditional on a positive pilot phase) will be 35%.

In addition to the number of responders, totality of data including tumor dynamics response (depth, durability) and overall safety data will be considered to make a determination to move forward to the expansion phase.

A one-sided exact binomial test with a type-I error of 2.5% will be conducted at the end of the expansion phase to test the hypothesis.

9.1 Statistical Hypotheses

There will be no statistical hypothesis testing done in the pilot phase of the study.

The primary hypotheses to be tested in the expansion phase of the study is

$$H_0: ORR_{Combination} \leq 20\% \text{ vs. } H_1: ORR_{Combination} > 20\%$$

The primary hypothesis will be tested by an exact binomial test. The significance level will be a 1-sided alpha of 2.5%.

9.2 Sample Size Determination

It is expected that approximately 170 participants will be screened to achieve the 119 evaluable participants for both study phases combined.

Pilot phase: A total of approximately 52 participants will be enrolled to receive regorafenib in combination with pembrolizumab divided in two cohorts: 26 of them after atezolizumab plus bevacizumab treatment combination (cohort 1); and 26 after any IO containing first line treatment (cohort 2), excluding atezolimab plus bevacizumab treatment combination.

Expansion phase: 2 scenarios should be considered depending on the pilot phase results.

- **Scenario 1**: if in the pilot phase at least 8 responders out of the 26 treated in cohort 1 are observed
- **Scenario 2**: if in the pilot phase at least 8 responders in each cohort are observed

In scenario 1, the study can continue to accrue 67 new additional participants after atezolizumab in combination with bevacizumab (i.e. a total of 93 participants after prior treatment with atezolizumab in combination with bevacizumab will be enrolled, representing the patient population of cohort 1). If 27 or more participants respond out of 93 evaluable participants (i.e. ORR 29%), the study will have ruled out an ORR ≤ 20% (with 1-sided alpha of 0.025), using an exact binomial test.

In scenario 2, the study can continue to accrue 67 new additional participants after any immune checkpoint inhibitor as defined in the pilot phase (i.e. a total of 119 participants will be enrolled, representing the patient population of cohort 1 and cohort 2). If 34 or more participants respond out of 119 evaluable participants (i.e. ORR 29%), the study will have ruled out an ORR ≤ 20% (with 1-sided alpha of 0.025), using an exact binomial test.

In case cohort 2 meets the response rate criterion and cohort 1 does not, the future direction for further evaluation in the expansion phase will be decided based on the totality of data and treatment landscape at the time.

If the true underlying response rate is 35%, given that at least 8 responders are observed in stage 1, the conditional power for the final analysis is at least 95%, under both scenarios above.

9.3 Populations for Analyses

The populations for analyses are defined in Table 9–1.

Table 9–1: Populations for Analyses

Population	Description
Enrolled	All participants who sign the ICF
Full Analysis Set	All participants who take at least 1 dose of study intervention will be included in the efficacy and safety evaluation

ICF = Informed consent form

All analyses will be performed on the Full Analysis Set.

9.4 Statistical Analyses

Analyses will be performed using SAS (SAS Institute, Cary, North Carolina, USA), Version 9.2 or higher. The specific version used will be mentioned in the statistical analysis plan (SAP).

This section is a summary of the planned statistical analyses of the most important endpoints including primary and secondary endpoints. The SAP will be finalized prior to first patient first visit (FPFV) and it will include a more technical and detailed description of the statistical analyses described in this section.

9.4.1 Efficacy Analyses

9.4.1.1 General Considerations

All analyses will be conducted at one-sided type-I error level of 2.5% or two-sided type-I error level of 5% respectively. A one-sided exact binomial test will be conducted in the expansion phase to analyze the primary endpoint. Confidence intervals will be presented for selected variables.

9.4.1.2 Primary Efficacy Endpoint

The primary endpoint of the study is ORR based on RECIST 1.1 assessed by central review. ORR is defined as the proportion of participants with best overall response of confirmed CR or PR. Participants for whom best overall tumor response is not CR or PR, as well as participants without any post-baseline tumor assessment will be considered non-responders.

In both study phases, the primary efficacy variable will be analyzed after all participants are available for efficacy. The analysis will be done on the Full Analysis Set. In the pilot phase, the analysis will be done by cohort. In the expansion phase, the analysis will be done on the participants who received the first line treatment determined in the pilot phase of the study.

Methods used will include frequency tables (with the ORR table also including all “Best overall response” categories) as well as 95% two-sided Clopper-Pearson confidence intervals and the results of an exact binomial test.

9.4.1.3 Secondary Efficacy Endpoints

The secondary efficacy endpoints in this study are DOR as per RECIST 1.1 by investigator assessment and central review and ORR as per RECIST 1.1 by investigator assessment.

DOR (for PR and CR) is defined as the time (in days) from the first documented objective response of PR or CR, whichever is noted earlier, to disease progression or death (if death

occurs before progression is documented). DOR will be defined for responders only, i.e. participants with a CR or PR. The actual dates the tumor scans were performed will be used for this calculation. DOR for participants who have not progressed or died at the time of analysis will be censored at the date of their last tumor evaluation.

The analysis will be done on the Full Analysis Set. In the pilot phase, the analysis will be done by cohort. In the expansion phase, the analysis will be done on participants who received the first line treatment determined in the pilot phase of the study.

For analyses of the secondary endpoints, proportion-based efficacy variables will be using frequency tables as well as 95% two-sided Clopper-Pearson confidence intervals. With regard to time to event data, these will be summarized descriptively using Kaplan Meier methodology and plots, as well as median estimates based on Greenwood's formula, including 95% two-sided confidence interval.

9.4.1.4 Tertiary/Exploratory Endpoints

All other endpoints will be analyzed by means of descriptive statistics using frequency tables for response endpoints and summary statistics for continuous endpoints. Further analyses will be described in the SAP.

9.4.2 Safety Analyses

All safety analyses will be done on the Full Analysis Set. In the pilot phase, the analysis will be done by first line treatment (atezolizumab plus bevacizumab vs. other first line treatments).

In the expansion phase, the analyses will be done on participants who received the first line treatment determined in the pilot phase of the study.

The incidence of TEAEs (new or worsening from baseline) will be summarized by system organ class and preferred term, severity (based on CTCAE grades), type of AE, and relation to study treatment. Deaths reportable as SAEs and non-fatal serious AEs will be listed by participant and tabulated by type of AE. AEs leading to study intervention withdrawal and/or modifications will be summarized.

Laboratory abnormalities will be summarized by severity. Frequency and incidence rates will be provided. Frequency tables will also be provided for changes in severity from baseline to worst value post-baseline. The following summaries will be generated separately for hematology and biochemistry:

- Worst change from baseline of abnormal hematological and biochemical laboratory values during treatment period
- Incidence of abnormal hematological and biochemical laboratory values during the treatment period

9.4.3 Other Analyses

PK and biomarker exploratory analyses will be performed and described in separate reports.

9.5 Interim Analyses

An interim analysis will be performed to determine the participant population (participants after treatment with atezolizumab in combination with bevacizumab, or after any first line treatment) for the expansion phase of the study.

Both cohorts from the pilot phase will continue to be expanded until a sample size of 26 evaluable participants per cohort is reached. Participants are considered evaluable for efficacy when:

- they have completed at least two post-baseline scans; or
- they have been followed for approximately 14 weeks from the first study intervention dose; or
- they have discontinued due to progression or any other reason before 14 weeks from the first study intervention dose.

The interim analysis is planned when the last participant enrolled in each of the cohorts from the pilot phase has reached the evaluation criteria outlined above. The interim analysis will be conducted on the Full Analysis Set. Both cohorts will be analyzed separately.

For this futility analysis, no formal adjustment of the type-I error will be performed.

9.6 Data Monitoring Committee (DMC) or other Review Board

Not applicable.

A Steering Committee may considered by the sponsor for the expansion phase.

10. Supporting Documentation and Operational Considerations

10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations

The protocol, protocol amendments, ICF, IB, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.

- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

10.1.2 Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

All relevant documentation will be filed in the TMF.

10.1.3 Informed Consent Process

The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative (if acceptable by local law) and answer all questions regarding the study.

Participants must be informed that their participation is voluntary. Participants or their legally authorized representative (if acceptable by local law) will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.

A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative (if acceptable by local law).

Participants who are re-screened are required to sign a new ICF.

10.1.4 Data Protection

Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5 Committees Structure

Not applicable.

10.1.6 Dissemination of Clinical Study Data

Result summaries of Bayer's sponsored clinical trials in drug development Phases 2, 3 and 4 and Phase 1 studies in patients are provided in the Bayer Trial Finder application after marketing authorization approval, in line with the position of the global pharmaceutical industry associations laid down in the "Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases". In addition, results of clinical drug trials will be provided on the publicly funded website www.ClinicalTrials.gov and EU Clinical Trials Register in line with the applicable regulations.

Bayer commits to sharing upon request from qualified scientific and medical researchers patient-level clinical trial data, study-level clinical trial data, and protocols from clinical trials in patients for medicines and indications approved in the US and EU on or after 01 JAN 2014 as necessary for conducting legitimate research.

All Bayer-sponsored clinical trials are considered for publication in the scientific literature irrespective of whether the results of the clinical trials are positive or negative.

10.1.7 Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF. The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities and requirements, including handling of non-compliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan.

The sponsor or designee is responsible for the data management of this study including quality checking of the data. The sponsor assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations).

