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Title Page

Protocol Title:	A Multi-indication, Single-treatment Arm, Open-label Phase 2 Study of Regorafenib and Nivolumab in Combination in Patients with Recurrent or Metastatic Solid Tumors
Protocol Number:	21136 Global Amendment 1
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Short Title:	Multi-indication study of regorafenib plus nivolumab for recurrent or metastatic solid tumors
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Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Amendment 1	27 JAN 2021
Original Protocol	09 SEP 2020

Amendment 1 (27 JAN 2021)

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

Overall Rationale for the Amendment:

The protocol amendment 01 was triggered by an amendment to nivolumab IB version 19, that includes updates to the management guidance for immune-mediated adverse events related to nivolumab and to male contraception guidance.

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities	Table 1-2 Schedule of activities Updated mention of footnotes on tumor assessment (CT/MRI) visits Footnote e – updated to point out which AEs are collected Table 1-3 Schedule of Biomarker Blood Sampling Updated footnote	Schedule of Activities updated to more clearly define the timing of the CT/MRIs and the collection of AEs during follow-up. Footnote removed as it does not apply to study population.
4.1.3 Active FU	Added sentence on AE documentation after start of new anti-cancer treatment	Wording was updated so only related AEs are collected during the follow-up period once new anti-cancer treatment is started.
4.4 End of Study Definition	Additional wording on trial stop added.	To clarify options in case the trial is stopped.
5.1 Inclusion Criteria Cohort 1 (HNSCC, IO naïve)	Inclusion criteria number 102 edited.	Additional inclusion criteria for stage 2 participants to clarify previous therapies allowed.
5.1 Inclusion Criteria Cohort 3 (ESCC)	Inclusion criteria number 302 edited.	Additional inclusion criteria for stage 2 participants to clarify previous therapies allowed.

Section # and Name	Description of Change	Brief Rationale
5.1 Inclusion Criteria For all cohorts	Inclusion criteria 9: Updated guidance on contraception after study intervention regarding nivolumab	Updated guidance regarding male contraception based on updated nivolumab IB.
5.2 Exclusion Criteria For all cohorts	Exclusion criteria 1: Updated definition Exclusion criteria 12: Definition of poorly controlled hypertension updated to 'above **140**/90 mmHg'	To clearly specify that participants that have known NTRK **fusions** are excluded. Updated according to most recent guidelines and recommendations.
6 Study Intervention	Definition of light meal added	Additional text inserted to further define light meal.
6.5.3 Prohibited Prior and Concomitant Therapies	Strong UGT1A9 inhibitors included as prohibited therapy.	Updated to remain consistent with current regorafenib label.
6.6.1 Toxicity Management	Table 6-3 Dose Modification/ Dose Interruption Guide for Regorafenib-Related Toxicities Table 6-5 Regorafenib Dose Modification Guidance: Non-Immune Toxicities: Hypertension	Tables updated as per HA request.
6.6.2 Toxicity Management 6.6.2.1	Note referring to CTCAE v5 deleted.	Nivolumab toxicity management guidelines were updated to reflect incorporation of CTCAE v5 as well as changes consistent with updated nivolumab immune-mediated AE management algorithms. Guidance in section 10.9 was updated accordingly.
	Table 6-7 updated Reference to Nivolumab management algorithm added	Recommended dose modification for nivolumab was updated according to the newest management algorithms for studies, under CTCAE v5. Section edited to be consistent with newest Nivolumab management algorithm.

Section # and Name	Description of Change	Brief Rationale
6.6.2.2 Management of Immune-Mediated AEs	Definition of immune-mediated AE added	Make description clearer and more precise for the reader.
7.1 Discontinuation of Study Intervention	Section Withdrawal from active FU edited.	Wording updated to further clarify when patients must be withdrawn from active FU.
8 Study Assessments and Procedures	Sentence added on trial-continuity issues.	To specify possible measures in the event of a significant trial-continuity issue (e.g. caused by a pandemic).
8.1 Efficacy Assessments	Use of oral contrasts	Specification that oral contrast agents are required unless inconsistent with local regulations.
10.1.1 Regulatory and Ethical Considerations	Section edited regarding amendments.	Section updated to clarify that substantial amendments to the protocol require regulatory authority approval before implementation.
10.2 Appendix 2	Wording updated Updated Table 10-1 Protocol-Required Safety Laboratory Assessments	Wording updated to clarify which assessments are performed in the local laboratory. Table footnote updated: Amylase and lipase will be part of safety blood test conducted in each treatment cycle. GGT will be assessed if clinically indicated.
10.6 Appendix 6 10.6.3 RANO	Definitions added and table updated.	Section was updated to improve readability and clarify on RANO criteria definitions.
10.9 Appendix 9	Update of AE management algorithms	AE management algorithms were all updated and apply criteria from NCI-CTCAE v5. Tables were exchanged accordingly.

Section # and Name	Description of Change	Brief Rationale
Throughout	Minor editorial and clerical errors and document formatting revisions	Minor, therefore have not been summarized

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

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1. Protocol Summary

1.1 Synopsis

Protocol Title:
A Multi-indication, Single-treatment Arm, Open-label Phase 2 Study of Regorafenib in Combination with Nivolumab in Patients with Recurrent or Metastatic Solid Tumors

Short Title:
Multi-indication study of regorafenib plus nivolumab for recurrent or metastatic solid tumors

Rationale:

Immune checkpoint inhibitors (ICI) have been shown to be effective anticancer therapy and are approved as standard treatment in several tumor types. However, approximately 60-70% of tumors do not respond to single agent ICI therapy and among the tumors that respond, resistance to therapy can develop over time. A high unmet need remains to improve clinical outcomes for cancer patients. One such strategy to improve outcomes is combining ICI with a multi-kinase inhibitor (MKI) targeting vascular endothelial growth factor (VEGF) which are predicted to have complementary anti-tumor effects and potential enhancement of tumor-directed immune response. In preclinical and clinical studies, the combination of an ICI and anti-VEGF MKI has demonstrated promising results showing enhanced tumor response in different cancers and improvement of clinical measures (Khan and Kerbel 2018).

To explore the potential to enhance anti-tumor response through combining of an ICI with an anti-VEGF MKI, this open-label, multi-center Phase 2 study of regorafenib and nivolumab aims to evaluate the safety and efficacy of the combination in multiple cohorts of participants with selected advanced solid tumors.
The combination of regorafenib with nivolumab is predicted to enhance tumor-directed immune response by relieving immunosuppression through the reduction of tumor associated macrophages (TAMs), regulatory T cells (T_{reg}), and expression of programmed cell death protein 1 ligand 1 (PD-L1) and indoleamine 2, 3-dioxygenase 1 (IDO-1), along with inhibition of VEGF signaling. In addition, tumor immunity may be enhanced by the increased infiltration of cytotoxic T cells mediated by increased expression of the chemoattractant C-X-C motif chemokine ligand 10 (CXCL10), the ligand for CXC-motif-chemokine receptor 3 (CXCR3), which occurs on T cells (data on file).
Therefore, novel therapies using regorafenib with programmed cell death protein 1 (PD-1) antibody, such as nivolumab, present a unique opportunity to address a high unmet need and improve clinical outcomes in multiple advanced solid tumor indications.

Objectives and Endpoints

Table 1–1 Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate efficacy of the regorafenib and nivolumab combination by cohort	• ORR per RECIST 1.1[a] by local assessment for all solid tumors except GBM/AA • ORR per RANO[a] by local assessment for GBM/AA
Secondary	
• Evaluation of the additional efficacy measures of the regorafenib and nivolumab combination	• DOR[a] • DCR[a] • PFS[a,] • 6 months PFS[a] • OS • 1yr OS
• To evaluate safety of the combination by cohort and overall	• Frequency and severity of AEs per CTCAE v 5.0
Tertiary/Exploratory	
• To characterize the PK and immunogenicity of the regorafenib and nivolumab combination	• Exposure of regorafenib and nivolumab and detection of anti-drug antibodies (ADA) (immunogenicity)
• To evaluate the relationship between regorafenib exposure and relevant biomarkers for efficacy and/or safety	• Retrospective analysis of the relationship between regorafenib exposure and biomarker, safety and/or efficacy measures
• To assess efficacy of regorafenib and nivolumab combination using immune related response criteria in solid tumors	• ORR per iRECIST or per iRANO for GBM/AA[a]
• To identify biomarkers in baseline tumor materials, blood and/or stool samples that may associate with response	• Correlation of biomarkers in tumor, blood or stool samples before treatment with other study endpoints
• To explore pharmacodynamic effects of regorafenib and nivolumab combination on e.g. immune environment, signaling pathway activity, and downstream processes	• Change from baseline in levels of biomarkers in tumor, blood or stool samples
• To further investigate the study intervention and similar drugs (i.e., mode-of-action-related effects and / or safety) and to further investigate patho-mechanisms deemed relevant to cancer and associated health problems	• Various biomarkers (e.g., diagnostic, safety, pharmacodynamic, monitoring, or potentially predictive biomarkers)

Abbreviations: AA = Anaplastic astrocytoma; ADA = Anti-drug antibody; AE = Adverse event; CTCAE = Common terminology criteria for adverse events; DCR=Disease Control Rate; DOR = Duration of response; GBM = Gliobastoma multiforme; iRANO = Immune response assessment in neuro-oncology; iRECIST = Response evaluation criteria in solid tumors for trials testing immunotherapeutics; ORR = Objective response rate; OS = Overall survival; PFS = Progression free survival; PK = Pharmacokinetics; RANO = Response assessment in neuro-oncology; RECIST 1.1 = Response evaluation criteria in solid tumors 1.1

a) The efficacy endpoints will be based on the local Investigator's assessment. Imaging data on tumor assessment will be collected for a potential central review of tumor evaluation by blinded readers.

Overall Design:

Disclosure Statement: This is a multi-indication, single-treatment arm, open-label Phase 2 study of regorafenib in combination with nivolumab in participants with recurrent or metastatic solid tumors

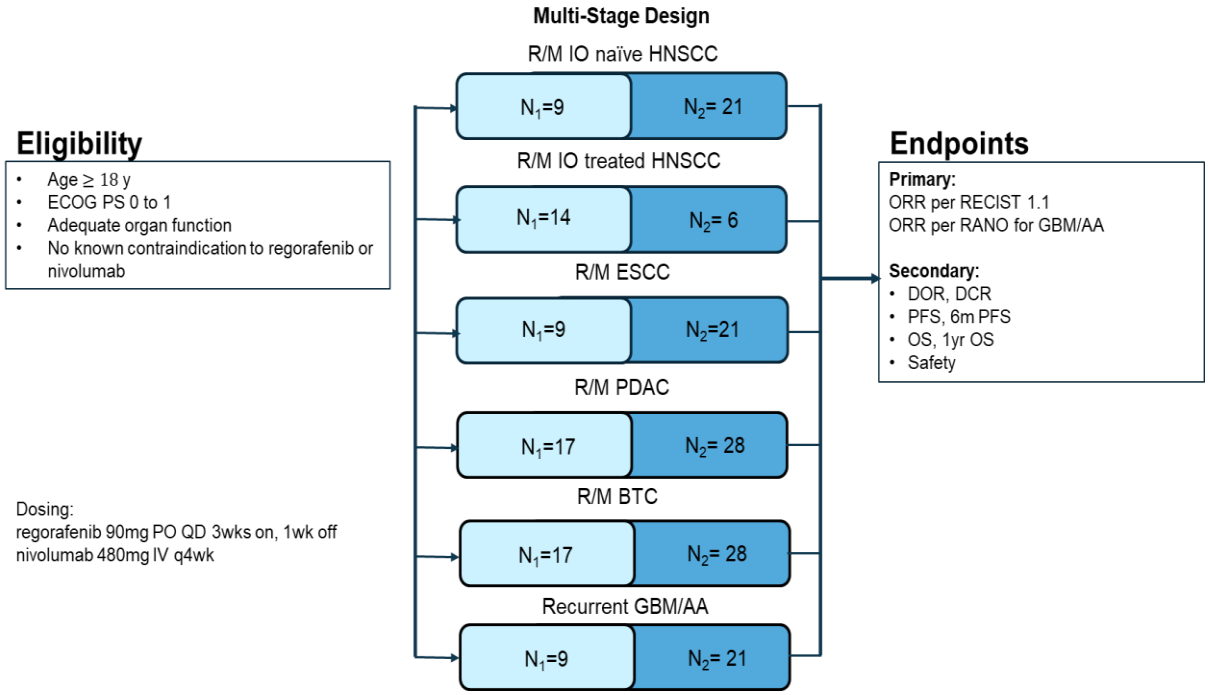
Number of Participants:

Approximately 286 participants will be screened to achieve up to approximately 200 treated participants. For cohort-specific details on treated participants see Figure 1-1.

Data Monitoring Committee: Not applicable.

1.2 Schema

Figure 1–1 Study Schema



Abbreviations: AA = Anaplastic Astrocytoma; BTC = Biliary Tract Carcinoma; ChT = Chemotherapy; DCR = Disease control rate; DOR = Duration of response; ECOG PS = Eastern Cooperative Oncology Group Performance Status; ESCC = Esophageal Squamous Cell Carcinoma; GBM = Glioblastoma Multiforme; HNSCC = Head and Neck Squamous Cell Carcinoma; IO = Immune oncology; IV = Intravenous; ORR= Overall Response Rate; OS = Overall survival; PDAC= Pancreatic ductal adenocarcinoma; PFS = Progression free survival; PK = Pharmacokinetics; PO = Per oral; q4wk = Every 4 weeks; QD = Once daily; RECIST 1.1 = Response Evaluation Criteria In Solid Tumors 1.1; RANO = Response assessment in neuro-oncology; R/M = Recurrent/Metastatic

1.3 Schedule of Activities (SoA)

Table 1–2 Schedule of Activities

Procedure	**Screening**		**Treatment period**								**EoT visit**	**Active FU[a]**			**Long-term FU**	**Comments**
			Cycle1				Cycle 2			Cycle ≥3						
	within **28 d** prior to first dose	within **7 d** prior to first dose	D 1	D 8	D15	D22	D1	D8	D15	D1	within 14 d after permanent study treatment discontinuation	**Safety FU visit** 30 d after permanent study treatment discontinuation	**Safety FU visit** 100 d after LD for nivolumab[a]	**Efficacy FU visit** (between EoT and confirmed radiological PD)	every 3 months **(phone call)**	
acceptable deviation (days)				± 2 d			± 2 d			± 3 d		+ 7 d	+ 14 d	± 14 d	± 14 d	
Informed consent	X															
Contact IxRS[b]	X		X				X			X	X					
General																
Inclusion and exclusion criteria	X	X	X													Section 5
Cancer classification[c]	X															
Tumor molecular and cellular data collection MSI status, TMB and PD-L1 if available	X															Section 8.2.7
GBM/AA: IDH mutation and MGMT methylation status by historical test or local test in tumor tissue if available	X															Section 8.8.2

Procedure	Screening		Treatment period								EoT visit	Active FU[a]			Long-term FU	Comments
			Cycle1				Cycle 2			Cycle ≥3						
	within **28 d** prior to first dose	within **7 d** prior to first dose	D 1	D 8	D15	D22	D1	D8	D15	D1	within 14 d after permanent study treatment discontinuation	**Safety FU visit** 30 d after permanent study treatment discontinuation	**Safety FU visit** 100 d after LD for nivolumab[a]	**Efficacy FU visit** (between EoT and confirmed radiological PD)	every 3 months **(phone call)**	
acceptable deviation (days)				± 2 d			± 2 d			± 3 d		+ 7 d	+ 14 d	± 14 d	± 14 d	
HNSCC (oropharyngeal): HPV/p16 status by historical test or local test in tumor tissue (mandatory)[d]	X															Section 8.8.2
Primary tumor diagnosis using complete pathological report	X															
Prior anti-cancer treatment (therapy, surgery, radiotherapy)	X															
Demography	X															
Full physical examination	X		X				X			X	X					Section 8.2.1
Limited physical examination				X	X	X		X	X			X	X			Section 8.2.1
Neurological examination for GBM/AA	X		X				X			X	X	X	X	X		Section 8.2.1

Procedure	Screening		Treatment period								EoT visit	Active FU[a]			Long-term FU	Comments
			Cycle1				Cycle 2			Cycle ≥3						
	within **28 d** prior to first dose	within **7 d** prior to first dose	D 1	D 8	D15	D22	D1	D8	D15	D1	within 14 d after permanent study treatment discontinuation	**Safety FU visit** 30 d after permanent study treatment discontinuation	**Safety FU visit** 100 d after LD for nivolumab[a]	**Efficacy FU visit** (between EoT and confirmed radiological PD)	every 3 months **(phone call)**	
acceptable deviation (days)				± 2 d			± 2 d			± 3 d		+ 7 d	+ 14 d	± 14 d	± 14 d	
Relevant medical history	X															
Safety																
AE review[e]	X	X	←==========										==========→			
ECOG performance status		X	X				X			X	X	X	X			Section 8.2.5
Serum pregnancy test if applicable (WOCBP only)[f]		X					X			X	X	X	X			Section 8.2.6 Table 10–1
Serology testing for Hepatitis B/C and HIV	X	If clinically indicated														at screening if history or symptoms of Hep B/C or HIV
Clinical chemistry expanded[g]		X	X		X		X		X	X	X	X	X			Table 10–1
Clinical chemistry limited				X		X		X								Table 10–1
Hematology expanded[g]		X	X		X		X		X	X	X	X	X			Table 10–1
Hematology limited				X		X		X								Table 10–1
PT-INR and aPTT[g]		X	X				X			X	X	X	X			Table 10–1

Procedure	**Screening**		**Treatment period**								**EoT visit**	**Active FU[a]**			**Long-term FU**	**Comments**
			Cycle1				Cycle 2			Cycle ≥3						
	within **28 d** prior to first dose	within **7 d** prior to first dose	D 1	D 8	D15	D22	D1	D8	D15	D1	within 14 d after permanent study treatment discontinuation	**Safety FU visit** 30 d after permanent study treatment discontinuation	**Safety FU visit** 100 d after LD for nivolumab[a]	**Efficacy FU visit** (between EoT and confirmed radiological PD)	every 3 months **(phone call)**	
acceptable deviation (days)				± 2 d			± 2 d			± 3 d		+ 7 d	+ 14 d	± 14 d	± 14 d	
Urine analysis by dipstick[g]		X	X				X			X	X	X	X			Table 10–1
Thyroid function testing[g]		X					X			X	X	X	X			Table 10–1
12-lead ECG[h]	X		X				X			X	X	X	X			Section 8.2.3
Vital signs (including weight)		X	X				X			X	X	X	X			Section 8.2.2
Efficacy																
Tumor assessments – (CT/MRI)[i]	X									X	X[a,i]	X[a,i]	X[a,i]	X[a,i]		Section 8.1
Bone scan[i]	X		←========== If indicated, see section 8.1 ==========→													Section 8.1
Brain scan (MRI/CT)[i]	X		←========== If indicated, see section 8.1 ==========→													Section 8.1
Survival status															X	
1st subsequent anti-cancer treatment											X	X	X	X	X	
Study intervention administration																
Study treatment: Nivolumab[j]			X				X			X						Section 6.1
Study treatment: Regorafenib[j]			←==========→ 3 weeks on/ 1 week off													Section 6.1

Procedure	Screening		Treatment period								EoT visit	Active FU[a]			Long-term FU	Comments
			Cycle1				Cycle 2			Cycle ≥3						
	within **28 d** prior to first dose	within **7 d** prior to first dose	D 1	D 8	D15	D22	D1	D8	D15	D1	within 14 d after permanent study treatment discontinuation	**Safety FU visit** 30 d after permanent study treatment discontinuation	**Safety FU visit** 100 d after LD for nivolumab[a]	**Efficacy FU visit** (between EoT and confirmed radiological PD)	every 3 months **(phone call)**	
acceptable deviation (days)				± 2 d			± 2 d			± 3 d		+ 7 d	+ 14 d	± 14 d	± 14 d	
Drug accountability (regorafenib and nivolumab)[k]							X			X	X					
Drug dispensing (regorafenib)[k]			X				X			X						
Prior/Concomitant medications and radiotherapy review (including vaccination)	X	X	←==========													
Research sample collection																
Regorafenib PK sample collection			X	X	X		X		X							see Table 1–4
Nivolumab PK sample collection			X				X			X						see Table 1–4
Immunogenicity			X				X			X						see Table 1–4
Biomarker blood sampling		for sampling details, see Table 1–3.														see Table 1–3
Tumor tissue	X							X			X					
Stool sample collection[l]	X							X			X					

