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Official Title:	An Open-label, Single-arm, Phase II Study of Regorafenib and Nivolumab in Patients with Mismatch Repair-Proficient (pMMR)/Microsatellite Stable (MSS) Colorectal Cancer (CRC)
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Title Page

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Sponsor Name and Legal Registered Address:	**Sponsor (Non-US):** Bayer AG, 51368 Leverkusen, Germany **Sponsor (US territory):** Bayer HealthCare Pharmaceuticals Inc., 100 Bayer Boulevard, P.O. Box 915, Whippany NJ 07981-0915, USA
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Current Version Amendment 2	 18 NOV 2020
Previous Version Amendment 1: Original Protocol:	 08 JAN 2020 12 JUL 2019

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 TMF and available on request.

Protocol Global Amendment 2 Summary of Changes Table

Current Version
Amendment 2: 18 NOV 2020
Previous Versions
Amendment 1: 08 JAN 2020
Original Protocol: 12 JUL 2019

Amendment 2 (18 NOV 2020)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis, **Table 1-1: Objectives and Endpoints** **3. Objectives and Endpoints,** **Table 3-1: Objectives and Endpoints** **4.1.2 Treatment Phase**	Blinded independent central review (BICR) was removed from the assessment of primary (ORR per RECIST v1.1) endpoint and secondary endpoints (Duration of Response (DOR); Disease control rate (DCR) at 8 and 16 weeks; Progression free survival (PFS)). Respective table footnotes were deleted.	CCI
8.1 Efficacy Assessments	Text was reverted to wording in the original protocol.	CCI
1.1 Synopsis, **Overall Design, Number of Participants** **4.1 Overall Design** **5. Study Population**	Recruitment has been stopped at 70 treated participants. The number of participants has been changed throughout, accordingly.	CCI
9.2 Sample Size Determination	Recruitment has been stopped at 70 treated participants. With this sample size of 70 participants, when the true underlying ORR is 17% or higher and a baseline response rate of 5% is assumed, a one-sided exact binomial test at a type-I error of at approximately 2.5% would result in a power of 92.6%, with at least 8 responders needed to achieve significance. The location of the primary tumor is a factor and it is expected that 40%-45% of participants will have the primary tumor on the right side. With 31 participants with right-sided tumors, the probability of observing 4 or more responders (ORR 13%) is approximately 80% when the true underlying response rate is 17%, and the probability of observing 2 or fewer responders (ORR 6.5%) is approximately 80% when the true ORR is 5%. With 39 participants with left-sided tumors, the probability of observing 6 or more responders (ORR 15%) is approximately 67% when the true underlying response rate is 17%, and the probability of observing 2 or fewer responders (ORR 5.1%) is approximately 70% when the true ORR is 5%.	CCI
1.2 Schema **Figure 1-1: Study Schema** **4.1.1 Screening Phase,** **Figure 4-1: Study Schema**	This study is composed of the following periods: Screening, treatment, active follow-up (FU), and long-term follow up. Participants will be considered “on study” during these periods. Wording was clarified “Completion of active follow-up”.	CCI

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities (SoA), Footnote m)	Footnote was clarified with a reference to Pharmacokinetic and Immunogenicity Sample Collection Plan.	CCI
4.4 End of Study Definition	Language defining end of study (EOS) was clarified using appropriate terminology.	CCI
5.1 Inclusion Criteria	12. Women of childbearing potential (WOCBP) must agree to follow instructions for method(s) of contraception for the duration of study intervention and **210** ~~120~~ d after last dose of regorafenib and 5 months after the last dose of nivolumab. 7-month contraception period, after last dose of nivolumab, is no longer required for male study participants during sexual activity with a WOCBP partner.	CCI
6. Study Intervention	Language defining continuation of study intervention after full treatment term (24 infusions/approximately 2 years of treatment) was clarified using appropriate terminology.	CCI
6.7 Intervention after the End of the Study	Language was clarified on further therapeutic options after EOS, with the discretion of the Investigator.	CCI
7. Discontinuation of Study Intervention, 7.1 Withdrawal from active FU	Language on withdrawal from active follow-up (FU) was updated by adding a requirement of performed safety visits.	CCI

Section # and Name	Description of Change	Brief Rationale
10.1.3 Informed Consent Process	Wording for reconsent for participants continuing study treatment following disease progression was clarified**:** In order to continue treatment after initial documentation of disease progression as per RECIST 1.1, participant must be re-consented **once**.	CCI [redacted]
Sponsor Signatory page	The signature of the Sponsor's medically responsible person was removed from the clinical study protocol.	CCI [redacted].

In addition to the substantive changes summarized in above table, several changes were made to update administrative details, correct typographical errors, and add clarity; such changes are not itemized in the table.

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1. Protocol Summary

1.1 Synopsis

Protocol Title: An Open-label, Single-arm, Phase II Study of Regorafenib and Nivolumab in Patients with mismatch repair-proficient (pMMR)/Microsatellite Stable (MSS) Colorectal Cancer (CRC)

Short Title: Regorafenib and Nivolumab in pMMR/MSS CRC

CCI

Objectives and Endpoints:

Table 1–1: Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate efficacy of the regorafenib and nivolumab combination[a]	• ORR per RECIST v1.1[a]
Secondary	
• Further evaluation of the efficacy of the regorafenib and nivolumab combination by measuring progression and survival intervals • To evaluate safety of the combination	• Duration of Response (DOR)[a] • Disease control rate (DCR) at 8 and 16 weeks[a] • Progression free survival (PFS)[a] • Overall survival (OS) • Incidence and severity of AEs per CTCAE v5
CCI	
CCI	

CCI AE = adverse event; CTCAE = common terminology criteria for adverse events; iRECIST = response evaluation criteria in solid tumors for trials testing immunotherapeutics; DCR = disease control rate; DOR = duration of response; ORR = objective response rate; OS = overall survival; PFS = progression free survival; CCI RECIST = response evaluation criteria in solid tumors

a) The efficacy endpoints will be based on the local Investigator's assessment according to RECIST 1.1.

Overall Design:

Disclosure Statement:

This is an open-label, single-arm, Phase II Study of Regorafenib in combination with Nivolumab in participants with pMMR/MSS CRC.

Number of Participants: Recruitment has been stopped at 70 treated patients.

In Amendment 1, it was planned that: approximately 143 participants will be screened to achieve 100 treated participants of which approximately 50-60 participants would have a left sided primary tumor. In order to allow appropriate balance of participants with right and left sided primary tumors, enrollment may be restricted to either left or right sided tumors during the study. (Information about right and left sided primary tumors of the participant will be recorded by the investigator or delegate in the Interactive voice/web response system (IxRS) when the participant is registered in IxRS after signing off the PI/ICF.).

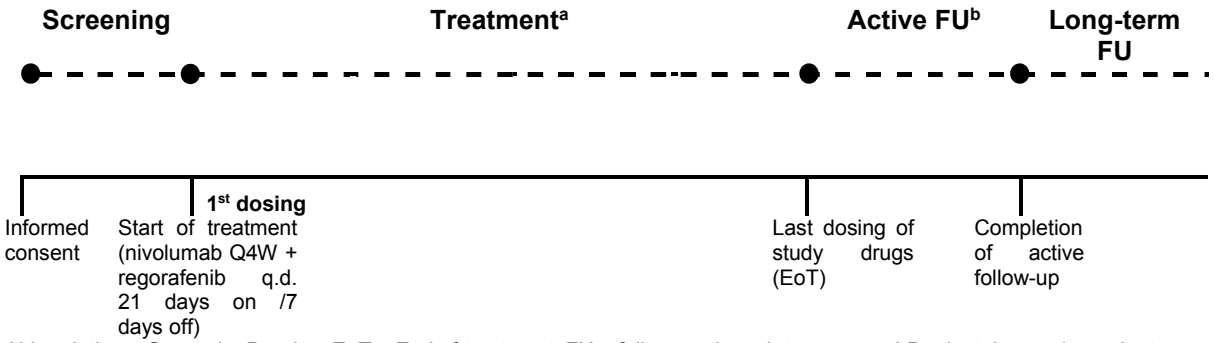
Data Monitoring Committee:

Not applicable.

1.2 Schema

This study is composed of the following periods: Screening, treatment, active follow-up (FU), and long-term follow up. Participants will be considered "on study" during screening, treatment ,active FU periods, and long-term FU periods. An overview of the study schema is presented in Figure 1–1.

Figure 1–1: Study Schema



Abbreviations: C = cycle; D = day; EoT = End of treatment; FU = follow-up; i.v. = intra venous; LD = last dose; min = minute; q.d. = *quaque die* (once daily); Q4W = every 4 weeks

a) Nivolumab 480 mg using a 30-min i.v. infusion every 4 weeks (Q4W). Regorafenib starting dose 80 mg orally every day (q.d.) for 21 days of each 28-day every 4 weeks (i.e. 21 days on, 7 days off). If starting dose is well tolerated (absence of any rash/HFSR any other or other Grade 2 or higher clinically significant toxicity) dose should be escalated to 120 mg orally daily starting with C2D1.

b) Mandatory safety FU visit (at least 30 d after LD of regorafenib/nivolumab and 100 d after LD of nivolumab) and other active FU visits to collect safety and efficacy information for participants who discontinue study treatment without disease progression, if applicable.

1.3 Schedule of Activities (SoA)

Table 1–2: Schedule of Activities

Procedure	Screening		Treatment period[a]								EoT visit	Active FU		Long-term FU	Notes
			Cycle1				Cycle 2			Cycle ≥3					
	within **28 d** prior to first dose	within **7 d** prior to first dose[c]	**D 1**	**D 8**	**D15**	**D22**	**D1**	**D8**	**D15**	**D1**	within **14 d** after permanent discontinuation of regorafenib and nivolumab	**30 d** after LD of regorafenib and nivolumab[b]	**100 d** after LD for nivolumab[b]	every **3 months**	
acceptable deviation				± 2 d			± 2 d			± 3 d		+ 7 d	+ 7 d	± 14 d	
Informed consent	X														
Contact IxRS[d]	X		X				X			X	X				
General															
Inclusion and exclusion criteria	X	X	X												Sections 5.1 and 5.2
Cancer classification (Stage per AJCC for CRC)	X														Section 8.2.7
Primary diagnosis using complete pathological report	X														
Demography	X														
Full physical examination	X		X				X			X	X				Section 8.2.1
Directed physical examination				X	X	X		X	X			X	X		Section 8.2.1
Relevant medical history	X														Section 8.2.7
Previous anti-cancer treatment	X														Section 6.5
Tumor molecular alteration data collection (MSI status, BRAF, extended RAS)[e]	X														
Safety															

Procedure	Screening		Treatment period[a]								EoT visit	Active FU		Long-term FU	Notes
			Cycle1				Cycle 2			Cycle ≥3					
	within **28 d** prior to first dose	within **7 d** prior to first dose[c]	**D 1**	**D 8**	**D15**	**D22**	**D1**	**D8**	**D15**	**D1**	within **14 d** after permanent discontinuation of regorafenib and nivolumab	**30 d** after LD of regorafenib and nivolumab[b]	**100 d** after LD for nivolumab[b]	every **3 months**	
acceptable deviation				± 2 d			± 2 d			± 3 d		+ 7 d	+ 7 d	± 14 d	
AE review[f]	X	X	←==========												Sections 8.3 and 10.3
ECOG performance status	X	X	X				X			X	X	X	X		Section 8.2.5
Serum pregnancy test if applicable (WOCBP only)[g]		X					X			X	X	X	X		Table 10–1
Serology testing for Hepatitis B/C incl. HIV-1 (if applicable)	X			If clinically indicated											
Clinical chemistry[h]	X	X	X	X	X	X	X	X	X	X	X	X	X		Section 8.2.4
Hematology	X	X	X	X	X	X	X	X	X	X	X	X	X		Table 10–1
PT/INR and aPTT	X	X	X	If clinically indicated											
Urine analysis by dipstick[i]	X		X				X			X	X				
Thyroid function testing	X						X			X	X				
12-lead ECG	X										X				Section 8.2.3
Vital signs (including weight)	X		X	X	X	X	X	X	X	X	X	X	X		Section 8.2.2
Efficacy															
Tumor assessment (CT/MRI)[j]	X									X	X	X	X		Section 8.1
Survival status												X	X	X	
Review of subsequent anti-cancer therapy												X	X	X	
CCI [redacted]		X	X				X			X	X	X	X		

Procedure	Screening		Treatment period[a]								EoT visit	Active FU		Long-term FU	Notes
			Cycle1				Cycle 2			Cycle ≥3					
	within **28 d** prior to first dose	within **7 d** prior to first dose[c]	**D 1**	**D 8**	**D15**	**D22**	**D1**	**D8**	**D15**	**D1**	within **14 d** after permanent discontinuation of regorafenib and nivolumab	**30 d** after LD of regorafenib and nivolumab[b]	**100 d** after LD for nivolumab[b]	every **3 months**	
acceptable deviation				± 2 d			± 2 d			± 3 d		+ 7 d	+ 7 d	± 14 d	
Study intervention administration															
Study treatment: Nivolumab[k]			X				X			X					Section 6.1
Study treatment: Regorafenib[k]			←==========→ 21 days on/ 7 days off												Section 6.1
Drug accountability			←==========→								X				
Concomitant medication review (including vaccination)	X		←==========→												Section 6.5
Research sample collection															
CCI															
CCI	X							X			X				Section 8.8
Baseline tumor tissue[o]	X														
On-treatment biopsy[o]								X							
Progression biopsy[o]											X				

Procedure	Screening		Treatment period[a]								EoT visit	Active FU		Long-term FU	Notes
			Cycle1				Cycle 2			Cycle ≥3					
	within **28 d** prior to first dose	within **7 d** prior to first dose[c]	**D 1**	**D 8**	**D15**	**D22**	**D1**	**D8**	**D15**	**D1**	within **14 d** after permanent discontinuation of regorafenib and nivolumab	**30 d** after LD of regorafenib and nivolumab[b]	**100 d** after LD for nivolumab[b]	every **3 months**	
acceptable deviation				± 2 d			± 2 d			± 3 d		+ 7 d	+ 7 d	± 14 d	

Abbreviations: AE = adverse event; AJCC = American Joint Committee on Cancer; aPTT = activated partial thromboplastin time; BRAF = proto-oncogen BRAF; C = cycle; CEA = carcinoembryonic antigen; CRC = colorectal cancer; CT = computed tomography; CTCAE = common terminology criteria for adverse events; D (d) = day; ECG = electro cardiogram; EoT = end of treatment; ECOG = Eastern Cooperative Oncology Group; FU = follow-up; GGT = gamma-glutamyl transferase; HIV = human immunodeficiency virus; hr = hour(s); INR = international normalized ratio; IxRS = interactive voice/web response system; LD = last dose; MRI = magnetic resonance imaging; MSI = microsatellite instability; PI/ICF = Participant information (informed consent form); PK = pharmacokinetics; PT = prothrombin time; RAS = proto-oncogen RAS; RECIST = response evaluation criteria in solid tumors; SAE = serious adverse event; WOCBP = women of childbearing potential.

a) Note: The ± 2 d and ± 3 d assessment windows do not apply to collection of PK blood samples.
b) A mandatory clinical visit to monitor safety will take place 30 d (window of +7 d) after the last administration of regorafenib/nivolumab and 100 d (window of +7 d) after the last dose of nivolumab, with the exception of death or withdrawal of consent.
c) If tested within 7 days prior to first dose no additional testing on D1 required except for pregnancy testing and abnormal liver function tests.
d) Contact IxRS to record the following: 1. to register the participant who has signed the PI/ICF f (a unique participant identifier will be assigned), 2. the patient is a screening failure (failed to meet the criteria during the screening period), 3. on D1 of every treatment cycle so that the specific participant drug bottle/vial can be provided for dispensing purposes and also in case the participant has discontinued the study treatment (EOT) for any reason.
e) Tumor genetic alteration(s), as determined by local testing results for MSI status, BRAF, extended RAS
f) Participant will be followed for treatment related toxicities until these toxicities resolve, return to baseline or are deemed irreversible. All AEs will be documented for a minimum of 100 d after LD of nivolumab or 30 d after LD of regorafenib, whatever occurs later. CTCAE v5.0 will be used.
g) Serum pregnancy test (for females of childbearing potential only). A negative pregnancy test must be available within 24 hr before study drug administration. Monthly pregnancy testing independent of study drug dosing should be conducted as per local regulations where applicable.
h) Amylase and GGT will be assessed if clinically indicated.
i) 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.
j) Tumor assessments should be performed according to RECIST v1.1 criteria. Obtain a contrast-enhanced CT scan and/or MRI with contrast of the chest, abdomen, and pelvis and any other known sites of disease (as clinically indicated) within 28 d prior to C1D1 (Scans can be used as baseline scans if not older than 4 weeks at C1D1), then in the first year every 8 weeks ± 7 d and thereafter every 12 weeks ±14 d. Radiological tumor evaluation within 14 days after last study treatment is not necessary if the previous tumor evaluation was performed within 4 weeks (for the first year) or within 8 weeks (thereafter). For participants who discontinue study treatment without disease progression, FU tumor evaluations will be performed until progression of malignancy and/or start of subsequent systemic anti-cancer treatment, whichever comes first, or any other criterion for withdrawal is met.
k) Regorafenib and Nivolumab will start on the same day C1D1. When the two study drugs are administered on the same day, regorafenib is to be taken first orally followed by nivolumab infusion. Participants who complete 24 infusions of nivolumab (after approximately 2 years of treatment) will discontinue treatment.
l) For PK collection details, see Section 8.5, Table 8–2. Pre- and end of infusion of nivolumab sampling C1D1 as well pre-infusion on C2, C5 and C19.
m) For Immunogenicity collection details, see Section 8.5, Table 8-2. Pre-infusion (C1, C2, C5 and C19)
n) Collection of stool can be performed at any time during visit or within ±7 d of the planned visit.
o) Tumor tissue requirement: Formalin-fixed paraffin-embedded block or minimum of 20 slides, obtained from core biopsy, punch biopsy, excisional biopsy or surgical specimen. Baseline: mandatory recent tumor tissue samples, defined as tumor tissue obtained within 180 d of enrollment and after the last dose of most recent anti-cancer therapy or tissue from a new biopsy. New tumor collection should be performed after confirmation of preliminary safety eligibility. Exceptions for patients with no recent baseline tumor tissues may be considered after documented discussion and approval by the sponsor. Archival tumor tissue must be provided if available. On treatment: C2D8 (+7d), mandatory if medically feasible. At progression: EoT (+7d), mandatory if medically feasible. The lesion accessible for biopsy may not be the only

Table 1–3: Schedule of Biomarker Blood Sampling

Procedure	Screening	Treatment							
		Cycle 1		Cycle 2		Cycle 4	Cycle 6	Cycle 8 and every even cycles	EoT
	within 7 d prior to 1st dose	D1	D8	D1	D8	D1	D1	D1	
		pre-dose	pre-dose	pre-dose	pre-dose	pre-dose	pre-dose	pre-dose	
acceptable deviation		- 30 min	- 30 min	- 30 min	- 30 min	- 30 min	- 30 min	- 30 min	
CCI									

Abbreviations: ctDNA =circulating tumor deoxyribonucleic acid; D (d) = Day; EoT = end of treatment; RNA = ribonucleic acid

a) For details please refer to the biomarker Section 8.8.

CCI

[redacted]

antibodies targeting VEGF pathway (bevacizumab, aflibercept, ramucirumab) and epidermal

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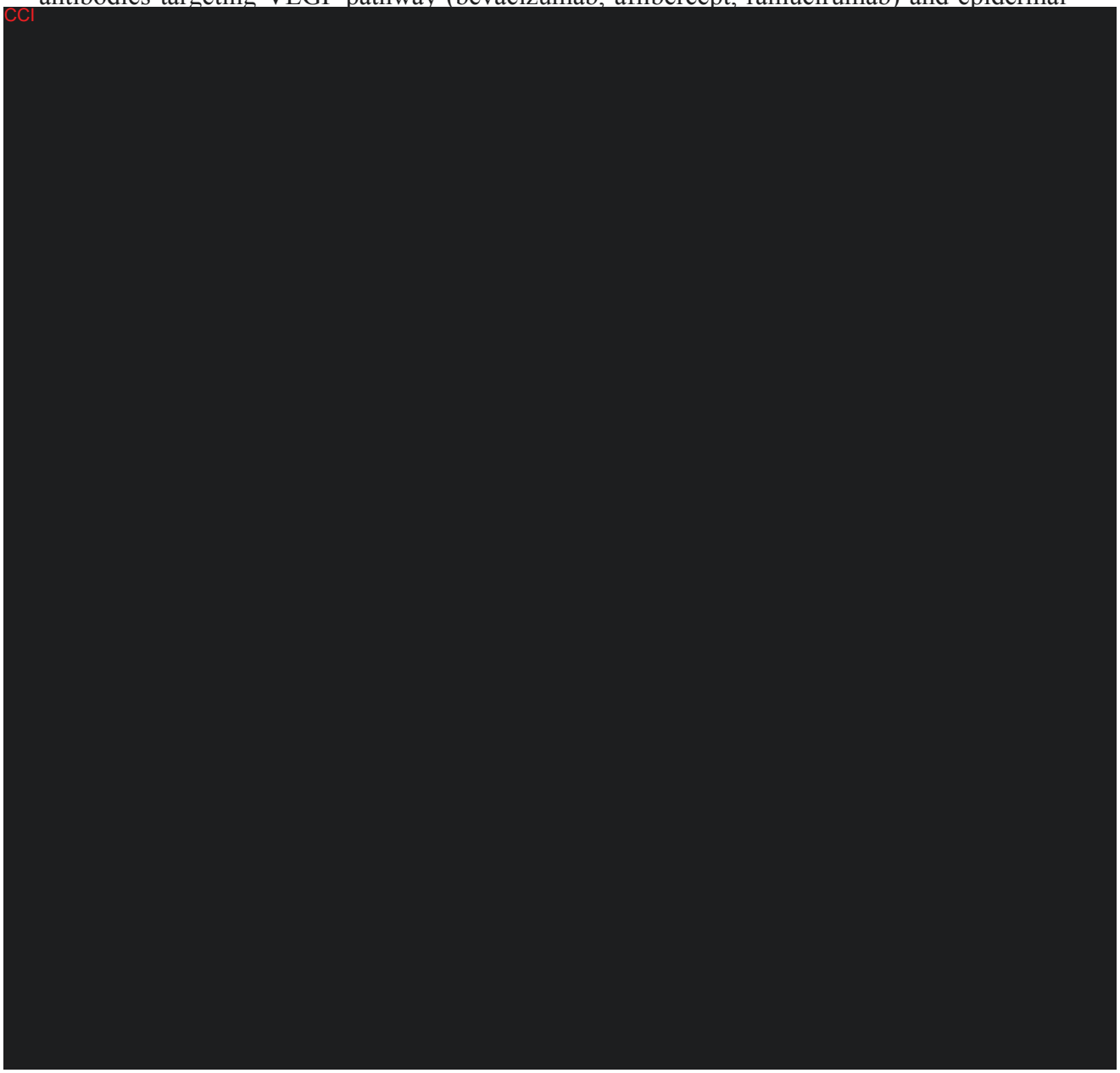

Even with the recent approvals of these two agents, a high unmet need remains in this patient

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angiogenic, inflammatory and immunosuppressive signature, with a high density of CCI