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator after study completion for the retention period as set forth in the Investigator Agreement unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

Data collection tool

The data collection tool for this study will be a validated electronic data capture system called RAVE. Participant data necessary for analysis and reporting will be transmitted into a validated database or data system (LSH).

Data required according to this protocol will be recorded by investigational site personnel via data entry into the internet-based electronic data capture (EDC) software system RAVE, which Bayer has licensed from Medidata Solutions Worldwide. RAVE has been validated by Medidata Solutions Worldwide and Bayer for use in its clinical studies. RAVE allows for the application of software logic to set-up data entry screens and data checks to ensure the completeness and accuracy of the data entered by the site personnel. Bayer extensively applies the logic to ensure data are complete and reflect the clinical data requirements of the study. Data queries resulting from the application of the software logic are resolved by the site personnel. The data are stored at a secure host facility maintained by Medidata Solutions Worldwide and transferred on a periodic basis to Bayer's internal computer system via a secure Virtual Private Network.

All access to the RAVE system is through a password-protected security system that is part of the RAVE software. All internal Bayer and external investigator site personnel seeking access must go through a thorough RAVE training process before they are granted access to RAVE for use in Bayer's clinical studies. Training records are maintained.

The RAVE system contains a system-generated audit trail that captures any changes made to a data field, including who made the change, why the change was made and the date and time it was made. This information is available both at the investigator’s site and at Bayer.

10.1.8 Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator’s site. The site must implement processes to ensure availability of all required source documentation. It is the expectation of the sponsor that all data entered into the eCRF have source documentation available at the site.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

The definition of what constitutes source data can be found in the source data location list (SDLL) (part of the monitoring plan, not part of the protocol) archived at site, and the monitor will work with the site to complete this checklist.

10.1.9 Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.

The investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participants and should assure appropriate therapy and/or follow-up.

Reasons for premature study termination or suspension may include but are not limited to:

- If the risk-benefit ratio becomes unacceptable owing to, for example,
    - Safety findings from this study (e.g. SAEs)
    - Results of parallel clinical Bayer studies or emerging data from literature
    - Results of parallel animal studies (on e.g. toxicity, teratogenicity, carcinogenicity or reproduction toxicity)
- If the study conduct (e.g. recruitment rate; dropout rate; protocol compliance) does not suggest a proper completion of the trial within a reasonable time frame
- Strategic reasons (e.g. the clinical development of the drug is stopped)

The site is entitled to end its participation in the study if necessary due to medical or ethical reasons.

For any of the above closures, the following applies:

- Closures should occur only after consultation between involved parties. The final decision on the closure must be in writing.
- All affected institutions (e.g. IEC(s)/IRB(s); competent authority(ies); study center; head of study center) must be informed as applicable according to local law.
- All study materials (except documentation that has to remain stored at site) must be returned to the sponsor. The investigator will retain all other documents until notification is given by the sponsor for destruction.

In the event of study closure, participants on treatment and those in post-study follow-up must be taken care of in an ethical manner.

10.1.10 Publication Policy

The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Investigators may publish or present individual study data (including case reports) obtained in the course of this study but only after the primary report and/or publication of the study results in their entirety. If publishing individual site data is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.

10.2 Appendix 2: Clinical Laboratory Tests

All laboratory analyses detailed in the SoA (Section 1.3.1) and in Table 10–2 and Table 10–3 will be performed locally.

Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol. Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

AFP will be assessed as described in the SoA (Section 1.3.1).

Serum or urine pregnancy tests are performed as outlined in the SoA (Section 1.3.1). The frequency of pregnancy tests may be higher if required by local regulations. Refer to Section 5.1 for screening pregnancy criteria. Details on Contraceptive Guidance and Collection of Pregnancy Information can be found in Section 10.4.

The schedule for testing and the laboratory tests included in Panel A and B are described in Table 10–1 and Table 10–2, respectively. The schedule and criteria for hepatitis virus testing is outlined in Table 10–3.

Investigators must document their review of each laboratory safety report.

Table 10–1: Laboratory Testing Standard Schedule

Visit	Panel A (see Table 10–2)	Panel B (see Table 10–2)
Screening (within 7 days of first study intervention)	X [a]	
Before each pembrolizumab infusion	X [b]	
Before each regorafenib dose after 7 days break		X [c]
Regorafenib D1 for in-between weeks within the first 8 weeks (first 2 cycles)		X
EoT visit		X
Safety follow-up visit	X	

D1 = Day 1; EoT = end of treatment; W1D1 = Week 1 Day 1
a: If for any reason tests were performed more than 7 days prior to the first dose of study intervention, they should be repeated on W1D1.
b: If there is a pembrolizumab dosing delay or pembrolizumab withdrawal, Panel A is required at least every 4 weeks on Day 1 before each regorafenib administration
c: Not required if sampling for Panel A has been done within the previous 5 days.

Table 10–2: Protocol-Required Safety Laboratory Assessments per panel

		Panel A	Panel B
Hematology	Hb	X	X
	Hct	X	
	Platelet count	X	X
	WBC	X	
	ANC	X	X
	ALC	X	
	AMC	X	
	ABC	X	
	AEC	X	
Biochemistry	Sodium	X	
	Potassium	X	
	AST	X	X
	ALT	X	X
	GGT	X	
	Total bilirubin	X	X
	Direct bilirubin	(X) if t-bilirubin elevated	
	ALP	X	
	Uric acid	X	
	Total protein	(X) if deemed clinically indicated	
	Albumin	X	
	Total calcium	X	
	Lipase	X	
	Amylase	X	
	Magnesium	X	
	Triglycerides	X	
	Phosphate	X	
	LDH	X[b]	X[b]
	Glucose (non-fasting)	X	
	Creatinine/CG [c]	X	
	Urea/BUN	X	

Table 10–2: Protocol-Required Safety Laboratory Assessments per panel

		Panel A	Panel B
Coagulation	INR	X	
	aPTT	X	
Thyroid	FT3	X	
	FT4	X	
	TSH	X	
Urinalysis [a] Analytes: *Urinalysis dipstick*: blood, glucose, ketones, bilirubin, protein, leukocytes, urobilinogen, nitrite, specific gravity, and pH *Microscopic urinalysis*: RBC microscopic, WBC microscopic, epithelial cells, casts, and crystals		X	

ABC = absolute basophil count; AEC = absolute eosinophil count; ALC = absolute lymphocyte count; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AMC = absolute monocyte count; ANC = absolute neutrophil count; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CG = Cockcroft-Gault (equation); EoT = end of treatment; FT3 = free triiodothyronine; FT4 = free thyroxine; GFR = glomerular filtration rate; GGT = gamma-glutamyl transferase; Hb = hemoglobin; Hct = hematocrit; INR = prothrombin time-international normalized ratio; LDH = lactate dehydrogenase; RBC = red blood cell count; TSH = thyroid stimulating hormone; WBC = white blood cell count.

a: If protein dipstick result is 3+ or abnormal (based on type of urine test strip used), a laboratory urine analysis should be done for the quantification of proteinuria by urinary protein/creatinine ratio on a random urine sample preferably taken at mid-morning.

b: At screening and EoT visit

c: Cockcroft-Gault formula for GFR:

$$GFR_{Cockcroft} = \frac{(140 - age) \times mass\ (kg)\ [\times 0.85 \text{ if female}]}{72 \times serum\ creatinine\ (mg/dl)}$$

Table 10–3: Hepatitis Virus Panel

Screening:

- Hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (HBsAb), hepatitis B core antibody (HBcAb) (total and IgM) and HBV-DNA viral load to be performed at baseline unless pre-study results are available within 3 months before informed consent and participants are clinically stable

If analysis results are:

  - (1) HBsAg+ or
  - (2) anti-HBc+ and anti-HBs-, HBsAg- and HBV-DNA viral load <100 IU/mL,
  - the following analyses are required: anti-HDV, anti-HBe and HBeAg

- Anti-HCV antibody (anti-HCV) to be performed at baseline unless pre-study results are available within 3 months before informed consent and participants are clinically stable
  - If the participant is found to be anti-HCV Ab positive, the following analyses are required: (HCV)-RNA viral load and HCV genotyping or serotyping (if genotyping is not available)

Intervention period + up to safety follow-up visit, if clinically indicated

- HCV recurrence/flare:
  - Measure HCV-RNA viral load (At the time of first detection of HCV RNA, send a specimen for HCV genotyping or serotyping (if genotyping is not available) (local laboratory))
  - Measure AST, ALT, ALP, Tbil, Dbil, and INR weekly
  - Measure HCV RNA levels every 2 weeks
  - Therapy with HCV antiviral treatments should be strongly considered
- HBV flare:
  - Measure HBV-DNA viral load.
  - Participants should undergo weekly laboratory tests including: AST, ALT, ALP, Tbil, Dbil, INR, HBsAg, HBV DNA (if detected at the onset of the flare).
  - Obtain anti-HBe, anti-HBs, and HBV-DNA levels (if not detected at the onset of the flare) every 2-3 weeks

See Table 6–6

Anti-HBc+ = hepatitis B core antibody positive; anti-HBe = hepatitis B e-antigen; anti-HBs- = hepatitis B surface antibody negative; anti-HCV = anti-hepatitis C virus antibody; anti-HDV = hepatitis D antibody; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; Dbil = direct bilirubin; DNA = deoxyribonucleic acid; HBcAb = hepatitis B core antibody; HBeAg = hepatitis B e-antigen; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; IgM = immunoglobulin M; INR = prothrombin time-international normalized ratio; RNA = ribonucleic acid; Tbil = total bilirubin

10.3 Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1 Definition of AE

AE definition
• An AE is any untoward medical occurrence in a participant or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention. **Treatment-emergent adverse event (TEAE) definition:** • A TEAE is defined as any AE arising or worsening after the start of first study intervention administration until 30 days after the last administration of any study intervention.