Abbreviations: AA =Anaplastic astrocytoma; AE = Adverse event; AJCC = American Joint Committee of Cancer; aPTT = Activated partial thromboplastin time; BTC = Biliary tract cancer; C = Cycle; CT = Computed tomography; CTCAE = Common terminology criteria for adverse events; D (d) = Day; ECG = Electro cardiogram; ECOG = Eastern Cooperative Oncology Group; EoT = End of treatment; ESCC = Esophageal squamous cell cancer; FU = Follow-up; GBM = Glioblastoma multiforme; GGT = Gamma-glutamyl transferase; Hep B/C = Hepatitis B/C virus; HIV = Human immunodeficiency virus; HNSCC = Head and neck squamous cell cancer; HPV = Human papilloma virus; hr = Hour(s); IDH = Isocitrate dehydrogenase; INR = International normalized ratio; IxRS = Interactive voice/web response system; LD = Last dose; MGMT= O^6-methylguanine DNA methyltransferase; MRI = Magnetic resonance; PDAC = Pancreatic ductal adenocarcinoma; PI/ICF = Participant information/informed consent form); PK = Pharmacokinetics; PT = Prothrombin time; WHO = World Health Organization; WOCBP = Women of childbearing potential.

a. Participants discontinuing study treatment without radiological disease progression should continue tumor evaluations (by CT/MRI) if at all possible until radiological progression and/or start of first subsequent systemic anti-cancer treatment whichever comes first, or until participant withdraws from study for any reason. During active FU, CT/MRI scans will be performed every 12 weeks +/-14d (see Section 8.1). Active FU will either be terminated by the last safety FU visit or thereafter by the last tumor assessment or documentation of first subsequent systemic anti-cancer treatment or any criterion for withdrawal is met.
   If nivolumab is permanently discontinued first and the day 100 safety FU visit after nivolumab discontinuation falls into regorafenib treatment period or day 30 safety FU period, no separate nivolumab day 100 safety FU visit is necessary as the information gathering and examinations will occur with regorafenib treatment cycle visit, EoT visit or day 30 safety FU visit (required after study treatment discontinuation).
b. Contact IxRS to record the following: **1**. to register the participant who has signed the PI/ICF **2**. the participant is a screening failure (failed to meet the criteria during the screening period), **3**. on D1 of every treatment cycle in order to register the cycle and to ensure the specific participant drug bottles/vials can be provided for dispensing purposes and also in case the participant has discontinued the study treatment (EoT) for any reason.
c. AJCC classification for HNSCC, ESCC, PDAC, BTC, and, WHO classification for GBM/AA.
d. Test results need to be available before start of study treatment.
e. Participants will be followed for intervention-related toxicities until these toxicities resolve, return to baseline or are deemed irreversible. All AEs will be documented for 30 d + 7 d after study treatment discontinuation or 100 d + 14 d after LD of nivolumab, whatever occurs later. After start of subsequent anti-cancer therapy only study intervention-related AEs should be collected. CTCAE v5.0 will be used.
f. A negative pregnancy test must be available within 24 h before the 1st study treatment administration. Monthly pregnancy testing independent of study treatment dosing should be conducted as per local regulations where applicable.
g. Need to be performed within 2 days prior to the study treatment administration. For thyroid function tests, results can also be analyzed retrospectively in case the results are not immediately available.
h. 12-lead ECG to be scheduled at every cycle on D1 until cycle 6, after which ECG can be performed at the discretion of the investigator if clinically indicated.
i. CT/MRI scans performed prior to the participant signing informed consent can be used as baseline scans if they are not older than 28 days from C1D1 and meet the requirements outlined in Section 8.1. Scans are to be performed every 8 weeks (± 7 d) through Cycle 8 (or until treatment discontinuation, if treatment discontinuation occurs before), afterwards every 12 weeks (± 14 d). See Section 8.1 for further details on the schedule of tumor assessments beyond progression per RECIST 1.1 or RANO criteria. For all participants with known bone metastases or clinically suspected of having bone disease, bone scans will be performed as outlined in Section 8.1. HNSCC, ESCC, PDAC, BTC participants with neurological symptoms and/or known CNS disease must undergo CT/ MRI scans of the brain as outlined in Section 8.1.
j. 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 nivolumab treatment and may continue on regorafenib monotherapy.
k. Participants will bring their medication at each visit. Drug accountability of regorafenib will be done on Day 1 of every cycle starting from Cycle 2, and at the EoT visit.
l. Collection of stool can be performed at any time during visit or within ±7 d of the planned visit.

Table 1–3 Schedule of Biomarker Blood Sampling

Procedure	Screening	Treatment							
		Cycle 1		Cycle 2		Cycle 4	Cycle 6	Cycle 8 and every even cycle	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	
Biomarker plasma for ctDNA		X		X		X	X	X	X
Biomarker blood for flow cytometry 1	X	X	X	X	X	X			X
Biomarker blood for flow cytometry 2	X	X	X	X	X	X			X
Biomarker serum[a]	X	X	X	X	X	X	X		X
Biomarker plasma [a]	X	X	X	X	X	X	X		X
Biomarker blood for RNA		X	X	X		X			X
Biomarker blood for pharmacogenetics		X							

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

Table 1–4 Pharmacokinetic and Immunogenicity Sample Collection Plan

Sampling time	Regorafenib, M-2 and M-5 PK	Nivolumab PK	Immunogenicity
C1 D1	pre-dose and at 0.5 hr[b] and 3-4 hr[b] after oral intake	pre-infusion and EoI[a]	pre-infusion
C1 D8	pre-dose		
C1 D15	pre-dose and 2-4 hr[b] after oral intake		
C2 D1	pre-dose and at 0.5 hr[b] and 3-4 hr[b] after oral intake	pre-infusion	pre-infusion
C2 D15	pre-dose and 2-4 hr[b] after oral intake		
C5 D1		pre-infusion	pre-infusion
C19 D1		pre-infusion	pre-infusion

Abbreviations: C = Cycle; D = Day; EoI = End of infusion; hr = Hour(s); PK = Pharmacokinetics

a) Nivolumab pre-dose samples should be taken just prior to start of infusion (preferably within 30 min). If the infusion is delayed and a pre-dose sample in already collected, there is no need to collect an additional pre-dose sample. EoI samples should be taken as close to EoI as possible (preferably 2 min prior to EoI) on the contralateral arm (i.e. the arm not used for the infusion). If nivolumab is not administered on the scheduled day PK, pre-dose samples should be collected. Otherwise PK sampling should always be linked to the nivolumab administration.

b) If regorafenib is not administered on the day of PK sampling, the pre-dose samples will be collected, the post-dose samples will not be collected. Pre-dose samples will also not be collected if participants have not taken regorafenib on the previous day. However, if regorafenib is re-started than PK sampling should resume as scheduled.

2. Introduction

2.1 Study Rationale

ICIs have been shown to be effective anticancer therapy and are approved as standard treatment in several tumor types. However, approximately 60-70% of tumors do not respond to single agent ICI therapy and among the tumors that respond, resistance to therapy can develop over time. A high unmet need remains to improve clinical outcomes.
One such strategy to improve outcomes is combining ICI with a MKI targeting VEGF which are predicted to have complementary anti-tumor effects and potential enhancement of tumor-directed immune response. In preclinical and clinical studies, the combination of an ICI and anti-VEGF MKI has demonstrated promising results showing enhanced tumor response in different cancers and improvement of clinical measures (Khan and Kerbel 2018).

Recently, combinations of anti PD-1antibodies and MKIs targeting VEGF pathway such as axitinib, lenvatinib, regorafenib and cabozantinib have shown encouraging activity in multiple solid tumors (Agarwal et al. 2020, Makker et al. 2019, Rini et al. 2019). In pre-clinical tumor models of various cancer types (colorectal cancer [CRC], hepatocellular carcinoma [HCC], melanoma) the combination of regorafenib and anti-PD-1 drugs was more effective compared to either monotherapy (Hoff et al. 2017, Wu et al. 2019). In a Phase 1b trial of Japanese patients with advanced microsatellite stable (MSS) colorectal and gastric cancer (GC), the combination of regorafenib and nivolumab was safe and demonstrated significant activity with confirmed overall response rate (ORR) of 33% and 44%, respectively (Fukuoka et al. 2020).

To explore the potential to enhance antitumor response through combining of an ICI with an anti-VEGF MKI, this open-label, multi-center Phase 2 study of regorafenib and nivolumab aims to evaluate the safety and efficacy of the combination in multiple cohorts of participants with selected advanced solid tumors.

The combination of regorafenib with nivolumab is predicted to improve efficacy through complementary anti-tumoral effects and to enhance tumor-directed immune response by relieving immunosuppression through the reduction of tumor associated macrophages, T_{reg}s, and expression of PD-L1 and IDO-1, along with inhibition of VEGF signaling. In addition, tumor immunity may be enhanced by the increased infiltration of cytotoxic T cells mediated by increased expression of the chemoattractant CXCL10, the ligand for CXCR3, which occurs on T cells (data on file).

Therefore, novel therapies using regorafenib with PD-1 antibody, such as nivolumab, present a unique opportunity to address a high unmet need and improve clinical outcomes in multiple advanced solid tumor indications.

2.2 Background

Regorafenib

Regorafenib (BAY 73-4506) is an oral small molecule tyrosine kinase inhibitor that potently blocks multiple protein kinases, including kinases involved in tumour angiogenesis (vascular endothelial growth factor receptor (VEGFR1), 2, 3, tyrosine kinase with immunoglobulin and epidermal growth factor homology domain 2 (TIE-2), oncogenesis [stem cell factor receptor (KIT)], rearranged during transfection (RET), rapidly accelerated fibrosarcoma 1 [RAF1],

type B of RAF kinase (BRAF), $BRAF^{V600E}$), metastasis (VEGFR3, platelet-derived growth factor receptor (PDGFR), fibroblast growth factor receptor (FGFR)] and tumour immunity [colony-stimulating factor 1 receptor (CSF1R)].

In preclinical studies, regorafenib has demonstrated potent antitumor activity as a single agent in a broad spectrum of tumour models, including models of head and neck squamous-cell carcinoma (HNSCC), glioblastoma multiforme/anaplastic astrocytoma (GBM/AA), pancreatic ductal adenocarcinoma (PDAC) and non-small cell lung cancer (NSCLC) (Daudigeos-Dubus et al. 2015, Klinghammer et al. 2015, Wilhelm et al. 2011), likely mediated by its anti-angiogenic and anti-proliferative effects. Regorafenib under trade name Stivarga is approved for pre-treated advanced CRC, pre-treated advanced gastro-intestinal stromal tumor (GIST), and pre-treated advanced hepatocellular carcinoma (HCC).

Regorafenib under the trade name Stivarga® is currently authorized in 96 countries for treatment of mCRC, 93 countries for treatment of GIST, and 86 countries for the treatment of HCC.

A detailed description of the chemistry, pharmacology, efficacy, and safety of regorafenib is provided in the most recent Investigator's Brochure (IB)

Nivolumab

Nivolumab (BMS-936558) is a fully human, immunoglobulin (IgG)4 (kappa) isotype monoclonal antibody that binds PD-1 on activated immune cells and disrupts engagement of the receptor with its ligands (PD-L1) (B7-H1/CD274) and PD-L2 (B7-DC/CD273), thereby abrogating inhibitory signals and augmenting the host antitumor response.

Nivolumab under the trade name Opdivo® is approved by the United States (US) Food and Drug Administration (FDA) for the treatment of multiple tumor types, unresectable or metastatic melanoma, adjuvant treatment of melanoma, metastatic NSCLC, small cell lung cancer (SCLC), advanced renal cell carcinoma (RCC), classical Hodgkin lymphoma, HNSCC, urothelial carcinoma (UC), microsatellite instability-high or mismatch repair deficient (MSI-H/dMMR) metastatic colorectal cancer (mCRC) and esophageal squamous cell carcinoma (ESCC).

A detailed description of the chemistry, pharmacology, efficacy, and safety of nivolumab is provided in the most recent IB.

Head and Neck Squamous Cell Carcinoma

Head and neck cancer is the seventh most common cancer worldwide with 890,000 newly diagnosed patients each year resulting in 450,000 death annually (Chow 2020). In the US, head and neck cancer incidence is estimated to be 65,000 with 15,000 deaths annually. HNSCC accounts for more than 90% of head and neck cancers and arises in the oral cavity, oropharynx, hypopharynx, and larynx. The two most common risk factors for HNSCC is tobacco and alcohol use (Hashibe et al. 2009), but Epstein-Barr virus (EBV) and human papilloma virus (HPV) also play a role in the development of carcinomas of the nasopharynx and the oropharynx, respectively. HPV infection is known to cause oropharyngeal cancer, especially those arising from the tonsils and tongue base but may also be associated with other HNSCC cancers as well (Ang et al. 2010, D'Souza et al. 2007). Oropharyngeal cancer associated with HPV infection as noted by HPV-positive or p16-positive status have better prognosis than those not associated with HPV.

Immunotherapy either alone or in combination with chemotherapy have improved the survival of patients with HNSCC regardless of PD-L1 status and have become part of standard of care in 1L and 2L. Despite these advances, patients with non-curative recurrent or metastatic disease have a median survival less than 16 months (Rischin et al. 2019) with 1L therapy and less than 9 months in the 2L setting, (Cohen et al. 2019, Ferris et al. 2016). Approximately 36% of HNSCC patients will respond to 1L systemic therapy and less than 13-18% of patients respond in the 2L setting when treated with an PD-1 inhibitor (Ferris et al. 2016, Mehra et al. 2018). With only a minority of patients benefitting from ICI, there is a need to explore additional strategies to improve outcomes.

Early results from clinical trial in subjects with advanced HNSCC treated with combination of anti-angiogenic MKI and PD-1 inhibitor (lenvatinib and pembrolizumab) suggest potential synergistic effect on response compared to the historical results of single agent PD-1 inhibitor (Taylor et al. 2020). Whereas clinical trials of single agent nivolumab and pembrolizumab in patients with advanced HNSCC showed an ORR of 13% to 18% (Ferris et al. 2016, Mehra et al. 2018), the study of the combination of lenvatinib and pembrolizumab resulted in an ORR of 46% (Taylor et al. 2020).
Nivolumab is approved for treatment of recurrent or metastatic HNSCC that are platinum-resistant based on data showing improved survival compared to treatment with single-agent chemotherapy (hazard ratio [HR] 0.70; 97.73% confidence interval [CI], 0.51 to 0.96; P = 0.01) (Ferris et al. 2016). The median OS for the nivolumab group was 7.5 months (95% CI, 5.5 to 9.1) and ORR was 13%. The activity of nivolumab as single agent and early clinical data from studies of PD-1 inhibitor in combination with an anti-angiogenic MKI suggest exploring the potential for combing nivolumab with regorafenib to improve clinical results for patients with advanced HNSCC.

Little is known regarding the effectiveness of ICI rechallenge after disease progression following initial ICI treatments in HNSCC and other solid tumors. Many previous trials involving ICI excluded patients who have received prior ICI. As ICIs have received expanded approval for different tumor indications including broader application for initial treatment in HNSCC, an unmet need exists to assess whether a rechallenge with an ICI in combination with another agent may overcome resistance to initial ICI treatment and improve response. There is early indication that a rechallenge with ICI in combination with a MKI may allow some solid tumors that have progressed on prior ICI to respond. In the REGONIVO study, 3 of 7 GC patients who were refractory to previous PD-1–targeted therapy achieved response with regorafenib plus nivolumab. The ORR was 42.8% (3 out of 7) for GC patients who progressed on prior ICI and 44% (11 out of 25) among all GC patients (Fukuoka, Hara et al. 2020). Among the 7 responders out of 21 patients with advanced NSCLC, 2 participants who progressed on prior ICI therapy achieved responses (1 complete response [CR] and 1 partial response [PR]) upon treatment with lenvatinib in combination with pembrolizumab (Taylor et al. 2020). These results are encouraging and warrant further study to address whether the combination regorafenib with nivolumab can elicit anti-tumor response in patients with HNSCC who have progressed on prior ICI therapy.

Esophageal Squamous Cell Carcinoma

Esophageal cancer, the sixth most common cause of cancer deaths worldwide, has an incidence of 570,000 cases annually (Bray et al. 2018, WHO-IARC 2018). The most common subtype globally is ESCC which accounts for 88% of all esophageal cancer (Abnet et al.

2018). ESCC occurs most commonly in Asia, Eastern Africa, and South America. The 5-year survival rate is 5% for patients diagnosed with metastatic disease (NIH-SEER 2020). In a randomized control Phase 3 trial (ATTRACTION-3), nivolumab improved survival versus chemotherapy (paclitaxel or docetaxel) (median OS 10.9 months vs 8.4 months, HR 0.77, 95% CI 0.62-0.96; p=0.019) irrespective of tumor PD-L1 expression in subjects with unresectable advanced, recurrent or metastatic ESCC previously treated with fluoropyrimidine- and platinum-based chemotherapy (Kato et al. 2019). Treatment with nivolumab was associated with an ORR of 19% and a favorable safety profile. Despite this progress, a high unmet need remains to explore a combinatorial approach to enhance the anti-tumor effects of PD-1 inhibition in patients with ESCC.

Pancreatic Duct Adenocarcinoma

PDAC, a highly lethal cancer associated with poor prognosis, is the seventh leading cause of cancer-related deaths worldwide and third leading cause of cancer-related deaths in the US (Rawla et al. 2019). Many patients present with advanced disease not eligible for curative treatment. Except for a small number of patients who qualify for targeted therapy based on selected tumor markers (e.g. MSI-H, tropomyosin receptor kinase [NTRK]) the treatment options for patients with non-curative advanced disease, include gemcitabine and fluoropyrimidine based chemotherapy regimens that are guided by performance status, (Ducreux et al. 2015, NCCN-Pancreatic-Cancer 2020). With these chemotherapy regimens, patients have associated hematological, gastrointestinal, and neurological toxicities and the overall 5-year survival rate has not improved markedly, remaining less than 10%. Although PD-1/PD-L1 inhibitors have shown efficacy in several different tumor indications, clinical trials have not shown effectiveness in PDAC (Henriksen et al. 2019). There exists a high unmet need to improve therapeutic options that lead to better clinical outcomes for patients with PDAC. Several potential mechanisms of pancreatic resistance to ICI exist including those related to T_{reg}s and tumor associated macrophages (TAMs) in the tumor microenvironment (Skelton et al. 2017). Regorafenib inhibits CSF1R, a receptor which in preclinical models of several cancers have been shown to reduce the number of immunosuppressive TAMs, thereby facilitating an immune response against tumors (Abou-Elkacem et al. 2013, Zopf et al. 2016). Pancreatic cancers have been shown to express high levels of serum CSF-1, the ligand for CSF1R (Groblewska et al. 2007). These findings form the rationale for a combination approach of using an anti-angiogenic agent such as regorafenib with CSF1R inhibition in combination with nivolumab to potentially overcome resistance to ICI therapy and fulfill the need to improve therapeutic options and clinical outcomes for patients with PDAC.

Biliary Tract Cancer

BTC is a group of rare heterogenous cancer that includes the subtypes intrahepatic cholangiocarcinoma (CCA), extrahepatic CCA, and gallbladder cancers (GBC). These cancers are more common in Asian countries than Western countries with an incidence age-standardized rate of 3 per 100,000 in South Korea and 0.66 per 100,000 in the United Kingdom (Wang et al. 2020). BTCs accounts for approximately 12,000 new cases and 4,000 deaths per year in the US (Siegel et al. 2019). Most patients are diagnosed with advanced disease and have poor prognosis, with 5-year survival rates of approximately 10% (Everhart

and Ruhl 2009, Ghosn et al. 2015). Chemotherapy typically with gemcitabine and cisplatin are first-line standard of care for patients with unresectable and metastatic BTC. Despite treatment advances, the survival for these patients is typically less than a year (Valle et al. 2010). Thus, there is a need to search for new and more effective therapeutic options for patients this rare and fatal cancer.

VEGF overexpression has been reported in BTC and appears to be a potential prognostic marker (Mobius et al. 2007, Yoshikawa et al. 2008). For this reason, regorafenib has been explored in several clinical studies which have shown encouraging efficacy in advanced BTC (Kim et al. 2020b, Sun et al. 2019). In a single arm Phase 2 trial of regorafenib in patients with advanced/unresectable or metastatic biliary tract cancer who failed at least 1 line of systemic chemotherapy, the median progression free survival (PFS) was 15.6 weeks (90% confidence interval, 12.9-24.7 weeks), and the median overall survival (OS) was 31.8 weeks (90% confidence interval, 13.3-74.3 weeks), with survival rates 40% at 12 months and 32% at 18 months, and ORR of 11%. Another single arm Phase 2 trial of single agent regorafenib in patients with advance BTC who have progressed after at least 1 prior line of therapy, the PFS and OS were 3.7 months and 5.4 months respectively, and the ORR was 9.1%. A multi-institution single arm study of nivolumab in patients with advanced BTC who have progressed after at least 1 line of standard of care (SOC) demonstrated, PFS of 3.7 months, OS 14.2 months, and ORR of 11% by central independent review (Kim et al. 2020a). The encouraging efficacy results from these trials and the tolerable profiles of regorafenib and nivolumab as single agent support exploration of the combination of these two agents to improve clinical responses for patients with advanced BTC.