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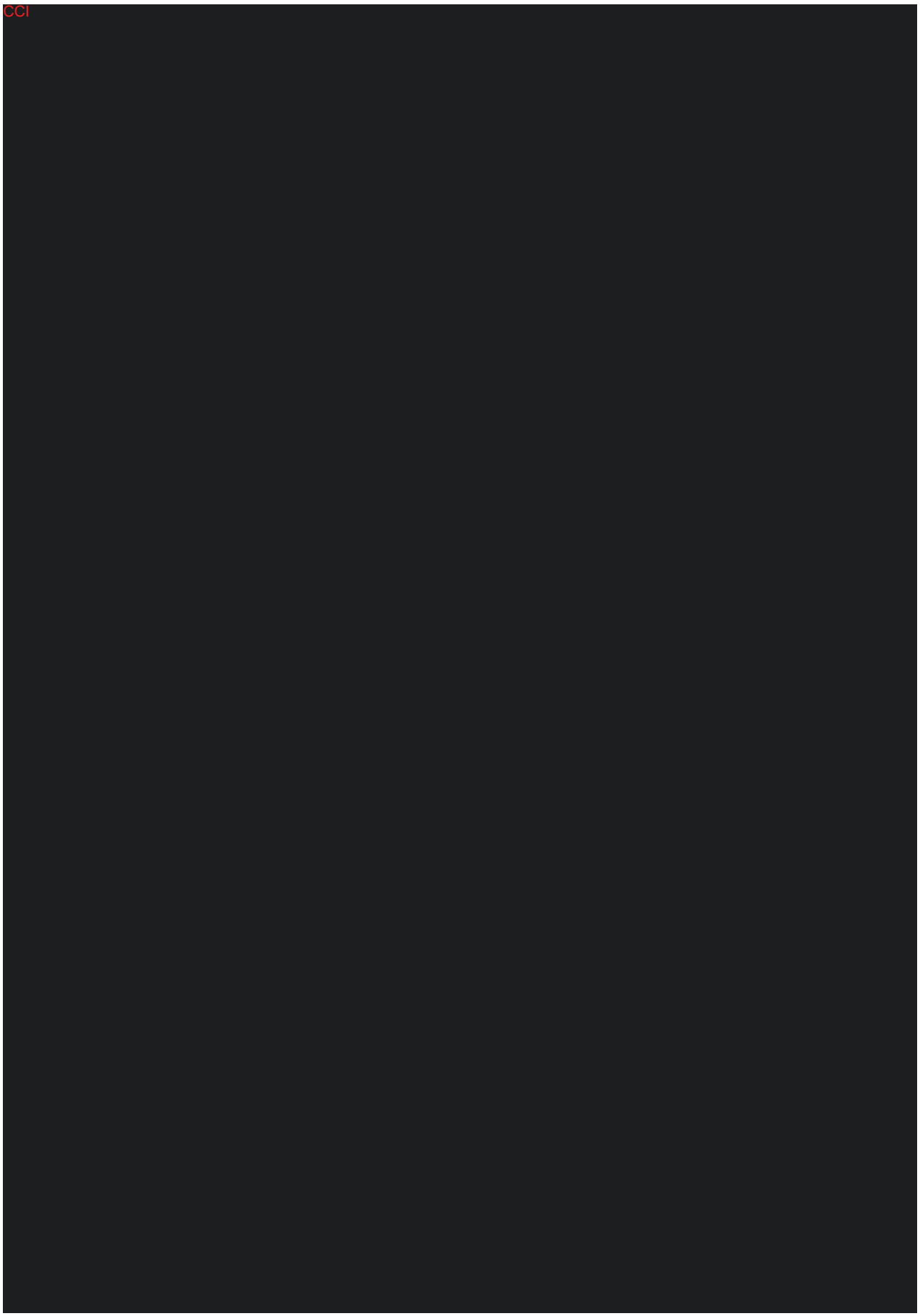
[redacted]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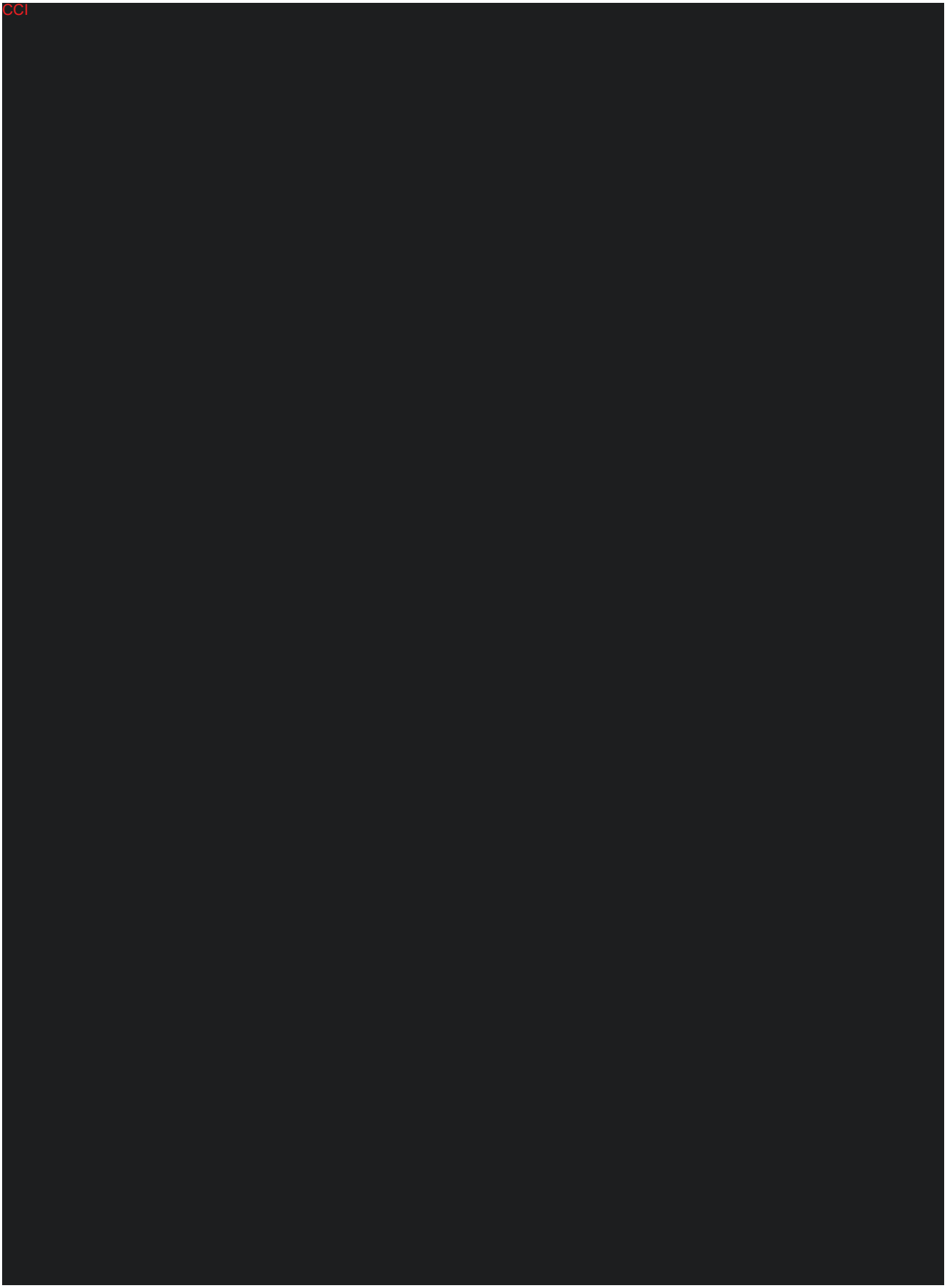
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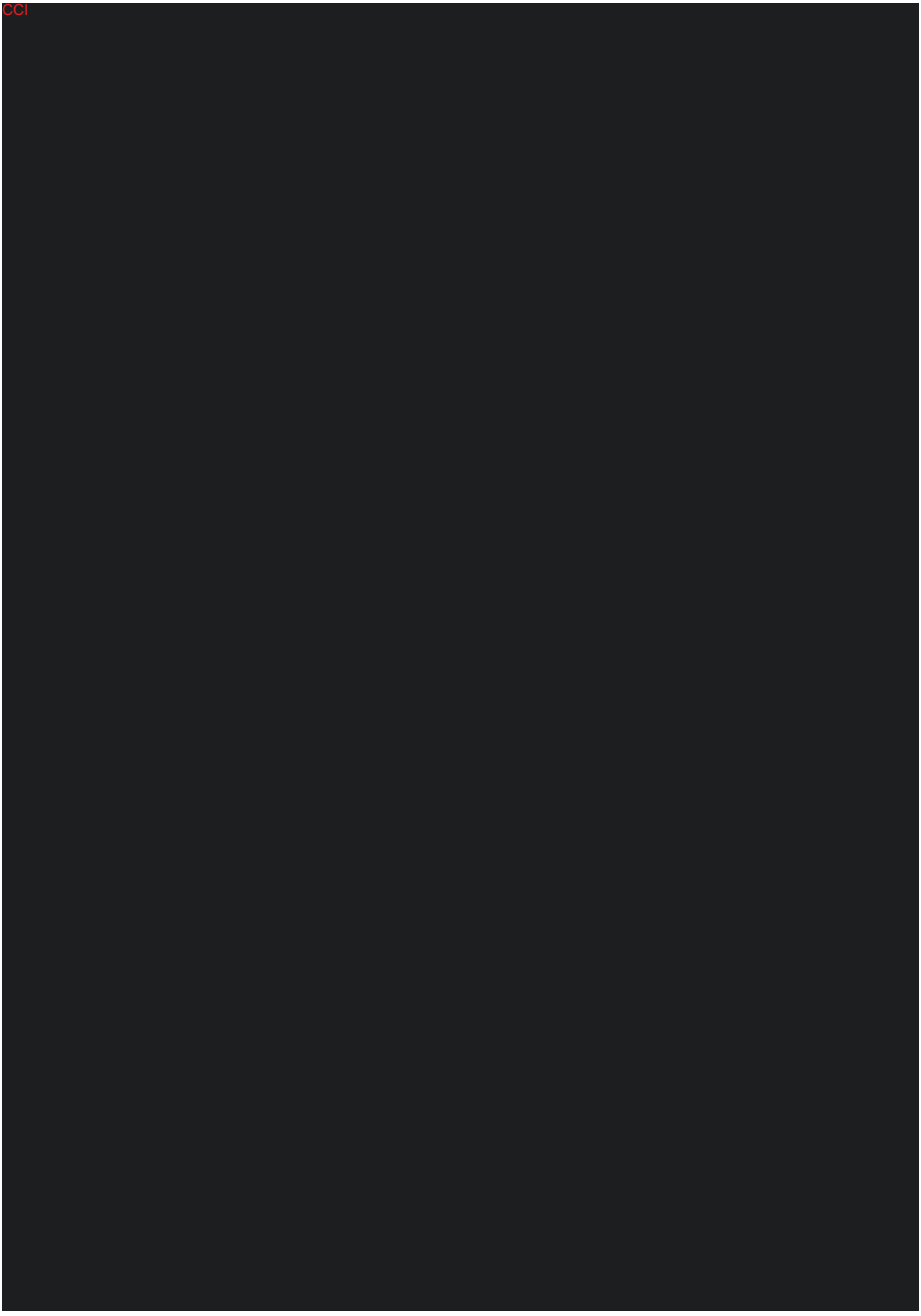
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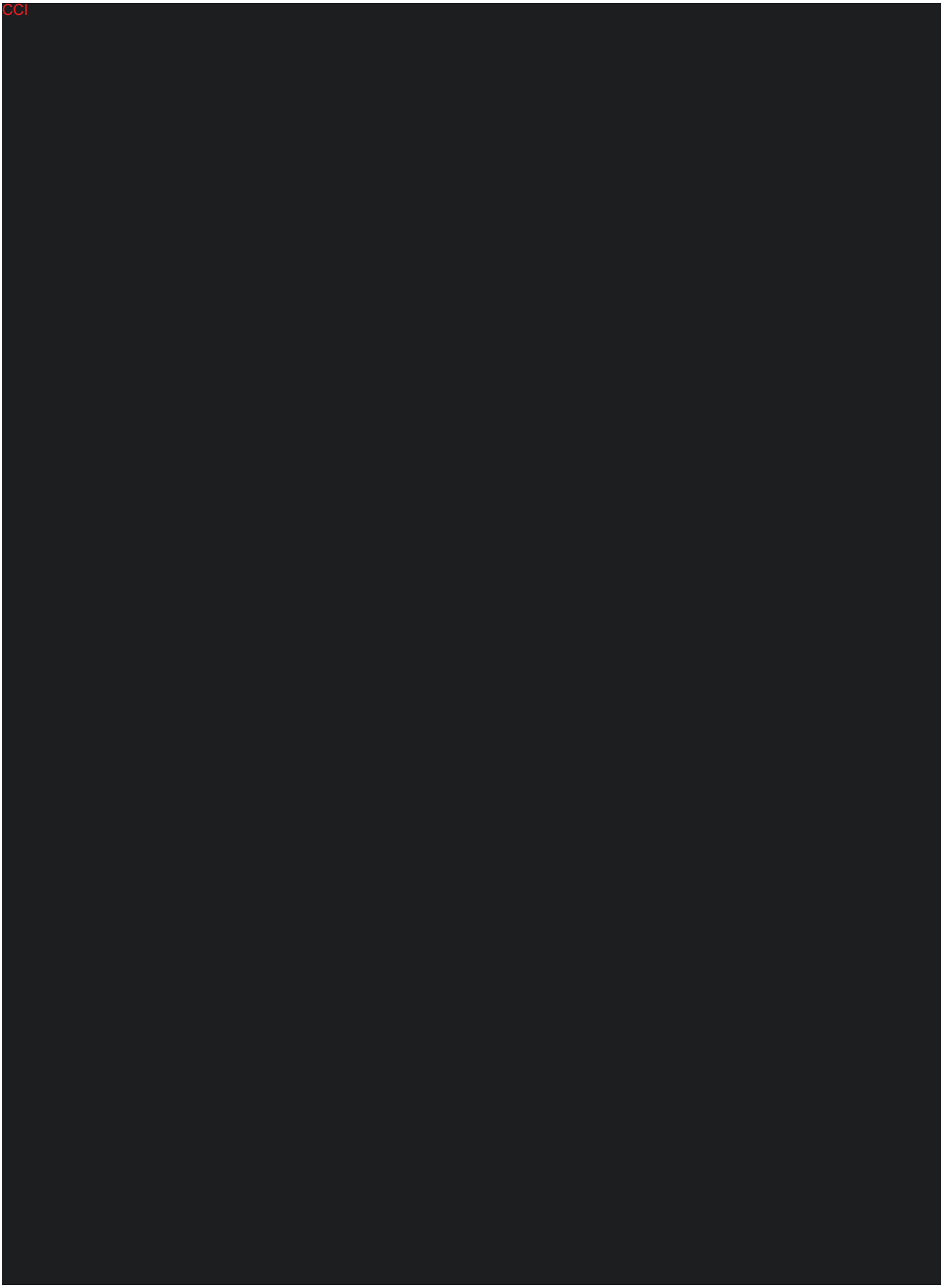
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[redacted]

randomization (i.e., 2 years after treatment initiation), suggesting that there may be minimal

CCI

CCI

[redacted]

3. Objectives and Endpoints

Table 3–1: Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate efficacy of the regorafenib and nivolumab combination[a]	• ORR per RECIST v1.1[a]
Secondary	
• Further evaluation of the efficacy of the regorafenib and nivolumab combination by measuring progression and survival intervals • To evaluate safety of the combination	• Duration of Response (DOR)[a] • Disease control rate (DCR) at 8 and 16 weeks[a] • Progression free survival (PFS)[a] • Overall survival (OS) • Incidence and severity of AEs per CTCAE v5
CCI	
CCI	
CCI	

AE = adverse event; CTCAE = common terminology criteria for adverse events; iRECIST = response evaluation criteria in solid tumors for trials testing immunotherapeutics; DCR = disease control rate; DOR = duration of response; ORR = objective response rate; OS = overall survival; PFS = progression free survival; PK = pharmacokinetics; RECIST = response evaluation criteria in solid tumors

a) The efficacy endpoints will be based on the local Investigator's assessment according to RECIST 1.1.

4. Study Design

4.1 Overall Design

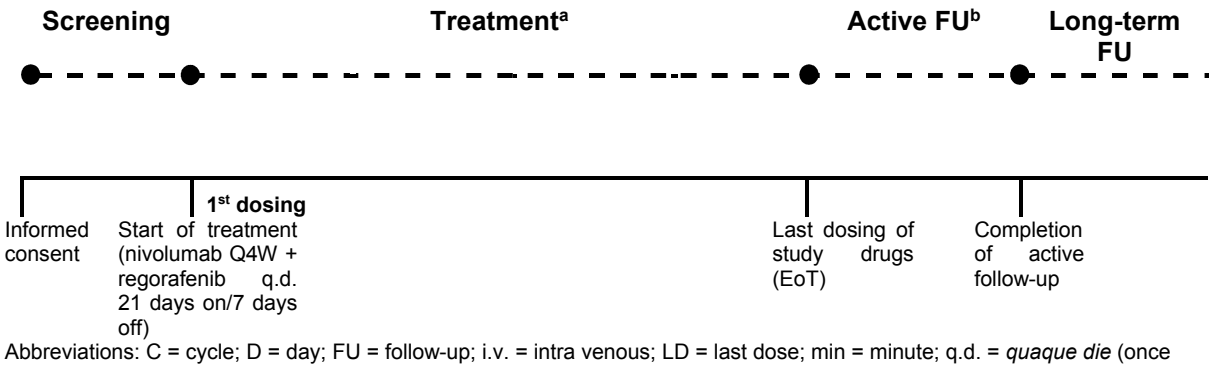
This is an open label, multicenter, single arm, Phase II study of regorafenib and nivolumab combination in participants with advanced or metastatic pMMR/MSS CRC who have been previously treated with no more than two (for extended RAS mutant) or three (for extended RAS wild type) lines of systemic chemotherapy. The study will be conducted at approximately 17 sites in North America. In Amendment 1, it was planned that at least 100

participants who qualify for the study will be treated with regorafenib plus nivolumab. Recruitment has been stopped at 70 treated patients.

4.1.1 Screening Phase

The start of the study period is defined by signing of the informed consent form (ICF). Participants with advanced pMMR/MSS colorectal cancer will be screened for eligibility up to 28 days (d) immediately prior to starting study intervention on cycle (C)1 day (D)1. 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 enrollment of each participant into the study to ensure that all inclusion and exclusion criteria have been satisfied.

Figure 4–1: Study Schema



Abbreviations: C = cycle; D = day; FU = follow-up; i.v. = intra venous; LD = last dose; min = minute; q.d. = *quaque die* (once daily); Q4W = every 4 weeks

a) Nivolumab 480 mg using a 30-min i.v. infusion every 4 weeks (Q4W). Regorafenib starting dose 80 mg orally every day (q.d.) for 21 days of every 28 -day cycle (i.e. 21 days on, 7 days off). If starting dose is well tolerated (absence of any grade rash/HFSR or other Grade 2 or higher clinically significant toxicity) dose should be escalated to 120 mg orally daily starting with C2D1.

b) Mandatory safety FU visit (at least 30 d after LD of regorafenib/ nivolumab and100 d after LD of nivolumab) and other active FU visits to collect safety and efficacy information for participants who discontinue study treatment without disease progression, if applicable.

4.1.2 Treatment Phase

Participants will be treated with nivolumab i.v. given on D1 and regorafenib orally every day for 21 days in a 28-d cycle. Nivolumab will be administered as a flat dose of 480 mg using a 30 min i.v. infusion Q4W. Regorafenib will be given at a starting dose of 80 mg for 21 days of every 28-day cycle (i.e., 21 days on, 7 days off). If the starting dose of 80 mg daily is well tolerated (absence of any grade rash/HFSR or other Grade 2 or higher clinically significant toxicity) the dose should be escalated to 120 mg orally daily starting with C2D1. Dose modification guidelines for dose reduction in case of toxicity are detailed in Section 6.6. The Sponsor should be consulted, if the Investigator decides to not escalate the dose to 120 mg despite meeting the criteria.

Participants will continue treatment until disease progression as defined by RECIST v1.1, unacceptable toxicity or consent withdrawal, withdrawal from the study at the discretion of the investigator or his/her designated associate(s) or any other withdrawal criteria are met. Treatment beyond radiological progression as per Response evaluation criteria in solid tumors for trials testing immunotherapeutics (iRECIST) is possible if the participant is still benefiting from treatment. For details please refer to Section 8.1.

Patients who complete 24 infusions of nivolumab (after approximately 2 years of treatment) need to discontinue treatment. Regorafenib monotherapy treatment can be continued beyond 2 years until discontinuation criteria are met.

During the study, participants will undergo evaluations for safety, efficacy, and tissue and blood for biomarker will be collected. Tumor assessments will be at baseline, every 8 weeks ± 7 d for the first year and thereafter every 12 weeks ±14 d until progressive disease. Treatment with individual drugs (regorafenib or nivolumab) may continue on schedule even if the other drug is interrupted or permanently discontinued due to toxicity.

Primary endpoint of the study is ORR measured by RECIST v1.1 as determined by investigator. Scans will be prospectively collected and stored by a vendor in case independent central review is needed.

4.1.3 Active Follow-Up

A mandatory clinical visit to monitor safety will take place 30 d (window of +7 d) after the last administration of regorafenib/nivolumab and 100 d (window of +7 d) after the last dose of nivolumab. Longer safety FU for nivolumab is required due to the long half-life of the antibody.

Participants who discontinue study intervention due to radiologically progressive disease will terminate the active FU period after the clinical safety visits.

Participants, who have not progressed clinically or radiologically or have discontinued study intervention for reasons other than death, withdrawal of consent or lost to FU, will continue with radiological tumor assessments. During the active follow-up period, CT (computed tomography) /MRI (magnetic resonance imaging) evaluations will be performed at the same intervals as during study treatment (every 8 weeks for the first year, and thereafter, every 12 weeks). In addition, study intervention-related toxicity/AE and information about survival status and subsequent anti-cancer therapy will be followed up until completion of the active FU.

4.1.4 Long-Term Follow-Up

All surviving participants will enter the long-term FU period after discontinuing from the active FU period except for participants who explicitly withdraw consent or are lost to FU. Participants will be followed for overall survival and subsequent anti-cancer therapy at 3-month intervals (± 14 d) until end of study, 2 years after the last participant started study intervention (telephone contact is sufficient) or consent withdrawal or death or lost to FU. Participants may be contacted at additional times throughout the course of the study in order to collect survival data to ensure that long-term FU data is current.