Events <u>meeting</u> the AE definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE.

Events NOT meeting the AE definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2 Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

A SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d. Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3 Recording and Follow-up of AE and/or SAE

AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to the sponsor in lieu of completion of the AE/SAE.
- There may be instances when copies of medical records for certain cases are requested by the contract research organization (CRO) and/or sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the CRO/sponsor.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study based on NCI-CTCAE v. 5.0.

An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.

Assessment of causality
• Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated. • The investigator will also consult the IB and/or Product Information, for marketed products, in his/her assessment. • For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality for regorafenib and pembrolizumab. • There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.** • The investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment. • The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs
• Immune-related AEs (also called immune-mediated AEs) are AEs consistent with an immune-mediated mechanism or immune-mediated component for which non-inflammatory etiologies (e.g., infection or tumor progression) have been ruled out. irAEs can include events with an alternate etiology which were exacerbated by the induction of autoimmunity. • Every AE must be assessed by the investigator with regard to whether it is considered immune-mediated. • The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. • If a participant dies during participation in the study or during a recognized follow-up period, the investigator should provide access to any post mortem findings including histopathology • New or updated information will be recorded in the originally completed CRF. • The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

10.3.4 Reporting of SAEs

SAE reporting to the sponsor via an Electronic Data Collection Tool
• The primary mechanism for reporting a SAE to the sponsor will be the electronic data collection tool.

SAE reporting to the sponsor via an Electronic Data Collection Tool
• If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours. • The site will enter the SAE data into the electronic system as soon as it becomes available. • After the study is completed at a given site, the electronic data collection tool will be taken offline to prevent the entry of new data or changes to existing data. • If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken offline, then the site can report this information on a paper SAE form (see next section) or to the sponsor by telephone. • Contacts for SAE reporting can be found in Investigator Site File.

SAE reporting to the sponsor via Paper CRF
• Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the sponsor. • In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames. • Contacts for SAE reporting can be found in the Investigator Site File.

10.4 Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

10.4.1 Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

Women in the following categories are not considered WOCBP:

1. Premenarchal
2. Premenopausal female with 1 of the following:
    - Documented hysterectomy
    - Documented bilateral salpingectomy
    - Documented bilateral oophorectomy

    Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
3. Postmenopausal female
    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
    - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Fertile Man

A man is considered fertile after puberty unless permanently sterile by bilateral orchidectomy.

10.4.2 Contraception

Regorafenib and pembrolizumab may have adverse effects on a fetus *in utero*. Furthermore, it is not known if pembrolizumab has transient adverse effects on the composition of sperm.

Participants should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study, male participants must agree to use highly effective contraception during the treatment period and for 120 days after the last dose of regorafenib. Female participants of childbearing potential must adhere to the contraception requirement (from the day of study intervention initiation, or 14 days prior to the initiation of study intervention for oral contraception) throughout the study period and for 120 days after the last dose of pembrolizumab, and 210 days after the last dose of regorafenib, whichever occurs last. If there is any question that a participant of childbearing potential will not reliably comply with the requirements for contraception, that participant should not be enrolled in the study.

Contraception guidance:

The investigator or a designated associate is requested to advise the participants how to achieve highly effective birth control.

Male participants

Male participants with female partners of childbearing potential are eligible to participate if they agree to the following (as applicable) during the protocol-defined time frame in Section 5.1:

- Are abstinent from sexual intercourse as their usual and preferred lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent.
- Agree to use a male condom plus partner use of a contraceptive method with a failure rate of <1% per year as described in Table 10–4 when having sexual intercourse with a WOCBP who is not currently pregnant.
- Men with a pregnant or breastfeeding partner must agree to remain abstinent or use barrier contraception during each episode of sexual intercourse during the protocol-defined time in Section 5.1.
- Refrain from donating sperm during the protocol-defined time frame in Section 5.1.

Female participants

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in Table 10–4 and during the protocol-defined time frame in Section 5.1:

Table 10–4: Highly Effective Contraceptive Methods

Highly effective contraceptive methods that are user dependent [a] *Failure rate of <1% per year when used consistently and correctly.*
Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation[b] • Oral • Intravaginal • Transdermal
Progestogen only hormonal contraception associated with inhibition of ovulation • Oral • Injectable
Highly effective methods of low user dependency[a]
Implantable progestogen only hormonal contraception associated with inhibition of ovulation[b] • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) Bilateral tubal occlusion
Vasectomized partner *A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.*
Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.*

Table 10–4: Highly Effective Contraceptive Methods

WOCBP = woman of childbearing potential
a. Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies.
b. Hormonal contraception may be susceptible to interaction with the study treatment, which may reduce the efficacy of the contraceptive method. In this case, two highly effective methods of contraception should be utilized during the protocol-defined time frame in Section 5.1.

10.4.3 Pregnancy

10.4.3.1 Pregnancy testing

WOCBP should only be included after a confirmed menstrual period and a negative highly sensitive urine or serum pregnancy test.

Additional pregnancy testing should be performed as outlined in the SoA (Section 1.3.1). The frequency of pregnancy tests may be higher if required by local regulations.

Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected.

10.4.3.2 Collection of Pregnancy Information

Female participants who become pregnant

- The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the sponsor within 24 hours of learning of a participant's pregnancy.
- The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate, after obtaining the signed informed consent from both parents of the neonate, unless local law or specific circumstances of the respective case allow otherwise, and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any post-study pregnancy related SAE considered reasonably related to the study treatment by the investigator will be reported to the sponsor as described in Section 8.3.4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will be immediately discontinued from study treatment.

Male participants with partners who become pregnant

- The investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive study intervention.
- After obtaining the necessary signed informed consent from both the study participant and the pregnant female partner, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

10.5 Appendix 5: Tumor response criteria (RECIST 1.1, mRECIST for HCC, and iRECIST)

Response and progression will be evaluated in this study using RECIST 1.1 (Section 10.5.1). Modified RECIST for HCC (Section 10.5.2) and iRECIST (Section 10.5.3) will be used as exploratory analyses.

10.5.1 RECIST 1.1

The RECIST 1.1 criteria, based on the measurement of the longest diameter of tumor lesions, were designed and validated to assess treatment response in solid tumors (Eisenhauer et al. 2009).

Measurable Disease:

Non-nodal tumor lesions: Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) with a minimum size of:

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm) or MRI. If scans with slice thicknesses greater than 5mm are used, the minimum size should be twice the slice thickness.
- 20 mm by chest X-ray
- 10 mm caliper measurement by clinical examination (lesions which cannot be accurately measured with calipers should be recorded as non-measurable)

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components that can be evaluated by CT or MRI, can be considered as measurable lesions if the soft tissue component meets the definition of measurability.

Tumor lesions situated in a previously irradiated area are not considered measurable unless there has been demonstrated progression in the lesion.

Baseline assessment

Non-Measurable Disease: All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to < 15mm short axis) are considered non-measurable disease. Leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitic involvement of skin or lung, inflammatory breast disease, abdominal masses/ abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques and blastic bone lesions are all non-measurable.

Target Lesions: All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs should be identified as *target lesions* and be recorded and measured at baseline. These 5 lesions should be selected on the basis of their size (lesion with the longest diameter), be representative of all involved organs and should be suitable for reproducible repeated measurements. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for *all target lesions* will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression of the measurable dimension of the disease. If there are >5 measurable lesions, those not selected as *target lesions* will be considered together with non-measurable disease as *non-target lesions*.

Non-target Lesions: All non-measurable lesions (or sites of disease) plus any measurable lesions over and above the 5 listed as *target lesions,* including pathological lymph nodes (with short axis ≥10 mm and < 15 mm) should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required but these lesions should be noted at baseline and should be followed as "present", "absent" or in rare cases "unequivocal progression". In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the eCRF (e.g.; 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

Best Response

The best overall response is the best response recorded from the start of the study intervention until the end of intervention. The participant's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions. While some non- target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

All participants will have their best response on study classified as outlined below:

Complete Response (CR): Disappearance of all clinical and radiological evidence of tumor (both *target* and *non-target*). Any pathological lymph nodes (whether target or non-target) must have a reduction in short axis to < 10mm.

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions taking as reference the baseline sum, no unequivocal progression of existing non-target lesions and no appearance of new lesions.

Stable Disease (SD): Steady state of disease. Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, no unequivocal progression of existing non-target lesions and no appearance of new lesions.

Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate

an absolute increase of at least 5mm. Unequivocal progression of existing non-target lesions or the appearance of one or more new lesions will also constitute progressive disease. (Note: the appearance of one or more new lesions is also considered progression). Ascites or pleural effusion will be recorded as disease progression only if proven malignant.

Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of <10mm.

To achieve unequivocal progression in participants with measurable disease on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit withdrawal of study intervention. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal.

In the absence of measurable disease, the same general concepts apply here as noted above.

Response duration

The duration of overall response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded on study).

The duration of overall complete response is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Stable disease duration

Stable disease is measured from treatment allocation until the criteria for progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, this is the reference for calculation of PD).

The following text descriptions of the visit response are logically equivalent to the tables below.