Recurrent Glioblastoma and Anaplastic Astrocytoma

There are more than 300,000 tumors of the brain and central nervous system worldwide each year, and approximately 240,000 deaths (Bray et al. 2018). The prognosis for patients diagnosed with GBM is poor, with 5-year survival rates of approximately 5% (Tykocki and Eltayeb 2018). The SOC for patients with GBM following surgical resection is radiation therapy (RT) with concomitant and adjuvant temozolomide (TMZ). Methylation of the promoter of the O6-methylguanine-DNA methyltransferase (MGMT) deoxyribonucleic acid (DNA)-repair gene is an independent favorable prognostic factor for patients treated with RT and TMZ. The standard of care in patients with recurrent GBM is less clear. Bevacizumab is approved in the U.S. and Japan for the treatment of recurrent GBM based on PFS but has not been shown to improve OS when compared to single agent nitrosourea-based chemotherapy (Friedman et al. 2009, Wick et al. 2017)

GBM is a highly vascularized tumor and is characterized by the expression of VEGF and other proangiogenic cytokines (Wong et al. 2009). Regorafenib alone significantly inhibited tumor growth in glioma tumor xenografts and antitumor activity was associated with decreased vascularization and inhibition of the platelet-derived growth factor receptor (PDGFR) pathways (Daudigeos-Dubus et al. 2015) A randomized, controlled Phase 2 trial of regorafenib showed OS benefit in a patient with recurrent GBM compared to lomustine (HR 0.50, 95% CI 0.33–0.75; log-rank p=0·0009) (Lombardi et al. 2019). Nivolumab was shown to have comparable median OS to bevacizumab in a randomized, controlled Phase 3 study of patient with first recurrence of GBM. Based on the high unmet need that exists for patients with recurrent GBM and demonstrated activity by regorafenib and nivolumab as single agent,

further study to assess the effectiveness of the combination of these two agents is warranted to improve outcomes for patients with this fatal tumor.

2.3 Benefit/Risk Assessment

ICIs have been approved for treatment in a broad range of cancers. However, approximately 60-70% of tumors do not respond to single agent ICI therapy and among the tumors that respond, resistance to therapy can develop over time. An approach that combines ICI with regorafenib, which blocks multiple protein kinases, including kinases involved in anti-tumor pathways including tumour angiogenesis, oncogenesis, metastasis, and immunity (Section 2.2), has the potential to improve tumor response in patients with advanced cancers.

Combination of regorafenib and nivolumab was evaluated in a Phase 1b trial of Japanese patients with advanced proficient mismatch repair (pMMR)/MSS CRC and gastric cancer and demonstrated clinically relevant activity greater than that expected from either agent alone with confirmed ORR of 33% and median PFS of 7.9 months in CRC and 44% for gastric cancer and median PFS 5.6 months (Fukuoka et al. 2020). The combination was well tolerated and had a manageable safety profile. In addition, a Phase 1b study combining regorafenib with a PD-1 inhibitor pembrolizumab for the treatment of patients with HCC without prior systemic therapy demonstrated encouraging anti-tumor activity and no new safety signals than what is expected from the safety profile of either drug alone (El-Khoueiry et al. 2020, Fukuoka et al. 2020).
Nivolumab is approved for treatment of recurrent or metastatic HNSCC that are platinum-resistant and unresectable advanced, recurrent or metastatic ESCC after prior fluoropyrimidine- and platinum-based chemotherapy. The therapeutic benefits of nivolumab for these indications apply to a minority of patients. Thus, additional strategies are needed to allow more patients to benefit from ICI therapy. Encouraging data (as discussed in Section 2.2) demonstrate that combining a MKI and PD-1 inhibitor may improve anti-tumor response over single agent PD-1 inhibitor. In one study, the combination of lenvatinib and pembrolizumab lead to an higher response rate (ORR of 46%) than what has been reported from trials of single agent PD-1 inhibitors (ORR 13-18%) for the treatment of advanced HNSCC (Ferris et al. 2016, Mehra et al. 2018). This clinical data as well as additional data as discussed in Section 2.2 suggest that combining a PD-1 inhibitor nivolumab with a MKI such as regorafenib has the potential for mechanistic synergy and enhanced the anti-tumor response which may lead to improved clinical outcomes.
Patients with recurrent GBM/AA and BTC typically have median survival of less a year and many of these patients fail to respond to therapy or develop progression after initial response. Trials of regorafenib or nivolumab as single agents for the treatment of advanced BTC and recurrent GBM have demonstrated some encouraging responses (as discussed in Section 2.2). These early indications of efficacy form the rationale to further investigate whether combining regorafenib and nivolumab can enhanced anti-tumor effects and address the high need for better therapeutic options for patients with these fatal cancers.
Advanced pancreatic cancers are highly lethal due to resistance to many classes of therapy. Despite ICI working in a broad range of cancers, PDAC remains fairly resistant to ICI therapy. Several potential mechanisms of PDAC resistance exist. Preclinical models show that regorafenib inhibits CSF1R, a receptor which in several cancers have been shown to reduce the number of immunosuppressive TAMs (see Section 2.2). This observation suggests that regorafenib has the potential to facilitate an immune response against tumors and to

enhance the immune-mediated action of nivolumab (Abou-Elkacem et al. 2013, Zopf et al. 2016).
The safety profiles from studies of regorafenib in combination with a PD-1 inhibitor (nivolumab or pembrolizumab) have shown that toxicities are consistent with those of regorafenib or nivolumab monotherapy (El-Khoueiry et al. 2020, Fukuoka et al. 2020). In the Phase 1b REGONIVO study of patients with CRC or GC treated with regorafenib plus nivolumab, the common grade ≥3 treatment-related AEs were rash (12%), proteinuria (12%), and palmar-plantar erythrodysesthesia (10%). In the Phase 1b study of patients with advanced HCC treated with regorafenib plus pembrolizumab, grade ≥3 treatment-related AEs were AST increase (20%), lipase increase (17%), hypertension (14%), ALT increase (17%), and bilirubin increase (11%).

Regorafenib has shown in clinical trials a positive benefit-risk across different tumor types, including CRC, GIST and HCC. The incidence, severity and relationship of adverse events (AEs) were generally similar across dose levels and tumor types. The development of some AEs (e.g. diarrhea, hyperbilirubinemia, increase in transaminases, hand foot skin reaction [HFSR], rash) are common in regorafenib clinical trials.

Overall, the safety profile of nivolumab monotherapy as well as in combination with other agents is manageable and generally consistent across completed and ongoing clinical trials with no maximal tolerated dose (MTD) reached at any dose tested up to 10 mg/kg. Most AEs were low-grade (Grade 1 to 2) with relatively few related high-grade (Grade 3 to 4) AEs. There was no pattern in the incidence, severity, or causality of AEs with respect to nivolumab dose level. A pattern of immune-related AEs has been defined. Most high-grade events were manageable with the use of corticosteroids or hormone replacement therapy for endocrinopathies. Additional details on the safety profile of nivolumab, including results from other clinical studies, are also available in the nivolumab IB.

Potential overlapping side effects of regorafenib and nivolumab such as transaminitis, diarrhea, and skin reactions may be possible. Safety will be monitored closely on an ongoing basis.

For patients with advanced or metastatic HNSCC, ESCC, PDAC, BTC, and recurrent GBM/AA who have failed systemic 1L therapy, the prognosis is poor. Although ICIs have shown benefit in many different tumors, including HNSCC and ESCC, it is common for primary and second resistance to occur and limit the therapeutic success of immunotherapy. The combination of regorafenib and nivolumab has potential for synergy which can improve anti-tumor immune response (as discussed above and Section 2.1 and 2.2). Early data suggest that the combination of regorafenib and nivolumab have a manageable safety profile. Taken together the safety profile, potential for benefit, and high unmet need for patients with advanced HNSCC, ESCC, PDAC, BTC, and recurrent GBM/AA, the overall benefit-risk assessment is favorable and supports the conduct of this Phase 2 study.

3. Objectives and Endpoints

Table 3–1 Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate efficacy of the regorafenib and nivolumab combination by cohort[a]	• ORR per RECIST 1.1[a] by local assessment for all solid tumors except GBM/AA • ORR per RANO[a] by local assessment for GBM/AA
Secondary	
• Evaluation of the additional efficacy measures of the regorafenib and nivolumab combination	• DOR[a] • DCR[a] • PFS[a,] • 6 months PFS[a] • OS • 1yr OS
• To evaluate safety of the combination by cohort and overall	• Frequency and severity of AEs per CTCAE v 5.0
Tertiary/Exploratory	
• To characterize the PK and immunogenicity of the regorafenib and nivolumab combination	• Exposure of regorafenib and nivolumab and detection of anti-drug antibodies (ADA) (immunogenicity)
• To evaluate the relationship between regorafenib exposure and relevant biomarkers for efficacy and/or safety	• Retrospective analysis of the relationship between regorafenib exposure and biomarker, safety and/or efficacy measures
• To assess efficacy of regorafenib and nivolumab combination using immune related response criteria	• ORR per iRECIST or per iRANO for GBM/AA[a]
• To identify biomarkers in baseline tumor materials, blood and/or stool samples that may associate with response	• Correlation of biomarkers in tumor, blood or stool samples before treatment with other study endpoints
• To explore pharmacodynamic effects of regorafenib and nivolumab combination on e.g. immune environment, signaling pathway activity, and downstream processes	• Change from baseline in levels of biomarkers in tumor, blood or stool samples
• To further investigate the study intervention and similar drugs (i.e., mode-of-action-related effects and / or safety) and to further investigate pathomechanisms deemed relevant to cancer and associated health problems	• Various biomarkers (e.g., diagnostic, safety, pharmacodynamic, monitoring, or potentially predictive biomarkers)

Abbreviations: AA = Anaplastic astrocytoma; ADA = Anti-drug antibody; AE = Adverse event; CTCAE = Common terminology criteria for adverse events; DCR=Disease Control Rate; DOR = Duration of response; GBM = Gliobastoma multiforme; iRECIST = Response evaluation criteria in solid tumors for trials testing immunotherapeutics; iRANO = Immune response assessment in neuro-oncology; ORR = Objective response rate; OS = Overall survival; PFS = Progression free survival; PK = Pharmacokinetics; RANO = Response assessment in neuro-oncology; RECIST 1.1 = Response evaluation criteria in solid tumors 1.1

a) The efficacy endpoints will be based on the local Investigator's assessment. Imaging data on tumor assessment will be collected for a potential retrospective central review of tumor evaluation by blinded readers.

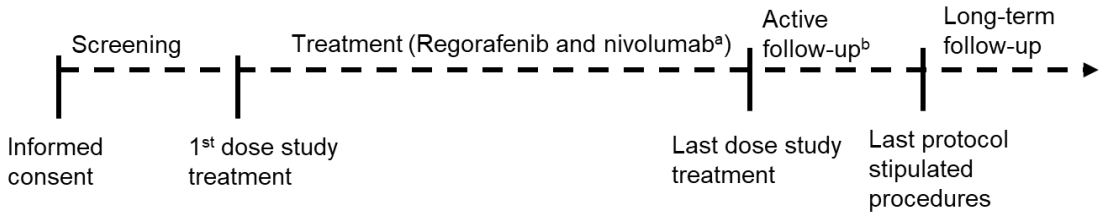
4. Study Design

4.1 Overall Design

This study is a multi-center, multi-indication, open-label, single-treatment arm, parallel-cohort Phase 2 study of regorafenib in combination with nivolumab in adult participants with selected recurrent or metastatic tumors (HNSCC, ESCC, PDAC, BTC, and GBM/AA) who have been previously treated with one or more systemic therapy for the selected tumor indication. An overview of the study schema is presented in Figure 4–1.
The study will be conducted at approximately 60 sites in North America, Europe and Asia/Pacific. Up to 200 participants who qualify for the study will be treated with regorafenib plus nivolumab.

This study is composed of the following periods: Screening, treatment, active follow-up (FU), and long-term follow up. An overview of the study schema is presented in Figure 4–1.

Figure 4–1 Study Design Overview

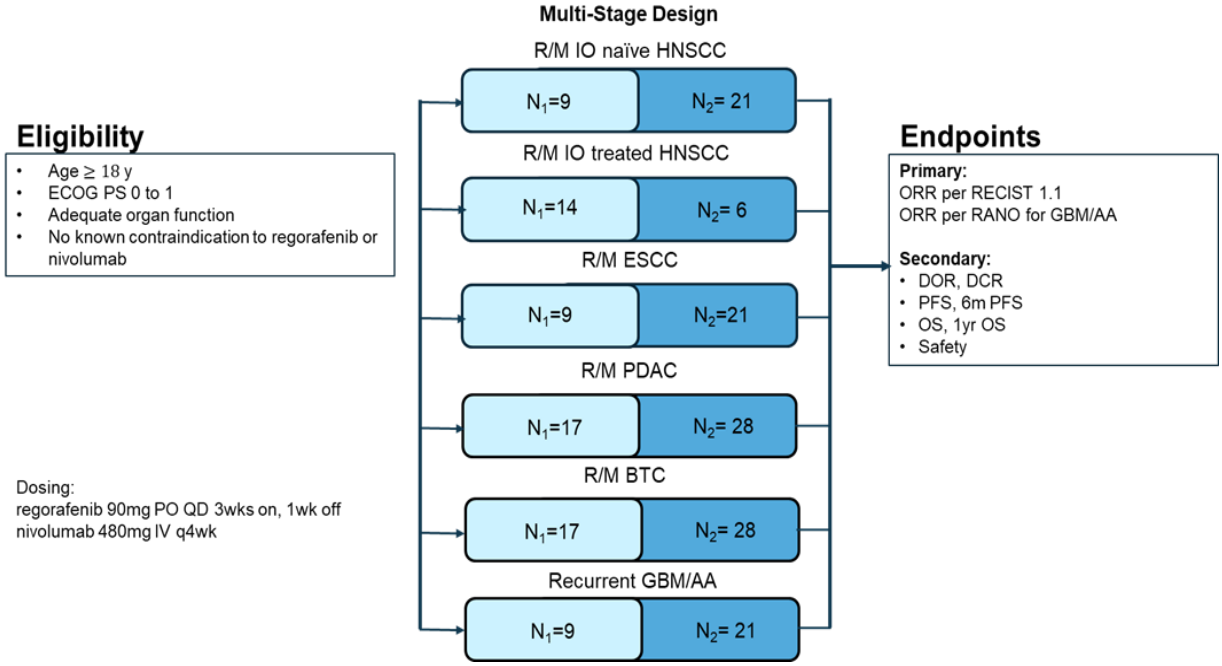


Abbreviations: C = Cycle; FU = Follow-up; LD = Last dose; Q4W = Every 4 weeks; QD = Daily

a) Nivolumab 480 mg using a 30-min i.v. infusion every 4 weeks (Q4W). Regorafenib starting dose 90 mg orally every day (QD) for 3 weeks of every 4 weeks (i.e. 21 days on, 7 days off). If starting the dose of 90 mg is well tolerated (absence of any grade rash/HFSR or other Grade 2 or higher clinically significant toxicity. Lab abnormalities of any grade that resolve to ≤G1 within 72 hours are acceptable) the dose can be escalated to 120 mg orally daily anytime after C1, starting with C2D1.

b) Mandatory safety FU visit (30 d + 7 d after study treatment discontinuation and 100 d + 14 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

Figure 4–2 Study Schema



Abbreviations: AA = Anaplastic Astrocytoma; BTC = Biliary Tract Carcinoma; ChT = Chemotherapy; DCR = Disease control rate; DOR = Duration of response; ECOG PS = Eastern Cooperative Oncology Group Performance Status; ESCC = Esophageal Squamous Cell Carcinoma; GBM = Glioblastoma Multiforme; HNSCC = Head and Neck Squamous Cell Carcinoma; IO = Immune oncology; IV = Intravenous; ORR= Overall Response Rate; OS = Overall survival; PDAC= Pancreatic ductal adenocarcinoma; PFS = Progression free survival; PK = Pharmacokinetics; PO = Per oral; q4wk = Every 4 weeks; QD = Once daily; RECIST 1.1 = Response Evaluation Criteria In Solid Tumors 1.1; RANO = Response assessment in neuro-oncology; R/M = Recurrent/Metastatic

Each cohort starts with the Stage 1 and may continue to the Stage 2 if sufficient efficacy will be observed.

Stage 1 of the study:
Tumor based cohorts will recruit as follows:

- approximately 9 participants will be treated for the HNSCC (IO naïve), ESCC and GBM/AA (participants with AA are included only in Stage 2) cohorts
- approximately 14 participants will be treated for the HNSCC (IO treated) cohort
- approximately 17 participants will be treated for the PDAC and BTC cohorts

Stage 2 of the study:
Tumor based cohorts that pass the pre-defined ORR threshold of the Stage 1 may expand as follows:

- approximately 21 participants will be treated for the HNSCC (IO naïve), ESCC and GBM/AA cohorts
- approximately 6 participants will be treated for the HNSCC (IO treated) cohort
- approximately 28 participants will be treated for the PDAC and BTC cohorts

Information about the respective Cohort of the participant will be recorded by the investigator or delegate in IxRS after signing off the participant information/informed consent form (PI/ICF).

All participants will be assessed for efficacy and safety during Stage 1 and Stage 2. Enrollment may be discontinued for those cohorts that will not pass the pre-defined ORR threshold for Stage 1. In addition, the totality of the data, including the duration and depth of response and overall risk-benefit assessment may be considered in the decision to terminate or continue the expansion after Stage 1.

4.1.1 Screening Phase

The screening period for a specific participant will start after signing the ICF and after a specific slot has been provided by the Sponsor. Participants will be screened for eligibility up to 28 days (d) 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. Recruitment is competitive on study, country and site level. As only a few patients will start treatment within one cohort, the participant slot allocation form is used to provide a slot for a defined cohort for a specific patient to avoid over-recruitment.

4.1.2 Treatment Phase

The start of the treatment period is defined by the first administration of study treatment. The length of a cycle is 28 days (plus a potential time window, for acceptable deviation see Section 1.3 SoA). Participants will be treated with nivolumab intravenously given on Day 1 and regorafenib orally every day for 3 weeks of a 4 week 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 90 mg for 21 days of every 28-day cycle (i.e., 21 days on, 7 days off). If the starting dose of 90 mg daily is well tolerated (absence of any grade rash/hand foot skin reaction (HFSR) or other Grade 2 or higher clinically significant toxicity) the dose can be escalated to 120 mg orally daily anytime after Cycle 1, starting with Cycle 2 Day 1. The Sponsor will be immediately informed, if the Investigator decides not to escalate the dose to 120 mg on C2D1 despite meeting the criteria.
Dose modification guidelines for dose reduction in case of toxicity are detailed in Section 6.6. Treatment with individual drugs (regorafenib or nivolumab) may continue on schedule even if the other drug is interrupted or permanently discontinued due to toxicity.

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

During the study, participants will undergo evaluations for safety, efficacy, pharmacokinetics and tissue and blood for biomarker will be collected.

Response will be assessed by imaging and participants may continue treatment until confirmation of disease progression per response evaluation criteria in solid tumors for trials testing immunotherapeutics (iRECIST; Section 10.6.2) or per immune response assessment in neuro-oncology (iRANO; Section 10.6.4), unacceptable toxicity or any other protocol defined criterion for withdrawal occurs. See Section 8.1 for further details on treatment continuation and tumor assessments beyond progression per RECIST 1.1 or RANO criteria. Primary endpoint of the study for all cohorts is ORR as measured by RECIST 1.1 or RANO for GBM/AA as determined by the investigator. For GBM/AA tumor assessment per RANO will

also include use of corticosteroids and neurological status. Imaging data on tumor assessment will be collected for a potential central review of tumor evaluation by blinded independent readers.

4.1.3 Active FU

Safety FU visits:

A mandatory clinical visit to monitor safety will take place 30 d (window of +7 d) after study treatment discontinuation and 100 d (window of +14 d) after the last dose of nivolumab. Longer safety FU for nivolumab is required due to the long half-life of the antibody.

If the study treatment was permanently discontinued after dose interruption/delay of more than 28 days (including drug holiday for regorafenib), the safety FU visit should occur within 14 days of the discontinuation. If the EoT and safety FU visits will be scheduled at the same time, the visits can be combined.

If nivolumab is permanently discontinued first and the day 100 safety follow up visit after nivolumab discontinuation falls into regorafenib treatment period or day 30 safety FU period, no separate day 100 safety FU visit for nivolumab is necessary as the information gathering and examinations will occur with regorafenib treatment cycle visit, EoT visit or day 30 safety FU visit.

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

During the safety FU, all AEs will be documented until the start of new anti-cancer treatment. Once new anti-cancer treatment is started, only study intervention related AEs should be documented.