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patients with mCRC. Primary endpoint for the study is ORR by RECIST, which is an

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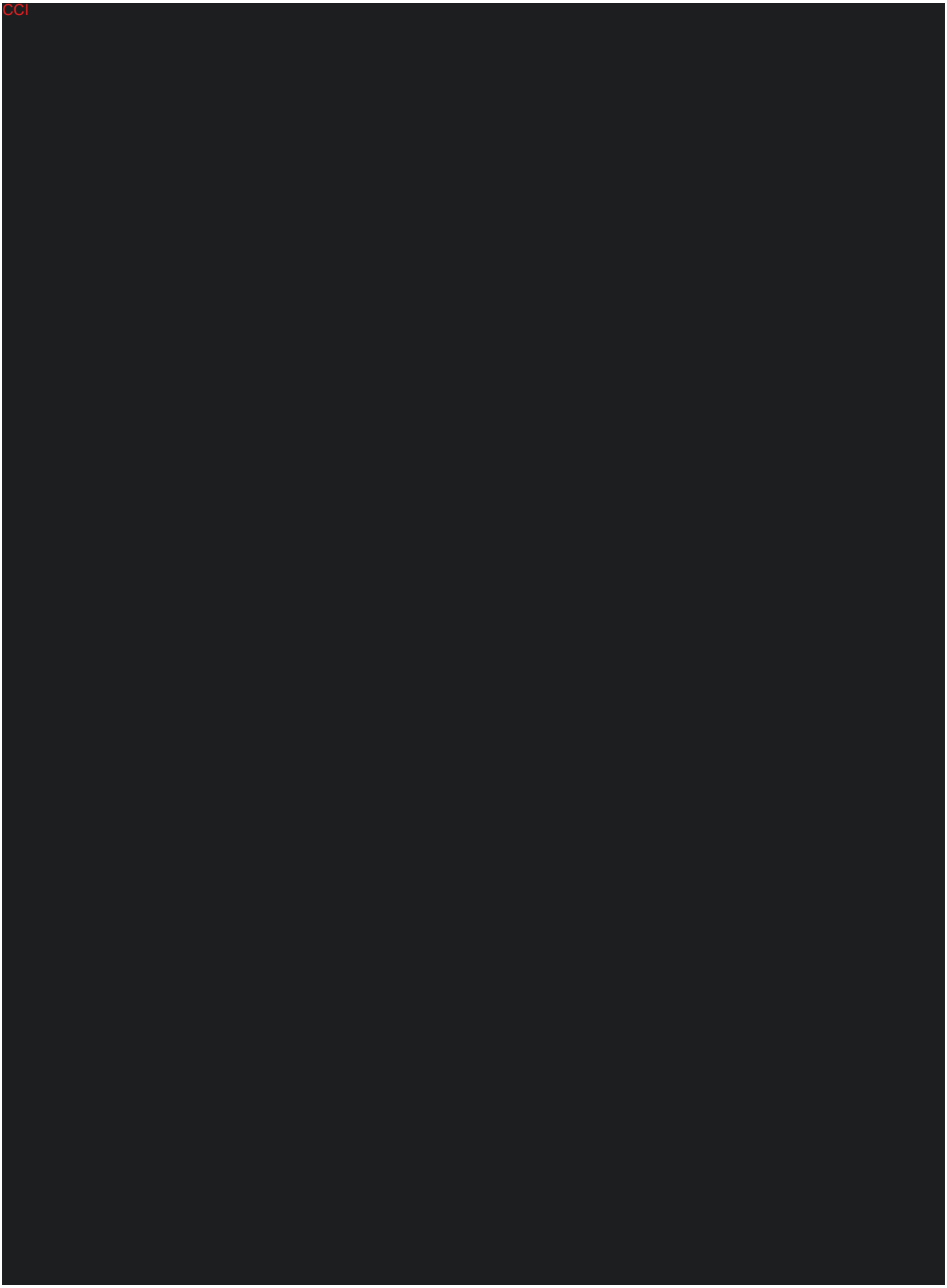
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4.4 End of Study Definition

The end of the study (EOS) is defined as the date when the last visit of the last participant has been achieved in all participating centers.

Last patient last visit (LPLV) of a participant is reached if he/she has completed the last scheduled procedure shown in the Schedule of Activities (this also includes phone contacts during long-term FU) unless the patient died or withdrew consent or is lost to FU.

The LPLV date may also be reached based on the last participant switching to a roll-over study or being switched to commercial drug supply with no cost to the participant.

Furthermore, to reach EOS, the following criteria need to be satisfied in this study:

- All participants have discontinued nivolumab treatment.
- The last included participant has been followed for at least 24 months since first study treatment administration.

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 10.1.9).

Primary completion

The primary completion is defined by the event when all participants have been assessed for response rate (as defined by RECIST v1.1) by at least 5 post-baseline scans unless they have discontinued before due to progression or any other reason i.e., have been followed for approximately 10 months from 1st dose.

5. Study Population

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

Recruitment has been stopped at 70 treated patients.

In Amendment 1, it was planned that approximately 143 participants would be screened to achieve 100 treated participantsof which approximately 50-60 participants would have a left sided primary tumor. In order to allow appropriate balance of participants with right and left sided primary tumors, enrollment may be restricted to either left or right sided tumors during the study. (Information about right and left sided primary tumors of the participant will be recorded by the investigator or delegate in IxRS when the participant is registered in IxRS after signing off the PI/ICF.).

5.1 Inclusion Criteria

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

1. Capable of giving signed informed consent as described in Section 10.1.3 which includes compliance with the requirements and restrictions listed in the ICF and in this

protocol. A signed informed consent must be obtained prior to conducting any study-specific procedures.

2. Male and female adult participants 18 years of age or older on day of signing informed consent.
3. Histological or cytological confirmed advanced, metastatic, or progressive pMMR/MSS adenocarcinoma of colon or rectum.
   a) Microsatellite status should be performed per local standard of practice. (e.g., IHC and/or PCR, next-generation sequencing). Only participants with pMMR/MSS mCRC are eligible.
4. Known extended RAS and BRAF status as per local standard of practice.
5. Participant must have progressed (radiologically or clinically) or been intolerant to no more than two (for extended RAS mutant) or three (for extended RAS wild type) lines of systemic chemotherapy regimens for advanced or metastatic CRC. Maintenance regimens, such as 5-fluorouracil or capecitabine, with or without bevacizumab, should not be counted as separate lines of treatment. Reintroduction of previously administered chemotherapy containing oxaliplatin, irinotecan or 5-fluorouracil/capecitabine, without newly added biologics like EGFR inhibitor for RAS wild type patients and locoregional treatments such as hepatic arterial infusion therapy or Yttrium-90 radioembolization should not be counted as separate lines of treatment.
   - Prior line of therapy must include ALL of the following agents
     a) Fluoropyrimidines
     b) Irinotecan
     c) Oxaliplatin
     d) anti-VEGF therapy, and, if extended RAS wild type, an anti-EGFR therapy (if appropriate and patient is eligible)
   - Patient must have evidence of progression on or after the last treatment regimen received and within 6 months prior to study enrollment
   - Patients who were intolerant to prior systemic chemotherapy regimens are eligible if there is documented evidence of clinically significant intolerance despite adequate supportive measures.
   - Adjuvant/neoadjuvant chemotherapy can be considered as one line of chemotherapy for advanced/metastatic disease if the participant had disease recurrence within 6 months of completion
6. ECOG (Eastern Cooperative Oncology Group) PS of 0 to 1.
7. Adequate hematologic and organ function as assessed by the following laboratory tests performed within 7 d before treatment initiation:
   - Total bilirubin ≤1.5 x the upper limit of normal (ULN). Total bilirubin (≤3 x ULN) is allowed if Gilbert's syndrome is documented.
   - Alanine transaminase (ALT) and aspartate aminotransferase (AST) ≤3 x ULN (≤5 x ULN for patients with liver involvement of their cancer)
   - Platelet count ≥100,000 /mm3, Hemoglobin (Hb) ≥9 g/dL, WBC ≥2000/µL absolute neutrophil count (ANC) ≥1500/mm3

- Serum creatinine ≤1.5 x ULN or creatinine clearance ≥40 mL/min (measured or calculated using the Cockroft-Gault formula)
- Prothrombin time-international normalized ratio (PT/INR) <2.3 and activated partial thromboplastin time (aPTT) <1.5 x ULN.

8. Measurable disease as determined by RECIST v1.1
9. Provision of recent tumor tissue (as defined below) is mandatory for all participants at screening (Formalin-fixed paraffin-embedded block or minimum of 20 slides).
   - Tumor tissue obtained within 180 d of enrollment and after the last dose of most recent anti-cancer therapy
   - Or a new biopsy

   Exceptions for patients with less than required tumor tissues may be considered after documented discussion and approval by the sponsor.
10. Anticipated life expectancy greater than 3 months
11. Be able to swallow and absorb oral tablets.
12. Women of childbearing potential (WOCBP) must agree to follow instructions for method(s) of contraception for the duration of study intervention and 210 d after last dose of regorafenib and 5 months after the last dose of nivolumab.

    Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of study intervention and 120 d after last dose of regorafenib. In addition, male participants must be willing to refrain from sperm donation during this time.

    Contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. Please refer to Section 10.4 for more information.

5.2 Exclusion Criteria

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

1. Participants with dMMR/MSI-H colorectal cancer.
2. Prior therapy with regorafenib, anti-PD-1, PD-L1, or CTLA-4 inhibitors, or any form of immunotherapy to treat cancer
3. Systemic anti-cancer treatment within 14 d or less than 5 half-lives (whichever is shorter) of the first dose of study treatment
4. Has unresolved clinically significant toxicity of greater than or equal to National Cancer Institute Common Terminology Criteria for AEs (NCI-CTCAE, v5.0) Grade 2 attributed to any prior therapies (excluding anemia, lymphopenia, alopecia, skin pigmentation, and platinum-induced neurotoxicity)
5. Arterial thrombotic or embolic events such as cerebrovascular accident (including transient ischemic attacks) within 6 months before the start of study medication. Active pulmonary emboli or deep vein thrombosis that are significant or not adequately controlled on anticoagulation regimen
6. Congestive heart failure ≥ New York Heart Association (NYHA) class 2

7. Unstable angina (angina symptoms at rest), new-onset angina (begun within the last 3 months), myocardial infarction less than 6 months before start of study drug
8. Uncontrolled cardiac arrhythmias
9. Poorly controlled hypertension, defined as a blood pressure consistently above 150/90 mmHg despite optimal medical management
10. Persistent proteinuria of NCI-CTCAE Grade 3. 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 hr
11. Major surgical procedure or significant traumatic injury within 28 d before start of study medication. Note: If participants received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy
12. Non-healing wound, non-healing ulcer, or non-healing bone fracture
13. Participants with evidence or history of any bleeding diathesis, irrespective of severity
14. Any hemorrhage or bleeding event ≥ NCI-CTCAE Grade 3 within 28 d prior to the start of study medication
15. Significant acute gastrointestinal disorders with diarrhea as a major symptom e.g., Crohn's disease, malabsorption, or ≥ NCI-CTCAE Grade 2 diarrhea of any etiology.
16. Participants with an active, known or suspected autoimmune disease. Participants with type I diabetes mellitus (T1DM), hypothyroidism only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.
17. Participants with a condition requiring systemic treatment with either corticosteroids (>10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 d of start of study treatment. Inhaled or topical steroids, and adrenal replacement steroid doses >10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.
18. History of (non-infectious) pneumonitis that required steroids or current pneumonitis
19. History of interstitial lung disease
20. Subjects 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.
21. Diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy.
22. Presence of symptomatic central nervous system (CNS) metastases, or CNS metastases that require local CNS-directed treatment (such as radiotherapy or surgery). Participants with stable CNS disease or previously treated lesions are eligible for study

entry. In addition, subjects must be either off corticosteroids, or on a stable or decreasing dose of 10 mg daily prednisone (or equivalent).

23. Ongoing infection > Grade 2 NCI-CTCAE requiring systemic therapy.
24. Known history of human immunodeficiency virus (HIV) infection (HIV 1/2 antibodies).
25. Any positive test result for hepatitis B virus (HBV) or hepatitis C virus (HCV) indicating presence of virus, e.g. Hepatitis B surface antigen (HBsAg, Australia antigen) positive, or Hepatitis C antibody (anti-HCV) positive (except if HCV-RNA negative).
26. Pregnancy or breast feeding.
27. Psychological, familial, or sociological condition potentially hampering compliance with the study protocol and FU schedule.
28. Previous treatment with live vaccine within 30 d of planned start of study drugs (seasonal flu vaccines that do not contain a live virus are permitted).
29. Known hypersensitivity to any of the study drugs, study drug classes, or excipients in the formulation.

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

For details please refer to Sections 6.1 and 6.5.

5.3.2 Caffeine, Alcohol, and Tobacco

Not applicable for this protocol.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently assigned to 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. Minimal information includes demography, screen failure details and any serious AE (SAE).

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once. Whether the participant can repeat the screening will be discussed with the Sponsor. Sponsor's approval of re-screening for a participant must be documented.

Also, for re-screening, the participant has to re-sign the informed consent form, even if it was not changed after the patient's previous screening. The screening failure will be registered in Interactive Voice/Web Response System (IxRS) to close the participant identification number (PID), and re-screening will start again by signing a new informed consent form and being assigned a new PID via IxRS.

6. Study Intervention

Study intervention is defined as any investigational intervention intended to be administered to a study participant according to the study protocol.

Participants will receive nivolumab intravenously on day 1 of every cycle. Nivolumab will be administered as a dose of 480 mg using a 30-min i.v. infusion Q4W.

Regorafenib will be given orally every day for 21 days of each 28-day cycle. Each treatment cycle will be 28 days in duration. Regorafenib will be given as 40 mg tablets q.d. for 21 days of every 28-day cycle (i.e., 21 days on, 7 days off) as a starting dose of 80 mg. If starting dose of 80 mg daily is well tolerated (absence of any grade rash/ HFSR or other Grade 2 or higher clinically significant toxicity) dose should be escalated to 120 mg orally daily starting with C2D1. Sponsor should be consulted, if the Investigator decides to not escalate the dose to 120 mg despite meeting the criteria.

When the two study drugs are administered on the same day, regorafenib is to be taken first orally followed by nivolumab infusion.

Regorafenib should be taken within 2 hr after a light meal with approximately 240 mL (8 fluid ounces) of water, preferably in the morning. If necessary, the study drug 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 hr interval between doses). Tablets should not be chewed. If a dose of regorafenib is missed, the missed dose should not be made up for (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 exceeded the scheduled dose.

On days when pre-dose PK blood samples will be collected (Table 8–2), participants will take the morning dose of regorafenib at the clinic after all required samples are collected. On days PK samples are not required, regorafenib can be taken at home or in clinic.

Participants will continue treatment until disease progression as defined by RECIST v1.1, unacceptable toxicity or consent withdrawal, withdrawal from the study at the discretion of the investigator or his/her designated associate(s) or any other withdrawal criteria are met. Treatment beyond radiological progression is possible if the participant is still benefiting from treatment. In order to continue treatment after initial documentation of disease progression, participant must be re-consented. In case of treatment interruption or discontinuation due to Nivolumab or Regorafenib related toxicities participants may continue treatment with either Nivolumab or Regorafenib single agent respectively.

Participants who complete 24 infusions of nivolumab (after approximately 2 years of treatment) need to discontinue treatment. Regorafenib treatment can be continued until clinical disease progression, or unacceptable toxicity, or any other withdrawal criteria are met.

6.1 Study Intervention(s) Administered

Table 6–1: Administration of Study Intervention

Study Intervention	Regorafenib	Nivolumab
Type	small molecule drug (MKI)	monoclonal antibody, biologic
Dose Formulation	tablet	concentrate for solution for infusion
Unit Dose Strengths	40 mg / tablet	240 mg / 24 mL vial (10 mg/mL)
Dosage Levels	2x 40 mg tablets every day (q.d.) for 21 days of every 28-day cycle (i.e. 21 days on, 7 days off) as a starting dose of 80 mg. If the starting dose is well tolerated dose should be escalated to 120 mg (3x40 mg tablets) starting with C2D1.	480 mg (2x240 mg / 24 mL vials) on D1 of each cycle
Route of Administration	oral	i.v. infusion
IMP and NIMP	IMP	IMP
Sourcing	Regorafenib will be provided centrally by the Sponsor.	Nivolumab 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 30 tablets Regorafenib 40 mg and a 3 g desiccant per bottle of Regorafenib 40 mg. The bottles will be labeled as required per country requirement.	Nivolumab will be provided in glass injection vial. Each glass injection vial will be labeled as required per country requirement.

Abbreviations: IMP = investigational medicinal product; i.v. = intravenous; MKI = multikinase inhibitor; NIMP = non-investigational medicinal product

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.

Study intervention should be stored in a secure locked location and at the recommended label temperature for the regorafenib 40 mg tablets in bottles and the nivolumab 240 mg / 24 mL vials.

Note: The regorafenib bottle contains a desiccant. Once the drug has been received it has to be kept in a secure, dry location. The tablets have to be stored in the original bottle according to the labelled storage advice. The tablets have to be stored in the original pack provided in order to protect from moisture and swallowed immediately after they have been taken out. The bottle has to be kept tightly closed after first opening and the desiccant has to remain in the bottle. Once the bottle is opened, tablets should be used within 7 weeks. Any unused tablets must be returned to study site by the patient. Beyond that, no special precautions are required, when handling the study drug.

The personnel will use the study intervention only within the framework of this clinical study and in accordance with this protocol. 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 a separate document.

6.3 Measures to Minimize Bias: Randomization and Blinding

Randomization and blinding are not applicable for this study.

This is an open-label study and all open label intervention at all visits must be assigned by the IxRS for tracking and accountability purpose.

Participant identification

After a participant has signed the PI/ICF, the participant identification number will be provided to the investigators through an IxRS. Participants will be identified by a 9-digit participant identification number consisting of:

Digits 1 to 5 = Unique center number

Digits 6 to 9 = Current patient number within the center

In order to allow appropriate balance of participants with right and left sided primary tumors, enrollment may be restricted to either left or right sided tumors during the study. Information about right and left sided primary tumors of the participant will be recorded by the investigator or delegate in IxRS when the participant is registered in IxRS after signing off the PI/ICF.

The IxRS procedure is described in detail in a separate IxRS instruction manual that will be maintained in the electronic trial master file (eTMF) and in each center's investigator site file.

6.4 Study Intervention Compliance

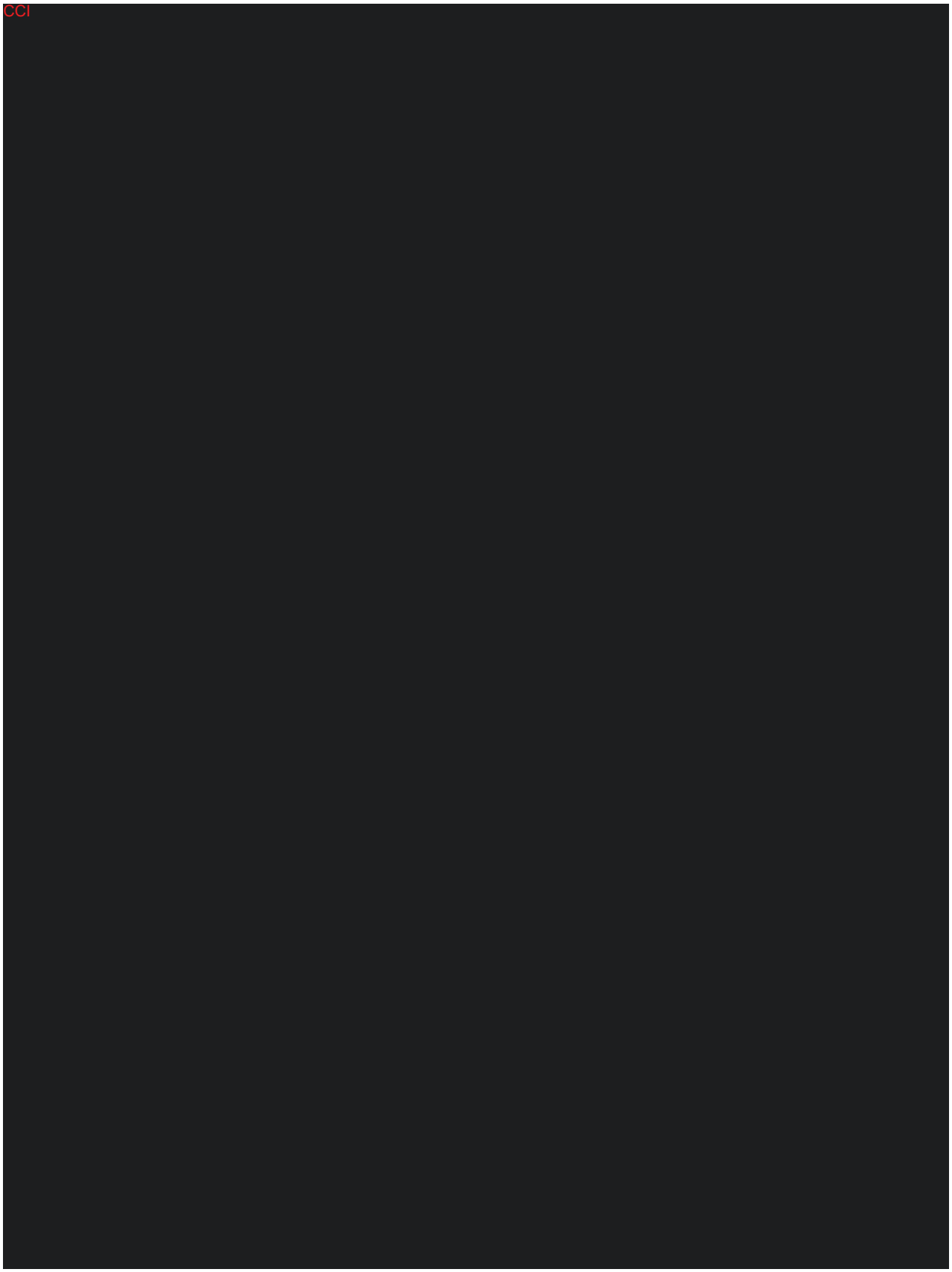
The administration of intravenous nivolumab will be performed in the clinic on D1 of every treatment cycle. The date and time of each infusion administered in the clinic will be recorded in the source documents and recorded in the electronic case report form (eCRF). Reasons for dose delay or infusion 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.

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

Additionally, for treatment compliance oral administration of regorafenib will be done under supervision of site staff on PK visit days, and the dosing and time must be documented in the source data and eCRF on the following days: D1, D8 and D15 of C1, and on D1 and D15 of C2.

When participants self-administer regorafenib at home, compliance with regorafenib will be assessed at each study visit. Compliance will be assessed by counting returned tablets. A record of the number of regorafenib tablets dispensed to and returned by each participant must be maintained and reconciled with regorafenib 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 medication 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.