Table 10–5: RECIST 1.1: Response for Participants with Target and Non-target Lesions

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Response for this category also requires
CR	CR	No	CR	
CR	Non-CR/Non-PD	No	PR	
CR	Not evaluated	No	PR	
PR	Non-PD or not all evaluated	No	PR	
SD	Non-PD or not all evaluated	No	SD	documented at least 6 weeks from treatment allocation
Not all evaluated	Non-PD	no	NE	
PD	Any	Yes or No	PD	
Any	PD	Yes or No	PD	
Any	Any	Yes	PD	

CR = complete response; NE = non-evaluable; PD = progressive disease; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; SD = stable disease

Participants with a global deterioration of health status requiring discontinuation of intervention without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration*". Every effort should be made to document the objective progression even after discontinuation of intervention.

Table 10–6: RECIST 1.1: Response for Participants with Non-target Lesions Only

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/Non-PD	No	Non-CR/non-PD*
Not evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

CR = complete response; NE = non-evaluable; PD = progressive disease; RECIST = Response Evaluation Criteria in Solid Tumors

* Non-CR/non-PD is preferred over "stable disease" for non-target disease.

Methods of Measurement

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. All measurements must be recorded in millimeters (or decimal fractions of centimeters), if applicable.

Clinical Lesions – Clinical lesions will only be considered measurable when they are superficial (e.g. skin nodules, palpable lymph nodes) and ≥ 10mm diameter as assessed using calipers. For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is recommended.

Chest X-ray – Lesions on chest X-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, chest CT is preferable.

CT / MRI – CT is the best currently available and reproducible methods to measure target lesions selected for response assessment. CT scans should be performed with cuts of 5 mm or less in slice thickness. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable. This

applies to the chest, abdomen and pelvis. Head & neck and extremities usually require specific protocols.

Ultrasound – Ultrasound is not useful in assessment of lesion size and should not be used as method of measurement. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised.

Endoscopy / Laparoscopy – The utilization of these techniques for objective tumor evaluation is not advised.

Cytology / Histology – These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (e.g. with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or stable disease in order to differentiate between response (or stable disease) and progressive disease.

10.5.2 mRECIST for HCC

The modified version of RECIST for HCC combines a quantitative assessment of a set of lesions using unidimensional measurements with a qualitative assessment of all other lesions.

The modifications introduced for the assessment of intrahepatic lesions are based on the modified RECIST criteria published in 2010 for the assessment of HCC (Lencioni and Llovet 2010).

Results from a number of previous clinical studies in HCC have demonstrated that RECIST does not adequately capture the extent of tumor necrosis induced by interventional therapies or new molecular targeting drugs. Only viable tumor, assessed by properly designed CT or MRI studies, should be included in the tumor burden, and viable tumor should be defined as uptake of contrast agent in the arterial phase of dynamic imaging studies. Consequently, a modification of RECIST was first proposed by a panel of experts, and further expanded. This proposal is based on the fact that the diameter of the target lesions with viable tumor tissue should be the basis of measurements for intrahepatic lesions. The measurement of the longest viable tumor diameter for the assessment of response according to mRECIST can be only applied in case of typical lesions. Conversely, for non-enhancing atypical lesions, as well as for any extrahepatic neoplastic niches, the measurements of the longest overall tumor diameter as per conventional RECIST should prevail. In addition, there are specific modifications of the original criteria regarding the assessment of vascular invasion, lymph nodes, ascites, pleural effusion, and new lesions (European Association for the Study of the Liver [EASL]- European Organisation for Research and Treatment of Cancer [EORTC] clinical practice guidelines) (EASL-EORTC 2012).

The expert panel has adopted the concept of viable tumor endorsed by EASL and proposed amendments to RECIST in the determination of tumor response for HCC, which have been incorporated into the criteria in this trial as described herein.

Definitions

Intrahepatic lesions: Malignant findings within the liver parenchyma, the portal vein, and the porta hepatis region. The rules for the assessment of intrahepatic lesions (including when a new lesion is considered to have appeared) incorporate the referenced modifications for HCC.

Extrahepatic lesions: All malignant lesions, other than those defined as intrahepatic as above. These lesions will be assessed using the standard RECIST 1.1 approach.

Measurable lesions: Lesions that, at baseline, meet the requirements for being reproducibly quantifiable. The requirements are different for intrahepatic and extrahepatic lesions, and are described below. Lesions that meet the requirements are considered eligible for quantitative assessment during the study.

Non-measurable lesions: Lesions that, at baseline, do not meet the below-described requirements, cannot be chosen for quantitative assessment, and must be assessed qualitatively.

Target lesions: Lesions that are chosen at baseline (from the set of measurable lesions) for quantitative assessment throughout the trial, using rules outlined below. A lesion that has been selected as a target lesion remains a target lesion for the rest of the trial.

Non-target lesions: Lesions that are not chosen at baseline for quantitative assessment, and must be assessed qualitatively throughout the trial. A lesion that has been selected as a non-target lesion remains a non-target lesion for the rest of the trial.

Typical HCC enhancement: A lesion is considered to have typical HCC enhancement if it shows enhancement during the arterial phase of contrast administration, with washout in the portal venous or late venous phase.

Baseline Assessment

Measurable disease:

Non-nodal tumor lesions: Measurable lesions are those that can be accurately measured in at least one dimension (longest diameter to be recorded) with a minimum size of:

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm) or MRI. If scans with slice thickness greater than 5mm are used, the minimum size should be twice the slice thickness.
- 20 mm by chest X-ray
- 10 mm caliper measurement by clinical examination (lesions which cannot be accurately measured with calipers should be recorded as non-measurable)
- For typical lesions within the liver parenchyma, only the portion of the lesion that shows typical HCC enhancement should be included in the measurement. For atypical lesions, the longest overall diameter should be measured.

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT or MRI scan

Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components that can be evaluated by CT or MRI, can be considered as measurable lesions if the soft tissue component meets the definition of measurability.

Tumor lesions situated in a previously irradiated area are not considered measurable unless there has been demonstrated progression in the lesion.

Non-measurable disease:

All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with short axis 10-14 mm) are considered non-measurable disease. Leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitic involvement of

skin or lung, inflammatory breast disease, abdominal masses/ abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques and blastic bone lesions are all non-measurable.

Intrahepatic lesions: For lesions in the liver parenchyma, those that show typical HCC enhancement with longest diameter <10 mm, as well as those that show typical enhancement in a complex pattern that does not lend itself to reproducible measurement are considered non-measurable.

Porta hepatis lymph nodes: Lymph nodes detected at the porta hepatis can be considered malignant, but not measurable, if the lymph node short axis is at least 2 cm. Nodes in the porta hepatis are never considered measurable.

Portal vein thrombosis: Malignant portal vein thrombosis should be considered a non-measurable lesion.

Selection of target and non-target lesions:

At baseline, lesions are divided into those that will be followed quantitatively (target lesions) and those that will be followed qualitatively (non-target lesions).

All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs should be identified as *target lesions* and be recorded and measured at baseline. These 5 lesions should be selected on the basis of their size (lesion with the longest diameter), be representative of all involved organs and should be suitable for reproducible repeated measurements. For the purposes of this selection, paired organs (such as the lungs) should be regarded as a single organ, and all lymph nodes should be regarded as a single organ.

If measurable lesions are present in the liver parenchyma, they should always be selected as target lesions before any other lesions are chosen. Up to 2 liver lesions can be selected, just as with any other organ. Typical liver lesions should be prioritized over atypical lesions when selecting target lesions.

The sum of the diameters (longest typically-enhancing diameter for typical liver lesions, longest diameter for atypical liver lesions and extrahepatic non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum of diameters. The baseline sum of diameters will be used as the reference measurement when looking for evidence of objective response at later visits.

If there are more than five measurable lesions, those not selected as target lesions will be considered together with non-measurable disease as non-target lesions.

Non-target lesions include all non-measurable lesions, plus any measurable lesions over and above the 5 listed as target lesions. It is possible to record multiple non-target lesions involving the same organ as a single item on the eCRF (e.g.; ‘multiple enlarged pelvic lymph nodes’ or ‘multiple liver metastases’).

Post-baseline assessment

At every planned follow-up scan visit as described in the protocol after baseline, the investigator will assess the target lesions selected at baseline quantitatively (as described below), assess the non-target lesions selected at baseline qualitatively, and search for new lesions. The lesion assessments are then combined into an assessment of the entire participant at that visit (called the visit response or the overall response).

Target lesion assessment

The investigator will measure each target lesion in the same manner as at baseline. Extrahepatic non-nodal lesions and atypical liver lesions will be measured using their longest diameter. Malignant lymph nodes (excluding those in the porta hepatis, which can never be target lesions) will be measured in short axis diameter. Intrahepatic typical lesions will be measured in the longest diameter that shows typical HCC enhancement (excluding areas of necrosis).

If a lesion decreases in size to the point where it is still present, but cannot be measured accurately, a default value of 5 mm should be recorded for its diameter. If a lesion has disappeared, a value of 0 mm should be recorded for its diameter. If a lesion has split into distinct fragments, the longest diameter of each fragment should be measured, and the diameters added together. If two lesions have merged, the longest diameter of the entire resulting lesion should be measured.