Efficacy FU visits:

For participants who discontinue study treatment without confirmed radiological disease progression every effort should be made to continue tumor evaluations (by computed tomography [CT]/magnetic resonance imaging [MRI]) until confirmation of radiological progression per RECIST 1.1 or RANO and/or start of first subsequent systemic anti-cancer treatment whichever comes first, or any other criterion for withdrawal is met. During the efficacy FU visits, CT/MRI evaluations will be performed every 12 weeks (+/-14 days). Following the occurrence of progression per RECIST 1.1 or RANO during efficacy FU, scans for tumor assessments may be obtained to confirm progression as per iRECIST or iRANO as detailed in Section 8.1. For GBM/AA tumor assessment per RANO will also include use of corticosteroids and neurological status. In addition, study intervention-related toxicity/AE and first subsequent anti-cancer therapy will be followed up until completion of the active FU. Active FU will either be terminated by the last safety FU visit or thereafter by the last tumor assessment or documentation of first subsequent systemic anti-cancer treatment or any criterion for withdrawal is met.

4.1.4 Long-Term FU

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 first subsequent anti-cancer therapy at 3-month intervals (± 14 d) at least for 1 year after starting treatment or until the last participant in the study has completed the active safety FU visit, or consent withdrawal or death or lost to follow up is reached for the last patient, whichever comes last. 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.

4.2 Scientific Rationale for Study Design

This study is a multi-center, multi-indication, open-label, single-treatment arm, parallel-cohort Phase 2 study of regorafenib in combination with nivolumab in adult participants with selected recurrent or metastatic tumors (HNSCC, ESCC, PDAC, BTC, and GBM/AA) who have been previously treated with one or more systemic therapy for the selected tumor indication. The open-label, single-treatment arm, multi-indication, parallel-cohort study design follows well-established Phase 1b/2 oncology trials, including studies that include combinations of a PD-1 inhibitor and a MKI with similar targets and mechanism of action as nivolumab and regorafenib (Taylor et al. 2020). This type of study is aimed at allowing for efficient evaluation of tumors types that will respond to the combination of a PD-1 inhibitor and a MKI.
Efficacy of each cohort will be examined in 2 stages based on a Sargent 3-outcome design with one-sided alpha of 0.1 (false positive rate), beta (false negative rate) of 0.1, power of 70% and likelihood of futility of 70% when the null hypothesis is true. Details of the statistical considerations, hypotheses, and sample size calculations are described in Section 9. The rationale for a 2-stage design is intended to allow an interim efficacy assessment based on the number participants enrolled in Stage 1 and early termination of a cohort if there is insufficient number of responders to meet the pre-defined low boundary for efficacy. Considerations were made so that the number of participants in Stage 1 needed for efficacy assessment was minimized. The ability to terminate a cohort early based on lack of efficacy based on Stage 1 is designed to efficiently assess efficacy while allowing for sufficient estimation of antitumor response to the study treatment.

4.3 Justification for Dose

Combination of regorafenib and nivolumab was evaluated in a Phase 1b trial of Japanese patients with advanced pMMR/MSS CRC and gastric cancer and demonstrated clinically relevant activity greater than that expected from either agent alone with confirmed ORR of 33% and median PFS of 7.9 months in CRC and 44% for gastric cancer and median PFS 5.6 months (Fukuoka et al. 2020). The combination was well tolerated at regorafenib starting dose of 80 mg once daily for 21 days on and 7 days off and nivolumab 3 mg/kg Q2W

In the dose escalation part of the study, regorafenib doses of 80, 120 or 160 mg were administered once daily for 21 days on and 7 days off with intravenous nivolumab 3 mg/kg Q2W. Three dose limiting toxicities (DLTs) were observed during dose-escalation with

regorafenib 160 mg, including Grade 3 maculopapular rash, colonic perforation and proteinuria. There was no DLT observed with 80 mg or 120 mg dose of regorafenib. Maximum tolerated dose for the combination based on pre-defined DLT criteria was deemed to be 120 mg. In the first 18 patients treated at 120 mg dose of regorafenib in the dose expansion cohort, all but one required dose reduction to 80 mg for AEs mostly related to frequent Grade 3 skin toxicities. All remaining 18 patients were treated with regorafenib starting dose of 80 mg and tolerated treatment well. Grade ≥ 3 treatment related adverse events occurred in 20 patients (6 at 80 mg, 11 at 120 mg and 3 at 160mg). The common Grade ≥ 3 events (> 10%) were rash (12%), palmar-plantar erythrodysesthesia (10%), and proteinuria (12%). None of the patients treated at 80 mg dose had Grade ≥ 3 rash or palmar-plantar erythrodysesthesia, while 5 events (20%) each were reported at 120 mg dose. Grade ≥ 3 treatment related adverse events among patients treated at 80 mg dose included 2 events each for hypertension, proteinuria and hepatic dysfunction.

Based on emerging data from ongoing clinical studies (Fukuoka et al. 2020) of regorafenib in combination with IO (e.g. nivolumab or pembrolizumab), 80 mg is the currently recommended starting dose with the option to escalate to 120 mg in patients who can tolerate it. However, a number of patients who start at a dose of 80 mg still require dose reductions due to safety/tolerability. With the currently available 40 mg tablet, the only options are to reduce to 40 mg QD which is a 50% dose reduction or to 80 mg every other day (QOD) which is more difficult for patient compliance and still a 50% dose reduction. Therefore, Bayer is proposing a new tablet strength of 30 mg for regorafenib in combination with IO. A 30 mg tablet would allow for a starting dose of 90 mg QD for the first 21 d of each 28 d cycle. Due to the high inter-subject PK variability, a dose of 90 mg is expected to provide very similar exposure to the currently recommended combination starting dose of 80 mg. A 30 mg tablet also will allow for a dose modification step to 60 mg which is a more conventional 33% dose reduction as compared to 50% with the 40 mg tablet. Based on data from the Phase 1 dose escalation study of regorafenib monotherapy, a dose of 60 mg showed a decrease in levels of sVEGFR2 that was in a comparable range to the 120 mg dose. This supports the pharmacological activity of a 60 mg dose (Mross et al. 2012). Further details on the 30 mg tablet are provided in the IB.

4.4 End of Study Definition

The end of the study is defined as the date of the last visit of the last participant (LPLV) in the study.
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.
If the trial is stopped but benefits are observed for patients, further treatment options may be discussed and agreed between the investigator, sponsor and the patients and continued treatment in a Roll Over Study (ROS) or with commercial supply will be offered.

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.

Primary completion

The primary completion of the study is defined by the event when all participants have been assessed for response rate (as defined by RECIST 1.1 or RANO) after the last participant has been followed for approximately 10 months unless they have discontinued before due to progression or any other reason.

5. Study Population

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

5.1 Inclusion Criteria

Participants are eligible to be included in the study only if all the following criteria apply (unless where specified for specific tumor indication). Reintroduction of the same chemotherapy in sequential order and locoregional treatments such as hepatic arterial infusion therapy is not considered as a new line of treatment:

Cohort 1 (HNSCC, IO naïve)

101 Cohort 1: Histologically confirmed recurrent or metastatic HNSCC (from any of the following primary sites only: oral cavity, oropharynx, hypopharynx and larynx) that is not amenable to curative intent surgery or chemoradiation.

102 Cohort 1: Progressed on or after 1, 2 or 3 lines of prior systemic therapy for recurrent or metastatic disease containing platinum chemotherapy or fluoropyrimidine or cetuximab, or a combination of these agents. Patients should receive standard of care treatment as initial treatment in accordance with local guidelines unless they are intolerant to standard first-line systemic chemotherapy as judged by their treating physician.

- For Stage 2, participants also qualify if they have recurrent disease within 6 months after the last dose of chemotherapy as part of definitive curative intent therapy (including patients who underwent chemoradiation with or without surgery).

103 Cohort 1: Documented HPV/p16 status for oropharyngeal cancer (historical results are acceptable if available).

104 Cohort 1: For Stage 2 participants only: Provision of recent tumor tissue 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.

Cohort 2 (HNSCC, IO treated)

201 Cohort 2: Histologically confirmed recurrent or metastatic HNSCC (from any of the following primary sites only: oral cavity, oropharynx, hypopharynx and larynx) that is not amenable to curative intent surgery or chemoradiation.

202 Cohort 2: Progressed on or after 1, 2 or 3 lines of prior systemic therapy for recurrent or metastatic disease containing PD-1/PD-L1 inhibitor alone or in combination with chemotherapy. One of these prior lines should contain a PD-1/PD-L1 inhibitor.

Progression on a prior PD-1/PD-L1 inhibitor regimen should meet the following criteria:

- Has received at least 2 doses of an anti-PD-1/PD-L1 mAb.
- Has demonstrated disease progression after anti-PD-1/PD-L1 therapy as defined by RECIST. Confirmation of radiographic progression on prior anti-PD-1/PD-L1 therapy is required with a scan confirming progression at least 4 weeks after the initial progression date. Screening scans can be used as the confirmation of progression.

203 Cohort 2: Documented HPV/p16 status for oropharyngeal cancer (historical results are acceptable if available).

204 Cohort 2: Provision of recent tumor tissue 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.

Cohort 3 (ESCC)

301 Cohort 3: Histologically or cytologically confirmed recurrent or metastatic ESCC that is not amenable to curative intent surgery or chemoradiation.

302 Cohort 3: Progression on or after 1 line of systemic therapy for recurrent or metastatic disease with platinum and/or fluoropyrimidine based regimen.

- For Stage 2, participants also qualify if they have recurrent disease within 6 months after the last dose of chemotherapy as part of definitive curative intent therapy (including patients who underwent chemoradiation with or without surgery).

Cohort 4 (PDAC)

401 Cohort 4: Histologically or cytologically confirmed recurrent or metastatic PDAC that is not amenable to curative intent surgery

402 Cohort 4: Progression on or after 1 or 2 lines of systemic therapy for recurrent or metastatic disease with gemcitabine or fluoropyrimidine based regimens

Cohort 5 (BTC)

501 Cohort 5: Histologically or cytologically confirmed recurrent or metastatic BTC, namely cholangiocarcinoma (intrahepatic or extrahepatic) or gall bladder cancer, that is not amenable to curative intent surgery, transplantation, or ablative therapies.

502 Cohort 5: Progression on or after 1 or 2 lines of systemic therapy for recurrent or metastatic disease containing gemcitabine or fluoropyrimidine or platinum therapy or a combination of these agents

Cohort 6 (GBM/AA)

601 Cohort 6: Histologically or cytologically confirmed Grade IV GBM or Grade III AA (World Health Organization [WHO] criteria) established following either a surgical resection or biopsy. This includes participants with prior diagnosis of lower grade astrocytoma from a biopsy that has been upgraded to a histologically verified glioblastoma or anaplastic astrocytoma after a subsequent definitive surgery. AA is only allowed in Stage 2.

602 Cohort 6: Unequivocal first progression after surgery followed by radiotherapy and temozolomide. Evidence of recurrent disease (RD) should be demonstrated by disease progression on biopsy or on MRI based on RANO criteria (using the post-chemoradiation or post-radiation scan as baseline).

For all cohorts

1. Capable of giving signed informed consent, including compliance with the requirements and restrictions listed in the informed consent form (ICF) and in the 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 age of legal maturity or older on day of signing the ICF
3. Eastern Cooperative Oncology Group（ECOG) Performance Status (PS) 0 to 1.
4. Adequate hematologic and organ function as assessed by the following laboratory tests performed within 7 d before start of study treatment:
    - 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 participants with liver involvement of their cancer)
    - Platelet count ≥100,000 /mm^3, Hemoglobin (Hb) ≥9 g/dL, white blood cell count (WBC) ≥2000/µL absolute neutrophil count (ANC) ≥1500/mm^3. Red blood cell (pRBC) transfusion is allowed if Hb meets the criteria for at least 14 days after transfusion.
    - Serum creatinine ≤1.5 x ULN or creatinine clearance ≥40 mL/min (measured or calculated using the Cockcroft-Gault formula)
    - Prothrombin time-international normalized ratio (PT-INR) <2.3 and activated partial thromboplastin time (aPTT)<1.5 x ULN.
5. Measurable disease by baseline CT or MRI per RECIST 1.1 criteria for all cohorts except GBM/AA. For GBM/AA, participants should have measurable disease as defined by RANO criteria at baseline by MRI. Previously irradiated lesions should not be counted as target lesions unless there have been demonstrated progression in the lesion since radiotherapy before study enrollment and no other lesions are available for selection as target lesions
6. Participants must consent to provide biopsy/tumor tissue of a primary tumor lesion or from metastases (e.g. liver, lung) and as defined below:
    - Provision of archival tumor tissue sample is mandatory if available.
    - 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, are mandatory in HNSCC (IO treated) cohort for Stage 1 and 2 and in HNSCC (IO naïve) cohort for Stage 2.
    - Recent tumor tissue samples as defined above are mandatory if medically feasible (as judged by the Investigator) for all participants in ESCC, PDAC, BTC, and for

participants in Stage 1 in HNSCC (IO naïve) cohort. For GBM/AA cohorts, recent tumor tissue samples are optional.

7. Anticipated life expectancy greater than 3 months
8. Be able to swallow and absorb oral tablets
9. Women of childbearing potential (WOCBP) must agree to follow instructions for method(s) of contraception (see Section 10.4) for the duration of study intervention and 7 months (or 210 days) 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 (see Section 10.4) for the duration of study intervention and 4 months (or 120 days) 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.

5.2 Exclusion Criteria

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

Cohort 1 (HNSCC IO naïve)

101 Cohort 1: Histologically confirmed non-squamous, nasopharyngeal, or salivary histology of head and neck cancer, or squamous cell carcinoma that originated from the skin, or of unknown primary origin.

102 Cohort 1: More than 3 prior lines of systemic anticancer therapy for recurrent/metastatic cancer

103 Cohort 1: Presence of symptomatic central nervous system (CNS) metastases, leptomeningeal metastases or spinal cord compression. Previously treated lesions should be stable for at least 6 weeks prior to study entry.

104 Cohort 1: Participants with a condition requiring systemic treatment with either corticosteroids (>10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days 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

105 Cohort 1: Prior therapy with PD-1/PD-L1 or cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibitors, or any form of immunotherapy to treat cancer.

Cohort 2 (HNSCC IO treated)

201 Cohort 2: Histologically confirmed non-squamous, nasopharyngeal, or salivary histology of head and neck cancer, or squamous cell carcinoma that originated from the skin, or of unknown primary origin.

202 Cohort 2: More than 3 prior lines of systemic anticancer therapy for recurrent/metastatic cancer

203 Cohort 2: Presence of symptomatic CNS metastases, leptomeningeal metastases or spinal cord compression. Previously treated lesions should be stable for at least 6 weeks prior to study entry.

204 Cohort 2: Participants with a condition requiring systemic treatment with either corticosteroids (>10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days 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

205 Cohort 2: More than one prior therapy with PD-1/PD-L1 or CTLA-4 inhibitors, or any other form of immunotherapy to treat cancer.

Cohort 3 (ESCC)

301 Cohort 3: More than 1 prior line of systemic anticancer therapy for recurrent/metastatic cancer

302 Cohort 3: Patients with apparent tumor invasion on organs located adjacent to the esophageal disease (e.g., the aorta or respiratory tract).

303 Cohort 3: Patients who have previously received taxane agents for recurrent/metastatic cancer.

304 Cohort 3: Presence of symptomatic CNS metastases, leptomeningeal metastases or spinal cord compression. Previously treated lesions should be stable for at least 6 weeks prior to study entry.

305 Cohort 3: Participants with a condition requiring systemic treatment with either corticosteroids (>10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days 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

306 Cohort 3: Prior therapy with PD-1/PD-L1 or CTLA-4 inhibitors, or any form of immunotherapy to treat cancer.

Cohort 4 (PDAC)

401 Cohort 4: More than 2 prior lines of systemic anticancer therapy for recurrent/metastatic cancer

402 Cohort 4: Presence of symptomatic CNS metastases, leptomeningeal metastases or spinal cord compression. Previously treated lesions should be stable for at least 6 weeks prior to study entry.

403 Cohort 4: Participants with a condition requiring systemic treatment with either corticosteroids (>10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days 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

404 Cohort 4: Prior therapy with PD-1/PD-L1 or CTLA-4 inhibitors, or any form of immunotherapy to treat cancer.

Cohort 5 (BTC)

501 Cohort 5: More than 2 prior lines of systemic anticancer therapy for recurrent/metastatic cancer

502 Cohort 5: Presence of symptomatic CNS metastases, leptomeningeal metastases or spinal cord compression. Previously treated lesions should be stable for at least 6 weeks prior to study entry.

503 Cohort 5: Participants with a condition requiring systemic treatment with either corticosteroids (>10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days 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

504 Cohort 5: Prior therapy with PD-1/PD-L1 or CTLA-4 inhibitors, or any form of immunotherapy to treat cancer.

Cohort 6 GBM/AA

601 Cohort 6: Primary tumors localized to the brainstem or spinal cord

602 Cohort 6: Locally directed therapies administered by injection convection-enhanced delivery within 6 months of start of study treatment.

603 Cohort 6: Presence of diffuse leptomeningeal disease or extracranial disease

604 Cohort 6: Participants requiring > 4 mg of dexamethasone or biologic equivalent per day to control symptoms related to brain tumor and cerebral edema within 21 days of starting study treatment. Also excluded are participants who have a condition (other than symptoms related to brain tumor and cerebral edema) requiring systemic treatment with either corticosteroids (>10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days 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.

605 Cohort 6: Major ongoing safety issues following surgery (e.g. infection requiring intravenous [IV]) antibiotics)

606 Cohort 6: CNS hemorrhage of Grade >1 on baseline MRI scan, unless subsequently documented to have resolved

607 Cohort 6: Prior therapy with PD-1/PD-L1 or CTLA-4 inhibitors, or any form of immunotherapy to treat cancer.

For all cohorts

1. Participants who have known dMMR/MSI-H cancers or NTRK fusions
2. Prior therapy with regorafenib
3. Uncontrolled hypercalcemia (e.g. causing signs and symptoms putting the participant at risk as judged by the investigator)
4. Uncontrolled pleural effusions (e.g. causing signs and symptoms putting the participant at risk as judged by the investigator)
5. Participants receiving any other investigational treatment at the time of informed consent

6. Systemic anti-cancer treatment within 14 days or less than 5 half-lives (whichever is shorter) of the first dose of study treatment
7. Previous radiotherapy is acceptable under the following conditions:
    - Therapy completed more than 4 weeks before the baseline (at screening) scan.
    - Palliative radiotherapy for bone metastases or soft tissue lesions is allowed and should be completed > 7 days prior to baseline scan.
    - Participants must have recovered from all therapy-related toxicities to Grade < 1.
    - If the site of previous radiotherapy is the only site of disease, it should show evidence of disease progression.
8. Participants having 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, platinum-induced neurotoxicity, and endocrine disorders due to prior IO treatment that are well controlled).
9. Participants who have permanent discontinuation of PD-1/PD-L1 therapy due to toxicity.
10. Arterial thrombotic or embolic events such as cerebrovascular accident (including transient ischemic attacks) within 6 months before the start of study treatment. Active pulmonary emboli or deep vein thrombosis that are significant or not adequately controlled on anticoagulation regimen as per investigator's judgement
11. History of cardiac disorders as defined by:
    - Congestive heart failure ≥ New York Heart Association (NYHA) class 2
    - 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
    - Uncontrolled cardiac arrhythmias (e.g. not well controlled on medications or causing signs and symptoms putting the participant at risk as judged by the investigator)
12. Poorly controlled hypertension, defined as a blood pressure consistently above 140/90 mmHg despite optimal medical management
13. Persistent proteinuria of NCI-CTCAE Grade 3 or higher. Urine dipstick result of 3+ or abnormal, based on type of urine test strip used, is allowed if protein excretion (estimated by urine protein/creatinine ratio on a random urine sample) is <3.5 g/24 hr
14. Major surgical procedure or significant traumatic injury within 28 days before start of study treatment. Note: If participants received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy. Central line placement and minor invasive biopsy are not considered major surgery
15. Non-healing wound, non-healing ulcer, or non-healing bone fracture
16. Participants with evidence or history of any bleeding diathesis, irrespective of severity
17. Any hemorrhage or bleeding event ≥ NCI-CTCAE Grade 3 within 28 days prior to the start of study treatment

18. 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
19. 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
20. History of (non-infectious) pneumonitis that required steroids, current pneumonitis or interstitial lung disease
21. Participants with previous malignancies (except superficial esophageal cancer, 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 informed consent signature and no additional therapy is required or anticipated to be required during the study period
22. Diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (for doses >10 mg daily prednisone equivalent) or any other form of immunosuppressive therapy
23. Active infection > NCI-CTCAE Grade 2
24. Positive test (from historical data or tested during screening) for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS)
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 (except for participants on anti-viral therapy for HBV with a viral load < 100 IU/mL), or Hepatitis C antibody (anti-HCV) positive (except if HCV-ribonucleic acid [RNA] negative)
26. Pregnancy or breast feeding
27. Psychological, familial, or sociological condition potentially hampering compliance with the study protocol
28. Previous treatment with live vaccine within 30 days of planned start of study treatment (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
30. History or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial or interfere with the participation for the full duration of the trial
31. Participants with a current or past history of interstitial lung disease or pulmonary fibrosis diagnosed based on imaging or clinical findings.