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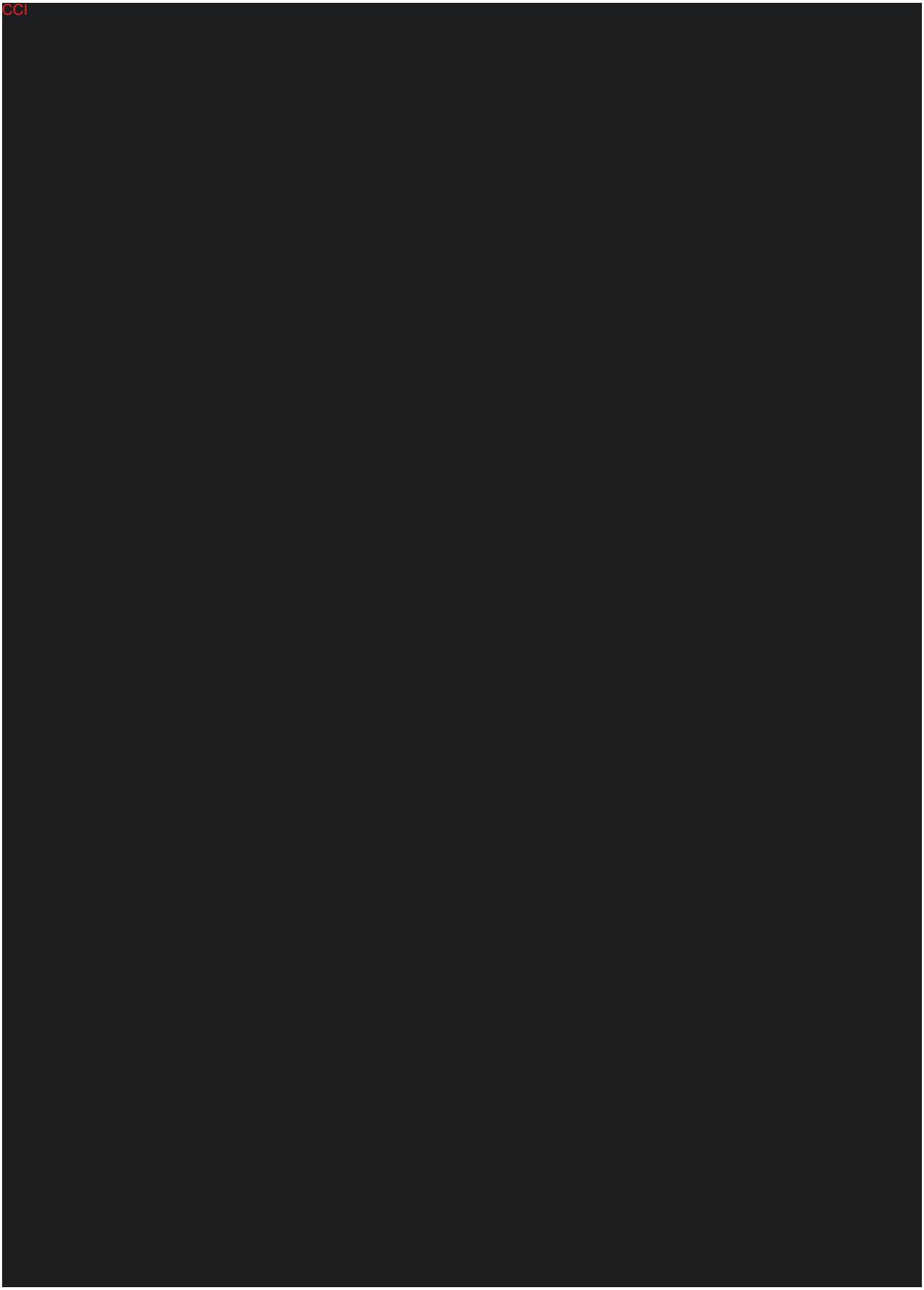
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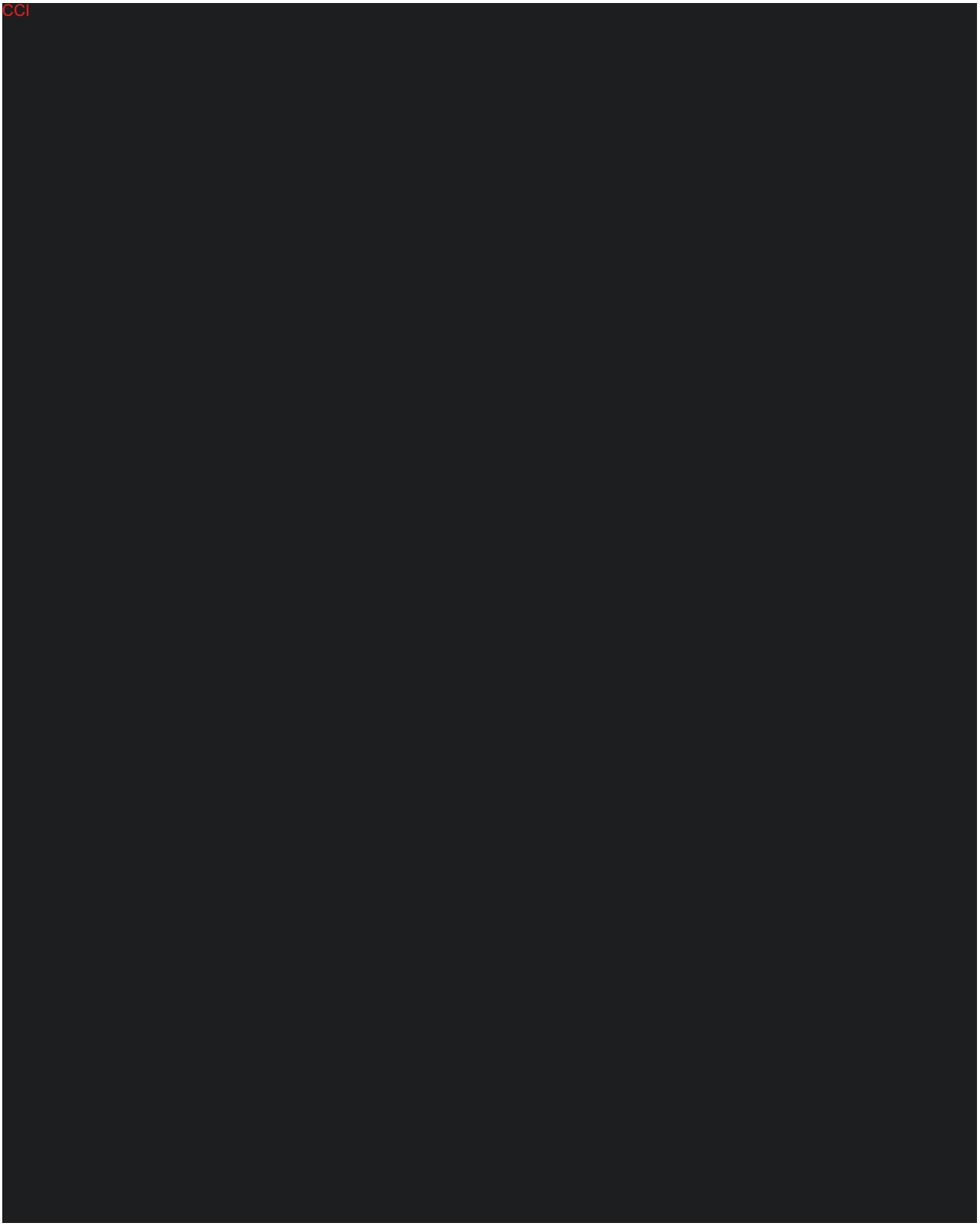

6.6 Dose Modification

Based on the known toxicity profiles of regorafenib and nivolumab, 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 nivolumab; similarly,

immune-related AEs are likely to be associated with nivolumab rather than regorafenib. However, some drug-related AEs such as diarrhea, abnormal thyroid function, and fatigue are overlapping. Therefore, it is important to evaluate each AE to confirm 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 must be based on the maximum toxicity experienced during a cycle. If appropriate, the Investigator may attribute each toxicity event to regorafenib or nivolumab alone or to the combination. In situations where clear attribution cannot be made to individual drugs, more conservative dose modification approach should be used for both drugs. In case of dose modifications, any efforts should be made to restart study intervention as per original schedules for regorafenib and nivolumab.

6.6.1 Toxicity Management and Dose Modification Recommendations for Regorafenib

Table 6–2 outlines different regorafenib dose levels for the purpose of dose modification. In case a dose reduction for regorafenib is necessary, the study intervention will be administered as outlined in Table 6–2 to Table 6–6.

Table 6–2: Dose Modification for Regorafenib

Dose Level	Daily Regorafenib (21 days on, 7 days off)	Daily Regorafenib (21 days on, 7 days off)
Current Dose	80 mg	120 mg
Dose Level -1	80 mg every other day[a]	80 mg
Dose Level -2	NA	80 mg every other day[a]

Abbreviations: mg = milligram; NA = not applicable

a) If reductions are required resulting in regorafenib daily dose of less than 80 mg every other day, the regorafenib will be permanently discontinued.

Table 6–3: Regorafenib Dose Modification/Dose Interruption Guide: (except HFSR, Hypertension, and Liver Function Test Abnormalities)

CTCAE Grade	Occurrences	Dose Interruption	Dose modification (when resuming treatment)
Grade 0-2	Any	No change	No change
Grade 3	1st and 2nd occurrence	Hold until recovery to <G2 or baseline[a]	Restart at same dose level or reduce 1 dose level (at the investigator's discretion)
	3rd occurrence	Hold until recovery to <G2 or baseline[a]	Reduce 1 dose level or consider permanent discontinuation[b]
Grade 4	1st occurrence	Hold until recovery to <G2 or baseline[a]	Reduce 1 dose level or consider permanent discontinuation[b]
	2nd occurrence	Hold until recovery to <G2 or baseline[a]	Discontinue

Abbreviations: CTCAE = common terminology criteria for adverse events; G = Grade; HFSR = hand-foot skin reaction

a) Excludes alopecia, non-refractory nausea/vomiting, lymphopenia and asymptomatic laboratory abnormalities. Treatment can be resumed with Grade 2 fatigue or hypothyroidism.

b) If reductions are required resulting in regorafenib daily dose of less than 80 mg eve ry other day, the regorafenib will be permanently discontinued. If toxicity returns to Grade 0-1 after dose reduction, dose reescalation is permitted in the subsequent cycle at the investigator's discretion. Subjects requiring a delay of >4 weeks should discontinue regorafenib treatment. However, continuation of regorafenib may be considered if, in the investigator's opinion, the patient may continue to benefit from the regorafenib treatment, and after consultation with Sponsor

Table 6–4: Regorafenib Dose Modification Guidance: HFSR/ Palmar-Plantar Erythrodysesthesia Syndrome

Skin toxicity grade (CTCAE)	Occurrence	Dose Interruption	Dose modification (when resuming treatment)
G1	Any	Maintain dose level and institute supportive measures immediately for symptomatic relief	No Change
G2	1st occurrence	Interrupt therapy for a minimum of 7 days, until toxicity resolves to Grade 0–1	Institute supportive measures and continue same dose or consider decrease by 1 dose level
	No improvement within 7 d or 2nd occurrence	Interrupt until toxicity resolves or improves to G1.	When resuming treatment, treat at reduced dose level or consider discontinuation[a]
	3rd occurrence	Discontinue	
G3	1st occurrence	Institute supportive measures immediately. Interrupt therapy for ≥ 7 d until toxicity resolves or improves to G1.	When resuming treatment, decrease by 1 dose level
	2nd occurrence	Institute supportive measures immediately. Interrupt therapy for ≥ 7 d until toxicity resolves or improves to G1.	When resuming treatment, decrease by 1 additional dose level or consider discontinuation[a]
	3rd occurrence	Discontinue	

Abbreviations: CTCAE = common terminology criteria for adverse events; G = Grade; HFSR = hand-foot skin reaction

a) If reductions are required resulting in regorafenib daily dose of less than 80 mg every other day, the regorafenib will be permanently discontinued. If toxicity returns to Grade 0-1 after dose reduction, dose reescalation is permitted in the subsequent cycle at the Investigator's discretion. Subjects requiring a delay of >4 weeks should discontinue regorafenib treatment. However, continuation of regorafenib may be considered if, in the investigator's opinion, the patient may continue to benefit from the regorafenib treatment, and after consultation with Sponsor.

Table 6–5: Regorafenib Dose Modification Guidance, Non-Immune Toxicities: Hypertension

CTCAE Grade	Suggested regorafenib dose interruption	Suggested regorafenib dose modification
Specific guidance for HYPERTESION		
G1	No change.	Consider increased BP monitoring
G2	If symptomatic, hold until symptoms resolve and diastolic BP ≤ 90 mmHg. Treat with anti-hypertensive medications	At restart, continue at the same dose level
G3	Hold until diastolic BP ≤ 90 mm Hg, and if symptomatic, until symptoms resolve. Treat with additional anti-hypertensive medications	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
	If G3 hypertension recurs despite dose reduction and optimal antihypertensive therapy	Reduce another dose level or consider discontinuation[a]
G4	Discontinue	

Abbreviations: BP = blood pressure; CTCAE = common terminology criteria for adverse events; G = Grade; Hg = mercury

a) If reductions are required resulting in regorafenib daily dose of less than 80 mg every other day, the regorafenib will be permanently discontinued. If toxicity returns to Grade 0-1 after dose reduction, dose reescalation is permitted in the subsequent cycle at the investigator's discretion. Subjects requiring a delay of >4 weeks should discontinue regorafenib treatment. However, continuation of regorafenib may be considered if, in the investigator's opinion, the patient may continue to benefit from the regorafenib treatment, and after consultation with Sponsor.

Table 6–6: Regorafenib Dose Modifications for Liver Function Test Abnormalities[a]

Increases in AST/ALT/Bilirubin	Occurrence	Dose Interruption	Dose Modification (when resuming treatment)
(from baseline within normal limits) AST and/or ALT < 3 times ULN or total bilirubin < 1.5 times ULN	Any	**Continue dosing**	No Change
(from baseline AST/ALT more than 1 and up to 3 times ULN) AST or ALT more than 3 and up to 5 times the ULN	Any	**Continue dosing**	No Change
(from baseline within normal limits) AST or ALT more than 3 and up to 5 times the ULN or total bilirubin more than 1.5 and up to 3 times the ULN	1st occurrence	**Delay dosing until return to Grade ≤ 1 or baseline**	Reduce 1 dose level[b]
	Re-occurrence	**Discontinue**	
(from baseline any grade) AST or ALT more than 5 times the ULN or total bilirubin more than 3 times the ULN	1st occurrence	**Delay dosing until return to Grade ≤ 1 or baseline**	If the potential to reinitiate regorafenib is considered to outweigh the risk of hepatotoxicity: reduce 1 dose level
	Re-occurrence	**Discontinue**	
(from baseline any grade)	Any	**Discontinue**	

Increases in AST/ALT/Bilirubin	Occurrence	Dose Interruption	Dose Modification (when resuming treatment)
AST and/or ALT > 20 x ULN			
AST and/or ALT > 3 x ULN with concurrent bilirubin > 2 x ULN	Any	**Discontinue**[c]	

Abbreviations: ALT=alanine aminotransferase; AST=aspartate aminotransferase; ULN = upper limit of normal

a) For any of the events listed above (dose interruption or modification): monitor liver function tests weekly or more frequently until recovery to baseline or stabilization
b) If all values remain stable for 2 full cycles, dose re-escalation may be considered at the discretion of the Investigator. After re-escalation AST, ALT, bilirubin should be checked 2×/week for 2 weeks, followed by weekly assessments for at least 4 weeks.
c) Exception: participants with Gilbert's syndrome who develop elevated transaminases should be managed as per the above outlined recommendations for the respective observed elevation of ALT and/or AST.

The dose modification can occur independently for the 2 drugs used if toxicity can be clearly attributed to one of the drugs. Resumption of regorafenib dosing is not required to receive further nivolumab dosing and vice versa. Treatment with individual drugs (regorafenib or nivolumab) may continue on schedule even if other drug is interrupted or permanently discontinued due to toxicity.

6.6.2 Toxicity Management and Dose Modification Recommendations for Nivolumab

AEs (both non-serious and serious) associated with nivolumab exposure may represent an immunologic etiology. These AEs may occur shortly after the first dose or several months after the last dose of treatment. Therefore, early recognition and initiation of treatment is critical to reduce complications.

There will be no dose reductions for nivolumab. Treatment can be delayed for nivolumab related AEs. If the criteria to resume treatment are met, the subject should restart treatment at the next scheduled time point per protocol.

Nivolumab administration should be delayed for the following:

- Grade 2 non-skin, drug-related AE, with the exception of fatigue
- Grade 2 drug-related creatinine, AST, ALT and/or Total Bilirubin abnormalities
- Grade 3 skin, drug-related AE
- Grade 3 drug-related laboratory abnormality, with the following exceptions:
  - Grade 3 lymphopenia or asymptomatic amylase or lipase does not require dose delay
  - Grade ≥ 3 AST, ALT, Total Bilirubin will require dose discontinuation (see Section 6.6.2.1)
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication.

There are no recommended dose modifications for hypothyroidism or hyperthyroidism. Interrupt or slow the rate of infusion in participants with mild or moderate (Grade 1-2)

infusion reactions. Discontinue nivolumab in participants with severe or life-threatening infusion reactions (Grade 3-4) (see Section 6.6.2.4).

Participants who require delay of nivolumab should be re-evaluated weekly or more frequently if clinically indicated and resume nivolumab dosing when re-treatment criteria are met (see Section 6.6.2.2). The dose modification can occur independently for the 2 drugs used if toxicity can be clearly attributed to one of the drugs. Resumption of regorafenib dosing is not required to receive further nivolumab dosing and vice versa. Treatment with individual drugs (regorafenib or nivolumab) may continue on schedule even if other drug is interrupted or permanently discontinued due to toxicity.

6.6.2.1 Nivolumab Treatment – Permanent Discontinuation

- Any Grade 2 drug-related uveitis, eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the re-treatment period OR requires systemic treatment
- Any Grade 3 non-skin, drug-related AE lasting >7 d or recurs, with the following exceptions for laboratory abnormalities, drug-related uveitis, pneumonitis, bronchospasm, neurologic toxicity, hypersensitivity reactions, infusion reactions, and endocrinopathies:
  - Grade 3 drug-related uveitis, pneumonitis, bronchospasm, neurologic toxicity, myocarditis, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation
  - Grade 3 drug-related endocrinopathies, adequately controlled with only physiologic hormone replacement do not require discontinuation. Adrenal insufficiency requires discontinuation regardless of control with hormone replacement.
  - Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except:
    - Grade 3 drug-related thrombocytopenia >7 d or associated with bleeding requires discontinuation
    - Grade ≥ 3 drug-related AST, ALT or total Bilirubin requires discontinuation
    - Concurrent AST or ALT > 3 x ULN and total bilirubin > 2x ULN
- In most cases of Grade 3 AST or ALT elevation, nivolumab treatment will be permanently discontinued. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of nivolumab treatment, a discussion between the investigator and the Sponsor must occur.
- Any Grade 4 drug-related adverse event or laboratory abnormality (including but not limited to creatinine, AST, ALT, or Total Bilirubin), except for the following events which do not require discontinuation:
  - Grade 4 neutropenia ≤7 d
  - Grade 4 lymphopenia or leukopenia or asymptomatic amylase or lipase
  - Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hr of their onset

- Grade 4 drug-related endocrinopathy adverse events, such as, hyper- or hypothyroidism, or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (corticosteroids, thyroid hormones) or glucose-controlling agents, respectively, may not require discontinuation after discussion with and approval from the Sponsor.

- Any event that leads to delay in dosing lasting >10 weeks from the previous dose requires discontinuation, with the following exceptions:
  - Dosing delays to allow for prolonged steroid tapers to manage drug-related adverse events are allowed.
  - Dosing delays lasting > 10 weeks from the previous dose that occur for non-drug-related reasons may be allowed if approved by the Sponsor.

Prior to re-initiating treatment in a participant with a dosing delay lasting > 10 weeks, the Sponsor must be consulted. Tumor assessments should continue as per protocol even if dosing is delayed.

- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the participant with continued nivolumab dosing.

6.6.2.2 Criteria to Resume Nivolumab Treatment

Participants may resume treatment with nivolumab when the drug-related AE(s) resolve to Grade ≤ 1 or baseline value, with the following exceptions:

Participants may resume treatment in the presence of Grade 2 fatigue

Participants who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity

For participants with Grade 2 AST, ALT and/or Total Bilirubin Abnormalities, dosing may resume when laboratory values return to baseline and management with corticosteroids, if needed, is complete.

Drug-related pulmonary toxicity, diarrhea or colitis must have resolved to baseline before treatment is resumed. Participants with persistent Grade 1 pneumonitis after completion of a steroid taper over at least 1 month may be eligible for retreatment if discussed with and approved by Sponsor.

Participants with drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment after consultation with the Sponsor. Adrenal insufficiency requires discontinuation regardless of control with hormone replacement.

6.6.2.3 Management of Immune-Mediated AEs

Because of the potential for clinically meaningful nivolumab related AEs requiring early recognition and prompt intervention, management algorithms have been developed for suspected pulmonary toxicity, GI toxicity, hepatotoxicity, endocrinopathy, skin toxicity, neurological toxicity, and renal toxicity. These adverse event management algorithms are included in Section 10.11.

These general guidelines constitute guidance to the Investigator and may be supplemented by discussions with the Sponsor. A general principle is that differential diagnoses should be

diligently evaluated according to standard medical practice. Non-inflammatory etiologies should be considered and appropriately treated. Corticosteroids are a primary therapy for immune related adverse events. The oral equivalent of the recommended IV doses may be considered for ambulatory patients with low-grade toxicity. The lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids. Consultation with a medical or surgical specialist, especially prior to an invasive diagnostic or therapeutic procedure, is recommended.

6.6.2.4 Treatment of Nivolumab related Infusion Reactions

Since nivolumab contains only human immunoglobulin protein sequences, it is unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypotension, hypertension, bronchospasm, or other allergic-like reactions. All Grade 3 or 4 infusion reactions should be reported within 24 hours to the Sponsor and reported as an SAE if it meets the criteria. Infusion reactions should be graded according to NCI CTCAE, v5.0 guidelines. Treatment recommendations are provided below and may be modified based on local treatment standards and guidelines, as appropriate:

For Grade 1 symptoms:

- Remain at bedside and monitor participant until recovery from symptoms. The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg at least 30 minutes before additional nivolumab administrations.

For Grade 2 symptoms:

- Stop the study drug infusion, begin an IV infusion of normal saline, and treat the participant with diphenhydramine 50 mg IV (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg; remain at bedside and monitor participant until resolution of symptoms. Corticosteroid and/or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor participant closely. If symptoms recur, then no further study medication will be administered at that visit.
- For future infusions, the following prophylactic premedications are recommended: Diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg should be administered at least 30 minutes before nivolumab and/or ipilimumab infusions. If necessary, corticosteroids (up to 25 mg of hydrocortisone or equivalent) may be used.

For Grade 3 or 4 symptoms:

- Immediately discontinue infusion of study drug. Begin an IV infusion of normal saline and treat the participant as follows: Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Participant should be monitored until the Investigator is comfortable that the symptoms will not recur. Study

drug will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor participant until recovery of the symptoms.

In case of late-occurring hypersensitivity symptoms (e.g., appearance of a localized or generalized pruritus within 1 week after treatment), symptomatic treatment may be given (e.g., oral antihistamine or corticosteroids).

Additional details on the immune mediated AEs of nivolumab, including results from other clinical studies, are also available in the nivolumab IB.

6.7 Intervention after the End of the Study

At the EOS intervention for each individual participant, further therapeutic options are at the discretion of the Investigator.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

General procedures

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

In rare instances, 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 for data to be collected at the time of discontinuation of study intervention, in FU, and for any further evaluations that need to be completed.

If the existing local governance (for example, Health Authorities or Ethics Committees) prohibits patients who withdraw consent from study drug treatment to continue into FU, additional consent processes should be implemented to invite patients to participate in the FU or to request that survival data will be available.

All patients 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 d after the last dose of regorafenib or within 100 d after the last dose of /nivolumab 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 hr of awareness on a Serious AE (SAE) Form and transmitted to the sponsor.

7.1 Discontinuation of Study Intervention

Withdrawal from study treatment period

Patients **MUST** be withdrawn from the study treatment combination if any of the following occurs:

- At their own request or at the request of their legally acceptable representative. At any time during the study and without giving reasons, a patient may decline to participate further. The patient will not suffer any disadvantage as a result.
- If, in the investigator's opinion, continuation of the study treatment would be harmful to the patient's well-being.
- Clinical progression as per iRECIST (every effort should be made to obtain radiological confirmation of disease progression [PD] during active FU). 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 subsequent systemic anti-cancer treatment
- 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
- *Withdrawal of regorafenib only*:
    - Patients 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 patient may continue to benefit from the regorafenib treatment, and after consultation with sponsor.
    - Unacceptable toxicity, i.e., event requiring permanent discontinuation of regorafenib according to dose modification guidance in Section 6.6.
- *Withdrawal of nivolumab only*:
    - Patients who experience a delay of more than 10 weeks to receive the subsequent nivolumab infusion due to treatment related toxicity (see exceptions in Section 6.6.2.1)
    - Patients who complete 24 infusions of nivolumab (after approximately 2 years of treatment)
    - Unacceptable toxicity, i.e. event requiring permanent discontinuation of nivolumab according to dose modification guidance in Section 6.6.2.1.

Withdrawal from active FU

Participants *must* be withdrawn from active FU if any of the following occurs:

- At their own request or at the request of their legally acceptable representative. 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 occurs (provided safety visits have been performed)
- Start of subsequent systemic anti-cancer treatment (provided safety visits have been performed)
- Development of a second primary malignancy that requires a different treatment
- Substantial non-compliance with the requirements of the study
- Withdrawal of consent to active FU visits

- If, in the investigator's opinion, continuation of the active FU visits would be harmful to the participant's well-being
- Participants lost to FU
- Death

Withdrawal from long-term FU

Participants *must* be withdrawn from long-term FU if any of the following occurs:

- Withdrawal of consent to long-term FU
- Participants lost to FU
- Death

Participants **MAY** be withdrawn from the study treatment combination for the following reasons:

- At the specific request of the sponsor and in liaison with the investigator (e.g., obvious non-compliance, safety concerns).
- Withdrawal of nivolumab only: discontinuation of nivolumab may be considered for participants who have attained a confirmed complete response (CR), that have been received at least 8 infusions (32 weeks) of nivolumab and had at least 2 infusions with nivolumab beyond the date when the initial CR was declared.