The sum of diameters will be calculated by adding all target lesion diameters. The sum of diameters is always compared to two reference points: the baseline sum of diameters, and the smallest sum of diameters seen during the trial (also called the nadir). The baseline may actually be the nadir, if there has been no reduction in the sum of diameters during the trial. The target lesion response is then classified as follows:

Table 10–7: mRECIST: Response for Participants with Target and Non-target Lesions

Complete response (CR)	Complete disappearance of target lesions outside the liver Complete disappearance of typical HCC enhancement from all target liver lesions All target lymph nodes <10 mm
Partial response (PR)	At least a 30% decrease in the sum of diameters from baseline
Progressive disease (PD)	At least a 20% increase in the sum of diameters from the smallest value seen during the trial (including baseline), with at least a 5 mm absolute increase in the sum
Stable disease (SD)	Neither enough shrinkage to qualify as PR, nor enough growth to qualify as PD
Non-evaluable (NE)	One or more target lesions not evaluated because of imaging issues, coverage, or change in imaging technique

CR = complete response; HCC = hepatocellular carcinoma; PD = progressive disease; PR = partial response; mRECIST = modified RECIST

Note that when lymph nodes are included as target lesions, a CR may occur even when the sum of diameters is not zero, since a normal lymph node will have a diameter greater than zero but less than 10 mm.

Non-target lesion assessment

Non-target lesions are assessed as a whole. After examining each non-target lesion, the investigator will classify the non-target lesion response as follows:

Table 10–8: mRECIST: Response for Participants with Non-target Lesions Only

Complete response (CR)	Complete disappearance of non-target lesions outside the liver Complete disappearance of typical HCC enhancement from all non-target liver lesions All non-target lymph nodes <10 mm (<20 mm for porta hepatis lymph nodes) Resolution of malignant portal vein thrombosis (if present)
Progressive disease (PD)	Unequivocal progression of non-target lesions as a whole
Non-CR/Non-PD	Non-target lesions still present, without unequivocal progression
Not all evaluated	One or more non-target lesions not evaluated because of imaging issues, coverage, or change in imaging technique

CR = complete response; HCC = hepatocellular carcinoma; PD = progressive disease; mRECIST = modified RECIST

To achieve unequivocal progression in participants with measurable disease on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit withdrawal of study intervention. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal.

Cytopathologic confirmation of the neoplastic nature of any effusion that appears or worsens during treatment is required to declare PD.

New lesions

Outside the liver, any new lesion that is considered unequivocally malignant is evidence of progression, with no minimum size requirement.

For lesions within the liver, a new lesion can be classified as HCC (and therefore evidence of progression) if its longest diameter is at least 1 cm and it shows typical HCC enhancement. A new lesion that is at least 1 cm without typical HCC enhancement can be diagnosed as HCC if it shows at least 1 cm growth in subsequent scans. A lesion that is smaller than 1cm in longest diameter is not considered a new lesion according to the rules of this protocol.

An individual radiological event will be adjudicated in retrospect as progression at the time it was first detected by imaging techniques, even if strict criteria were fulfilled only on subsequent radiological testing. This means that if a new lesion is not unequivocal at the time of initial detection, but later becomes unequivocal, the date of progression will be the date it was first detected.

Visit overall response

The response of the target lesions, the response of the non-target lesions, and the presence or absence of new lesions are combined into the visit overall response for the entire participant at this visit, using the tables below.

Best response

The best overall response is the best visit response recorded from the start of the study intervention until the end of intervention. If SD is the best response seen during the study, it must be maintained for at least 6 weeks (42 days) after the start of intervention.

Complete Response (CR): Disappearance of all clinical and radiological evidence of tumor (both target and non-target). Any pathological lymph nodes (whether target or non-target) must have a reduction in short axis to < 10mm (<20 mm for porta hepatis lymph nodes).

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions taking as reference the baseline sum, no unequivocal progression of existing non-target lesions and no appearance of new lesions.

Stable Disease (SD): Steady state of disease. Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, no unequivocal progression of existing non-target lesions and no appearance of new lesions.

Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions from the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. Unequivocal progression of existing non-target lesions or the appearance of one or more new lesions also constitute progressive disease. Ascites or pleural effusion will be recorded as disease progression only if proven malignant.

In the absence of measurable disease, the same general concepts apply as noted above.

Progression is assessed on the basis of intrahepatic and extrahepatic disease together. Either the growth of intrahepatic lesions with typical arterial enhancement, or the growth of extrahepatic tumors, can indicate progression, if the sum of diameters (for target lesions) or the qualitatively assessed total tumor burden (for non-target lesions) indicates progression.

Response duration

The duration of overall response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded on study).

The duration of overall complete response is measured from the time criteria are first met for CR until the first date that recurrent disease is objectively documented.

Stable disease duration

Stable disease is measured from assignment to treatment until the criteria for progression are met.

The following text descriptions of the visit response are logically equivalent to the tables below.

Table 10–9: Response for Participants with Target and Non-target Lesions

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Response for this category also requires
CR	CR	No	CR	
CR	Non-CR/Non-PD	No	PR	
CR	Not evaluated	No	PR	
PR	Non-PD or not all evaluated	No	PR	
SD	Non-PD or not all evaluated	No	SD	Documented at least 6 weeks from treatment allocation.
Not all evaluated	Non-PD	no	NE	
PD	Any	Yes or No	PD	
Any	PD	Yes or No	PD	
Any	Any	Yes	PD	

CR = complete response; NE = non-evaluable; PD = progressive disease; PR = partial response; SD = stable disease

Participants with a global deterioration of health status requiring withdrawal of intervention without objective evidence of disease progression at that time should be reported as "symptomatic deterioration". Every effort should be made to document the objective progression even after withdrawal of intervention.

Table 10–10: Response for Participants with Non-target Lesions Only

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/Non-PD	No	Non-CR/non-PD*
Not evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

CR = complete response; NE = non-evaluable; PD = progressive disease

* Non-CR/non-PD is preferred over "stable disease" for non-target disease.

10.5.3 iRECIST

iRECIST is RECIST 1.1 adapted as described below to account for the unique tumor response seen with immunotherapeutic drugs (Table 10–11). If the investigator considers radiographic changes secondary to drug-induced inflammation and not to tumor progression (i.e. in case of suspected pseudo-progression), the investigator may postpone a diagnosis of progressive disease until the next radiographic evaluation in the study, and further confirmation per iRECIST criteria. This decision by the investigator should be based on the participant's overall clinical condition.

Description of the iRECIST Process for Assessment of Disease Progression

Assessment at Screening and Prior to RECIST 1.1 Progression

Until radiographic disease progression based on RECIST 1.1, there is no distinct iRECIST assessment.

Assessment and Decision at RECIST 1.1 Progression

For participants who show evidence of radiological PD by RECIST 1.1, the investigator will decide whether to continue a participant on study intervention until repeat imaging is obtained

using iRECIST for participant management (see Table 10–11 and Figure 10–1). This decision by the investigator should be based on the participant's overall clinical condition.

Clinical stability is defined as the following:

- Absence of symptoms and signs indicating clinically significant progression of disease
- No decline in ECOG performance status
- No requirements for intensified management, including increased analgesia, radiation, or other palliative care

Any participant deemed **clinically unstable** should be discontinued from study intervention at site-assessed first radiologic evidence of PD, and is not required to have repeat tumor imaging for confirmation of PD by iRECIST.

If the investigator decides to continue treatment, the participant may continue to receive study intervention and the tumor assessment should be repeated 4 to 8 weeks later to confirm PD by iRECIST, per investigator assessment.

Tumor flare may manifest as any factor causing radiographic progression per RECIST 1.1, including:

- Increase in the sum of diameters of target lesion(s) identified at baseline to ≥20% and ≥5 mm from nadir
- Note: the iRECIST publication uses the terminology "sum of measurements", but "sum of diameters" will be used in this protocol, consistent with the original RECIST 1.1 terminology
- Unequivocal progression of non-target lesion(s) identified at baseline
- Development of new lesion(s)

iRECIST defines new response categories, including iUPD (unconfirmed progressive disease) and iCPD (confirmed progressive disease). For purposes of iRECIST assessment, the first visit showing progression according to RECIST 1.1 will be assigned a visit (overall) response of iUPD, regardless of which factors caused the progression.

At this visit, target and non-target lesions identified at baseline by RECIST 1.1 will be assessed as usual.

New lesions will be classified as measurable or non-measurable, using the same size thresholds and rules as for baseline lesion assessment in RECIST 1.1. From measurable new lesions, up to 5 lesions total (up to 2 per organ), may be selected as New Lesions – Target. The sum of diameters of these lesions will be calculated, and kept distinct from the sum of diameters for target lesions at baseline. All other new lesions will be followed qualitatively as New Lesions – Non-target.

Assessment at the Confirmatory Imaging

On the confirmatory imaging, the participant will be classified as progression confirmed (with an overall response of iCPD), or as showing persistent unconfirmed progression (with an overall response of iUPD), or as showing disease stability or response (iSD/iPR/iCR).

Confirmation of Progression

Progression is considered confirmed, and the overall response will be iCPD, if ANY of the following occurs:

- Any of the factors that were the basis for the initial iUPD show worsening
- For target lesions, worsening is a further increase in the sum of diameters of ≥5 mm, compared to any prior iUPD time point
- For non-target lesions, worsening is any significant growth in lesions overall, compared to a prior iUPD time point; this does not have to meet the "unequivocal" standard of RECIST 1.1

For new lesions, worsening is any of these:

- An increase in the new lesion sum of diameters by ≥5 mm from a prior iUPD time point
- Visible growth of new non-target lesions
- The appearance of additional new lesions

Any new factor appears that would have triggered PD by RECIST 1.1

Persistent iUPD

Progression is considered not confirmed, and the overall response remains iUPD, if:

- None of the progression-confirming factors identified above occurs AND
- The target lesion sum of diameters (initial target lesions) remains above the initial PD threshold (by RECIST 1.1)

Additional imaging for confirmation should be scheduled 4 to 8 weeks from the imaging on which iUPD is seen. This may correspond to the next visit in the original visit schedule. The assessment of the subsequent confirmation imaging proceeds in an identical manner, with possible outcomes of iCPD, iUPD, and iSD/iPR/iCR.