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

For details please refer to Section 6.

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 treatment. 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, date of informed consent, inclusion/exclusion criteria with at least one of them failed, the reason for premature discontinuation, cancer classification), and any serious AE (SAE) information.

Individuals who do not meet the criteria for participation in this study 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. All expired tests/assessments must be repeated to fall within the protocol-defined time window as specified in SoA and the investigator should ensure that the repeated screening procedures do not expose the patient to unjustifiable health risks.

The screening failure will be registered in Interactive Voice/Web Response System (IxRS) to close the participant identification number (PID). Re-screening will start by signing a new informed consent form, even if the content was not changed after the patient's previous screening, 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.

A cycle will be defined as 28 days (plus a potential time window, for acceptable deviation see Section 1.3 SoA) regardless of interruptions. Accordingly, a new cycle will start, even if one or both study drugs are interrupted.

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 IV infusion every 4 weeks (Q4W)

Regorafenib will be given orally every day for 3 weeks of each cycle. Each treatment cycle will be 28 d in duration. Regorafenib will be given as 30 mg tablets QD for 3 weeks of every 4 weeks (i.e., 3 weeks on, 1 week off) as a starting dose of 90 mg. If starting dose of 90 mg daily is well tolerated (absence of any grade rash/HFSR or other Grade 2 or higher clinically significant toxicity; lab abnormalities of any grade that resolve to ≤Grade 1 within 72 hours are acceptable) dose can be escalated to 120 mg orally daily anytime after Cycle 1 starting with C2D1. Sponsor should be informed immediately, 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. A light meal contains less than 600 calories and less than 30% fat. 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 of pre-dose PK all blood samples will be collected at the clinic prior to the morning dose of regorafenib. When participants are dosed at the site, they will receive regorafenib directly from the Investigator or designee.

Participants will continue treatment until any treatment discontinuation criteria apply as specified in Section 7.1.

Treatment with individual drugs (regorafenib or nivolumab) may continue on schedule even if the other drug is interrupted or permanently discontinued due to toxicity.

Participants who complete 24 infusions of nivolumab (after approximately 2 years of treatment) need to discontinue nivolumab treatment. Regorafenib treatment can be continued until clinical or radiological disease progression or unacceptable toxicity.

Treatment beyond radiological progression is possible. See Section 8.1 for additional details. In order to continue treatment after initial documentation of disease progression as per RECIST 1.1 or RANO, participant must be re-consented. Re-consent also covers a potential treatment continuation with regorafenib after confirmed radiological progression (according to iRECIST or iRANO).

6.1 Study Intervention(s) Administered

Table 6–1 Administration of Study Intervention

Study Intervention	Regorafenib	Nivolumab
Type	small molecule drug (MKI)	monoclonal antibody (mAB), biologic
Dose Formulation	tablet	solution for infusion
Unit Dose Strengths	30 mg / tablet	100 mg / 10 mL vial (10 mg/mL)
Dosage Levels	3x 30 mg tablets every day (q.d.) for 21 days of every 28-day cycle (21 days on, 7 days off) as a starting dose of 90 mg. If the starting dose is well tolerated dose should be escalated to 120 mg (4x30 mg tablets) starting with C2D1.	480 mg (5x100 mg / 10 mL vials) on D1 of each cycle
Route of Administration	oral	i.v. infusion
Use	experimental	experimental
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 21 tablets Regorafenib 30 mg and a 3 g desiccant per bottle. 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.
Current/Former Name(s) or Alias (es)	Stivarga / BAY 73-4506	Opdivo®

Abbreviations: IMP = Investigational medicinal product; i.v. = Intravenous; mAB = Monoclonal antibody; 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 30 mg tablets in bottles and the nivolumab 100 mg / 10 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 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 participant. Beyond that, no special precautions are required, when handling the study intervention.

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 cycles must be assigned by the IxRS for tracking and accountability purposes.

Participant Identification

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

Digits 1 to 5 = Unique center number

Digits 6 to 7 = Indication (cohort) identifier and study stage

Digits 8 to 9 = Current patient number within the center and indication (cohort)

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 regorafenib pharmacokinetics (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 (see Table 1–4).

When participants self-administer regorafenib at home, compliance with regorafenib will be assessed at each D1 of a cycle. 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.

6.5 Concomitant Therapy

6.5.1 Drug-Drug Interactions Relevant for Regorafenib

6.5.1.1 Inhibitors / Inducers of CYP3A4

Administration of ketoconazole (400 mg for 18 d), a strong cytochrome p450 (CYP)3A4 inhibitor, with a single dose of regorafenib (160 mg on D5) resulted in an increase in mean exposure (area under the plasma concentration time curve [AUC]) of regorafenib of approximately 33%, and a decrease in mean exposure of the active metabolites, M 2 and M 5, of approximately 90%. It is recommended to avoid concomitant use of strong inhibitors of CYP3A4 activity (Section 10.8) as their influence on the steady state exposure of regorafenib and its metabolites has not been studied.

Administration of rifampicin (600 mg for 9 d), a strong CYP3A4 inducer, with a single dose of regorafenib (160 mg on D7) resulted in a reduction in AUC of regorafenib of approximately 50%, a 3- to 4-fold increase in mean exposure of the active metabolite M 5, and no change in exposure of active metabolite M 2. Other CYP3A4 inducers (Section 10.8) may also increase metabolism of regorafenib. Inducers of CYP3A4 should be avoided, or selection of an alternate concomitant medicinal product, with no or minimal potential to induce CYP3A4 should be considered.

Section 10.8 provides an overview of the most commonly used strong CYP3A4 inhibitors and CYP3A4 inducers) that should be avoided during the study.

6.5.1.2 UGT1A1 and UGT1A9 Substrates

In vitro data indicate that regorafenib as well as its active metabolites M-2 inhibit glucuronidation mediated by UDP-glucuronosyltransferase 1-1 (UGT1)A1 and UGT1A9 whereas M-5 only inhibits UGT1A1 at concentrations which are achieved in vivo at steady state.

Administration of regorafenib with a 5-day break prior to administration of irinotecan resulted in an increase of approximately 44% in mean exposure (AUC) of SN-38, a substrate of UGT1A1 and an active metabolite of irinotecan. An increase in mean exposure (AUC) of irinotecan of approximately 28% was also observed. This indicates that co-administration of regorafenib may increase systemic exposure to UGT1A1 and UGT1A9 substrates. The clinical significance is unknown and is dependent on the substrate.

6.5.1.3 Breast Cancer Resistance Protein and P-glycoprotein Substrates

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

6.5.1.4 CYP Isoform-Selective Substrates

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

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

6.5.1.5 Antibiotics

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

6.5.1.6 Bile Salt-Sequestering Agents

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

6.5.2 Permitted Concomitant Therapies

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

a) Treatment with non-conventional therapies (e.g., acupuncture) and vitamin/mineral supplements is acceptable provided that they do not interfere with the study endpoints, in the opinion of the Investigator.

b) Administration of contrast media for protocol-specified radiological procedures (CT scan or MRI) does not need to be reported on the concomitant medication eCRF page, unless there is an AE related to the contrast medium injection (e.g. allergic reaction).

c) Participants who are therapeutically treated with low molecular weight heparin or novel oral anticoagulants (NOACs) such as dabigatran or rivaroxaban will be allowed to participate provided that no prior evidence of underlying abnormality in coagulation parameters exists.

d) Participants may receive palliative or supportive care for any underlying illness (e.g.: anti-emetics, anti-diarrheal, IV fluids).

e) Bisphosphonates and/or receptor activator of nuclear factor kappa-B ligand (RANKL) inhibitor therapies (such as denosumab) for bone metastases may be continued if

treatment with an agent from one of these two classes was initiated prior to signing informed consent. Bisphosphonates and/or RANKL inhibitor therapies cannot be initiated after informed consent has been signed, unless in the opinion of the Investigator, the participant does not have PD.

f) Hematopoietic colony stimulating growth factors such as granulocyte colony stimulating factor (G-CSF) and other hematopoietic growth factors may be used during the study in the management of acute toxicity such as febrile neutropenia when clinically indicated or at the discretion of the Investigator; however, they may not be substituted for a required dose reduction or used prophylactically. Participants taking chronic erythropoietin are permitted.

g) Participants are permitted the use of topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption). Adrenal replacement steroid doses >10 mg daily prednisone are permitted in the absence of active autoimmune disease.

h) A brief (less than 3 weeks) course of corticosteroids for prophylaxis (e.g., contrast dye allergy) or for treatment of non-autoimmune conditions (e.g., delayed-type hypersensitivity reaction caused by a contact allergen) is permitted

i) Radiotherapy:

- Palliative radiotherapy during the study is allowed for local pain control after individual benefit-risk assessment provided that:
  - In the opinion of the Investigator, the participant does not have PD,
  - No more than 25% of the participant's bone marrow is irradiated
  - The radiation treatment field may not include a target lesion by RECIST 1.1.
- Nivolumab should be withheld for at least 1 week before, during and 1 week after radiation. Participants should be closely monitored for any potential toxicity during and after receiving radiotherapy, and AE should resolve to Grade ≤1 prior to resuming therapy. Regorafenib may only be continued during palliative radiotherapy after an individual benefit-risk assessment. The Investigator should consult the Sponsor

j) Analgesics

k) Nutritional support

l) Other medications that the Investigator deems to be medically necessary.

Major surgery should only be performed during the study period if, in the opinion of the Investigator and after careful individual benefit/risk assessment (taking into account the potential wound healing complications that have been described with all anti-VEGF drugs), the surgery will be beneficial for the participant (except surgery for symptom management or palliative tumor control).

It is recommended to stop regorafenib treatment at least two weeks before scheduled major surgery. Central line placement and minor invasive biopsy are not considered major surgery. The decision to resume regorafenib after major surgery should be no sooner than two weeks after major surgery and be based on clinical judgment of adequate wound healing. Patients should be placed back on study therapy within 4 weeks of the scheduled interruption of

regorafenib. The appropriate interval of time between minor procedure (biopsy) and regorafenib treatment required to minimize the risk of impaired wound healing and bleeding has not been determined. Treatment with regorafenib may be interrupted at least 24 hours before the procedure and the decision to reinitiate regorafenib treatment should be based upon a clinical assessment of satisfactory wound healing and recovery from the procedure.

6.5.3 Prohibited Prior and Concomitant Therapies

Patients are prohibited from receiving the following therapies during the course of the study:

a) Disease-specific anti-neoplastic therapies, including kinase inhibitors, immunotherapy, chemotherapy, hormonal therapy, non-palliative radiation therapy or experimental therapies other than regorafenib and nivolumab are not allowed.

b) Any botanical preparation (e.g., herbal supplements or traditional Chinese medicines) intended to treat the disease under study or provide supportive care. Use of marijuana and its derivatives for treatment of symptoms related to cancer or cancer treatment are permitted if obtained by medical prescription or if its use (even without a medical prescription) has been legalized locally.

c) Surgery for symptom management or tumor control.

d) Concomitant use of strong inhibitors of CYP3A4 and strong inducers of CYP3A4 (listed in Section 10.8) are not permitted for 2 weeks prior to start of study intervention or during the study.

e) Grapefruit and grapefruit juice (CYP3A4 inhibitor) consumption is not permitted during the study.

f) Excessive intake of biotin above the recommended daily dose of 30 µg. Biotin is found in multivitamins, including prenatal multivitamins, biotin supplements, and dietary supplements for hair, skin, and nail growth at levels that may interfere with laboratory tests.

g) Investigational anti-neoplastic chemo/hormonal/immunotherapy.

h) Any live/attenuated vaccine (e.g., varicella, zoster, yellow fever, rotavirus, oral polio and measles, mumps, rubella [MMR]) during treatment and until 100 days post last dose (LD) of nivolumab. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however intranasal influenza vaccines (e.g., FluMist®) are live attenuated vaccines and are not allowed.

i) Immunosuppressive agents and immunosuppressive doses of systemic corticosteroids (except as stated in Section 6.5.2 regarding permitted therapies and to treat a drug-related adverse event).

j) Co-administration of a strong UGT1A9 inhibitor (e.g. mefenamic acid, diflunisal, and niflumic acid) during regorafenib treatment should be avoided, as their influence on the steady-state exposure of regorafenib and its metabolites has not been studied.

6.5.4 Documentation of Prior and New Concomitant Therapies

All medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that may affect efficacy, toxicity or taken for any concurrent medical conditions at the time of enrollment or during the study must be recorded along with:

a) Reason for use

b) Dates of administration including start and end dates

c) Dosage information including dose and frequency

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.5.5 Rescue Medicine

Not applicable for this study intervention

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. The length of a cycle is 28 days (plus a potential time window, for acceptable deviation see Section 1.3 SoA). 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.

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 dependent on resumption of nivolumab 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.

A cycle will be defined as 28 days regardless of interruptions.

- In case of interruption regorafenib is allowed to be re-started during the cycle within day 1 and day 21, regorafenib should not be restarted in the off week. Missed doses of regorafenib will not be replaced in the off week.
- For nivolumab dosing occurs on day 1 of every cycle
- Per protocol dose reduction or increase of nivolumab is not allowed

6.6.1 Toxicity Management, Dose Modification and Permanent Discontinuation 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 Levels for Regorafenib

Dose Level	Daily Regorafenib (21 days on, 7 days off)	Daily Regorafenib (21 days on, 7 days off from cycle 2 onwards if escalation if feasible)
Dose Level 0	90 mg	120 mg
Dose Level -1	60 mg	90 mg
Dose Level -2	NA	60 mg[a]

Abbreviations: NA = Not applicable

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

Table 6–3 Dose Modification/Dose Interruption Guide for Regorafenib-Related Toxicities

CTCAE Grade	Occurrences	Dose Interruption	Dose modification (when resuming treatment)
Grade 0-2[c]	Any	No change	No change
Grade 3[c]	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[c]	Any	-	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 60 mg, then 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. Participants requiring a delay of >4 weeks should discontinue regorafenib treatment. However, continuation of regorafenib may be considered if, in the investigator's opinion, the participant may continue to benefit from the regorafenib treatment, and after consultation with Sponsor.

c) Discontinuation is required for severe bleeding necessitating urgent medical intervention, gastrointestinal perforation or fistula of any grade and posterior reversible encephalopathy syndrome (PRES) of any grade.

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

Skin toxicity grade (CTCAE)	Occurrence	Dose Interruption	Dose modification (when resuming treatment)
Grade 1	Any	Maintain dose level and institute supportive measures immediately for symptomatic relief	No Change
Grade 2	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	
Grade 3	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 60 mg, then 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. Participants requiring a delay of >4 weeks should discontinue regorafenib treatment. However, continuation of regorafenib may be considered if, in the investigator's opinion, the participant may continue to benefit from the regorafenib treatment, and after consultation with Sponsor.

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

CTCAE Grade	Suggested regorafenib dose interruption	Suggested regorafenib dose modification
Specific guidance for HYPERTENSION		
Grade 1	No change.	Consider increased BP monitoring
Grade 2	If symptomatic, hold until symptoms resolve and diastolic BP ≤ 90 mmHg. Treat with anti-hypertensive medications	At restart, continue at the same dose level
Grade 3	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]
Grade 4[b]	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 60 mg, then 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. Regorafenib cannot be interrupted for more than 28 consecutive days including the drug holidays. However, continuation of regorafenib may be considered if, in the investigator's opinion, the participant may continue to benefit from the regorafenib treatment, and after consultation with Sponsor.

b) This includes hypertensive crisis per CTCAE v 5.

Table 6–6 Dose Modification/Dose Interruption Guide for Regorafenib-related Toxicities: Liver Function Test Increases Related to Regorafenib[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) AST and/or ALT > 20 x ULN	Any	**Discontinue**	

Increases in AST/ALT/Bilirubin	Occurrence	Dose Interruption	Dose Modification (when resuming treatment)
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.

6.6.2 Toxicity Management, Dose Modification and Permanent Discontinuation Recommendations for Nivolumab

There will be no dose reductions for nivolumab. Recommendations for nivolumab delay and discontinuation are provided (Table 6–7) when the Investigator attributes toxicity event to nivolumab either alone or in combination with regorafenib. In situations where clear attribution cannot be made to an individual drug (regorafenib or nivolumab), a more conservative dose modification approach should be used for both drugs (Section 6.6).

Resumption of nivolumab dosing is not dependent on resumption of regorafenib 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. Further details regarding resumption of nivolumab are specified in Section 6.6.2.1.

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 (Section 6.6.2.2).

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). Additional information is in Section 6.6.2.3.

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Table 6–7 Recommended Dose Modification for Nivolumab[a]

Adverse Reaction	Severity (CTCAE v5)	Dose Modification
Colitis	Grade 2 diarrhea or colitis	Withhold dose[b]
	Grade 3 diarrhea or colitis	Withhold dose[b]
	Grade 4 diarrhea or colitis	Permanently discontinue
Pneumonitis	Grade 2 pneumonitis	Withhold dose[b]
	Grade 3 or 4 pneumonitis	Permanently discontinue
Hepatitis/non-hepatocellular carcinoma	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	Withhold dose[b]
	AST or ALT more than 5 times the ULN or total bilirubin more than 3 times the ULN	Permanently discontinue[c]
Hypophysitis/ Hypopituitarism	Grade 1-3 hypophysitis that is also associated with corresponding abnormal lab and/or pituitary scan	Withhold dose[b]
	Grade 4	Permanently discontinue
Hyperthyroidism or Hypothyroidism	Grade 2 or 3	Withhold dose[d]
	Grade 4	Withhold dose or permanently discontinue
Adrenal Insufficiency	Grade 2 adrenal insufficiency	Withhold dose[b]
	Grade 3 or 4 adrenal insufficiency	Permanently discontinue[e]
Hyperglycemia	Grade 2 or 3 hyperglycemia requiring initiation or change in daily management	Withhold dose[b]
	Grade 4 hyperglycemia	Permanently discontinue
Nephritis and Renal Dysfunction	Serum creatinine more than 1.5 and up to 6 times the ULN	Withhold dose[b]
	Serum creatinine more than 6 times the ULN	Permanently discontinue
Skin	Grade 2 rash covering >30% BSA or 3 rash or **suspected** SJS, TEN or DRESS	Withhold dose[b]
	Grade 4 rash or **confirmed** SJS, TEN or DRESS	Permanently discontinue
Myasthenia gravis, Guillain-Barre syndrome, treatment-related myelitis, or encephalitis	Any grade	Permanently discontinue
Neurological adverse reaction (other than Guillain-Barre syndrome, myasthenia gravis, encephalitis, or myelitis)	Grade 2	Withhold dose[b]
	Grade 3 or 4	Permanently discontinue
Other	Other Grade 3 adverse reaction: First occurrence Recurrence of same Grade 3 AR	Withhold dose[b] Permanently discontinue

	Life-threatening or Grade 4 AR	Permanently discontinue
	Grade 2 myocarditis	Withhold dose[b]
	Grade 3 or higher myocarditis	Permanently discontinue
	Requirement for 10 mg per day or greater prednisone or equivalent for more than 12 weeks	Permanently discontinue
	Persistent Grade 2 or 3 ARs lasting 12 weeks or longer	Permanently discontinue

Abbreviations: ALT = Alanine aminotransferase; AR = Adverse reaction; AST = Aspartate aminotransferase; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; SJS = Stevens-Johnson syndrome; TEN = Toxic epidermal necrolysis; DRESS = Drug Reaction with Eosinophilia and Systemic Symptoms; ULN = Upper limit of normal

a) For additional management recommendations, please see Appendix 9: Guidance for Management of Immune-Related Adverse Events Section 10.9.
b) Resume treatment when adverse reaction improves to Grade 0 or 1 (see further details in Section 6.6.2.1).
c) In most cases of AST or ALT > 5 x ULN, study treatment will be permanently discontinued. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study treatment, a discussion between the investigator and the Medical Monitor/ designee must occur and approval from Medical Monitor prior to resuming therapy.
d) Dosing may resume if endocrinopathy resolves to be asymptomatic, or is adequately controlled with only physiologic hormone replacement or other medical management.
e) If adrenal insufficiency resolves or is adequately controlled with physiologic hormone replacement, participant may not require discontinuation of study drug. Mandatory discussion with and approval from the Medical Monitor needed prior to resuming therapy.

Nivolumab Treatment – Permanent Discontinuation

In addition to nivolumab treatment discontinuation specified in Table 6–7, the following criteria of discontinuation are as follow:

a) Patients who complete 24 infusions of nivolumab (after approximately 2 years of treatment)

b) In the scenario when AST or ALT elevation fulfills the criteria of discontinuation and the investigator judges there is a possible favorable benefit/risk profile that warrants continuation of nivolumab treatment, a discussion between the investigator and the Sponsor must occur.

c) 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.

d) 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.