Discontinuation of study intervention for abnormal liver function should be considered by the Investigator when a participant meets one of the conditions outlined in Table 6–6 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 for data to be collected at the time of intervention discontinuation and FU and for any further evaluations that need to be completed.

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, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

7.2 Lost to Follow-up

A participant will be considered lost to FU 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 FU.

Discontinuation of specific sites or of the study as a whole are handled as part of Section 10.1.

8. Study Assessments and Procedures

- Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed (pre-specified exceptions requiring discussion with the Sponsor are not considered protocol waivers).
- 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 the SoA, 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.

8.1 Efficacy Assessments

Primary endpoint for efficacy assessment is ORR measured by RECIST v1.1 as determined by Radiologist/Investigator. DOR, DCR and PFS will be based on local radiologist/investigator assessment per RECIST v.1.1.

Scans will be prospectively collected and stored at vendor in case independent central review is needed.

All participants who received at least one dose of study drug (regorafenib and nivolumab) will be valid for efficacy evaluations. Contrast-enhanced multi-detector CT is the preferred method to measure lesions selected for response assessment. MRI (typically with gadolinium-based intravenous contrast) may be performed instead of CT (e.g., when local regulations or allergy to CT contrast media do not permit the use of CT as requested per protocol schedule, or when there is concern about radiation exposure from CT, or when MRI is deemed a more appropriate imaging method). Recommended slice thickness for CT/MRI is ≤5mm. PET-CT

scans may be used provided that measurements are obtained from the CT scan and the CT scan is of the same diagnostic quality as a diagnostic CT (with IV and oral contrast). If a CT scan for tumor assessment is performed in a positron-emission-tomography (PET)/CT scanner, the CT acquisition must be consistent with the standard for a diagnostic CT scan (i.e., adequate radiation dose and i.v. contrast) if intended to be used for target lesion measurements. The non-contrast low-dose CT performed as part of the PET scan for attenuation correction is not adequate as a diagnostic CT.

Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Previously irradiated lesions should not be counted as target lesions unless there has been demonstrated progression in the lesion since radiotherapy prior to study enrollment.

For consistency, the same imaging modality and equivalent technique (e.g., slice thickness, field of view) should be used for all scans performed on an individual participant, including baseline scans. At a minimum, anatomical regions that should be included in scans performed at baseline and during study treatment include the chest, abdomen and pelvis, as well as any other areas of known disease and areas prone to metastatic disease for pMMR/MSS CRC.

Tumor assessments will be performed locally by participating radiologists/ Investigators and whenever possible all scans taken at each clinical site will be interpreted by the same radiologist/Investigator at that site. Scans must meet the standard of care for imaging of lesions in the respective organ system(s). Unless progression is noted, all lesions will be assessed and reported at each scheduled scan.

All imaging scans (coded with study participant number and in digital imaging and communications in medicine [DICOM] format) as well as imaging-related adjunctive data (e.g., fluorodeoxglucose [FDG] dose and tracer uptake time) must be prospectively collected and transferred to Bayer, or Bayer-designated imaging core lab, in case independent central review is needed.

The tumor markers CEA and CA 19-9 will be evaluated on an exploratory basis in participants with CRC and will not be used to assess objective tumor response.

Assessment of disease

RECIST v1.1 will be applied by the Investigator as the primary measure for categorization of disease on the baseline imaging and assessment of tumor response until progressive disease (see Section 10.7). CR and PR must be confirmed with repeated imaging performed at least 4 weeks after initial documentation of response.

iRECIST is based on RECIST v1.1, but adapted to account for the unique tumor response seen with immunotherapeutic drugs. iRECIST will be used by the Investigator to assess tumor response and progression, and make treatment decisions (see Section 10.8).

Tumor scans are required at screening, during study treatment and at the End of Treatment: see section 1.3 SoA Table 1–2. Tumor scans are also required during active follow-up, if applicable.

- Baseline assessments will be conducted during the screening period and target lesions should to be selected, measured, and recorded before start of study intervention. Scans that were obtained prior to the participant signing the ICF document for this study can be used as baseline assessments provided that they were performed within 28 d of starting study treatment and meet the requirements for the study

- Assessments during study treatment will be performed every 8 weeks (±7d) for the first year and every 12 weeks ±14 d thereafter. Tumor assessment during the study intervention period includes the same anatomic areas as baseline and will be done until radiological disease progression or the end of the study.
- Radiological tumor evaluation (within 14 days after last study treatment is not necessary if the previous tumor evaluation was performed within 4 weeks (for the first year) or within 8 weeks (thereafter).
- For participants who discontinue study treatment without disease progression, FU tumor evaluations will be performed until progression of malignancy and/or start of subsequent systemic anti-cancer treatment, whichever comes first, or any other criterion for withdrawal is met. During the active FU period, CT/MRI evaluations will be performed at the same intervals as during study treatment.
- At the Investigator's discretion, tumor scans may be repeated at any time if progressive disease is suspected. For further details, see Sections 10.7 and 10.8.

For participants who show evidence of radiological PD by RECIST v1.1 and are clinically stable, the Investigator will decide whether to continue a participant on study treatment until repeat imaging is obtained using iRECIST for participant management. Participant must be re-consented for continuation of treatment beyond initial documentation of disease progression (If repeat imaging does not confirm PD per iRECIST (iCPD), as assessed by the Investigator, and the participant continues to be clinically stable, study treatment may continue and follow the regular imaging schedule. If PD is confirmed (iCPD), participants will be discontinued from study treatment).

Treatment beyond confirmed progression as per iRECIST is possible if the participant is still benefiting from treatment after documented discussion and approval by the Sponsor.

When clinically stable, participants should **not** be discontinued until progression is confirmed by the Investigator, working with local radiology, according to the rules outlined in Section 10.8. This allowance to continue treatment despite initial radiologic PD takes into account the observation that some participants can have a transient tumor flare in the first few months after the start of immunotherapy, and then experience subsequent disease response. This data will be captured in the clinical database.

For treatment beyond progression as per iRECIST the following needs to be fulfilled:

- Evidence of clinical benefit as assessed by the investigator
- Absence of symptoms and signs indicating unequivocal progression of disease.
- Absence of clinical signs or symptoms of progression despite a rising CEA level.
- No decline in ECOG PS that can be attributed to disease progression
- Absence of tumor progression at critical anatomical sites (e.g., leptomeningeal disease) that cannot be managed by protocol−allowed medical interventions

Participant must be re-consented once for continuation of treatment beyond initial documentation of disease progression. Tumor imaging beyond progression will follow the originally planned intervals and will be conducted using iRECIST.

8.2 Safety Assessments

Investigators should refer to the Safety Information section of the current IB of regorafenib and nivolumab 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, performance status, and any abnormal findings observed during the performance of physical examinations.

Planned time points for all safety assessments are provided in the SoA (Table 1–2).

Therapeutic monitoring should be performed following dose modification of study drugs 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 FU 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 at screening, start of each cycle and EOT visit. Full physical examination includes, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal and neurological systems and of skin status. Height will be measured at screening only.

On all other visits, the investigator or qualified designee will perform a symptom directed physical exam as clinically indicated. 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.

BP and heart rate measurements should be preceded by at least 5 min of rest for the participant in a quiet setting without distractions (e.g., television, cell phones).

When vital signs measurements and ECG measurements are scheduled at the same time point, ECG must be obtained before vital signs.

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

8.2.3 Electrocardiograms

12-lead ECG will be locally obtained as outlined in the SoA (Table 1–2) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals.

8.2.4 Clinical Safety Laboratory Assessments

- See Section 10.2 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.
- 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 eCRF. 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 laboratory tests with values considered clinically significantly abnormal during participation in the study or within 30 d (active FU period for regorafenib) or within 100 d (active FU period for nivolumab) after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator.
    - 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 Section 10.2, must be conducted in accordance with the SoA.

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 eCRF.

8.2.5 ECOG Performance Status

Participant’s ability to manage activities of daily living will be appraised utilizing the performance status scale by ECOG. The participant’s ECOG PS will be estimated according to the schedule summarized in Section 1.3. An ECOG PS score of 0 or 1 is required for study inclusion (see Section 5.1). Change of ECOG PS will be measured for safety reasons.

Grading definitions for ECOG PS are given in Table 8–1 below.

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.

Abbreviation.: ECOG PS = Eastern cooperative oncology group performance status.

8.2.6 Pregnancy Tests

Serum pregnancy tests are performed at Screening and during treatment. Specific time points can be found in the SoA in Section 1.3. The frequency of pregnancy tests may be higher, if required by local regulations. More details can be found in Section 10.4.

8.2.7 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 limit 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 liver and/or lung metastasis, tumor mutational burden (TMB) and PD-L1 expression

(if available), presence of extended RAS and BRAF mutation (when known), MSI status, date of most recent progression, prior cancer therapies and procedures

- All medications (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by the participant within 30 d 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 s ymptoms should be recorded as AEs.

The intensity of AEs should be documented using the NCI-CTCAE, v5.0.

The study treatment action should be recorded separately for each study treatment 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 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 (see Section 7).

Investigators should refer to the Safety Information section of the current IB of regorafenib and the current IB of nivolumab 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 the end of active FU visit (30 d after last dose of regorafenib and 100 d after last dose of nivolumab at the time points specified in the SoA (Section 1.3).

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 hr, as indicated in Section 10.3. The Investigator will submit any updated SAE data to the Sponsor within 24 hr 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 in 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 AEs of special interest will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to FU (as defined in Section 7.2). Further information on FU procedures is provided in 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

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.
If a pregnancy is reported, the Investigator should inform the Sponsor within 24 hr of learning of the pregnancy and should follow the procedures outlined in Section 10.4.
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, participant 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.

8.4 Treatment of Overdose

Overdose of regorafenib

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

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

1. Closely monitor the participant for any AE/SAE and laboratory abnormalities until study intervention can no longer be detected systemically.
2. Obtain a plasma sample for PK analysis within 3 d from the date of detection of overdose if requested by the Sponsor (determined on a case-by-case basis).
3. Any overdose or incorrect administration of study drug should be noted on the Study Drug Administration eCRF.
4. AE associated with an overdose or incorrect administration of study drug 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 please 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 q.d. 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.

There is no specific antidote for regorafenib overdose. Subjects who have overdosed should be treated with symptomatic support. No additional data concerning management of overdose are available at this time.

Overdose of nivolumab

An overdose is defined as the accidental or intentional administration of any dose of nivolumab that is considered both excessive and medically important. All occurrences of overdose must be reported as an SAE. In the event of an overdose, the investigator should:

1. Closely monitor the participant for any AE/SAE and laboratory abnormalities until study intervention can no longer be detected systemically, at least 28 days.
2. 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).
3. Any overdose or incorrect administration of nivolumab should be noted on the Study Drug Administration eCRF.
4. AE associated with an overdose or incorrect administration of study drug should be recorded on the AE eCRF.

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

For detailed guidance on overdosing please refer to the most current version of the nivolumab IB.

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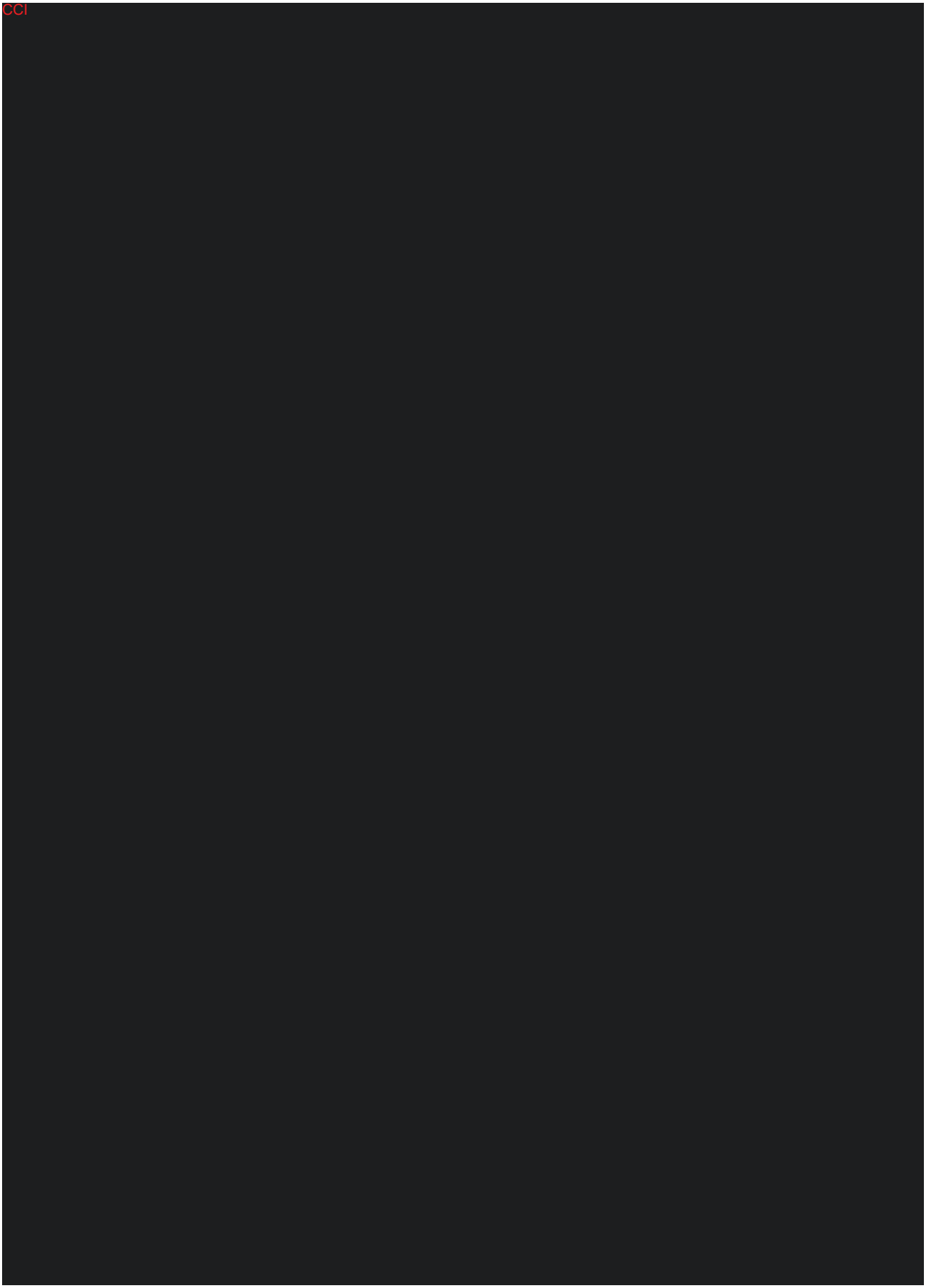
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Timing: See SoA (Table 1–2) and Schedule of Biomarker Blood Sampling (Table 1–3) for
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9. Statistical Considerations

This is a single arm, Phase II study with ORR as primary endpoint. Background response rate for the combination is estimated to be at most 5%. Target response rate for the combination treatment will be 17%.

A one-sided exact binomial test will be conducted to test the hypothesis.

9.1 Statistical Hypotheses

The underlying hypotheses to be tested in this study is

H0: $ORR_{Combination} \leq 5\%$ versus H1: $ORR_{Combination} > 5\%$

9.2 Sample Size Determination

As of amendment 2, it is decided to stop recruitment at 70 treated patients. With this sample size of 70 patients, when the true underlying ORR is 17% or higher, and a baseline response rate of 5% is assumed, a one-sided exact binomial test at a type-I error of at approximately 2.5% would result in a power of 92.6%, with at least 8 responders needed to achieve significance.

The location of the primary tumor is a factor and it is expected that 40%-45% of patients will have the primary tumor on the right side. With 31 patients with right-sided tumors, the probability of observing 4 or more responders (ORR 13%) is approximately 80% when the true underlying response rate is 17%, and the probability of observing 2 or fewer responders (ORR 6.5%) is approximately 80% when the true ORR is 5%.

With 39 patients with left-sided tumors, the probability of observing 6 or more responders (ORR 15%) is approximately 67% when the true underlying response rate is 17%, and the probability of observing 2 or fewer responders (ORR 5.1%) is approximately 70% when the true ORR is 5%.

For this calculation SAS PROC POWER was used.

9.3 Populations for Analyses

The following populations are defined:

Table 9–1: Populations for Analyses

Population	Description
Enrolled	All participants who sign the ICF
FAS	All participants who have received at least 1 dose of study intervention will be included in the efficacy and safety evaluation.
r-PKS	All patients who have received at least 1 dose of regorafenib and with at least 1 valid regorafenib concentration after dosing and no protocol deviations affecting the validity of the regorafenib PK will be included in the regorafenib PK analysis set.
n-PKS	All patients who have received at least 1 dose of nivolumab and with at least 1 valid nivolumab concentration after dosing and no protocol deviations affecting the validity of the nivolumab PK will be included in the nivolumab PK analysis set.
IMS	All patients who have received at least one dose of nivolumab and have at least one ADA sample taken (during the treatment or follow-up observation period) that is appropriate for ADA testing (with reportable result) will be included in the analysis set for the immunogenicity analysis of nivolumab, which is defined as the immunogenicity analysis set.

Abbreviations: ADA = anti-drug antibodies; FAS = full analyses set; ICF = informed consent form; PK = pharmacokinetics; r-PKS = regorafenib PK analysis set; n-PKS = nivolumab PK analysis set; IMS = immunogenicity analysis set

9.4 Statistical Analyses

Analysis 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).

The SAP will be developed and finalized before FPFV and will describe the participant populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary, secondary and tertiary/exploratory endpoints (see also Section 2.3).

9.4.1 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. The primary endpoint will be tested by an exact binomial test. No further confirmatory analysis is intended, and no further tests are conducted. Confidence intervals will be presented for selected variables.

9.4.2 Primary Endpoint(s)

ORR based on RECIST v1.1 is the primary endpoint of the study and the population used for the primary analysis will be the Full Analysis Set (FAS). Response is defined as a best overall response of CR or PR.

The primary efficacy variable will be analyzed after all participants met the criteria for primary completion and the data base is closed. 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. The result of the exact binomial test will be presented in a separate table.

Descriptive statistics for the primary endpoint will be displayed by side of primary tumor (right vs. left).

9.4.3 Secondary Endpoint(s)

Secondary efficacy endpoints include duration of response (DOR), disease control rate at 8 and 16 weeks, progression free survival (PFS), and overall survival (OS). DOR is defined for responders only as the time from first documentation of response (i.e. CR or PR) until disease progression or death (if death without documented disease progression). Disease control is defined as tumor response of stable disease (SD) or better. PFS is the time from first dose of study medication to disease progression or death, whichever is earlier. For patients who did not progress or die, PFS will be censored at the last evaluable tumor assessment. For patients that started subsequent therapy, PFS will be censored at the start of subsequent therapy. OS is defined as time from first dose to death. For patients who did not die, OS will be censored at the last time point at which the survival status is known to be alive.

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. Continuous endpoints will be analyzed using summary statistics tables including 95% two-sided confidence intervals.

For the analysis of PFS and OS, PFS and OS rates at specific time points such as 6, 12, and 18 months will also be provided based on the Kaplan-Meier method.

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[redacted]

9.4.5 Other Safety Analyse(s)

For all safety analyses, the FAS will be used as the FAS definition matches the one of the safety set. The incidence of TEAE (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 treatment discontinuation 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. Laboratory data considered as AE will be graded according to CTCAE v. 5.0, if applicable. The following summaries will be generated separately for hematology and biochemistry, overall and by cohort with the same dose:

- Frequency table for newly occurring on-treatment all CTCAE grades and CTCAE Grades 3 or 4
- Shift tables using CTCAE grades to compare baseline to the worst on-treatment value

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[redacted]

9.5 Interim Analyses

No formal interim analysis is planned in this study.

However, it is planned to look at the data after approximately 30-40participants have had at least the first response evaluation, in order to get better information for the planning of the intended Phase III study.

No formal conclusions for this study will be drawn from this look at the data and no formal adjustment of the type-I error will be performed.

9.6 Data Monitoring Committee (DMC) or other Review Board

No DMC is planned for this study.

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

Each Investigator (including principal and/or any sub Investigators) who is directly involved in the treatment or evaluation of research participants has to provide a financial disclosure

according to all applicable legal requirements. All relevant documentation will be filed in the trial master file.

10.1.3 Informed Consent Process

All relevant information on the study will be summarized in an integrated patient information sheet and informed consent form provided by the Sponsor or the study center.

Sample patient information and informed consent forms are provided as documents separate to this protocol.

Based on this patient information sheet, the Investigator or designee will explain all relevant aspects of the study to each participant prior to his/her entry into the study (i.e. before any examinations and procedures associated with the selection for the study are performed or any study-specific data is recorded on study-specific forms).

The Investigator will also mention that written approval of the IRB/IEC has been obtained.

Each participant will be informed about the following aspects of premature withdrawal:

Each participant has the right to withdraw from the study at any time without any disadvantage and without having to provide reasons for this decision.

The participant's consent covers end-of-study examinations as specified in the visit description described in the SoA (Table 1–3) to be conducted after withdrawal of consent.

The participant's data that have been collected until the time of withdrawal will be retained and statistically analyzed in accordance with the statistical analysis plan.

Participant-specific data on the basis of material obtained before withdrawal may be generated after withdrawal (e.g., image reading, analysis of biological specimen such as blood, urine or tissues); these data would also be retained and statistically analyzed in accordance with the statistical analysis plan. The participant has the right to object to the generation and processing of this post-withdrawal data. The participant's oral objection may be documented in the patient's source data.

Each participant will have ample time and opportunity to ask questions:

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 will be informed that their participation is voluntary. Participants or their legally authorized representative 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.

Only if the participant voluntarily agrees to sign the general informed consent form and has done so, may he/she enter the study. Additionally, the Investigator or his/her representative will personally sign and date the form. The participant will receive a copy of the signed and dated form.

The signed informed consent statements are to remain in the Investigator site file or, if locally required, in the patient's note/file of the medical institution.

In the event that informed consent is obtained on the date that baseline study procedures are performed, the study record or participant's clinical record must clearly show that informed consent was obtained prior to these procedures.

If the participant is not capable of providing a signature, a verbal statement of consent can also be given in the presence of an impartial witness (independent of the Sponsor and the Investigator). This is to be documented by a signature from the informing physician as well as by a signature from the witness.

The informed consent forms and any other written information provided to participants will be revised whenever important new information becomes available that may be relevant to the participant's consent, or there is an amendment to the protocol that necessitates a change to the content of the patient information and / or the written informed consent form. The Investigator will inform the participant of changes in a timely manner and will ask the participant to confirm his/her participation in the study by signing the revised informed consent form. A PI/ICF on study updates may be used for update information (e.g. if new safety information is available) for patients who are already participating in the study.

Any revised written informed consent form and written information must receive the IEC/IRB`s approval / favorable opinion in advance of use.

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.

Participants who are rescreened are required to sign a new ICF. For details with regard to rescreening please refer to Section 5.4.

PI/ICF for continuing study treatment following disease progression

Treatment beyond radiological progression is possible if the participant is still benefiting from treatment. In order to continue treatment after initial documentation of disease progression as per RECIST 1.1, participant must be re-consented once.

PI/ICF for collection of data on pregnancy and birth

A PI/ICF for collection of data on pregnancy and birth will be used for female participants who become pregnant or for those fertile male patients whose female partner becomes pregnant. The PI/ICF will be signed by the female patient or the male patient and their pregnant female partner.

10.1.4 Data Protection

All records identifying the patient will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available.