Resolution of iUPD

Progression is considered not confirmed, and the overall response becomes iSD/iPR/iCR, if:

- None of the progression-confirming factors identified above occurs, AND
- The target lesion sum of diameters (initial target lesions) is not above the initial PD threshold.

The response is classified as iSD or iPR (depending on the sum of diameters of the target lesions), or iCR if all lesions resolve.

In this case, the initial iUPD is considered to be pseudo-progression, and the level of suspicion for progression is "reset". This means that the next visit that shows radiographic progression, whenever it occurs, is again classified as iUPD by iRECIST, and the confirmation process is repeated before a response of iCPD can be assigned.

Management Following the Confirmatory Imaging

If repeat imaging does not confirm PD per iRECIST, as assessed by the investigator, and the participant continues to be clinically stable, study intervention may continue and follow the regular imaging schedule. If PD is confirmed, participants will be discontinued from study intervention.

NOTE: If a participant has iCPD as defined above, but the participant is achieving a clinically meaningful benefit, an exception to continue study intervention may be considered following consultation with the sponsor. In this case, if study intervention is continued, tumor imaging

should continue to be performed following the intervals as outlined in this protocol (see Section 1.3.1)

Detection of Progression at Visits after Pseudo-progression Resolves

After resolution of pseudo-progression (i.e., achievement of iSD/iPR/iCR), iUPD is indicated by any of the following events:

Target lesions

- Sum of diameters reaches the PD threshold (≥20% and ≥5 mm increase from nadir) either for the first time, or after resolution of previous pseudo-progression. The nadir is always the smallest sum of diameters seen during the entire trial, either before or after an instance of pseudo-progression.

Non-target lesions

- If non-target lesions have never shown unequivocal progression, their doing so for the first time results in iUPD.
- If non-target lesions have shown previous unequivocal progression, and this progression has not resolved, iUPD results from any significant further growth of non-target lesions, taken as a whole.

New lesions

- New lesions appear for the first time
- Additional new lesions appear
- Previously identified new target lesions show an increase of ≥5 mm in the new lesion sum of diameters, from the nadir value of that sum
- Previously identified non-target lesions show any significant growth

If any of the events above occur, the overall response for that visit is iUPD, and the iUPD evaluation process (see Assessment at the Confirmatory Imaging above) is repeated. Progression must be confirmed before iCPD can occur.

The decision process is identical to the iUPD confirmation process for the initial PD, with one exception: if new lesions occurred at a prior instance of iUPD, and at the confirmatory imaging the burden of new lesions has increased from its smallest value (for new target lesions, the sum of diameters is ≥5 mm increased from its nadir), then iUPD cannot resolve to iSD or iPR. It will remain iUPD until either a decrease in the new lesion burden allows resolution to iSD or iPR, or until a confirmatory factor causes iCPD.

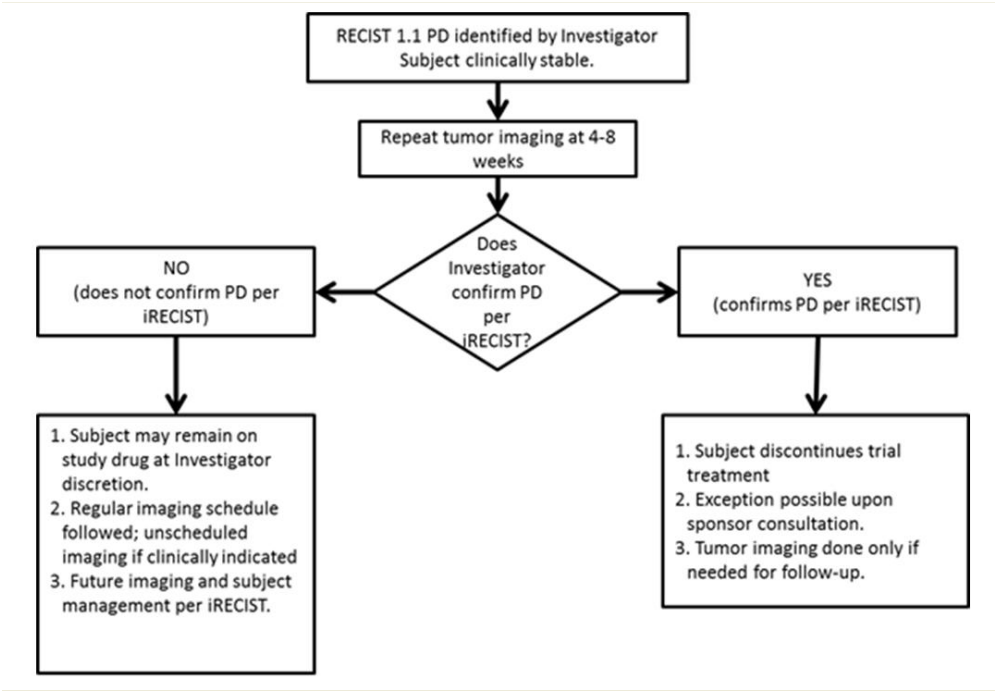
Additional details about iRECIST are provided in the iRECIST publication (Seymour et al. 2017).

Table 10–11: Imaging and Treatment after First Radiologic Evidence of PD

	Clinically Stable		Clinically Unstable	
	Imaging	**Treatment**	**Imaging**	**Treatment**
1st radiologic evidence of PD by RECIST 1.1	Repeat imaging at 4 to 8 weeks at site to confirm PD	May continue study intervention at the local site investigator's discretion while awaiting confirmatory tumor imaging by site by iRECIST.	Repeat imaging at 4 to 8 weeks to confirm PD per physician discretion only	Discontinue study intervention
Repeat tumor imaging confirms PD (iCPD) by iRECIST at the local site	No additional imaging required	Discontinue study intervention (exception is possible upon consultation with sponsor)	No additional imaging required	N/A
Repeat tumor imaging shows iUPD by iRECIST per investigator assessment	Repeat imaging at 4 to 8 weeks to confirm PD. May occur at next regularly scheduled imaging visit.	Continue study intervention at the investigator's discretion.	Repeat imaging at 4 to 8 weeks to confirm PD per investigator's discretion only.	Discontinue study intervention
Repeat tumor imaging shows iSD, iPR, or iCR by iRECIST per investigator assessment.	Continue regularly scheduled imaging assessments	Continue study intervention at the local site investigator's discretion	Continue regularly scheduled imaging assessments	May restart study intervention if condition has improved and/or clinically stable per investigator's discretion. The next tumor image should occur according to the schedule outlined in the SoA (Section 1.3.1).

iCPD = iRECIST confirmed progressive disease; iCR = iRECIST complete response; iRECIST = modified RECIST 1.1 for immune-based therapeutics; iPR = iRECIST partial response; iSD = iRECIST stable disease; iUPD = iRECIST unconfirmed progressive disease; N/A = not applicable; PD = progressive disease; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors 1.1

Figure 10–1: iRECIST: Process for Assessment of Disease Progression



iRECIST = immune RECIST; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors 1.1; PD = progressive disease

10.6 Appendix 6: CYP3A4 Inhibitors and Inducers

CYP3A4 inducers and inhibitors

Table 10–12 presents an overview of CYP3A4 inducers and **strong** CYP3A4 inhibitors. CYP3A4 inducers and **strong** CYP3A4 inhibitors are NOT allowed due to drug-drug-interaction with regorafenib.

Grapefruit juice (CYP3A4 inhibitor) should also be avoided.

Table 10–12: Overview of CYP3A4 Inducers and Strong CYP3A4 Inhibitors

Strong CYP3A4 Inhibitors	CYP3A4 Inducers
Boceprevir	Avasimibe
Clarithromycin	Bosentan
Cobicistat, only available in the combination with elvitegravir, emtricitabine, tenofovir or disoproxil fumarate	Carbamazepine
	Efavirenz
Conivaptan	Enzalutamide
Delavirdine	Etravirine
Idelalisib	Fosphenytoin
Indinavir	Hypericum perforatum (St John's Wort)
Itraconazole	
Ketoconazole	Lersivirine
Lopinavir	Lumacaftor
Mibefradil	Methylphenobarbital
Miconazole	Mitotane
Nefazodone	Modafinil
Nelfinavir	Nafcillin
Posaconazole	Phenobarbital
Ritonavir	Phenytoin
Saquinavir	Primidone
Telaprevir	Rifabutin
Telithromycin	Rifampicin
Tipranavir	Rifamycin
Troleandomycin	Semagacestat
Voriconazole	Thioridazine

CYP3A4 = cytochrome P450 3A4
Strong CYP3A4 inhibitors are NOT allowed during this clinical trial.
CYP3A4 inducers are NOT allowed during this clinical trial.