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.

6.6.2.1 Criteria to Resume Nivolumab Treatment

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 at D1 of a next planned cycle.

Participants may resume treatment with nivolumab when the drug-related AE(s) resolve to Grade ≤ 1 or baseline value (please refer to Appendix 9: Guidance for Management of Immune-Related Adverse Events), with the following exceptions:

Participants may resume treatment in the presence of Grade 2 fatigue

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.

6.6.2.2 Management of Immune-Mediated AEs

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 case report form.

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, cardiac toxicity and renal toxicity. These adverse event management algorithms are included in Section 10.9.

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.

6.6.2.3 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 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 End of Treatment

At the EoT for each individual participant, further therapeutic options with drugs other than regorafenib and/or nivolumab are at the discretion of the Investigator.

An EoT visit will be performed within 14 days after permanent discontinuation of study treatment. Note: If the study treatment was permanently discontinued after dose interruption of more than 28 days (including drug holiday for regorafenib), the active FU visit should also occur within 14 days of discontinuation. If the EoT and active FU visits will be scheduled at the same time, the visits can be combined.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

General procedures

Discontinuation of one study drug does not constitute withdrawal from study treatment period. Permanent discontinuation of both study drugs (regorafenib and nivolumab) constitutes withdrawal from treatment period of the study. Withdrawal from treatment period (all study drugs are discontinued) does not constitute withdrawal from the study. Patients who withdraw from study treatment period for any reason should complete the active safety FU visit and should be encouraged to remain on the study for FU of primary, secondary and other objectives (i.e. continue in the active FU and long-term FU periods). Patients are expected to participate in the FU unless they explicitly object. Withdrawal of consent to treatment should be documented in the patient's medical record. If the patient does not wish to be followed up further, this additional consent withdrawal for FU must also be documented.

The criteria for withdrawal from the study are listed in Section 7.2, and the criteria for permanent discontinuation of each study drug are listed in Section 6.6.1 for regorafenib and in Section 6.6.2 for nivolumab.

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 from study, no further study related procedures will be allowed. The patient will not suffer any disadvantage as a result.

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.

All patients who discontinue due to AEs should be followed up until they recover or stabilize, and the subsequent outcome is recorded. If any participant dies during treatment, or within 30 d + 7 d after the last dose of regorafenib if a patient was on regorafenib monotherapy or within 100 d + 14 d after the last dose of regorafenib/nivolumab combination treatment or nivolumab monotherapy, 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 both, regorafenib and nivolumab, if any of the following occurs:

- At their own request. 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.
- Confirmed PD as per iRECIST or iRANO criteria; however, treatment may be continued provided that the patient derives ongoing clinical benefit as determined by the treating physician (Participants who complete 24 infusions of nivolumab [after approximately 2 years of treatment] need to discontinue nivolumab treatment. Regorafenib monotherapy treatment can be continued beyond 2 years until discontinuation criteria are met).
- Clinical progression (every effort should be made to obtain radiological confirmation of 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.
- Substantial non-compliance with the requirements of the study.
- If all study drugs (regorafenib and nivolumab) have to be permanently discontinued. Requirements for discontinuation of individual study drugs are described in Section 6.6.1 for regorafenib and in Section 6.6.2 for nivolumab.
- 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 FU
- 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 > 10 weeks to receive the subsequent nivolumab infusion due to treatment related toxicity (see exceptions in Section 6.6.1)
    - 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 Medical Monitor (or designee).
  - 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 6.6.1.

Withdrawal from active FU

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

- At their own request. 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 per iRECIST or iRANO (Participants who discontinue study intervention due to confirmed radiological PD per iRECIST or iRANO will terminate the active FU period after the safety FU visits are completed
- Start of subsequent systemic anti-cancer treatment after the safety FU visits are completed
- Development of a second primary malignancy that requires a different treatment after the safety FU visits are completed
- 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 both, regorafenib and nivolumab, for the following reasons:

- At the specific request of the sponsor and in liaison with the investigator (e.g., obvious non-compliance, safety concerns).
- Discontinuation of study intervention for toxicity should be considered by the Investigator when a participant meets one of the conditions outlined in Section 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 (QT interval corrected for heart rate F [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 Participant Discontinuation/Withdrawal from the Study

For details on participant discontinuation and withdrawal from the study please refer to section 7.1.

7.3 Lost to FU

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 table (Section 1.3). 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 (Section 1.3), is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA (Section 1.3).
- In the event of a significant trial-continuity issue (e.g. caused by a pandemic), alternate strategies for participant visits, assessments, medication distribution and monitoring may be implemented by the sponsor or the investigator, as per local health authority / ethics requirements.

8.1 Efficacy Assessments

For HNSCC (IO-naïve), HNSCC (IO-treated), ESCC, PDAC and BTC, RECIST 1.1 (Section 10.6.1) and iRECIST (Section 10.6.2) criteria will be used to determine the efficacy. iRECIST will be used to make treatment-related decisions beyond initial RECIST 1.1 progression.

For GBM/AA, tumor response and efficacy variables will be evaluated using the RANO (Section 10.6.3) and iRANO criteria (Section 10.6.4). iRANO will also be used to make treatment-related decisions beyond initial progression for GBM/AA.

Imaging acquisitions:
The following anatomic coverage is required:

- HNSCC (IO-naïve and IO-treated): At screening, neck, chest, abdominal and pelvic CT with oral and intravenous (IV) contrast. During treatment and follow-up, neck and chest CT with oral and IV contrast should be performed. Abdominal and pelvic scans should be done if disease is present at screening. Otherwise, abdominal and pelvic scans may be done as clinically indicated if disease was absent at screening. For HNSCC, the anatomic coverage for the neck scan should typically include from the base of the skull to the base of the neck. The reconstructed slice thickness for this

anatomic coverage is highly recommended to be ≤ 3 mm. For the CT scans of the chest, abdomen and pelvis, reconstructed slice thickness should be ≤ 5 mm.

- ESCC: Neck, chest, abdominal and pelvic CT with oral and IV contrast.
- PDAC, BTC: CT of chest, abdomen and pelvis with oral and IV contrast.
- GBM/AA: Brain MRI with and without IV gadolinium-based contrast agent.

When intravenous and oral agents are required per protocol, oral contrast agents may be omitted if the requirement for oral contrast administration is inconsistent with local regulations.

HNSCC, ESCC, PDAC, BTC participants with known or suspected CNS tumor lesions should undergo contrast enhanced MRI (preferred)/CT scans of the brain. Participants with new brain metastases on screening scan are excluded. Participants with known CNS tumor lesions on screening scan should have stable lesions for at least 6 weeks, confirmed by comparison to prior brain MRI/CT scans. If CNS lesion stability is confirmed at screening, participants are eligible to undergo study treatment and brain MRI/CT should be repeated at every tumor assessment time point on study. If any participants develop CNS symptoms during the study, brain MRI/CT should be performed if clinically indicated.
For all cohorts, the anatomic coverage should further include any other anatomic areas of known or suspected disease at baseline and throughout the study.

The slice thickness for CT and MRI is strongly recommended to be ≤ 5mm without gap. MRI should be performed instead of CT when institutional policy does not recommend the use of CT or there is a contraindication to iodinated CT contrast. It is recommended, that when MRI is used instead of CT, MRI of the abdomen and pelvis (and neck, when applicable) should be performed with a gadolinium-based contrast agent. However, the chest should still be assessed with a CT scan (without contrast if contrast allergy exists). MRI of the chest can be performed in extenuating circumstances (e.g. local health regulations).

Whole-body bone scans with both anterior and posterior projection using a technetium-99m phosphonate tracer (methylene diphosphonate [MDP], hydroxymethylene diphosphonate [HMDP], hydroxyethylene diphosphonate [HDP], or 2,3-dicarboxypropane-1,1-diphosphonate [DPD]) will be performed within 28 days prior to the start of study treatment to establish baseline presence or absence of bone lesions for all participants with known bone metastases or clinically suspected of having bone disease. Bone scans should be repeated when CR or PR is identified in the CT/MRI assessments to confirm the absence of new bone lesion(s) disease or when progression in bone is suspected.

For primary brain tumors (GBM/AA), MRI of the brain should be performed with and without a gadolinium-based contrast agent. Recommended sequences are the following: pre-contrast axial 3D T1, axial T2 fluid-attenuated inversion recovery (FLAIR) and axial diffusion-weighted imaging (DWI); post-contrast sequences are an axial T2 and a 3D T1. Slice thickness should typically be ≤ 5mm without a gap (1mm is optimal for 3D T1 and 3mm for T2, FLAIR and DWI).

For consistency, the same imaging modality and equivalent technique (e.g. slice thickness, field of view, contrast agent, bone scan radiotracer, magnet strength) should be used for all scans across all time points (including baseline scans) performed on an individual participant.

Imaging time-points:
The time-points for CT, MRI and bone scans, if applicable, are described in the SoA (Section 1.3). Baseline radiological tumor assessments will be conducted within 28 days before C1D1.

Scans performed prior to the participant signing informed consent may be used for baseline tumor assessments provided:

- CT/MRI scans were conducted within 28 days of C1D1
- Bone scans were conducted within 42 days of C1D1
- There has been no intervening therapy between the scans and C1D1
- The scans meet the imaging requirements of this protocol (Section 8.1)

Tumor assessments during the treatment period will occur every 8 weeks (± 7 days) through Cycle 8 (or until treatment discontinuation, if treatment discontinuation occurs before) and every 12 weeks (± 14 days) thereafter during the treatment period until initial criteria for disease progression are met. When disease progression occurs, tumor assessments should follow the iRECIST (Section 10.6.2) or iRANO timing (Section 10.6.4) as described below.

Tumor assessment will be repeated at the EoT visit or safety follow-up visit if not performed within 12 weeks since the most recent tumor assessment. For participants who discontinue study treatment without radiological disease progression, every effort should be made to perform CT/MRI tumor assessments every 12 weeks (± 14 days) during active-FU until radiological progression of the disease occurs or the start of a new anti-cancer treatment. The schedule of tumor assessments beyond unconfirmed progression per RECIST 1.1 or RANO during the active FU is described below.

Tumor response assessments for all participants except those with GBM/AA:
The primary endpoint for efficacy assessment is ORR measured by RECIST 1.1 (Section 10.6.1) as determined by local assessment. ORR measured by iRECIST (Section 10.6.2) will also be included as an exploratory endpoint. Tumor response using RECIST 1.1 criteria will continue until disease progression (PD) occurs. The minimum time interval required between two tumor assessments for determination of stable disease is 6 weeks per RECIST 1.1. CT/MRI scans for confirmation of PR or CR should be performed no sooner than 4 weeks after the initial scan demonstrating PR or CR.

Please note that chest X-rays should not be used at baseline in lieu of chest CT assessments. However, if an unequivocal new tumor lesion(s) is identified on at a chest X-ray during the study and that lesion which was not present on the most recent prior CT chest assessment, this chest X-ray is acceptable as imaging evidence for PD. FDG PET/CT scans may be used to complement CT or MRI scans for the assessment of progression (e.g., for the detection of new lesions) as described in the RECIST 1.1 criteria (Eisenhauer et al. 2009). Changes in FDG uptake in known lesions should not be used to define a positive response or progression. The low dose or attenuation correction CT portions of a combined PET/CT are of limited use in anatomically based efficacy assessments and it is therefore suggested that they should not be

substituted for dedicated diagnostic contrast enhanced CT scans for anatomically based RECIST 1.1 measurements. However, if a site can document that the CT performed as part of a PET/CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast) then the CT portion of the PET/CT can be used for response assessments.

NOTE: Lesions selected as target (measurable) lesions per RECIST 1.1 should not be biopsied. Additional guidance will be provided to the site on decisions about performing biopsies on potential target lesions when only one potential target lesion exists at baseline.

For treatment beyond RECIST 1.1 progression:
For participants who show evidence of PD by RECIST 1.1, the Investigator may decide to continue a participant on study treatment using the iRECIST guidelines (Section 10.6.2) if the participant signs a new consent for continuation of treatment beyond initial documentation of disease progression and if the following features are fulfilled:

- No worsening of performance status has occurred
- No clinically relevant increases in disease-related symptoms
- No requirement for intensified management of disease-related symptoms exists
- Absence of tumor progression at critical anatomical sites that cannot be managed by protocol−allowed medical interventions

For participants who continue treatment beyond unconfirmed progressive disease (iUPD), the next imaging assessment should be performed ≥ 4 weeks and no longer than 8 weeks later. Participants should discontinue study treatment upon confirmed progression per iRECIST (iCPD). During the treatment phase, if immune complete response (iCR), immune partial response (iPR) or immune stable disease (iSD) is determined following iUPD, imaging assessments should continue as originally planned (8 weeks (± 7 days) through Cycle 8 (or until treatment discontinuation, if treatment discontinuation occurs before) and every 12 weeks (± 14 days) thereafter). During active FU, tumor assessments should also be performed ≥ 4 weeks and no longer than 8 weeks later following any determination of iUPD until determination of iCR, iPR, iSD or until iCPD occurs.

NOTE: If a participant has iCPD, but the participant is achieving a clinically meaningful benefit, an exception to continue treatment and tumor assessments until clinical disease progression may be considered following consultation with the sponsor.

Tumor response assessments for participants with GBM/AA:
The primary endpoint for efficacy assessment is ORR measured by RANO (Section 10.6.3) as determined by local assessment. ORR measured by iRANO (Section 10.6.4) will also be included as an exploratory endpoint. Tumor response using RANO criteria will continue until initial disease progression is detected. Both CR and PR responses should be confirmed ≥ 4 weeks later. If PR or CR is not confirmed, response will be considered only SD. If PD occurs beyond 6 months after initiation of treatment, the participant should be discontinued from treatment. For any participant deemed clinically unstable (provided that their decline is attributable to the disease and not comorbid events or changes in medication), the investigator should discontinue the participant from study treatment at site-assessed first radiologic evidence of PD without need for repeat tumor imaging for confirmation of PD and regardless of whether the PD occurs within the first 6 months after initiation of study treatment. For

these participants, the date of progression is the date the patient developed substantial neurological decline attributable to their underlying tumor.

For treatment beyond initial RANO progression:
When a participant has an initial unconfirmed PD by RANO that is within the first 6 months of starting treatment, the investigator may consider treating past this unconfirmed PD using iRANO criteria (Section 10.6.4) if the participant is clinically stable according to the following criteria:

- No decline in ECOG PS
- No clinically relevant increase in symptoms related to the participant's cancer
- No requirement for intensified management of disease related symptoms, including increased analgesia, radiation, or other palliative care

If it is decided that the participant may continue treatment, the participant must be re-consented for continuation of treatment beyond initial RANO-based unconfirmed disease progression.
Treatment may continue for 12 weeks as long as no significant clinical decline unrelated to comorbid event or concurrent medication occurs. Participants who develop substantial clinical decline at any time, should be classified as having progressive disease with the date of disease progression back-dated to the first date that the patient met criteria for radiographic progression. For these participants, treatment should be discontinued. If progression is not confirmed, the participant may continue treatment with brain imaging every 12 weeks (± 14 days) in the absence of increased corticosteroid dosing. Note: Unscheduled brain MRI within this 12-week treatment period may be done as medically appropriate at the discretion of the investigator. If PD is assessed and judged by the investigator to be true disease progression rather than pseudoprogression due to immunotherapy, the participant should discontinue treatment. During active FU, within 6 months of initiation of treatment, tumor assessments should also be performed every 12 weeks (± 14 days) until confirmation of progressive disease, so long as the participant is clinically stable as defined above and no other therapy has been initiated. Confirmation of progressive disease is not necessary during active FU beyond 6 months after initiation of treatment.

The doses and duration of use of corticosteroids should be limited to the minimum amount needed to control neurologic symptoms. Participants who need increased corticosteroid use within 2 weeks of MRI assessment relative to the dose taken at the time of the previous assessment, cannot be classified as having a CR, PR, or SD and should be classified as non-evaluable at that timepoint. Conversely, patients who decrease corticosteroid use within 2 weeks of MRI assessment relative to the dose taken at the time of the previous assessment cannot be classified as having PD and should be classified as non-evaluable.

Image scan collection:
All imaging scans (coded with study participant number and in digital DICOM format for CT/MRIs) as well as imaging-related adjunctive data (e.g. dose of contrast) will be prospectively collected and stored at an imaging core laboratory designated by the sponsor in the event that an independent central review of the scans is warranted.

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 IBs 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 (Section 1.3).

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. Planned time points for all safety assessments are provided in the SoA.

8.2.1 Physical Examinations

For physical examinations please refer to Section 1.3 (SoA).

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.

A limited physical exam is based on symptom-directed findings or 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.

For GBM and AA, neurologic examinations (via Neurologic Assessment in Neuro-Oncology (NANO) Scale) in addition to the physical examinations will be performed that will include assessments of mental status and neurologic functions (motor and sensory systems, cranial nerves, reflexes, or other symptom-directed findings as clinically indicated).

8.2.2 Vital Signs

Body temperature, heart rate, blood pressure, height (only at screening) and weight 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 (Section 1.3) 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.

An isolated laboratory abnormality that meets the criteria for a CTCAE Grade 4 classification is not reportable as an SAE, unless the investigator assesses that the event meets standard ICH criteria for an SAE (see SAE definition in Section 10.3.2).

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 30 d (active FU period after study treatment discontinuation) 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 SoA (see 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-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g., light 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 and safety FU. 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:

- Year of birth and age
- Gender
- Race, if legally allowed
- Ethnicity, if legally allowed
- Child bearing 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 (and sub-location if applicable) of the primary tumor, histology, tumor stage at study entry, date of diagnosis of first metastasis, presence of liver and/or lung metastasis. Date of most recent progression/relapse, prior cancer therapies.

- Tumor mutational burden (TMB) (if available) and PD-L1 expression (if available), MSI status (if available).
- All medications (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by the participant within the screening period prior to the study intervention.

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

8.3 Adverse Events and Serious Adverse Events

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

AEs should be assessed in terms of their seriousness, intensity (according to NCI-CTCAE, v5.0), and relationship to the study drugs, or other treatment.

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 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 informed consent form (ICF) until the end of active safety FU visits 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 Appendix 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 FU 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, will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to FU (as defined in Section 7.3). 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. Participants 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.

8.5 Pharmacokinetics

In all participants enrolled, sparse pharmacokinetic samples will be collected for determination of regorafenib and its metabolites M-2 and M-5 (in plasma) and nivolumab (in serum) as specified in Table 1–4.

Deviations from planned sampling time intervals will not be considered as protocol deviations. However, omission of samples other than specified in the PK sampling Table 1–4 will be considered a protocol deviation. The date and clock time of each sample as well as dates and times of the regorafenib administration and start and stop times of nivolumab infusion will be recorded in the eCRF as PK estimates will be based on the sampling times relative to dosing times.

For regorafenib, meal intake time should be collected on PK sampling days together with the dosing time.

Samples may be collected irrespective of any dose modifications during the treatment cycle. If regorafenib is not administered on the day of PK sampling, the pre-dose samples will be collected, the post-dose samples will not be collected. Pre-dose samples will also not be collected if participants have not taken regorafenib on the previous day. However, if regorafenib is re-started than PK sampling should resume as scheduled. Pre-dose samples will also not be collected if participants have not taken regorafenib on the previous day. However, if regorafenib is re-started than PK sampling should resume as scheduled

The regorafenib dose that separates the pre- and post-dose sample needs to be taken under supervision and the time of dosing should be recorded.

Regorafenib data from this study will be pooled with data from other clinical studies for pharmacometric analysis. The nivolumab serum concentration may be analyzed using a previously developed population PK model to determine measures of individual exposure.

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

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

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

8.6 Pharmacodynamics

Pharmacodynamic biomarkers will be evaluated in this study and are described in Section 8.8.

8.7 Genetics

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

8.8 Biomarkers

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

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

All biomarker analyses are covered by the main study informed consent. No separate consent is required as no whole genome sequencing will be performed. The investigator will assess if tumor specimen acquisition is medically feasible.

Timing:

The following samples for biomarker research are required and will be collected from all participants as specified in the SoA (Table 1–2) and schedule of Biomarker Blood Sampling (Table 1–3).

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

At screening:

- Archival tumour tissue sample is mandatory if available for all cohorts.
  - HNSCC IO treated cohort: the archival tissue shall be preferably before IO treatment if available.