- 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

The Sponsor has made the information regarding the study protocol publicly available on the internet at www.clinicaltrials.gov. All data and results and all intellectual property rights in the data and results derived from the study will be the property of the Sponsor who may utilize them in various ways, such as for submission to government regulatory authorities or disclosure to other Investigators. Regarding public disclosure of study results, the Sponsor will fulfill its obligations according to all applicable laws and regulations. The Sponsor is interested in the publication of the results of every study it performs.

The Sponsor recognizes the right of the Investigator to publish the results upon completion of the study. However, the Investigator, whilst free to utilize study data derived from his/her center for scientific purposes, must obtain written consent of the Sponsor on the intended publication manuscript before its submission. To this end, the Investigator must send a draft of the publication manuscript to the Sponsor within a time period specified in the contract. The Sponsor will review the manuscript promptly and will discuss its content with the Investigator to reach a mutually agreeable final manuscript.

Result Summaries of Bayer's sponsored clinical trials in drug development phases II, III and IV and phase I trials in participants 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".

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 participants for medicines and indications approved in the US and EU on or after January 01, 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 eCRF 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 eCRF.

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

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.

- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- 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 noncompliance 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 eCRF 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.

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).

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.
- Definition of what constitutes source data can be found in the Monitoring Plan.
- The site must implement processes to ensure availability of all required source documentation. A source document checklist (not part of this protocol) will be used at the site to identify the source data for key data points collected and the monitor will work with the site to complete this.
- 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 eCRF 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.

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 principal Investigator of each center must sign the protocol signature page and must receive all required external approvals (e.g., health authority, ethics committee, Sponsor) before patient recruitment may start at the respective center. Likewise, all amendments to the protocol must be signed by the principal Investigator and must have received all required external approvals before coming into effect at the respective center.

Study Closure

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
- The study is terminated due to safety concerns or lack of proven efficacy;
- The participant can obtain medication used in this study as treatment from a government sponsored or private health program;
- The clinical development of the study treatment is stopped, no marketing authorization is pursued, and therapeutic alternatives are available in the local market.

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 subject and should assure appropriate subject therapy and/or FU.

10.1.10 Publication Policy

All data and results and all intellectual property rights in the data and results derived from the study will be the property of the Sponsor who may utilize them in various ways, such as for submission to government regulatory authorities or disclosure to other Investigators. Regarding public disclosure of study results, the Sponsor will fulfill its obligations according to all applicable laws and regulations. The Sponsor is interested in the publication of the results of every study it performs.

- 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.
- The Sponsor recognizes the right of the Investigator to publish the results upon completion of the study. 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

The laboratory analyses detailed in Table 1–2 and Table 1–3 will be performed by the local laboratory. These tests will not be performed centrally. Testing will generally be performed at a laboratory associated with each participating clinical site. In some cases, participants may have testing performed at a location other than the participating clinical site (e.g., at their local hospital), and in these cases the results are to be sent to the relevant participating clinical site.

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

Table 10–1: Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	• Platelet count • RBC count • Hemoglobin • Hematocrit		WBC count with differential: • Neutrophils • Lymphocytes • Monocytes • Eosinophils • Basophils	
Chemistry panel	• BUN • Creatinine/CG[b] • Lipase • LDH • Albumin	• Potassium • Sodium • Chloride • Amylase[c] • Phosphate	• AST/SGOT • ALT/SGPT • Total protein • Calcium (total calcium), calcium ionized or adjusted calcium • Uric acid • Magnesium	• Total and direct bilirubin • ALP • Glucose (fasting or non-fasting) • Triglycerides • GGT[c]
Routine Urinalysis[a]	• Specific gravity, pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick • Microscopic examination (if blood or protein is abnormal)			
Coagulation	• aPTT • PT/INR			
Thyroid	• FT3 • FT4 • TSH			
Other Screening Tests	Serum human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential) At screening if status is unknown or if a previous test is >3 months old • HIV antibody, Hepatitis B surface antigen, and Hepatitis C virus antibody			

Abbreviations: ALT = alanine aminotransferase; ALP = alkaline phosphatase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CG = Cockcroft-Gault (equation); FT3 = free triiodothyronine; FT4 = free thyroxine; hCG = human chorionic gonadotropin; LDH = lactic dehydrogenase; PT/INR = prothrombin time-international normalized ratio; PTT = partial thromboplastin time; RBC = red blood cell count; SGOT = serum glutamic-oxaloacetic transaminase; SGPT = serum glutamic-pyruvic transaminase; 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) Cockcroft Gault formula for GFR:

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

c) Will be assessed if clinically indicated.
d) Fasting or non-fasting glucose per local practice.

Investigators must document their review of each laboratory safety report.

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 patient 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.

Events Meeting 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" (i.e. disease progression) 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.

Events NOT Meeting the AE Definition
• 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 eCRF.
- It is **not** acceptable for the Investigator to send photocopies of the participant's medical records to Bayer in lieu of completion of the AE/SAE eCRF page.
- There may be instances when copies of medical records for certain cases are requested by Bayer. 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 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 version 5.0. and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

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 (regorafenib and nivolumab) 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.

Assessment of Causality
• The Investigator will use clinical judgment to determine the relationship. • 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 IBs and/or Product Informations, 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 both, regorafenib and nivolumab. • There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report to Bayer. 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 Bayer.** • The Investigator may change his/her opinion of causality in light of FU information and send a SAE FU report with the updated causality assessment. • The causality assessment is one of the criteria used when determining regulatory reporting requirements. • Immune-mediated adverse events (IMAEs) 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. IMAEs can include events with an alternate etiology which were exacerbated by the induction of autoimmunity. Information supporting the assessment will be collected on the participant's eCRF. • Every AE must be assessed by the investigator with regard to whether it is considered immune-mediated.

FU of AEs and SAEs
• The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Bayer 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 FU period, the Investigator should provide access to any post-mortem findings including histopathology • New or updated information will be recorded in the originally completed eCRF. • The Investigator will submit any updated SAE data to Bayer within 24 hr of receipt of the information.

10.3.4 Reporting of SAEs

SAE Reporting to Bayer via an Electronic Data Collection Tool
• The primary mechanism for reporting a SAE to Bayer will be the electronic data

SAE Reporting to Bayer via an Electronic Data Collection Tool
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 hr. • 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 off-line 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 off-line, then the site can report this information on a paper SAE form (see next section) or to the Medical Monitor by telephone. • Contacts for SAE reporting can be found in the Monitoring Plan.

SAE Reporting to Bayer via Paper eCRF
• Facsimile transmission of the SAE paper eCRF is the preferred method to transmit this information to the Medical Monitor. • 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 eCRF pages within the designated reporting time frames. • Contacts for SAE reporting can be found in the Monitoring Plan.

10.4 Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

Definitions:

Woman of Childbearing Potential (WOCBP)

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

If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

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

   For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., mullerian agenesis, androgen insensitivity), Investigator discretion should be applied to determining study entry.

   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 in a woman over age 45 years
     - 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, confirmation with more than one FSH measurement is required. In addition, females under the age of 55 years must have a serum follicle stimulating hormone, (FSH) level > 40 mIU/mL to confirm menopause
   - 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.

Contraception Guidance: Please refer to the inclusion criteria for details (Section 5.1).

The Investigator or a designated associate is requested to advise the participants how to achieve highly effective birth control. Highly effective (failure rate of less than 1% per year) contraception methods include:

- Combined (estrogen and progesterone containing: oral, intravaginal, transdermal) or progesterone-only (oral, injectable, implantable) hormonal contraception.
    - Hormonal contraception may be susceptible to interaction with the study treatment, which may reduce the efficacy of the contraceptive method. Hormonal contraception is permissible only when there is sufficient evidence that the investigational medicinal product (IMP) and other study medications will not alter hormonal exposures such that contraception would be ineffective or result in increased exposures that could be potentially hazardous. In this case, alternative methods of contraception should be utilized.
- Bilateral tubal occlusion or vasectomized partner (provided that partner is the sole sexual partner and has received medical assessment of the surgical success).
- Intrauterine devices and intrauterine hormone releasing systems are acceptable methods of contraception in the absence of definitive drug interaction studies when hormone exposures from intrauterine devices do not alter contraception effectiveness
- Sexual abstinence (reliability to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the participant
    - Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

Collection of Pregnancy Information

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 Bayer within 24 hr 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 FU 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.

Female Participants who become pregnant

- The Investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. The initial information will be recorded on the appropriate form and submitted to Bayer within 24 hr of learning of a participant's pregnancy.
- The participant will be followed to determine the outcome of the pregnancy. The Investigator will collect FU 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, FU 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 for medical reasons will be reported as an AE or SAE.
- A spontaneous abortion (occurring at <22 weeks gestational age) or still birth (occurring at >22 weeks gestational age) 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 intervention 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 discontinue study intervention.

CCI [redacted]

[redacted]

10.6 Appendix 6: FU Assessments

Active FU visits

All participants who withdraw from study treatment period for any reason (except death or lost to FU) will be followed for safety at mandatory active FU visits, which will be performed 30 d (+7 d) after the last administration of study treatment regorafenib/nivolumab and 100 d (+7 d) after the last dose of nivolumab.

If the treatment was permanently discontinued after the maximal allowed dose interruption/delay period, 28 d for regorafenib and 6 weeks for nivolumab, the 1st active FU visit should occur within 14 d of the permanent discontinuation. AE assessment and concomitant medication review must be updated at these active follow-up visits and all AEs starting within 30 d after the last dose of study treatment regorafenib (100 d after the last dose nivolumab) should be collected and recorded in the eCRF.

Additionally, for participants who discontinue study treatment without radiological disease progression, drug-related AEs will continue to be collected FU tumor evaluations (by CT or MRI with contrast unless contraindicated) will be performed until radiological progression, occurrence of secondary malignancy and/or start of first subsequent systemic anticancer treatment, whichever comes first, or any other criterion for withdrawal is met.

During the efficacy FU visits, CT/MRI evaluations will be performed at the same intervals as during study treatment (see Table 1–2). Note: all images still need to be prospectively collected and submitted in DICOM format in case independent central review is needed.

Long-term FU

All participants who withdraw from study treatment period with radiological PD, or from active FU for any reason will be followed for survival and first subsequent anti-cancer treatment, every 3 months (±14 d) during the long-term FU period, until either data

maturation for the final analysis is reached, or death of the patient, or any other criterion for withdrawal from long-term FU is met. The long-term FU contacts may occur at more frequent intervals at the discretion of the Sponsor. If a patient is lost to FU, the site will try to contact the patient, the patient's relatives, or another doctor treating the patient, unless prohibited by local requirements.

All participants in the long-term FU period will be contacted (telephone contact is sufficient) every month (±7 d) to determine survival status and obtain information on subsequent systemic anti-cancer treatment.

10.7 Appendix 7: Response Assessment for CRC - RECIST v1.1 Criteria

Efficacy response and progression for participants with CRC will be evaluated using RECIST v1.1 criteria (59). Contrast-enhanced multi-detector CT is the preferred method to measure lesions selected for response assessment. MRI (typically with gadolinium-based intravenous contrast) may be performed instead of CT (e.g., when local regulations or allergy to CT contrast media do not permit the use of CT as requested per protocol schedule, or when there is concern about radiation exposure from CT, or when MRI is deemed a more appropriate imaging method). At a minimum, anatomical regions that should be included in scans performed at baseline and during study intervention treatment include the chest, abdomen and pelvis, as well as any other areas of known disease and areas prone to metastatic disease for the particular tumor type under evaluation. CT scans of the chest, abdomen and pelvis should be contiguous throughout all the anatomic region of interest. Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. X-ray is not an accepted method for lesion assessment in this study. Recommended slice thickness for CT/MRI is ≤ 5mm. PET-CT scans may be used provided that measurements are obtained from the CT scan and the CT scan is of the same diagnostic quality as a diagnostic CT (with IV and oral contrast and diagnostic quality radiation dose). The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during study conduct. When lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective. Previously irradiated lesions should not be counted as target lesions unless there has been demonstrated progression in the lesion post radiotherapy before study enrollment and no other lesions are available for selection as target lesions. Lesions identified later during the study in a part of the body not scanned at baseline would be considered as a new lesion representing disease progression.

The tumor marker carcinoembryonic antigen (CEA) will be evaluated on an exploratory basis in participants with CRC and will not be used to assess objective tumor response.

RECIST

Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST v1.1 criteria (long axis diameter for non-nodal lesions; short axis diameter for lymph nodes). Rules described below for CT are also valid for MRI.

Measurable disease

Selection of target lesions should be based on lesion size (the largest lesions, with at least 10mm at longest diameter if non-nodal lesions, and 15mm at short axis if nodal lesions), organ representation of involved organs (up to a maximum of two per organ and five total) and suitability for repeated evaluations.

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.

Cystic lesions thought to be cystic metastases can be considered as measurable lesions if they meet the definition of measurability. However, if non-cystic lesions are present in the same participant, those lesions should be preferably selected for 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 <15 mm short axis) are considered non-measurable disease. In addition, leptomeningeal disease, ascites, pleural or pericardial effusion, lymphangitic involvement of skin or lung, inflammatory breast disease, lesions that meet radiographic criteria for simple cysts and blastic bone lesions are all non-measurable.

Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable (previously treated lesions can only be selected as target lesions when they have progressed post radiotherapy until baseline).

Target lesions

When more than one measurable lesion is present at baseline, all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) will be identified as target lesions and will be recorded and measured at baseline. Thus, in instances where participants have only one or two organ sites involved, a maximum of two and four lesions, respectively, will be recorded. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and should be representative of all involved organs and amenable to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which case the next largest lesion which can be measured reproducibly should be selected. 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 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 in 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.

Optimally, lesions selected as target lesions should not be biopsied. In this study, tumor biopsies for biomarker analysis are optional and biopsies for biomarker analysis should not be performed on target lesions.

Non-target lesions

All other lesions (or sites of disease) including pathological lymph nodes (with short axis ≥ 10 mm and < 15 mm) any measurable lesions over and above the 5 listed as target lesions are to be identified as non-target lesions and should also be recorded at baseline. Measurements are not required, and these lesions 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’).

Evaluation of response in target lesions

Best Response

The best overall response is the best response recorded from the start of the study intervention until the end of treatment. 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 according to the RECIST v1.1 criteria as outlined below and summarized in Table 10–3.

Complete Response (CR)

Disappearance of all target and non-target lesions. Any pathological lymph nodes (whether target or non-target) must have decreased in size to have a short axis of < 10 mm.

Partial Response (PR)

At least a 30% decrease in the sum of diameters of target lesions taking as reference the baseline sum diameters.

Stable Disease (SD)

Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Non-CR/Non-PD

To be used for participants with non-target lesions only at baseline**.** Persistence of one or more non-target lesion(s).

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 5 mm. Unequivocal progression of existing non-target lesions (see comments below), or the appearance of one or more new lesions, also constitutes progressive disease.

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 < 10 mm.

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 discontinuation of therapy. 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.

Table 10–2: Target and Non-Target Lesion Response

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Response requires
CR	CR	No	CR	Tumor response is to be documented approximately every 2 cycles (6 weeks) from C1D1. SD requires documentation at least once approximately 2 cycles (6 weeks) from C1D1.
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	
PD	Any	Yes or No	PD	
Any	PD	Yes or No	PD	
Any	Any	Yes	PD	

Abbreviations: C= cycle; CR = complete response; D = day; PD = progressive disease; PR = partial response; SD = stable disease.
Participants with a global deterioration of health current to the objective progression even after discontinuation of treatment without current 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 treatment

Table 10–3: Assessment of Best Response According to RECIST v1.1 Criteria for Participants with Non-Target Lesions Only

Non-target lesions	New lesions	Overall response
Complete response	No	Complete response
Non-complete response / Non-progressive disease	No	Non-complete response / non-progressive disease [a]
Not evaluated	No	Not evaluable
Unequivocal progressive disease	Yes or No	Progressive disease
Any	Yes	Progressive disease

a) Non-complete response / non-progressive disease" is preferred over “stable disease” for non-target lesions.

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 sum of diameters (nadir) 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 the start of the treatment 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).

10.8 Appendix 8: Response Assessment for CRC - iRECIST

iRECIST is RECIST v1.1 adapted as described below to account for the unique tumor response seen with immunotherapeutic drugs (Table 10–4). iRECIST will be used by site Investigator/local radiology review to make treatment decisions. This data will be collected in the clinical database

Description of the iRECIST Process for Assessment of Disease Progression

Assessment at Screening and Prior to RECIST v1.1 Progression

Until radiographic disease progression based on RECIST v1.1, there is no distinct iRECIST assessment.

Assessment and Decision at RECIST v1.1 Progression

For participants who show evidence of radiological PD by RECIST v1.1, the Investigator will decide whether to continue a participant on study treatment until repeat imaging is obtained using iRECIST for participant management (see Table 10–4 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 PS

No requirements for intensified management, including increased analgesia, radiation, or other palliative care

Any participant deemed **clinically unstable** should be discontinued from study treatment 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 treatment 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 v1.1, 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 v1.1 terminology.
- Unequivocal progression of non-target lesion(s) identified at baseline
- Development of new lesion(s)

iRECIST defines new response categories, including unconfirmed progressive disease by iRECIST (iUPD) and iCPD. For purposes of iRECIST assessment, the first visit showing progression according to RECIST v1.1 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 v1.1 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 v1.1. 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 v1.1

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 v1.1

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 v1.1)

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 treatment may continue and follow the regular imaging schedule. If PD is confirmed, participants will be discontinued from study treatment.

NOTE: If a participant has iCPD as defined above, but the participant is achieving a clinically meaningful benefit, an exception to continue study treatment may be considered following consultation with the Sponsor. In this case, if study treatment is continued, tumor imaging should continue to be performed following the intervals as outlined in this protocol (See SoA Table 1–2)

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.

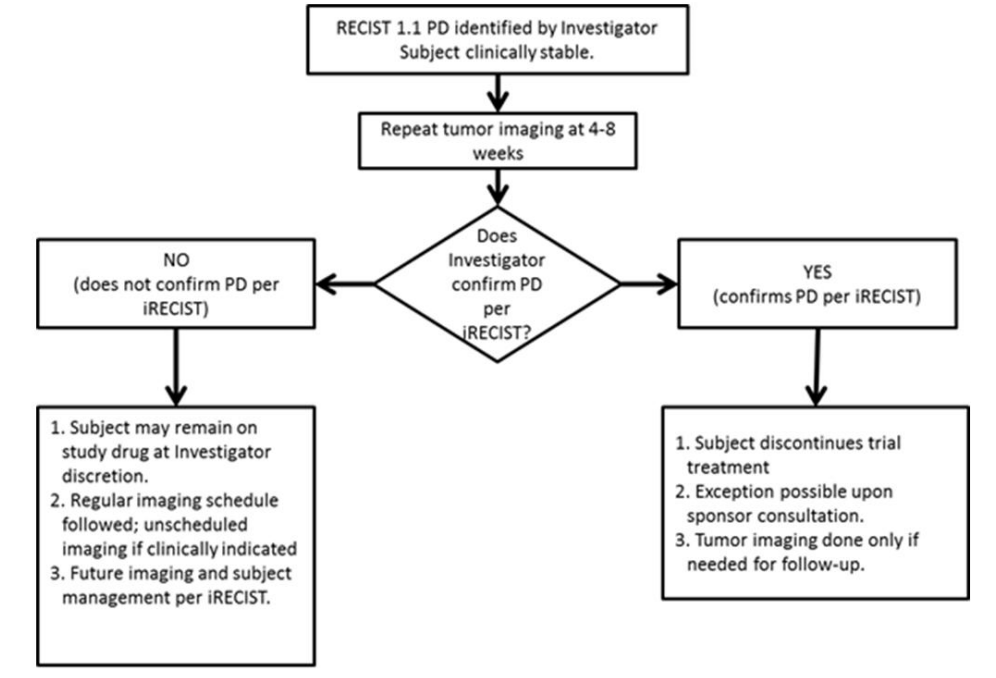
Additional details about iRECIST are provided in the iRECIST publication (60).

Table 10–4: Imaging and Treatment after First Radiologic Evidence of PD

	Clinically Stable		Clinically Unstable	
	Imaging	**Treatment**	**Imaging**	**Treatment**
1st radiologic evidence of PD by RECIST v1.1	Repeat imaging at 4 to 8 weeks at site to confirm PD	May continue study treatment 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 treatment
Repeat tumor imaging confirms PD (iCPD) by iRECIST at the local site	No additional imaging required	Discontinue treatment (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 treatment at the Investigator's discretion.	Repeat imaging at 4 to 8 weeks to confirm PD per Investigator's discretion only.	Discontinue treatment
Repeat tumor imaging shows iSD, iPR, or iCR by iRECIST per Investigator assessment.	Continue regularly scheduled imaging assessments	Continue study treatment at the local site Investigator's discretion	Continue regularly scheduled imaging assessments	May restart study treatment if condition has improved and/or clinically stable per Investigator's discretion. Next tumor image should occur according to the every 6 weeks (±7 d) imaging schedule for the 32 weeks (until Week 31 D1 ± 7 d) and 12 weeks (±14 d) thereafter

Abbreviations: D/d = day(s); iCPD = iRECIST confirmed progressive disease; iCR = iRECIST complete response; iRECIST = modified Response Evaluation Criteria in Solid Tumors v1.1 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 v1.1 = Response Evaluation Criteria in Solid Tumors v1.1

Figure 10–1: iRECIST: Process for Assessment of Disease Progression



Abbreviation: iRECIST = immune RECIST; PD = progressive disease

10.9 Appendix 9: New York Heart Association (NYHA) Classification

The stages of heart failure will be assessed according to the NHYA functional classification system. This system relates symptoms to everyday activities and the participant's quality of life.

Table 10–5: New York Heart Association (NYHA) Classification

Class	Participant symptoms
Class I (mild)	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea (shortness of breath).
Class II (mild)	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea.
Class III (moderate)	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea.
Class IV (severe)	Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.

10.10 Appendix 10: CYP3A4 Inhibitors and Inducers

CYP3A4 inducers and inhibitors

Table 10–6 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.

Table 10–6: An 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

A STRONG inhibitor is **NOT allowed during this clinical trial**.
CYP3A4 inducers are **NOT allowed during this clinical trial**.

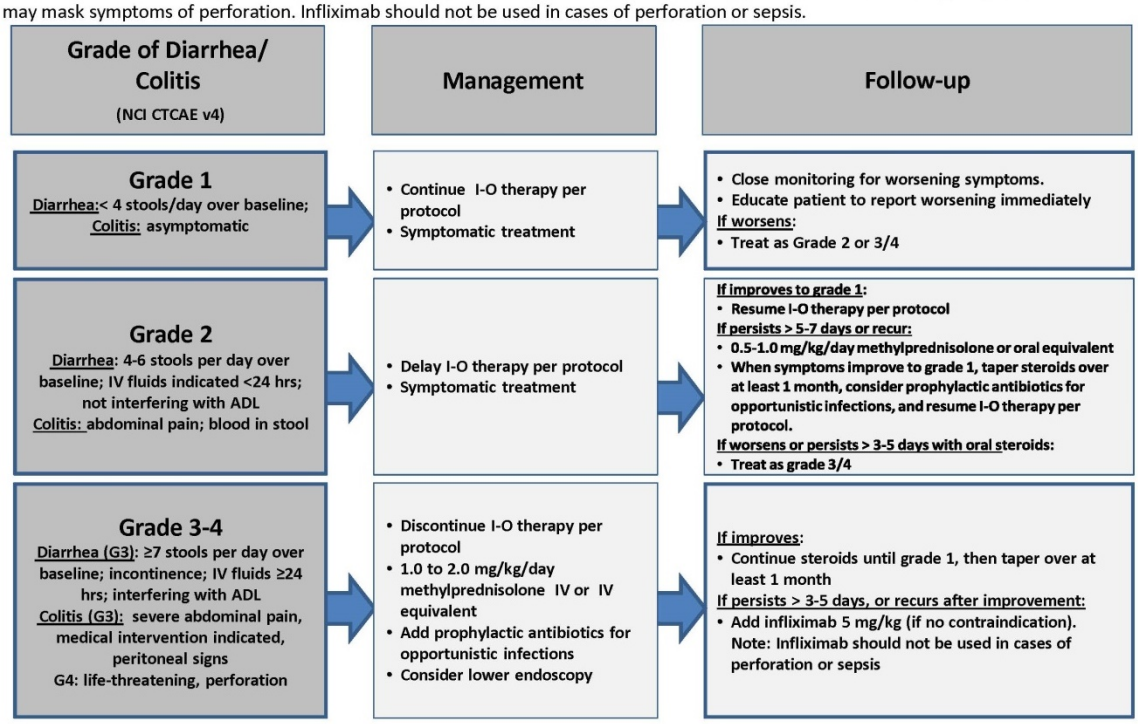
The CYP3A4 inducers and strong CYP3A4 inhibitors in Table 10–6 were identified using the Bayer-World Health Organization's Drug Dictionary (WHO-DD) and Bayer drug groupings for CYP3A4 inducers and CYP3A4 inhibitors.