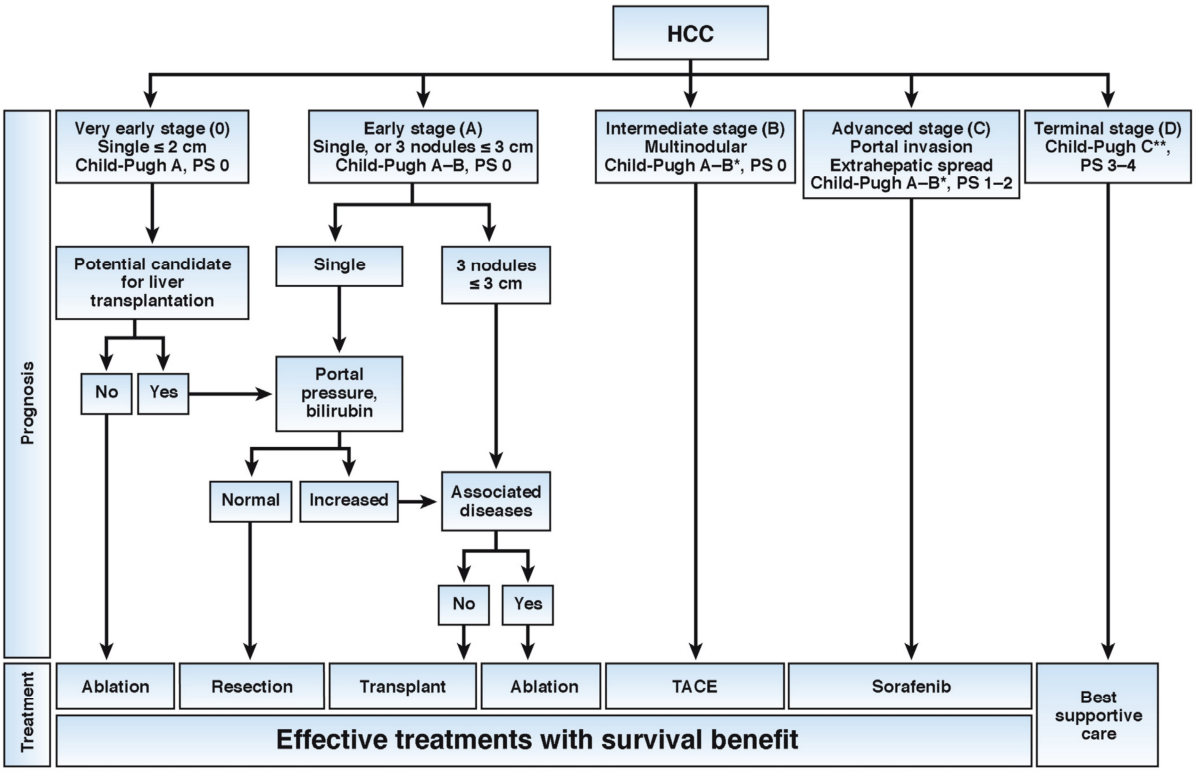
The CYP3A4 inducers and strong CYP3A4 inhibitors in Table 10–12 were identified using the Bayer-World Health Organization's Drug Dictionary (WHO-DD) and Bayer drug groupings for CYP3A4 inducers and CYP3A4 inhibitors.

10.7 Appendix 7: New York Heart Association Functional Classification

NYHA Class	Symptoms
I	No symptoms and no limitation in ordinary physical activity, e.g. shortness of breath when walking, climbing stairs etc.
II	Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.
III	Marked limitation in activity due to symptoms, even during less-than-ordinary activity, e.g. walking short distances (20–100 m). Comfortable only at rest.
IV	Severe limitations. Experiences symptoms even while **at rest**. Mostly bedbound patients.

10.8 Appendix 8: Barcelona Clinic Liver Cancer (BCLC) Classification

Figure 10–2: BCLC Staging and Treatment Strategy



*Note that Child-Pugh classification is not sensitive to accurately identify those patients with advanced liver failure that would deserve liver transplant consideration.

**Patients with end stage cirrhosis due to heavily impaired liver function (Child-Pugh C or earlier stages with predictors of poor prognosis, high MELD score) should be considered for liver transplantation. In them, HCC may become a contraindication if exceeding the enlistment criteria.

HCC = hepatocellular carcinoma; MELD = model for end-stage liver disease; PS = performance status; TACE = transarterial chemoembolization
Source: (Bruix et al. 2016)

The BCLC classification divides HCC patients in 5 stages (0, A, B, C and D) according to pre-established prognostic variables, and allocates therapies according to treatment-related status. Thus, it provides information on both prognostic prediction and treatment allocation. Prognosis prediction is defined by variables related to tumor status (size, number, vascular invasion, N1, M1), liver function (Child–Pugh's) and health status (ECOG). Treatment allocation incorporates treatment dependent variables, which have been shown to influence

therapeutic outcome, such as bilirubin, portal hypertension or presence of symptoms-ECOG (EASL-EORTC Clinical Practice Guidelines) (EASL-EORTC 2012).

10.9 Appendix 9: Child-Pugh Classification

	Points Scored for Observed Findings		
	1	**2**	**3**
Encephalopathy grade [a]	None	1 or 2	3 or 4
Ascites	Absent	Slight	Moderate
Serum bilirubin, mg/dL	< 2	2 to 3	> 3.0
Serum albumin, g/dL	> 3.5	2.8-3.5	< 2.8
Prothrombin time-international normalized ratio (INR)	< 1.7	1.7 - 2.3	> 2.3

a Grade 0: normal consciousness, personality, neurological examination, electroencephalogram
Grade 1: restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting, 5 cps waves
Grade 2: lethargic, time-disoriented, inappropriate, asterixis, ataxia, slow triphasic waves
Grade 3: somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity, slower waves
Grade 4: unrousable coma, no personality/behavior, decerebrate, slow 2-3 cps delta activity

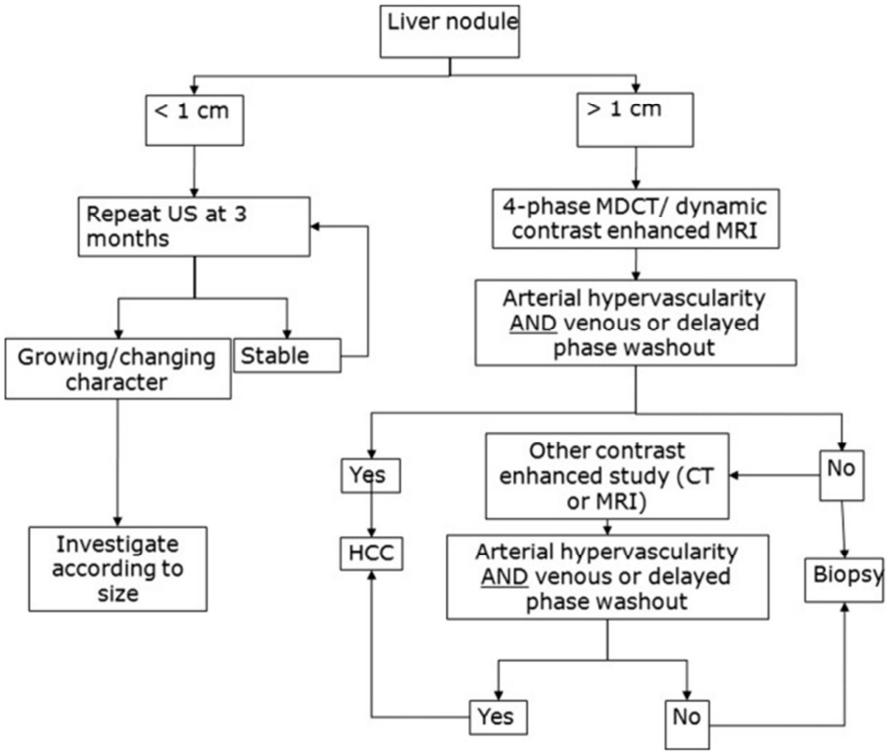
Assessment as good operative risk (A) if 5 or 6 points; moderate risk (B) if 7 to 9 points, and poor operative risk (C) if 10 to 15 points (developed for surgical evaluation of alcoholic cirrhotics).