  AND
- Provision of recent tumor tissues (defined as an archival biopsy not older than 180 day and after last anti-tumor treatment; or a new biopsy) are
  - mandatory for all participants in HNSCC (IO treated) in Stage 1 and 2
  - mandatory for HNSCC (IO naïve) in Stage 2
  - mandatory if medically feasible (as judged by the Investigator) for all participants in the ESCC, PDAC, and BTC cohorts and for participants in Stage 1 of the HNSCC (IO naïve) cohort.
  - Optional for GBM/AA cohort and should only be considered if tumor is accessible and biopsy is deemed safe by the Investigator

C2D8 (+7 days):

- In Stage 1: mandatory if medically feasible (as judged by the Investigator) for all participants in HNSCC (IO treated); optional for all other cohorts
- In Stage 2: mandatory if medically feasible (as judged by the Investigator) for all participants in all cohorts except the GBM/AA cohort. For the GBM/AA cohort, tumor tissue collection is optional and should only be considered if tumor is accessible and biopsy is deemed safe by the Investigator.

EoT:

- Optional for all cohorts.

Table 8–2 Requirements for Tumor Tissue Collection

	HNSCC IO Naïve Stage 1	HNSCC IO naïve Stage 2	HNSCC IO treated Stage 1+2	ESCC Stage 1+2	PDAC Stage 1+2	BTC Stage 1+2	GBM/AA Stage 1+2
Archival tumor tissue	Mandatory if available	Mandatory if available	Mandatory if available, preferably before IO treatment	Mandatory if available	Mandatory if available	Mandatory if available	Mandatory if available
Recent tumor tissues[a]	Mandatory if medically feasible	Mandatory	Mandatory	Mandatory if medically feasible	Mandatory if medically feasible	Mandatory if medically feasible	Optional
C2D8 Stage 1 participants	Optional	NA	Mandatory if medically feasible	Optional	Optional	Optional	Optional
C2D8 Stage 2 participants	NA	Mandatory if medically feasible	Mandatory if medically feasible	Mandatory if medically feasible	Mandatory if medically feasible	Mandatory if medically feasible	Optional
EoT	Optional	Optional	Optional	Optional	Optional	Optional	Optional

Abbreviations: AA= Anaplastic astrocytoma; BTC = Biliary Tract Carcinoma; C = Cycle; D = Day; EoT = End of treatment; ESCC = Esophageal squamous cell carcinoma, HNSCC = Head and neck squamous cell cancer; IO = Immune oncology; NA = not applicable; PDAC= Pancreatic ductal adenocarcinoma

a) archival biopsy not older than 180 day and after last anti-tumor treatment; or a new biopsy
Note: Medically feasible as judged by the Investigator

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

Medical history information – if any additional molecular information about the tumor was collected in the course of treatment prior to entry of the participant in the study, the results may be collected in order to include this data in biomarker analyses.

Sample handling and storage:

Tumor tissue requirement for archival tissue: Formalin-fixed paraffin-embedded block or minimum of 20 slides if available. Less slides are acceptable if provision of a block or 20 slides is not feasible.
Tumor tissue requirement for recent tissue at baseline, C2D8 and EoT tissue: Formalin-fixed paraffin-embedded block or minimum of 20 slides, obtained from core needle biopsy, punch biopsy, excisional biopsy or surgical specimen. Fine needle aspirates or other cytology samples are not acceptable.

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

Reporting:

Some of the results of biomarker investigations may be reported separately (e.g., in a biomarker evaluation report).

8.8.1 Pharmacodynamics Biomarker

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

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

- Intra-tumor PD biomarkers such as immune cell infiltrations (e.g. effector T cells [T_{eff}], T_{reg}, marcophages), expression of immune genes/signatures, and/or parameters in the regorafenib targeted pathways in paired tumor biopsies (pre- and on-treatment)
- Quantification and characterization of immune cell populations in blood (e.g. T cells, Myeloid-Derived Suppressor Cells [MDSC], etc.) analyzed e.g., by flow-cytometry
- Systemic levels of immune mediators (e.g., cytokines, chemokines) from serum or plasma and tumor markers from circulating tumor deoxyribonucleic acid (ctDNA)
- Plasma proteins of interest for regorafenib (e.g., TIE-1, sVEGFR1, sVEGFR2, VEGF, angiopoietin 1 [Ang1])
- Circulating miRNA
- Composition of gut microbiome by e.g., bacterial taxonomy profiling in stool sample

8.8.2 Biomarkers that may associate with Response

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

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

- Tumor immune status (e.g., PD-L1 expression, immune gene expression profiles, immune cell infiltration e.g. T_{eff}, T_{reg}, macrophages) at baseline
- Expression of parameters of interest for regorafenib (e.g., ligands of targeted receptor tyrosine kinases) in baseline tumor materials
- Baseline TMB/ tumor mutations (e.g. B2M, JAK1/2/3) as detected in tumor and/or ctDNA
- Baseline immune cell populations in blood and baseline systemic levels of immune mediators (e.g., cytokines/chemokines)
- Germline genetic variants in genes of interest (e.g., cc-chemokine ligands CCL4 and CCL3, cc-chemokine receptor 5 (CCR5))
- Baseline circulating miRNA markers
- MGMT methylation status and IDH mutation status (GBM/AA only)
- HPV/p16 (oropharyngeal HNSCC only)
- Baseline composition of gut microbiome by e.g., bacterial taxonomy profiling in stool sample

8.8.3 Other Biomarkers

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

8.9 Immunogenicity Assessments

Blood (serum) samples will be collected from all participants treated with nivolumab for analysis of anti-drug-antibodies (ADAs) and neutralizing antibodies (NABs) in Cycles 1, 2, 5 and 19, pre-infusion (Table 1–4).

Serum samples will be screened for ADAs and the titer of confirmed positive samples will be reported. Other analyses may be performed to verify the stability of ADAs and/or further characterize the immunogenicity of nivolumab.

The detection and characterization of ADAs will be performed using a validated assay method. ADAs may be further characterized and/or evaluated for their ability to neutralize the activity of nivolumab.

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

9. Statistical Considerations

This is a single arm, open-label Phase 2 study with ORR per RECIST1.1 per local assessment for all solid tumors except GBM/AA or RANO per local assessment for GBM/AA as primary endpoint.

Each cohort will be examined in 2 stages based on a Sargent 3-outcome design (Sargent et al. 2001) with one-sided alpha of 0.1 (false positive rate), beta (false negative rate) of 0.1, power of 70% and likelihood of futility of 70% when the null hypothesis is true. At the end of Stage 2, 3 outcomes are possible based on 2 efficacy boundaries. The first outcome is considered negative if there is an insufficient number of responders to pass the pre-defined low boundary for efficacy. The second outcome is considered a positive outcome if the number of responders meets or surpasses the pre-defined target boundary for efficacy. The third outcome is a result in which the number of responders lies between the two boundaries and is considered inconclusive for declaring a positive outcome based on the pre-defined target.

If Stage 1 does not show the targeted level of activity after 2 tumor assessments, recruitment into Stage 2 may be discontinued. In addition, the totality of the data, including the duration and depth of response and overall risk-benefit assessment may be considered in the decision to terminate or continue the expansion after Stage 1. The complete cohort of participants from Stage 1 and Stage 2 will be tested at the one-sided alpha of 0.1. A one-sided exact binomial test will be conducted to test the hypotheses.

All participants treated will be included in the evaluation of response rate, not treated participants will be replaced. Any treated participant who does not qualify as a responder according to the tumor assessment criteria will be considered as non-responder.

9.1 Statistical Hypotheses

The underlying hypotheses to be tested in this study are

HNSCC (IO naïve): H0: $ORR_{Combination} \leq 15\%$ versus H1: $ORR_{Combination} \geq 30\%$

HNSCC (IO treated): H0: $ORR_{Combination} \leq 5\%$ versus H1: $ORR_{Combination} \geq 19\%$

ESCC: H0: $ORR_{Combination} \leq 15\%$ versus H1: $ORR_{Combination} \geq 30\%$

PDAC: H0: $ORR_{Combination} \leq 10\%$ versus H1: $ORR_{Combination} \geq 20\%$

BTC: H0: $ORR_{Combination} \leq 10\%$ versus H1: $ORR_{Combination} \geq 20\%$

GBM/AA: H0: $ORR_{Combination} \leq 15\%$ versus H1: $ORR_{Combination} \geq 30\%$

9.2 Sample Size Determination

Cohort: HNSCC (IO naïve), ESCC and GBM/AA
In Stage 1, a total of 9 participants should be targeted for each cohort. To target 30% of ORR at least 1 responder out of the 9 participants is needed per cohort.
In Stage 2, per cohort, 21 additional participants should be added in order to target 30 participants. If 8 or more out of the 30 participants respond, the cohort is considered as showing a positive outcome. If 5 or less out of the 30 participants respond, the cohort is considered as showing a negative outcome. If 6 or 7 participants respond, outcome is inconclusive.

Cohort: HNSCC (IO treated)
In Stage 1, a total of 14 participants should be targeted in the cohort. To target 19% of ORR at least 1 responder out of the 14 participants is needed.
In Stage 2, 6 additional participants should be added in order to target 20 participants. If 3 or more out of the 20 participants respond, the cohort is considered as showing a positive outcome. If 1 or less out of the 20 participants respond, the cohort is considered as showing a negative outcome. If 2 participants respond, outcome is inconclusive.

Cohort: PDAC and BTC
In Stage 1, a total of 17 participants should be targeted in the cohort. To target 20% of ORR at least 1 responder out of the 17 participants is needed.
In Stage 2, 28 additional participants should be added in order to target 45 participants. If 8 or more out of the 45 participants respond, the cohort is considered as showing a positive outcome. If 5 or less out of the 45 participants respond, the cohort is considered as showing a negative outcome. If 6 or 7 participants respond, outcome is inconclusive.

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 (full analysis set)	All participants who have received any dose of study intervention
SAF (safety analysis set)	All participants who have received any dose of study intervention
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 (at baseline and during the treatment or FU 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; FU = Follow-up; ICF = Informed consent form; IMS = Immunogenicity analysis set; PK = Pharmacokinetics; n-PKS = Nivolumab PK analysis set; r-PKS =Regorafenib PK analysis set; SAF = Safety analysis set

As the safety analysis set (SAF) equals the full analysis set (FAS), all analyses related to safety will be performed on the Full 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 statistical analysis plan will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and secondary endpoints.

9.4.1 General Considerations

All analyses will be conducted at one-sided type-I error level of 10% or two-sided type-I error level of 20% respectively. A one-sided exact binomial test will be conducted in the Stage 2 to test the primary endpoint. Confidence intervals will be presented for selected variables.

9.4.2 Primary Endpoint(s)

The primary endpoint of the study is ORR defined as the proportion of participants with best overall response of confirmed CR or partial response (PR). ORR is based on RECIST 1.1. for all solid tumors by local assessment and for the GBM/AA cohort ORR is based on RANO by local assessment. Participants for whom best overall tumor response is not CR or PR, as well as participants without any post-baseline tumor assessment will be considered non-responders.
The primary endpoint is ORR based on RECIST 1.1 or RANO as assessed by the investigator. The primary efficacy variable will be analyzed per cohort. The primary analysis will be done on the Full Analysis Set.

Methods used will include frequency tables (with the ORR table also including all "Best overall response" categories) as well as 80% two-sided Clopper-Pearson confidence intervals and the results of an exact binomial test.

9.4.3 Secondary Endpoint(s)

The secondary efficacy endpoints in this study are Duration of Response (DOR), Disease Control Rate (DCR), PFS, 6 month PFS, according to RECIST 1.1 or RANO and additionally OS and 1 year OS in the Stage 2.

DOR (for PR and CR) is defined as the time (in days) from the first documented objective response of PR or CR, whichever is noted earlier, to first documented objective disease progression or death (if death occurs before progression is documented). DOR will be defined for responders only, i.e. participants with a CR or PR. The actual dates the tumor scans were performed will be used for this calculation. DOR for participants who have not progressed or died at the time of analysis will be censored at the date of their last tumor evaluation.

PFS is defined as the time (in days) from start of study intervention to the date of first objectively documented PD or death from any cause (if no progression is documented). The actual date of tumor assessments will be used for this calculation. PFS for participants without PD or death at the time of analysis will be censored at the date of their last tumor evaluation. PFS for participants who have neither tumor assessments nor death after baseline will be censored at Day 1.

OS is defined as the time (in days) from start of study intervention to the date of death due to any cause. If a participant is not known to have died, then OS will be censored at the date of last known date participant alive. If a participant is lost to FU before any assessment after assignment to study intervention, this participant will be censored at Day 1.

Safety is also considered as secondary endpoint. For details please refers to Section 9.4.5.

The secondary efficacy endpoints will be based on investigator assessments. Analyses will be done on the Full Analysis Set per cohort.

For analyses of the secondary endpoints, proportion-based efficacy variables will be using frequency tables as well as 80% 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 80% two-sided confidence interval

9.4.4 Tertiary/Exploratory Endpoint(s)

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

For further information on PK and biomarkers refer to Section 9.4.6.

9.4.5 Safety Analyse(s)

All safety analyses will be done on the Safety Analysis Set as defined in Table 9–1, analysis will be done by cohort and overall.

The incidence of treatment-emergent adverse events (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 or other measured values will be summarized in frequency tables. Where applicable, laboratory measurements will be summarized by severity, cohort, and changes in severity from baseline to worst post-baseline value. Laboratory data considered as AE will be graded according to CTCAE v. 5.0, if applicable.

9.4.6 Other Analyses

PK, pharmacodynamic, and biomarker exploratory analyses will be described in a separate statistical analysis plan finalized before database release. The population PK analysis and pharmacodynamic analyses will be presented separately from the main clinical study report (CSR).

9.5 Interim Analyses

At stage 1, an interim futility analysis for response rate will be conducted per cohort based on patients in the full analysis set (FAS). The evaluation will be based on a clean database of Stage 1 with cut-off date when the last participant of the respective cohort has had the chance to complete 4 cycles of treatment.

At Stage 2, response rates will be analyzed per cohort based on the FAS. Data read out is planned after the last participant of the respective cohort has had the chance to complete 4 cycles of treatment.

9.6 Data Monitoring Committee (DMC) or other Review Board

Not applicable.

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, Investigator Brochure, 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 and require regulatory authority approval.
- Any amendments to the protocol will require IRB/IEC and regulatory authority 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 and answer all questions regarding the study

Participants will be informed that their participation is voluntary. Participants 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.

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

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.

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/RANO, participant must be re-consented. Re-consent also covers a potential

treatment continuation with regorafenib after confirmed radiological progression (according to iRECIST/iRANO) until clinical progression.

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.

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

Bayer commits to sharing upon request from qualified scientific and medical researchers patient-level clinical trial data, study-level clinical trial data, and protocols from clinical trials in patients for medicines and indications approved in the United States (US) and European Union (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. The sponsor has the right to close this study (or, if applicable, individual segments thereof [e.g. treatment arms; dose steps; centers]) at any time, which may be due but not limited to the following reasons. 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 participant and should assure appropriate participant 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 (except PK, immunogenicity, tumor tissue, stool sample and items mentioned in 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. 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 expanded	• Platelet count • Hemoglobin		WBC count with differential: • Neutrophils • Lymphocytes • Monocytes • Eosinophils • Basophils	
Hematology limited	• Platelet count • Hemoglobin • WBC count			
Chemistry panel expanded	• BUN or Urea • Creatinine and eGFR [a] • Lipase • LDH • Albumin	• Potassium • Sodium • Chloride • Amylase • Phosphate	• AST/SGOT • ALT/SGPT • Total protein • Total calcium, calcium ionized or adjusted • Uric acid • Magnesium	• Total and direct bilirubin • ALP • Glucose (fasting or non-fasting according to local standards) • GGT [b]
Chemistry panel limited			• AST/SGOT • ALT/SGPT	• Total and direct bilirubin • Glucose (fasting or non-fasting according to local standards)
Routine Urinalysis[a]	• Dipstick: pH, glucose, protein, blood, ketones, • 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. • Microscopic examination (if blood or protein is abnormal)			
Coagulation	• PT-INR • aPTT			
Thyroid	• FT3 • FT4 • TSH			
Pregnancy Test	Serum human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential) • A negative pregnancy test must be available within 24 hr before the 1st study treatment administration. Monthly pregnancy testing independent of study treatment dosing should be conducted as per local regulations where applicable.			

Abbreviations: ALT = Alanine aminotransferase; ALP = Alkaline phosphatase; aPTT = Activated partial thromboplastin time; AST = Aspartate aminotransferase; BUN = Blood urea nitrogen; eGFR = Estimated glomerular filtration rate; FT3 = Free triiodothyronine; FT4 = Free thyroxine; GGT = Gamma-glutamyl transferase; hCG = Human chorionic gonadotropin; LDH = Lactic dehydrogenase; PT-INR = Prothrombin time-international normalized ratio; SGOT = Serum glutamic-oxaloacetic transaminase; SGPT = Serum glutamic-pyruvic transaminase; TSH = Thyroid stimulating hormone; WBC = White blood cell count

a) Cockcroft Gault formula for GFR:

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

a.

b) GGT will be assessed if clinically indicated.

Investigators must document their review of each laboratory safety report.

10.3 Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, FU, 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 signature of the ICF even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

Events NOT Meeting the AE Definition
• The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2 Definition of SAE

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

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

may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

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

10.3.3 Recording and FU of AE and/or SAE

AE and SAE Recording

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

Assessment of Intensity

The intensity of AEs should be documented using the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI-CTCAE, version 5.0).
The intensity of AEs is classified according to the following categories for events not listed in the CTCAE v.5.0:

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL (ADL: Activities of Daily Living; instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.).
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL (Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden).

- Grade 4: Life-threatening consequences; urgent intervention indicated.
- Grade 5: Death related to AE.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- 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 Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report to the Sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.**
- The investigator may change his/her opinion of causality in light of 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.

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 the Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized FU period, the Investigator should provide access to any postmortem findings including histopathology

FU of AEs and SAEs
• New or updated information will be recorded in the originally completed case report form (CRF). • The investigator will submit any updated SAE data to Bayer within 24 hours of receipt of the information.

10.3.4 Reporting of SAEs

SAE Reporting to the Sponsor via an Electronic Data Collection Tool
• The primary mechanism for reporting a SAE to the Sponsor will be the electronic data collection tool. • If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours. • The site will enter the SAE data into the electronic system as soon as it becomes available. • After the study is completed at a given site, the electronic data collection tool will be taken 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 Sponsor by telephone. • Contacts for SAE reporting can be found in the Investigator file.

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

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).

Women in the following categories are not considered WOCBP:

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

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

Fertile Man

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

Contraception Guidance:

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

Male participants

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

- Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent

- Agree to use a male condom plus partner use of a contraceptive method with a failure rate of <1% per year as described in Table 10–2 when having penile-vaginal intercourse with a woman of childbearing potential who is not currently pregnant
- Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration [during the protocol-defined time frame]
- Refrain from donating sperm for the duration of the study and for a period after study completion or the last dose of study treatment as specified in Section 5.1.

Female participants

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in Table 10–2 and during the protocol-defined time frame in Section 5.1.

Table 10–2 Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of <1% per year when used consistently and correctly.*
Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation • Oral • Intravaginal • Transdermal
Progestogen only hormonal contraception associated with inhibition of ovulation • Oral • Injectable
Highly Effective Methods of Low User Dependency[a]
Implantable progestogen only hormonal contraception associated with inhibition of ovulation • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) Bilateral tubal occlusion Vasectomized partner • A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.*
NOTES: a) Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies.

Pregnancy Testing

Highly sensitive serum testing is mandatory if required by local regulations or ethics committees, or to resolve an indeterminate test or to confirm a positive urine test.

- WOCBP should only be included after a confirmed menstrual period and a negative highly sensitive [serum] pregnancy test.
- Additional pregnancy testing should be performed at monthly intervals, during the treatment period and at safety FU after the last dose of study treatment as specified in Section 1.3 (SoA) and as required locally.

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

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 treatment.
- After obtaining the necessary signed informed consent from both the study participant and the pregnant female partner, the investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female Participants who become pregnant

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

- Any post-study pregnancy related SAE considered reasonably related to the study treatment by the investigator will be reported to the Sponsor as described in Section 8.3.4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study treatment or be withdrawn from the study.

10.5 Appendix 5: Genetics

Genetic as well as non-genetic analyses will be part of the biomarker investigations in this study. See Section 8.8 for details.

10.6 Appendix 6: Response Evaluation Criteria in Solid Tumors

For participants with HNSCC, ESCC, PDAC, and BTC, response and progression will be evaluated using the RECIST 1.1 (Eisenhauer et al. 2009) as well as the modified iRECIST guidelines for immune-based therapeutics (Seymour et al. 2017).

For participants with GBM/AA, response and progression will be evaluated using the RANO (Wen et al. 2010) and the iRANO criteria (Okada et al. 2015).

10.6.1 RECIST 1.1

Definition of Measurable disease:

- Soft tissue/ visceral tumor lesions: Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of 10 mm by CT scan. If scans with slice thicknesses greater than 5mm are used, the minimum size should be twice the slice thickness.
- Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in *short axis* when assessed by CT scan (for CT scan slice thickness of 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease

All other lesions are considered non-measurable. This includes small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis) and also truly non-measurable lesions, such as: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung.