10.11 Appendix 11: Guidance for Management of Immune-Related Adverse Events

The following AE management algorithms apply criteria from NCI-CTCAE v4

GI Adverse Event Management Algorithm

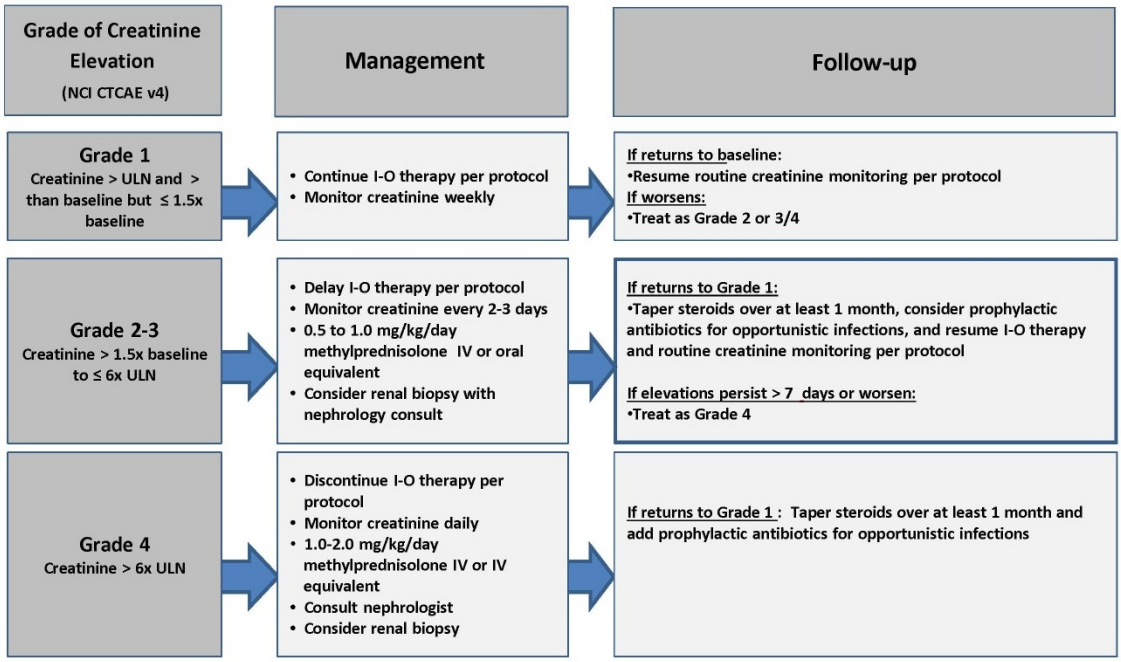
Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Renal Adverse Event Management Algorithm

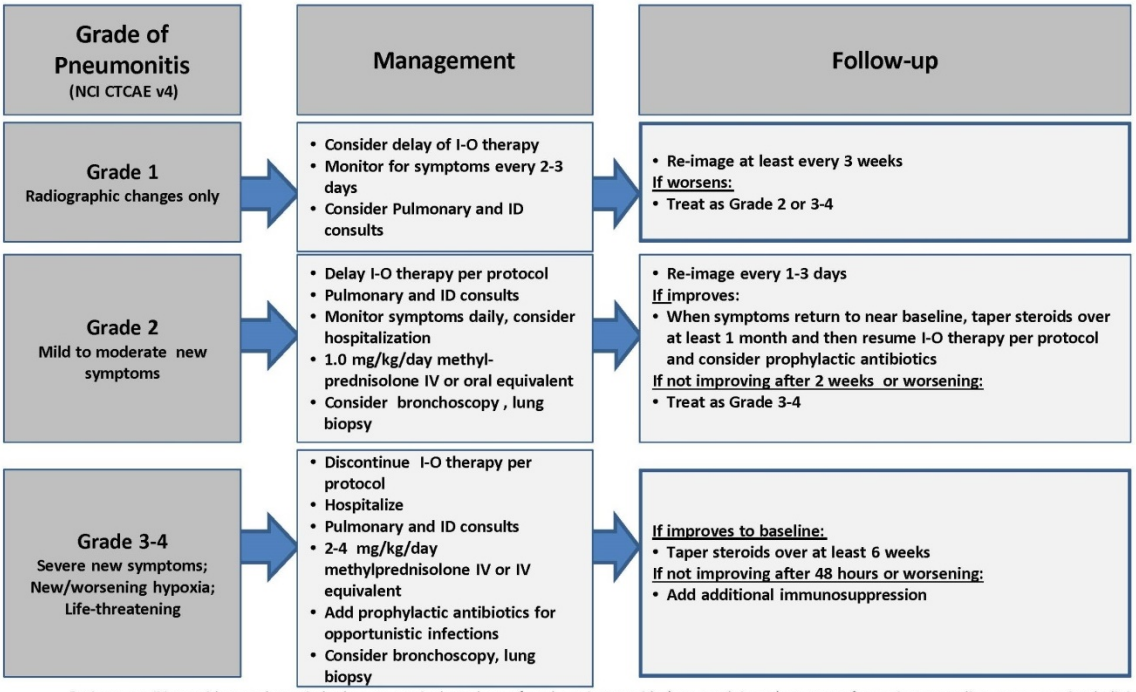
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Pulmonary Adverse Event Management Algorithm

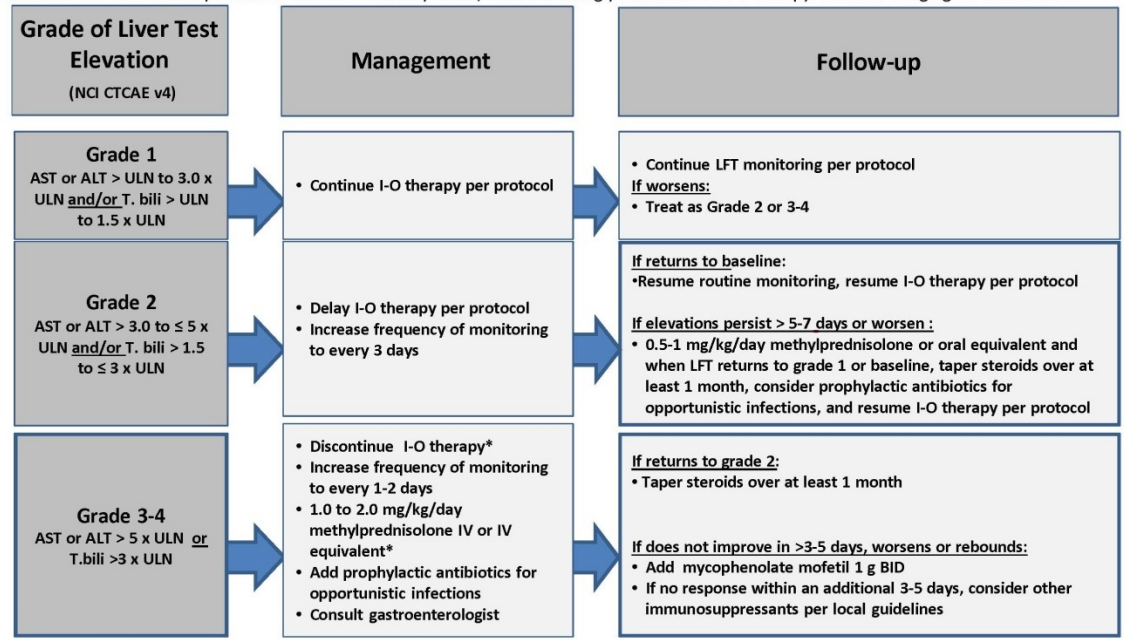
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Evaluate with imaging and pulmonary consultation.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids

Hepatic Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider imaging for obstruction.

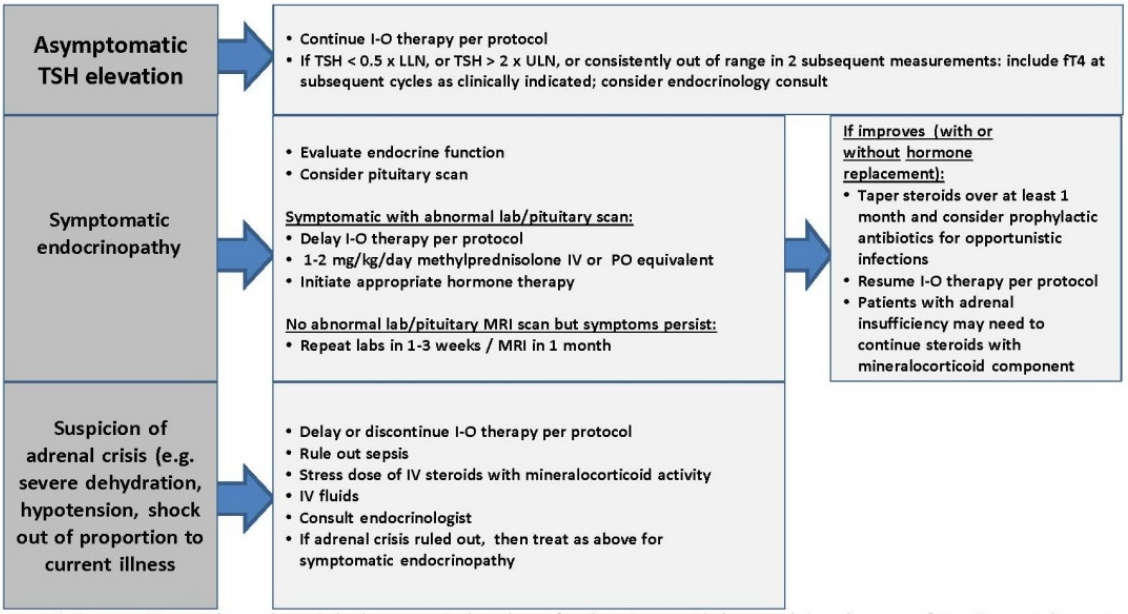


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

*The recommended starting dose for grade 4 hepatitis is 2 mg/kg/day methylprednisolone IV.

Endocrinopathy Adverse Event Management Algorithm

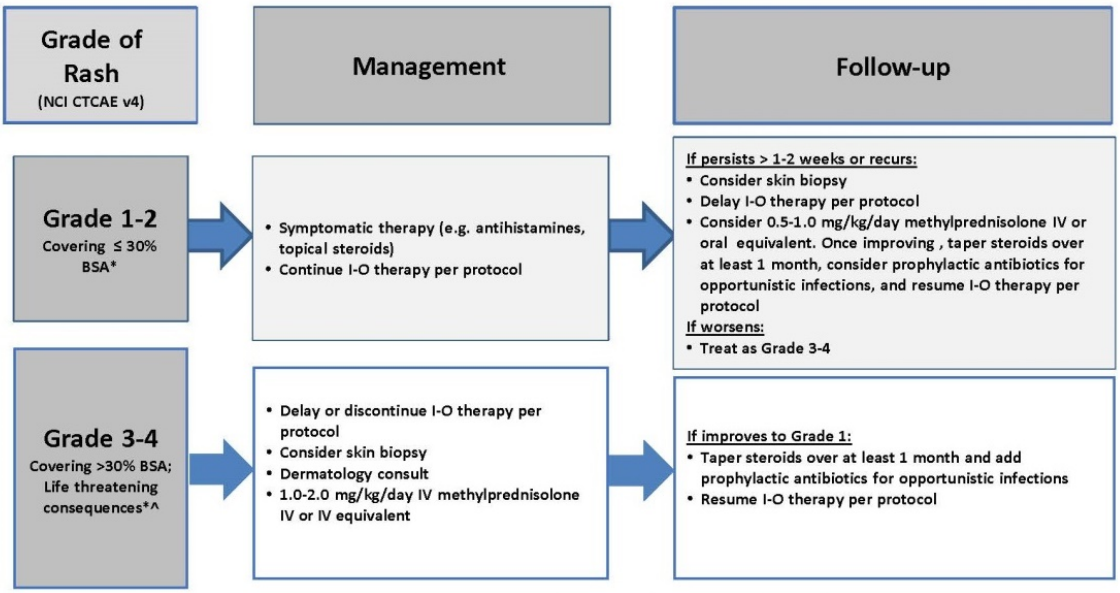
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider visual field testing, endocrinology consultation, and imaging.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Skin Adverse Event Management Algorithm

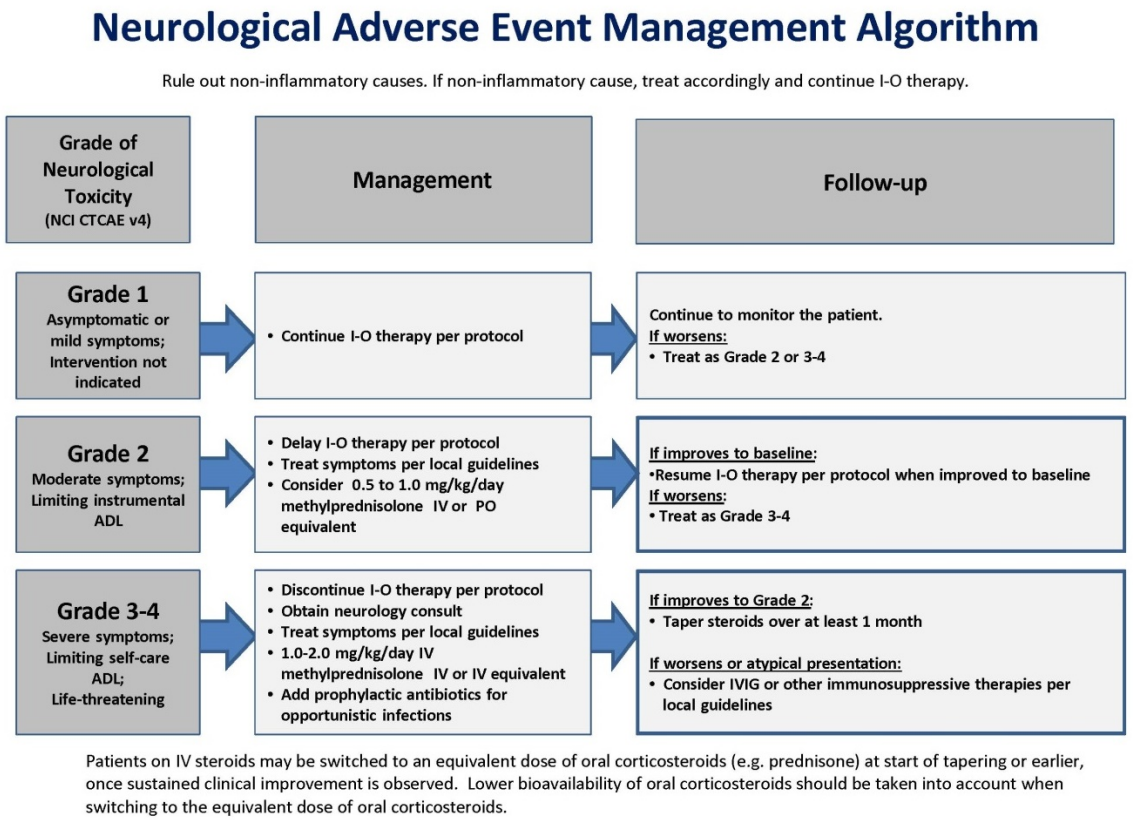
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

*Refer to NCI CTCAE v4 for term-specific grading criteria.

^If SJS/TEN is suspected, withhold I-O therapy and refer patient for specialized care for assessment and treatment. If SJS or TEN is diagnosed, permanently discontinue I-O therapy.



10.12 Appendix 12: Abbreviations

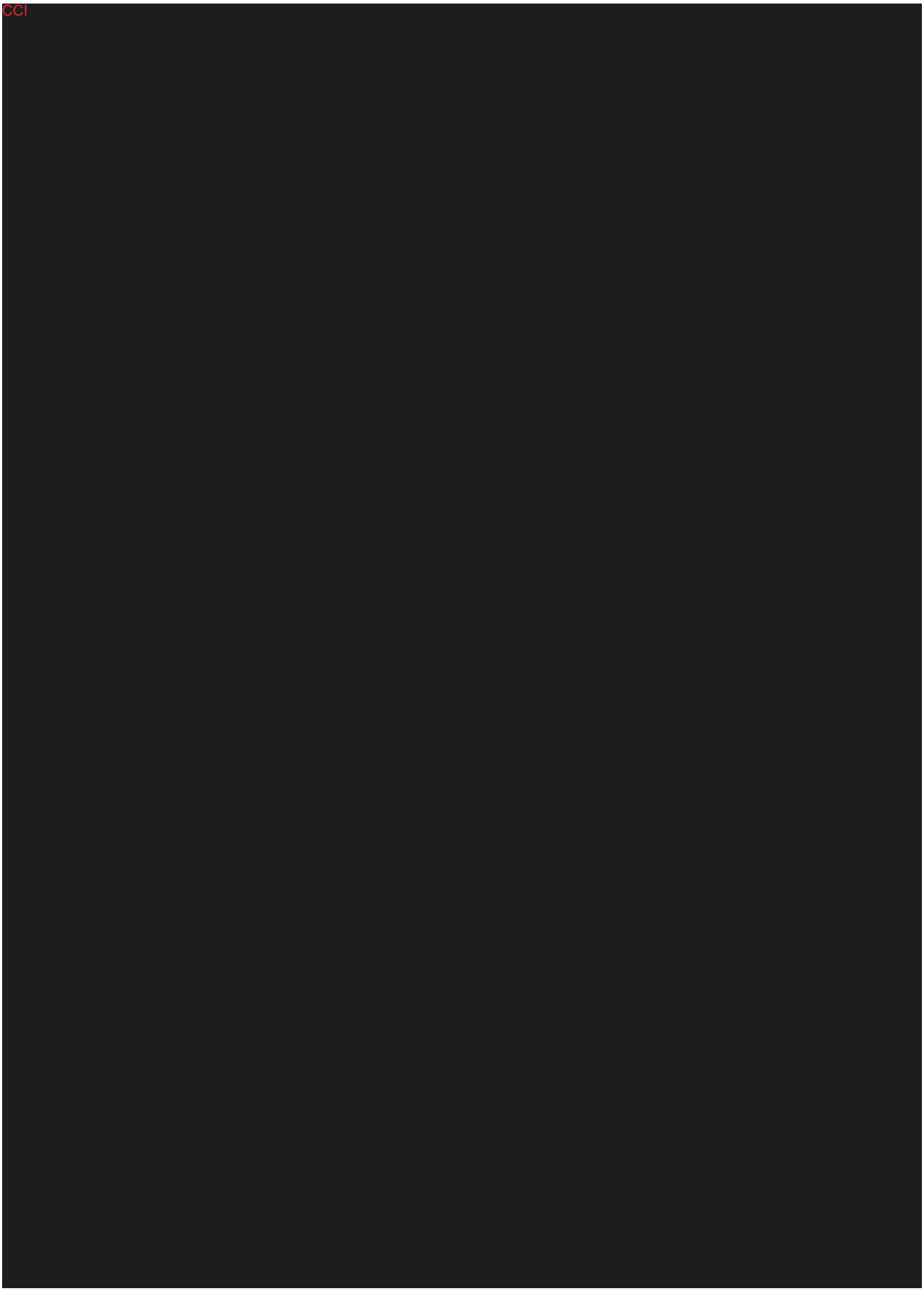
Table 10–7: Abbreviations

5-FU	5-fluorouracil
ADA	Anti-drug-antibodies
AE	Adverse event
AJCC	American Joint Committee on Cancer
ALT	Alanine aminotransferase
ALP	Alkanine phosphatase
Ang1	Angiopoietin 1
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration time curve
BCRP	Breast cancer resistance protein
BICR	Blinded independent central review
BP	Blood pressure
BRAF	Proto-oncogen BRAF
BUN	Blood urea nitrogen
BTLA	B- and T-lymphocyte attenuator
C	Cycle
CCL	cc-chemokine ligand
CD	Cluster of differentiation

CEA	Carcinoembryonic antigen
CI	Confidence interval
C_{max}	maximum observed drug concentration
CMS	Consensus molecular subtypes
CMV	Cytomegalovirus
CNS	Central nervous system
CR	Complete response
c-RAF	Proto-oncogen c-RAF
CRC	Colorectal cancer
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
CYP	Cytochrome P450 (derivates)
D / (d)	Day(s)
DCR	Disease control rate
DICOM	Digital imaging and communication in medicine
DLT	Dose limiting toxicity
DMC	Data monitoring committee
dMMR	Mismatch repair deficient
DOR	Duration of response
EC_{50}	Half maximal effective concentration
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EGFR	Epidermal growth factor receptor
EU	European Union
FAS	Full analyses set
FDA	Food and Drug Administration
FSH	Follicle stimulating hormone
FU	Follow-up
GC	Gastric cancer
GCP	Good clinical practice
GIST	Gastrointestinal stroma tumor
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HFSR	Hand foot skin reaction
HIV	Human immunodeficiency virus
HNSCC	Head and neck squamous-cell carcinoma
HR	Hazard ratio
HRT	Hormonal replacement therapy
IB	Investigators brochure
IC_{50}	Half maximal inhibitory concentration
ICF	Informed consent form
ICH	International Conference on Harmonization
ICOS	Inducible T-cell co-stimulator
iCPD	Confirmed radiographic progression by iRECIST
IEC	Independent Ethics Committees
IFN-γ	Interferon-gamma

IgG	Immunoglobulin
IL	Interleukin
IMAE	Immune-mediated adverse event
INR	International normalized ratio
IRB	Institutional Review Board
iRECIST	Response evaluation criteria in solid tumors for trials testing immunotherapeutics
iUPD	Unconfirmed progressive disease by iRECIST
i.v.	Intravenous
IxRS	Interactive voice/web response system
LPLV	Last patient last visit
M-2	N-oxide
M-5	N-oxide plus N-desmethyl
mCRC	Metastatic colorectal cancer
pMMR	Mismatch repair-proficient
MRI	Magnetic resonance imaging
MSI	Microsatellite instable
MSS	Microsatellite stable
NCI	National Cancer Institute
NSCLC	Non-small cell lung cancer
NYHA	New York Heart Association
ORR	Overall response rate
OS	Overall survival
PCR	Polymerase chain reaction
PD	Progressive disease
PD-1	Programmed cell death protein 1
PD-L1	Programmed cell death protein 1 ligand 1
PET	Positron-emission tomography
PFS	Progression free survival
PID	Participant identification number
PK	Pharmacokinetics
PPK	Population pharmacokinetics
PR	Partial response
PS	Performance status
q.d.	Quaque die (once daily)
RANKL	receptor activator of nuclear factor kappa-B ligand
RAS	rat sarcoma viral oncogene homolog
RCC	Renal cell cancer
RECIST	Response evaluation criteria in solid tumors
RET	Rearranged during transfection
r-PKS	Regorafenib PK analysis set
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Stable disease
TIL	Tumor infiltrating lymphocytes
TMB	Tumor mutational burden
UGT	UDP-glucuronosyltransferase (derivates)
ULN	Upper limit of normal
UPD	Unconfirmed progressive disease
US	United States