10.10 Appendix 10: Guideline for Diagnosing Esophageal Varices

1	**A screening esophagogastroduodenoscopy (EGD) for the diagnosis of esophageal and gastric varices is recommended when a diagnosis of cirrhosis has been made**		
2	**Surveillance endoscopies are recommended on the basis of the level of cirrhosis and the presence and size of the varices:**		
	Patients with	*and*	*Repeat EGD*
—	Compensated cirrhosis	No varices	Every 2–3 years
		Small varices	Every 1–2 years
	Decompensated cirrhosis		Yearly intervals
3	**Progression of gastrointestinal varices can be determined on the basis of the size classification at the time of EGD. In practice, the recommendations for medium-sized varices in the three-size classification are the same as for large varices in the two-size classification:**		
	Size of varix	*Two-size classification*	*Three-size classification*
	Small	< 5 mm	Minimally elevated veins above the esophageal mucosal surface
	Medium	–	Tortuous veins occupying less than one-third of the esophageal lumen
	Large	> 5 mm	Occupying more than one-third of the esophageal lumen
4	**Variceal hemorrhage is diagnosed on the basis of one of the following findings on endoscopy:**		
	• Active bleeding from a varix • "White nipple" overlying a varix • Clots overlying a varix • Varices with no other potential source of bleeding		

Source: (WGO 2014)

10.11 Appendix 11: AASLD Practice Guideline (Diagnostic Algorithm for HCC)



CT = computed tomography; HCC = hepatocellular carcinoma; MDCT = multidetector CT; MRI = magnetic resonance imaging; US = ultrasound
Source: (Bruix et al. 2011)

10.12 Appendix 12: Abbreviations

AASLD	American Association for the Study of Liver Diseases
ABC	Absolute basophil count
ADA	Anti-drug-antibody
AE	Adverse event
AEC	Absolute eosinophil count
AESI	Adverse event of special interest
AFP	Alpha-fetoprotein
AG	Joint stock company, *Aktiengesellschaft*
ALC	Absolute lymphocyte count
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AMC	Absolute monocyte count
ANC	Absolute neutrophil count
Ang1	Angiopoietin 1
Anti-HBc+	Hepatitis B core antibody positive
Anti-HBe	Hepatitis B e-antigen
Anti-HBs-	Hepatitis B surface antibody negative
Anti-HCV	Anti-hepatitis C virus antibody
Anti-HDV	Hepatitis D antibody
aPTT	Activated partial thromboplastin time

AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
BCG	Bacillus Calmette-Guérin
BCLC	Barcelona Clinic Liver Cancer staging;
BCRP	Breast cancer resistance protein
BM	Biomarker
BP	Blood pressure
BRAF	Proto-oncogene BRAF
BSC	Best supportive care
BUN	Blood urea nitrogen
C_{avg}	Average concentration over the dosing interval
CBC	Complete blood count
CCL3/CCL4	Chemokine ligand 3 / 4
CCR5	Chemokine receptor 5
CD	Compact disk
CD28 / CD3 / CD8	Cluster of differentiation 28 / 3 / 8
CFR	Code of Federal Regulations
CG	Cockcroft-Gault (equation)
CI	Confidence interval
CIOMS	Council for International Organizations of Medical Sciences
C_{max}	Maximum/peak concentration
C_{min}	Minimum/trough concentration
CMV	Cytomegalovirus
CONSORT	Consolidated Standards of Reporting Trials
CNS	Central nervous system
COPD	Chronic obstructive pulmonary disease
CP	Child-Pugh (score)
CR	Complete response
CRC	Colorectal cancer
CrCl	Creatinine clearance
CRF	Case report form
CRO	Contract research organization
CSF1R	Colony stimulating factor 1 receptor
CT	Computed tomography
CTCAE	Common terminology criteria for adverse events
ctDNA	Circulating tumor DNA
CTLA-4	Cytotoxic T-lymphocyte-associated protein 4
CXCL10	C-X-C motif chemokine 10
CXCR3	C-X-C Motif Chemokine Receptor 3
CYP	Cytochrome P450 (derivates)
DAA	Direct acting antiviral
DC	Discontinuation of study intervention
DCR	Disease control rate
DICOM	Digital Imaging and Communications in Medicine
DLT	Dose-limiting toxicity
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
DOR	Duration of response
DPD	2,3-dicarboxypropane-1,1-diphosphonate
DRESS	Drug rash with eosinophilia and systemic symptoms
DVD	Digital versatile disk
EASL	European Association for the Study of the Liver
EBV	Epstein-Barr virus

ECG	Electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group performance status
eCRF	Electronic case report form
EDC	Electronic data capture
EOI	End of infusion
EORTC	European Organisation for Research and Treatment of Cancer
EoS	End of study
EoT	End of treatment
E-R	Exposure-response
EU	European Union
FDA	Food and Drug Administration
FGFR	Fibroblast growth factor receptor
FoxP3	Forkhead box P3
FPFV	First patient first visit
FSH	Follicle stimulating hormone
FT3	Free triiodothyronine
FT4	Free thyroxine
FU	Follow-up
GCP	Good clinical practice
G-CSF	Granulocyte colony stimulating factor
GFR	Glomerular filtration rate
GGT	Gamma-glutamyl transferase
GI	Gastrointestinal
GIST	Gastrointestinal stromal tumor
GM-CSF	Granulocyte-macrophage colony stimulating factor
Hb	Hemoglobin
HBcAb	Hepatitis B core antibody
HBeAg	Hepatitis B e-antigen
HBsAb	Hepatitis B surface antibody
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
hCG	Human chorionic gonadotropin
HCV	Hepatitis C virus
HDP	Hydroxyethylene diphosphonate
HDV	Hepatitis D virus
HECI	Hepatic events of clinical interest
HFSR	Hand-foot skin reaction
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
HMDP	Hydroxymethylene diphosphonate
HR	Hazard ratio
IB	Investigators brochure
HRT	Hormonal replacement therapy
ICI	Immune checkpoint inhibitor
ICF	Informed consent form
ICH	International Conference on Harmonization
iCPD	Confirmed progressive disease by iRECIST
iCR	iRECIST complete response
IDO1	Indolamine-2,3-dioxygenase
IEC	Independent Ethics Committee
IFN-γ	Interferon gamma
IgG	Immunoglobulin G

IgM	Immunoglobulin M
IgV	Immunoglobulin variable
ILD	Interstitial lung disease
IMP	Investigational medicinal product
IND	Investigational New Drug
INR	International normalized ratio
IO	Immune oncology
iPR	iRECIST partial response
irAE	Immune-related adverse event
IRB	Institutional Review Board
iRECIST	Response evaluation criteria in solid tumors, adapted to account for tumor response seen with immunotherapeutic drugs
iSD	iRECIST stable disease
IU/mL	International units per milliliter
IUD	Intrauterine device
iUPD	Unconfirmed progressive disease by iRECIST
IUS	Intrauterine hormone-releasing system
IV	Intravenous
IxRS	Interactive Voice/Web Response System
KIT	v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog
LDH	Lactate dehydrogenase
LFT	Liver function test
LPLV	Last patient last visit
LSH	Life Sciences Data Hub
M-2, M-5	Metabolites of regorafenib
M&S	Modeling and simulation
mAb	Monoclonal antibody
MAD	Maximum administered dose
mCRC	Metastatic colorectal cancer
MDCT	Multidetector computed tomography
MDP	Methylene diphosphonate
MDSC	Myeloid-derived suppressor cells
MedDRA	Medical Dictionary for Regulatory Activities
MHC1	Major histocompatibility complex 1
miRNA	Micro RNA
MKI	Multi-kinase inhibitor
mRECIST	Modified response evaluation criteria in solid tumors
MRI	Magnetic resonance imaging
MSI	Microsatellite instability
MTD	Maximum tolerated dose
mTPI	Modified toxicity probability interval
MVI	Macrovascular invasion
NCI	National Cancer Institute
NE	Non-evaluable
NIMP	Non-investigational medicinal product
NOACs	Novel oral anticoagulants
NSAID	Nonsteroidal anti-inflammatory drug
NSCLC	Non-small cell lung cancer
NYHA	New York Heart Association
ORR	Objective response rate
OS	Overall survival
p.o.	Per os (oral)
PBMC	Peripheral blood mononuclear cells

PD	Progressive disease
PD-1	Programmed cell death 1
PDGFR	Platelet-derived growth factor receptor
PD-L1	Programmed death-ligand 1
PD-L2	Programmed death-ligand 2
PFS	Progression-free survival
PI/ICF	Patient information / informed consent form
PID	Participant identification number
PK	Pharmacokinetics
PKCθ	Protein kinase C-theta
PR	Partial response
pRBC	Packed red blood cell
PS	Performance status
PT	Partial thromboplastin
Q2W	Every 2 weeks
Q3W	Every 3 weeks
Q4W	Every 4 weeks
Q6W	Every 6 weeks
QD	Once daily
QOD	Every other day
QRS	QRS interval in ECG
QT	QT interval in ECG
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected using Fridericia's formula
RAF	Rat fibrosarcoma
RANKL	Receptor activator of nuclear factor kappa-B ligand
RAVE	Electronic data capture software
RBC	Red blood cell count
RCC	Renal cell carcinoma
RECIST	Response evaluation criteria in solid tumors
RET	Rearranged during transfection
RNA	Ribonucleic acid
RP2D	Recommended Phase 2 dose
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Statistical software suite developed by SAS Institute
SD	Stable disease
SDLL	Source data location list
SHP-1, SHP-2	Src homology region 2 domain-containing phosphatase-1 / 2
SIM	Site imaging manual
SJS	Stevens-Johnson Syndrome
SmPC	Summary of Product Characteristics
SN-38	Active metabolite of irinotecan
SoA	Schedule of activities
SRC	Sarcoma
SUSAR	Suspected unexpected serious adverse reactions
sVEGFR	Soluble vascular endothelial growth factor receptor-1
SVR	Sustained virological response
T1DM	Type 1 Diabetes Mellitus
TACE	Transarterial chemoembolization
TEAE	Treatment-emergent adverse event
Teff	Effector T cells
TEN	Toxic epidermal necrolysis

TIE2	Tyrosine kinase with Ig and EGF homology domains
TM	Trademark
TMB	Tumor mutational burden
TMF	Trial master file
Treg	Regulatory T cells
TSH	Thyroid stimulating hormone
UGT1A1, UGT1A9	Uridine 5'-diphospho-glucuronosyltransferase family 1 A1 / A9
ULN	Upper limit of normal
US(A)	United States of America
v.	Version
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor
WxDx	Week x, day x
WBC	White blood cell count
WHO-DD	World Health Organization's Drug Dictionary
WOCBP	Woman of childbearing potential
ZAP70	Zeta-chain-associated protein kinase 70

10.13 Appendix 13: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents.

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