VEGFR	Vascular endothelial growth factor receptor
WOCBP	Woman of childbearing potential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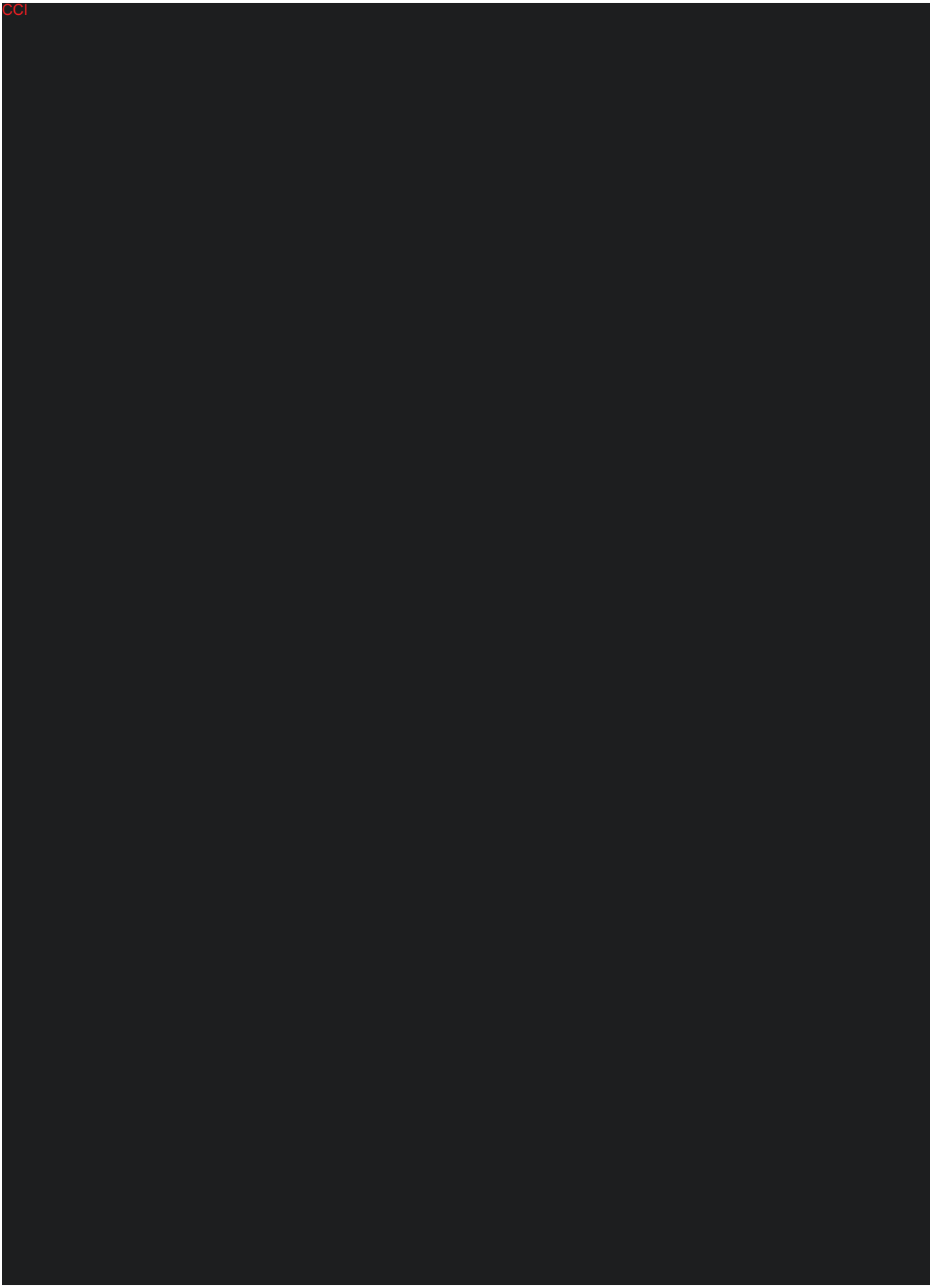
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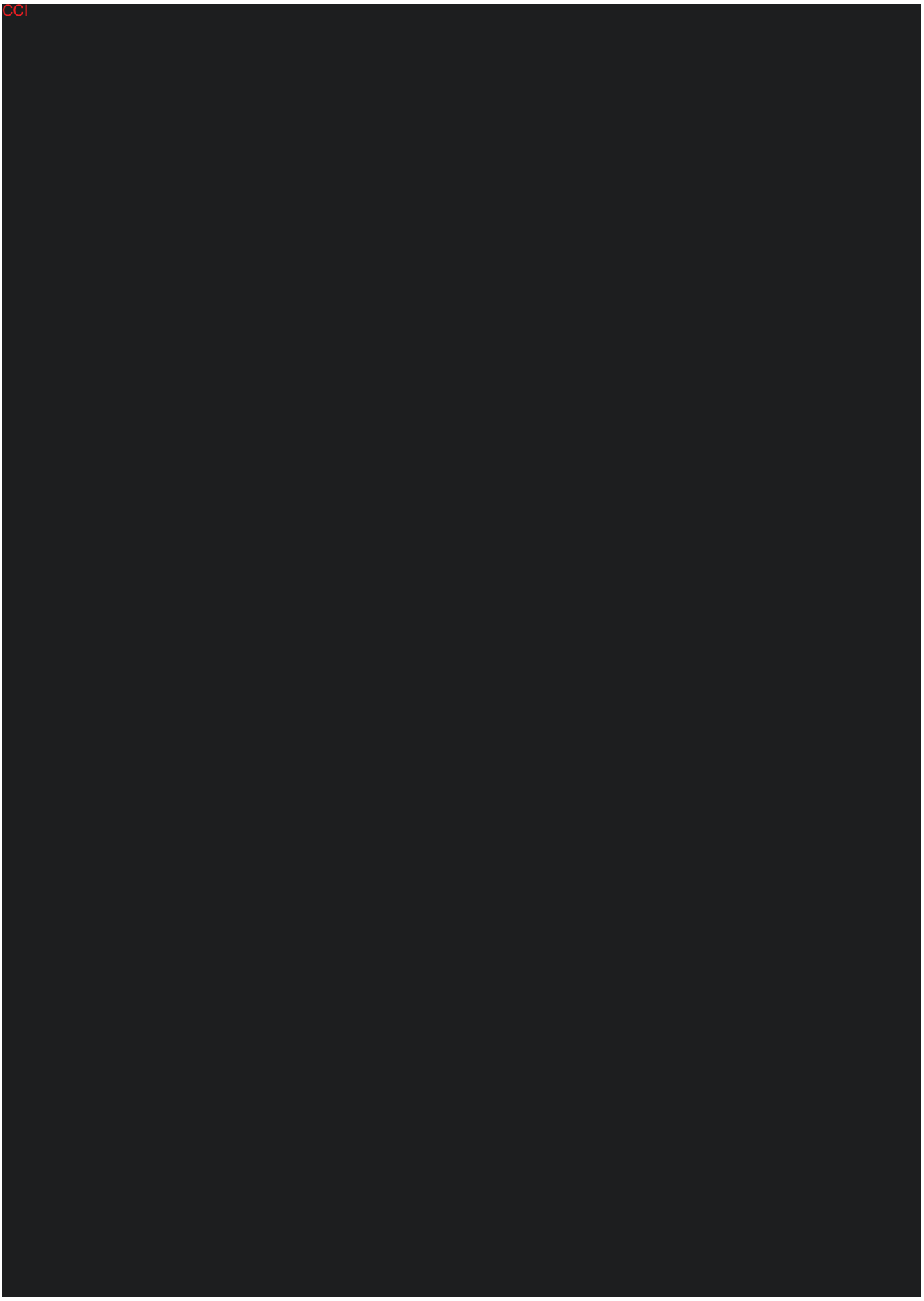
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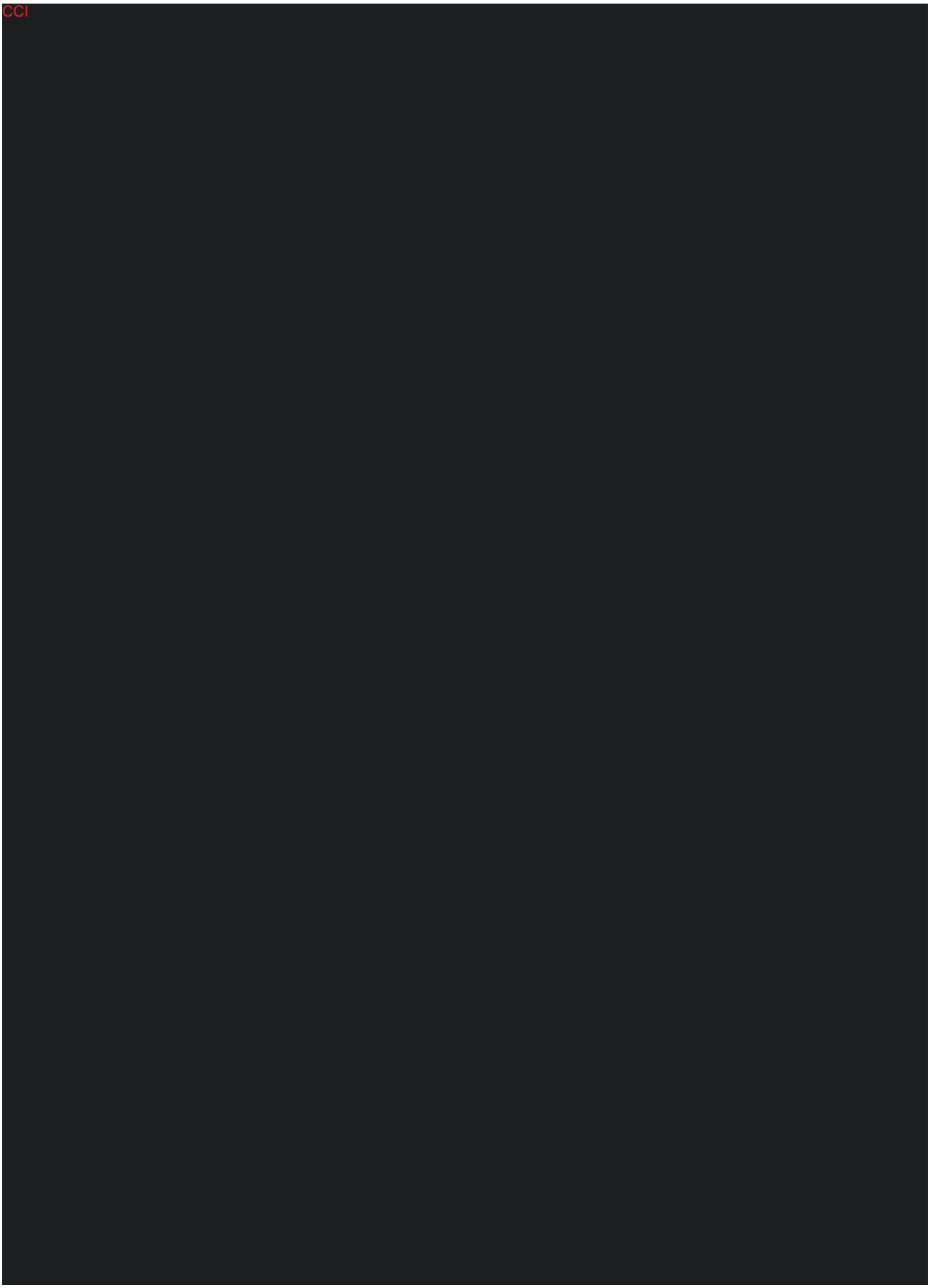
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12. Protocol Amendments

12.1 Amendment History

Current Version
Amendment 2: 18 NOV 2020
Previous Versions
Amendment 1: 08 JAN 2020
Original Protocol: 12 JUL 2019

12.2 Global Amendment 1

Amendment 1 is a global amendment forming integrated protocol Amendment 1, dated 08 JAN 2020.

Overall rationale for the amendment

The primary purpose of this amendment is to:

1) To further evaluate safety and efficacy of the regorafenib and nivolumab combination, sample size of the study will be increased from 53 to approximately 100 treated patients. The primary completion is defined by the event when the last enrolled participant was assessed for response rate as defined by RECIST v1.1 during at least 5 post-baseline scans i.e., has been followed for approximately 10 months from the first dose. With increased sample size of 100 patients, when the true underlying ORR is 17% or higher, there is >95% likelihood that the lower bound of the 95% CI will be above 5%. For this ORR analysis, the primary analysis will be based on blinded independent central review. In addition to ORR, duration of response will also be analyzed and reported descriptively.
2) To clarify inclusion criteria 5 regarding prior lines of treatment.
3) To modify exclusion criteria 5 to allow inclusion of patients with deep vein thrombosis and pulmonary emboli who have been adequately treated with anticoagulation.
4) To remove exclusion of participants with BRAF V600E mutation
5) To provide guidance regarding interrupting regorafenib treatment during on treatment biopsy.
6) To modify criteria for nivolumab discontinuation due to delay in dosing. Delay in nivolumab dosing that requires discontinuation has been changed to 10 weeks instead of 6 weeks to be consistent with other nivolumab studies using 480 mg dose Q4W.
7) To align wording for tolerance and escalation of regorafenib starting dose. Tolerance defined as: Absence of any grade rash/HFSR or other Grade 2 or higher clinically significant toxicity.

Changes to the protocol text

Changes to the protocol text are provided in a separate track-changes version.

High-level description of the changes and the affected sections are listed in the table below.

Table 12–1: Summary of Changes to the Protocol

Protocol Section	Amendment 1 Revisions
Throughout	Use **RECIST v1.1** and **iRECIST**
1.1 Synopsis **3. Objectives and Endpoints**	Modified footnote of **Tables 1.1** and **3-1 Objectives and Endpoints**: **ORR and DOR will be based on blinded independent central review (BICR) and local investigator assessment per RECIST 1.** ~~The primary efficacy endpoint (ORR) will be based on the local investigator's assessment on blinded local investigator's assessment. Central independent central review (BICR) may be implemented as needed for ORR assessment by RECIST 1.1~~.**DCR and PFS will be based on local investigator assessment.**
1.1 Synopsis **4.1 Overall Design** **5. Study Population** **9.2 Sample Size Determination**	Adjusted/modified wording to account for increased participant numbers (...approximately **143 instead of 80**; treated **100 instead of 53,** approximately **50-60** instead of **30-35** for left sided tumor) and to reflect statistical implications for right- and left sided tumors, ORR and true underlying response rate: Approximately **143** participants will be screened to achieve 100 treated participants. Approximately **50-60** participants with left sided primary At least **100** participants who qualify for the study will be treated As of amendment 1, additional 47 patients will be treated to achieve approximately **100** treated patients. With increased sample size of 100 patients The location of the primary tumor is a factor and it is expected that **50-60** patients will have the primary tumor on the left side
1.2 Schema, Figure 1-1 **4.1.1 Screening Phase, Figure 4-1, footnote a** **4.1.2 Treatment Phase** **4.3 Justification of Dose** **6 Study Intervention**	Alignment of wording for tolerance and escalation of regorafenib starting dose: **Absence of any grade rash/HFSR or other Grade 2 or higher clinically significant toxicity**
1.3 Schedule of Activities	Updated sampling timepoint for several screening assessments from 7 days prior to **28 days prior to first dose** to allow more time for planning biopsy Added footnote 'c': **If tested within 7 days prior to first dose no additional testing on D1 required except for pregnancy testing and abnormal liver function tests** Added to footnote 'b: **If disease progression and start of a new anti-cancer treatment happens before the 30/100 d safety visit, the safety visits should still be performed**.
3 Objectives and Endpoints, Table 3-1	Removed reference to iRECIST v.1.1 as **iRECIST** is used.
4.1 Study Design **5.1 Inclusion Criteria #5**	Modified details on prior lines of treatment: …treated with no more than two (for extended RAS mutant) ~~and~~ **or** three (for extended RAS wild type) lines of systemic chemotherapy
4.1.2 Treatment Phase	Deleted **"as determined by investigator"** and **central review is needed**: Primary endpoint of the study is ORR measured by RECIST v1.1 ~~as determined by investigator~~. … by a vendor for BICR. ~~central review is needed~~.
4.1.4 Long-Term Follow-Up	Added detail on consent withdrawal: Participants will be followed for overall survival …. or **consent withdrawal or** death or lost to FU
4.4 End of Study Definition	Modified definition of primary completion/clarification of appropriate terminology: **The primary completion is defined by the event when** ~~the last~~ **all** ~~enrolled~~ **participants have been** ~~was~~ **assessed for response rate (as defined by RECIST v1.1) during at least** ~~3~~ **5 post-baseline scans unless they have discontinued before due to progression or any other reason i.e. have been followed for approximately** ~~6~~ **10 months from 1st dose**
5.1 Inclusion Criteria #5	Added details on progression: Participant must have progressed

Protocol Section	Amendment 1 Revisions
	(radiologically or clinically) or **been** ~~was~~ intolerant to no more than two (for extended RAS mutant) ~~and~~ **or** three (for extended RAS wild type) lines of systemic chemotherapy … Added details on prior lines of treatment: **Reintroduction of previously administered chemotherapy containing oxaliplatin, irinotecan or 5-fluorouracil/capecitabine, without newly added biologics like EGFR inhibitor for RAS wild type patients and locoregional treatments such as hepatic arterial infusion therapy, or Yttrium-90 radioembolization should not be counted as separate lines of treatment.** **Added:** Adjuvant/neoadjuvant …considered as one line **of chemotherapy** ...
5.1 Inclusion Criteria #9	Modified wording on tumor tissue requirements: Exceptions for patients with **less than required** ~~no recent baseline~~ tumor tissue may be considered …
5.2 Exclusion Criteria #1	Added **dMMR** to reflect the IHC testing methodology and deleted **BRAF V600E mutation** to be consistent with Phase III protocol: Participants with **dMMR**/MSI-H colorectal cancer or ~~BRAF V600E mutation~~
5.2 Exclusion Criteria #5	Modified language to allow inclusion of patients with deep vein thrombosis and pulmonary emboli who have been adequately treated with anticoagulation: **Arterial thrombotic or embolic events such as cerebrovascular accident (including transient ischemic attacks) within 6 months before the start of study medication. Active pulmonary emboli or deep vein thrombosis that are significant or not adequately controlled on anticoagulation regimen**
CCI [redacted]	CCI [redacted]
6.6.1.1 Nivolumab Treatment – Permanent Discontinuation **7.1 Discontinuation of Study Intervention**	To modify criteria for Nivolumab discontinuation due to delay in dosing. Delay in nivolumab dosing that requires discontinuation has been changed from 6 weeks to **10 weeks**.
7.1 Discontinuation of Study Intervention	Harmonized wording throughout section 7.1: Start of **subsequent systemic anti-cancer treatment** ~~a new anti-cancer therapy~~.
8.1 Efficacy Assessment	Deleted: **"as determined by Radiologist/Investigator"** Specified wording on tumor assessment: **Primary endpoint for efficacy assessment is ORR based on BICR** ~~measured by~~ **per RECIST 1.1**. ~~as determined by Radiologist/Investigator~~. **Radiological tumor assessments will be done locally by the investigator, and in addition centrally by a blinded independent central imaging review. Scans will be prospectively collected and stored at vendor** ~~in case~~ **for** ~~independent central review is needed~~ **BICR**. ~~Treatment response for primary efficacy endpoint (ORR) will be based on BICR.~~**ORR and DOR will be assessed by BICR and local**

Protocol Section	Amendment 1 Revisions
	investigator per RECIST 1.1. DCR and PFS will be based on local investigator assessment. … scans … must be collected ... **for** ~~in case~~ **blinded** independent central review ~~is needed~~**. For patients with objective response (CR and PR), scans will be collected till start of subsequent systemic anti-cancer treatment.** Moved up subsection "**Assessment of disease**" for better understanding and added "**CR and PR must be confirmed with repeated imaging performed at least 4 weeks after initial documentation of response**." to description of RECIST v1.1
9.2. Sample Size Determination	Rewrote and adjusted section to account for changed patient numbers: **As of amendment 1, additional 47 patients will be treated to achieve approximately 100 treated** ~~response evaluable~~ **patients. With increased sample size of 100 patients, when the true underlying ORR is 17% or higher, there is >95% likelihood that the lower bound of the 95% CI will be above 5%.** **The sample size of 100 patients for a one-sided exact binomial test at a type-I error of at most 2.5% would result in a power of 96.4%, with at least 11 responders needed to achieve significance.** ~~The sample size in this study was determined by the need to have a sufficient number of patients with the primary tumor located on each side (right and left).~~ **The location of the primary tumor is a factor and it is expected that 50-60 patients will have the primary tumor on the left side.** ~~This sample size of 53 patients for a one-sided exact binomial test at a type-I error of at most 5% would result in a power of 90.6%. Approximately 30-35 participants with left-sided primary tumor will be treated. In order to allow appropriate balance of participants with right and left sided primary tumors, enrollment may be restricted to either left or right sided tumors during the study.~~ With **45** ~~18~~ patients with right-sided tumors, the probability of observing **5** ~~2~~ or more responders (ORR 11%) is approximately **90%** ~~83%~~ when the true underlying response rate is 17%, and the probability of observing **3** ~~1~~ or fewer responders (ORR **6.6%**) is approximately **81%** ~~77%~~ when the true ORR is 5%. With **55** ~~35~~ patients with left-sided tumors, the probability of observing **6** ~~4~~ or more responders (ORR 11%) is approximately **92%** ~~87%~~ when the true underlying response rate is 17%, and the probability of observing **3** ~~2~~ or fewer responders (ORR 6%) is approximately **70%** ~~75%~~ when the true ORR is 5%. ~~The critical number of responders to be achieved or surpassed to reject the null hypothesis of a 5% response rate for overall population is 6 patients.~~ For this calculation SAS PROC POWER was used.
9.4 Statistical Analysis	Correction; SAP will be finalized before ~~database lock~~ **FPFV** rather than at database lock as stated in the original version
9.4.1 General Considerations	Corrected error levels: All analyses will be conducted at one-sided type-I error level of **2.5%** ~~5%~~ or two-sided type-I error level of **5%** ~~10%~~ respectively
9.4.2 Primary Endpoints **9.4.3 Secondary Endpoints**	Corrected confidence intervals to **95%** from 50%. Added to 9.5.3: **For patients that started subsequent therapy, PFS will be censored at the start of subsequent therapy**.
9.5 Interim Analysis	Modified …after approximately ~~50% of the~~ **30-40** participants Correction; main data analysis may be conducted by study statistician and does not require an external statistician. Analyses do not require to be pre-specified in SAP. Deleted: ….~~due to the exploratory nature of this study…~~ ~~In order to avoid bias during the main analysis, the data look will be conducted by a statistician not involved in the study and the analyses to~~

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	~~be conducted will be pre-specified in an interim SAP.~~
10.1.3 Informed Consent Process	Deleted non-required details: ~~Only if the participant voluntarily agrees to sign the pharmacogenetics (PGx) research project informed consent form and has done so, optional study procedures can be performed (e.g., sample collection for optional biomarker testing).~~
10.2 Appendix 2: Clinical Laboratory Tests	Total Calcium assessment of chemistry panel changed to **Calcium (total calcium), calcium ionized or adjusted calcium**. Total bilirubin and indirect bilirubin changed to: **total and direct bilirubin.** Deleted assessments not required; ~~RBC Indices, MCV, MCH, %Reticulocytes~~

In addition to the substantive changes summarized in above table, several changes were made to update administrative details, correct typographical errors, and add clarity; such changes are not itemized in the table.