Bone lesions, cystic lesions and lesions previously treated with local therapy require particular comment:

Bone lesions:

- Lytic bone lesions, with an identifiable soft-tissue component, (e.g., lytic bone lesions in renal cell carcinoma) evaluated by CT or MRI can be considered as measurable lesions if the soft-tissue component otherwise meets the definition of measurability
- Blastic bone lesions are considered as non-measurable

Cystic lesions:

- Lesions that meet radiographic criteria for simple cysts should not be considered malignant lesions (neither measurable nor non-measurable)
- "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 participants, these should be preferably selected for assessment

Lesions with prior local treatment:

- 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 prior to baseline.

Target lesions

When more than one measurable lesion is present at baseline, all lesions up to a maximum of 5 lesions total (and a maximum of 2 lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline (this means in instances where participants have only 1 or 2 organ sites involved a maximum of 2 and 4 lesions respectively will be recorded). Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance 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 as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective change in the measurable dimension of the disease.

Non-target lesions

All other lesions (or sites of disease) including pathological lymph nodes (with short axis ≥ 10 mm and < 15 mm) not considered as target should 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' (more details to follow). Please note that some non- target lesions may actually be measurable, but if they were chosen to be followed as non-target lesions, they should be assessed only qualitatively. In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (e.g. 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

Best Response: The best overall response for a participant is the best response recorded from the start of the study intervention until the end of treatment or A-FU, if applicable, taking into account any requirement for confirmation. 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.

Complete Response (CR): Disappearance of all non-nodal 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. In addition, there must be normalization of any applicable tumor marker.

Since lymph nodes are normal body structures, it is not expected that they disappear. Lymph nodes identified as target lesions should always have the 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 lymph node is defined as normal when having 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.

In participants with a bone/brain scan at baseline, a repeat bone/brain scan must be done at confirmation of response to ensure there is no bone progression before claiming PR or CR.

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**)**: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

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.

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.

The above text descriptions of the visit/time point response are logically equivalent to Table 10–3 below.

Table 10–3 RECIST 1.1 - Time Point Response for participants with target and non-target lesions

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

Abbreviations: C=Cycle; CR = Complete response; D=Day; NE = Not evaluated; PD = Progressive disease; PR = Partial response; SD = Stable disease.

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

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.

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 intervention 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). When SD is believed to be best response, it must also meet the protocol specified minimum time of 6 weeks from baseline.

10.6.2 iRECIST

iRECIST is RECIST 1.1 adapted as described below to account for the unique tumor response seen with immunotherapeutic drugs (Table 10–4). Responses assigned using iRECIST criteria will have an “i” prefix. 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 1.1 Progression

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

Assessment and Decision at RECIST 1.1 Progression

For participants who show evidence of radiological PD by RECIST 1.1, the Investigator will decide whether to continue a participant on study treatment until repeat imaging is obtained and response is evaluated using iRECIST for participant management (see Table 10–4 and Figure 10–1).

Regarding the decision to treat past PD (based on RECIST 1.1), the Investigator should consider the participant's clinical stability, which includes the following:

- No decline in ECOG PS
- No clinically relevant increase in symptoms related to patient's cancer
- No requirement for intensified management of disease related symptoms, including increased analgesia, radiation, or other palliative care

For any participant deemed **clinically unstable, the Investigator** should discontinue the participant from study treatment at site-assessed first radiologic evidence of PD without need for 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

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

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

iRECIST defines new response categories, including unconfirmed progressive disease by iRECIST (iUPD) and iCPD. For iRECIST assessments, the first visit showing progression according to RECIST 1.1 will be assigned a visit (overall) response of iUPD, regardless of the underlying cause of progression. At this visit, target and non-target lesions identified at baseline by RECIST 1.1 will be assessed as usual.

New lesions will be classified as measurable or non-measurable, using the same size thresholds and rules as for baseline lesion assessment in RECIST 1.1. From measurable new lesions, up to 5 lesions total (up to 2 per organ), may be selected as New Lesions – Target (NLT). 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 (NLNT).

Assessment at the Confirmatory Imaging

On the confirmatory imaging for iRECIST, the participant will be classified as progression confirmed (with an overall response of iCPD), or as showing persistent unconfirmed

progression (with an overall response of iUPD), or as showing disease stability or response (iSD/iPR/iCR).

Confirmation of Progression

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

- Any of the factors that were the basis for the initial iUPD show worsening
  - For target lesions, worsening is a further increase in the sum of diameters of ≥5 mm, compared to any prior iUPD time point
  - For non-target lesions, worsening is any significant growth in lesions overall, compared to a prior iUPD time point; this does not have to meet the "unequivocal" standard of RECIST 1.1
  - For new lesions, worsening is any of these:
    - an increase in the new lesion sum of diameters by ≥5 mm from a prior iUPD time point
    - visible growth of new non-target lesions
    - the appearance of additional new lesions
  - Any new factor appears that would have triggered PD by RECIST 1.1

Persistent iUPD

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

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

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

Resolution of iUPD

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

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

The response is classified as iSD or iPR (depending on the sum of diameters of the target lesions), or iCR if all lesions resolve. In this case, the initial iUPD is considered to be pseudo-progression, and the level of suspicion for progression is "reset". This means that the next visit that shows radiographic progression, whenever it occurs, is again classified as iUPD by iRECIST, and the confirmation process is repeated before a response of iCPD can be assigned.

Management Following the Confirmatory Imaging

If repeat imaging does not confirm PD per iRECIST, as assessed by the Investigator, and the participant continues to be clinically stable, study treatment may continue and follow the regular imaging schedule. If PD is confirmed (iCPD) via iRECIST, 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.

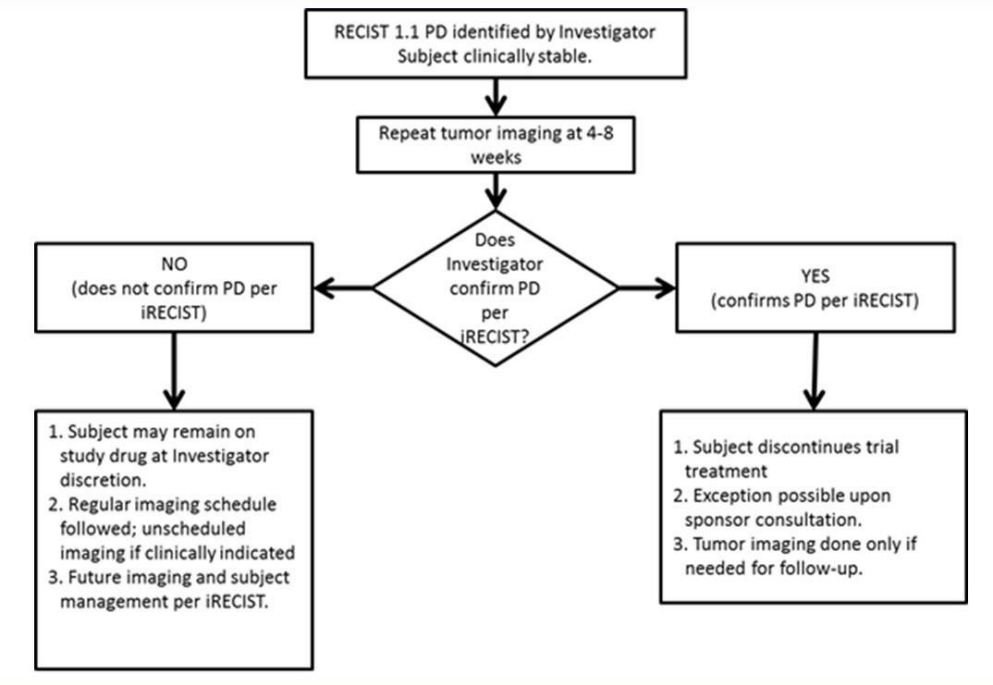
Additional details about iRECIST are provided in the iRECIST publication (Seymour et al. 2017).

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

Tumor Assessment	Clinically Stable		Clinically Unstable	
	Imaging	Treatment	Imaging	Treatment
1st radiologic evidence of PD by RECIST 1.1	Repeat imaging at 4 to 8 weeks to confirm PD	May continue study treatment at the Investigator's discretion while awaiting confirmatory tumor imaging 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 every 8 weeks (±7 d) according to the imaging schedule through Cycle 8 (or until treatment discontinuation, if treatment discontinuation occurs before) and 12 weeks (±14 d) thereafter

Abbreviations: D/d = day(s); iCPD = iRECIST Confirmed progressive disease; iCR = iRECIST complete response; iRECIST = Response Evaluation Criteria in Solid Tumors for immune-based therapeutics; iPR = iRECIST partial response; iSD = iRECIST stable disease; iUPD = iRECIST unconfirmed progressive disease; N/A = Not applicable; PD = Progressive disease; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors 1.1

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



iRECIST = Immune response evaluation criteria in solid tumors; PD = Progressive disease

10.6.3 RANO

The RANO criteria (Wen et al. 2010) were developed to evaluate efficacy of investigational agents in glioblastoma clinical trials and have been more broadly utilized for lower grade primary CNS malignancies. These criteria were developed in part to address issues faced when assessing some lesions based on MacDonald criteria, particularly lesions with central necrosis and with a T2 component.

RANO RESPONSE CRITERIA SUMMARY:

Table 10–5 RANO Response Criteria Incorporating MRI and Clinical Factor

Response Category	Criteria
CR	Requires all of the following: • Disappearance of all measurable and non-measurable enhancing disease sustained for at least 4 weeks* • Stable or improved non-enhancing T2/FLAIR lesions • No new lesions • Clinically stable or improved with no reliance on corticosteroids (except for physiological replacement)
PR	Requires all of the following: • ≥ 50% decrease from baseline in the SPPD of all measurable enhancing lesions sustained for at least 4 weeks* • No progression of non-measurable disease • Stable or improved non-enhancing T2/FLAIR lesions • No new lesions • Clinically stable or improved, with stable or reduced corticosteroids compared to baseline
PD	Defined by any of the following: • ≥ 25% increase in SPPD of enhancing lesions compared with the smallest tumor measurement obtained either at baseline (if no decrease) or best response despite stable or increasing steroid dose • Significant increase in non-enhancing T2/FLAIR lesions compared with baseline scan or best response after initiation of therapy not attributable to other non-tumor causes • Any new lesions • Clinical deterioration not attributable to other non-tumor causes and not due to steroid decrease • Failure to return for evaluation as a result of death or deteriorating condition • Clear progression of nonmeasurable disease
SD	Requires all of the following: • Does not meet other criteria for response or progression • Stable non-enhancing T2/FLAIR lesions • Clinically stable with stable or reduced corticosteroids compared to baseline NOTE: In the event the corticosteroid dose is increased for new symptoms and signs without confirmation of disease progression, and subsequent follow-up imaging shows that this increase in corticosteroids was required because of disease progression, the last scan considered to show stable disease will be that when the corticosteroid dose was equivalent to the baseline dose

Abbreviations: CR = Complete response; T2/FLAIR = T2-weighted fluid-attenuated inversion recovery; MRI = magnetic resonance imaging; PD = progressive disease; PR = Partial response; RANO = Response Assessment in Neuro-Oncology; SD = Stable disease; SPPD = Sum of products of perpendicular diameters.
* In the absence of a confirming scan 4 weeks later, this response will be considered only stable disease.

A measurable lesion is evaluated by contrast-enhancing MRI and:

- Has clearly defined margins
- Is visible on two or more axial slices, preferably < 5 mm thick
- Has two perpendicular diameters of at least 10 mm if slice thickness is < 5 mm (or 2 × slice thickness if > 5 mm)
- Does not measure a cystic cavity

Non-measurable lesions are those that do not fit the criteria above, and specifically lesions that are cystic, necrotic, or include a surgical cavity should not be considered measurable. Measurements are calculated by summing the products of perpendicular diameters of all measurable enhancing lesions.
All patients must have at least one measurable lesion as defined by RANO to enroll in the study.
If there are multiple contrast-enhancing lesions, a minimum of the two largest lesions should be measured. However, emphasis should be placed on selecting lesions that allow reproducible repeated measurements. For patients who have multiple lesions for which only one or two are increasing in size, the enlarging lesions should be considered the target lesions for evaluation of response.

10.6.4 iRANO

The iRANO criteria (Okada et al. 2015) were issued to aid the interpretation of imaging changes in patients with cancer undergoing immunotherapy. The key component of the iRANO criteria is specific additional guidance for the determination of progressive disease in patients with neuro-oncological malignancies undergoing immunotherapy.

iRANO criteria:
The iRANO guidelines incorporate criteria previously defined by the RANO working committee to define complete response, partial response, minor response, stable disease, progressive disease, and non-evaluable disease for patients with malignant glioma, low-grade glioma, and brain metastases (Table 10–6).

Table 10–6 RANO and iRANO Criteria

	Malignant glioma	Low-grade glioma	Brain metastases
CR	Disappearance of all enhancing disease for ≥ 4 weeks; no new lesions; stable or improved T2/FLAIR; no more than physiological steroids; clinically stable or improved	Disappearance of all enhancing and T2/FLAIR disease for ≥ 4 weeks; no new lesions; no more than physiological steroids; clinically stable or improved	Disappearance of all enhancing target and non-target lesions for ≥ 4 weeks; no new lesions; no steroids; clinically stable or improved
PR	≥ 50% decrease in the sum of biperpendicular diameters of enhancing disease for ≥ 4 weeks; no new lesions; stable or improved T2/FLAIR; stable or decreased steroid dose; clinically stable or improved	≥ 50% decrease in the sum of biperpendicular diameter of T2/FLAIR disease for ≥ 4 weeks; no new lesions; stable or decreased steroid dose; clinically stable or improved	≥ 30% decrease in sum of longest diameters of target lesions for ≥ 4 weeks; no new lesions; stable or decreased steroid dose; clinically stable or improved
MR	N/A	25-49% decrease in the sum of biperpendicular diameters of T2/FLAIR disease for ≥ 4 weeks; no new lesions; clinically stable or improved	N/A
SD	Does not qualify for complete response, partial response, or progressive disease; no new lesions; stable or improved T2/FLAIR; stable or decreased steroid dose; clinically stable or improved	Does not qualify for complete response, partial response, or progressive disease; no new lesions; stable or improved T2/FLAIR; stable or decreased steroid dose; clinically stable or improved	Does not qualify for complete response, partial response, or progressive disease
PD	≥ 25% increase in the sum of biperpendicular diameters of enhancing disease; or new lesions; or substantial worsened T2/FLAIR; or substantial decline	≥ 25% increase in the sum of biperpendicular diameters of T2/FLAIR disease; or new lesions; or substantial clinical decline	≥ 20% increase in the sum of longest diameters of target lesions; or unequivocal progression of enhancing non-target lesions; or new lesions; or substantial clinical decline

Abbreviations: CR = Complete response; FLAIR=fluid-attenuated inversion recovery; iRANO=immunotherapy Response Assessment in Neuro-Oncology; MR = Minor response; N/A=not applicable; PD = Progressive disease; PR = Partial response; SD = Stable disease.

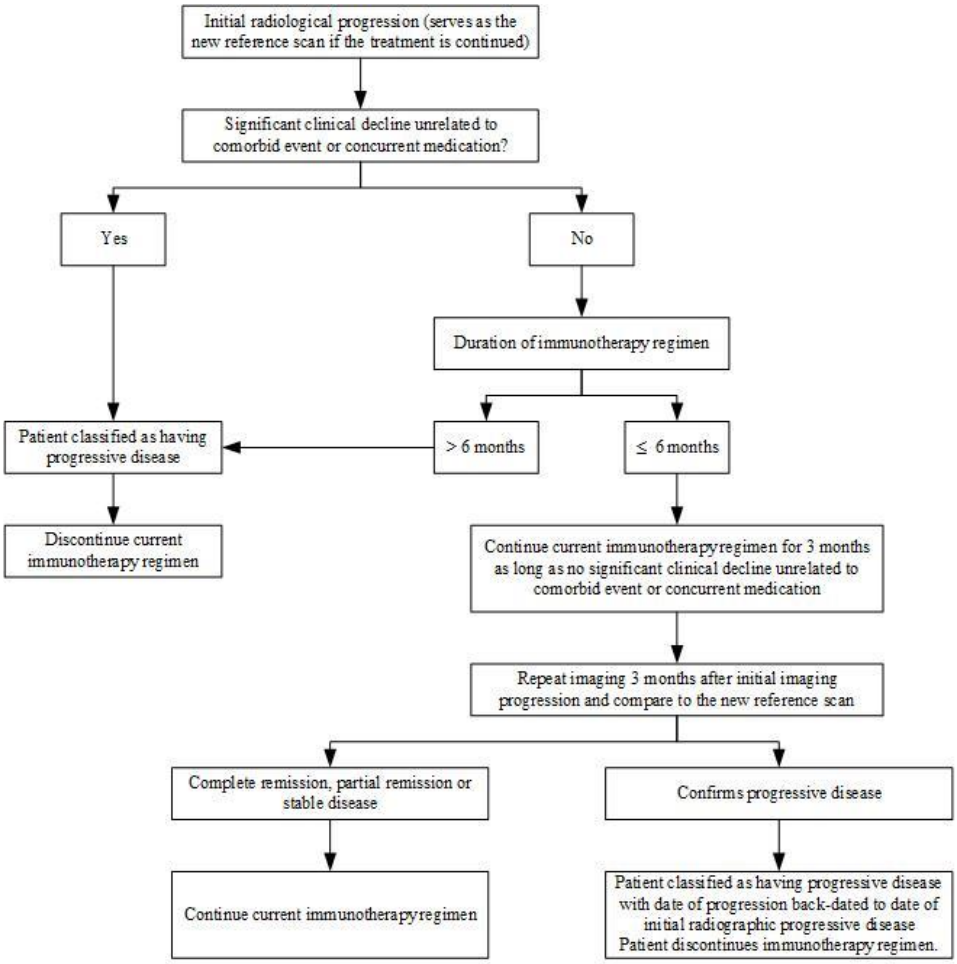
In patients who have imaging findings that meet RANO criteria for progressive disease within 6 months of starting immunotherapy, including the development of new lesions, confirmation of radiographic progression on follow-up imaging before defining the patient as nonresponsive to treatment might be needed, provided that the patient does not have new or substantially worse neurological deficits. Such patients might be allowed a window of 3 months before confirming disease progression with the scan that first showed initial progressive changes as the new reference scan for comparison with subsequent imaging studies.

If RANO criteria for progressive disease are met on the follow-up scan 3 months later, non-responsiveness to treatment should be assumed, and the date of progressive disease should be back-dated to the initial date when it was first identified (Table 10–6). Patients who develop

substantial new or worsened neurological deficits not due to comorbid events or a change in co-administered medication at anytime within the 3-month follow-up window should be designated as non-responsive to treatment and should discontinue immunotherapy. For these patients, the date of actual tumor progression should also be back-dated to the date when radiographic progressive disease was initially identified.

If radiographic findings at the 3-month follow-up meet RANO criteria for stable disease, partial response, or complete response compared with the original scan meeting criteria for progression, and no new or worsened neurological deficits are identified, such patients should be deemed as deriving clinical benefit from therapy and allowed to continue treatment. Patients who develop worsening radiographic findings compared with the pretreatment baseline scan more than 6 months from starting immunotherapy are expected to have a low likelihood of ultimately deriving clinical benefit and should be regarded as non-responsive to treatment with a recommendation to discontinue therapy.
The iRANO treatment algorithm is summarized in Figure 10–2.

Figure 10–2 iRANO Treatment Algorithm for the Assessment of Progressive Imaging Findings in Patients with Neuro-Oncological Malignancies Undergoing Immunotherapy



Corticosteroids:

Patients with brain tumors frequently develop peritumoral edema needing treatment with corticosteroids. Dexamethasone is the most commonly used corticosteroid. In addition to the systemic side-effects, dexamethasone can have profound effects on contrast enhancement for neuroimaging studies and on the immune system, including T cells, dendritic cells and natural killer cells. Therefore, dexamethasone doses and duration of therapy should be limited to the minimum amount needed to control neurologic symptoms. If pseudoprogression occurs during the course of treatment, higher doses of corticosteroids might be necessary to control symptoms.
Of note, patients who need increased corticosteroid use within 2 weeks of MRI assessment relative to the dose taken at the time of the previous assessment, cannot be classified as having a complete response, partial response, or stable disease and should be classified as non-evaluable at that timepoint. Conversely, patients who decrease corticosteroid use within 2 weeks of MRI assessment relative to the dose taken at the time of the previous assessment cannot be classified as having progressive disease and should be classified as non-evaluable.

10.7 Appendix 7: 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 10–7 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.

10.8 Appendix 8: CYP3A4 Inhibitors and Inducers

CYP3A4 inducers and inhibitors

Table 10–8 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 10–8 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
Conivaptan	Efavirenz
Delavirdine	Enzalutamide
Idelalisib	Etravirine
Indinavir	Fosphenytoin
Itraconazole	Hypericum perforatum (St John's Wort)
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**.

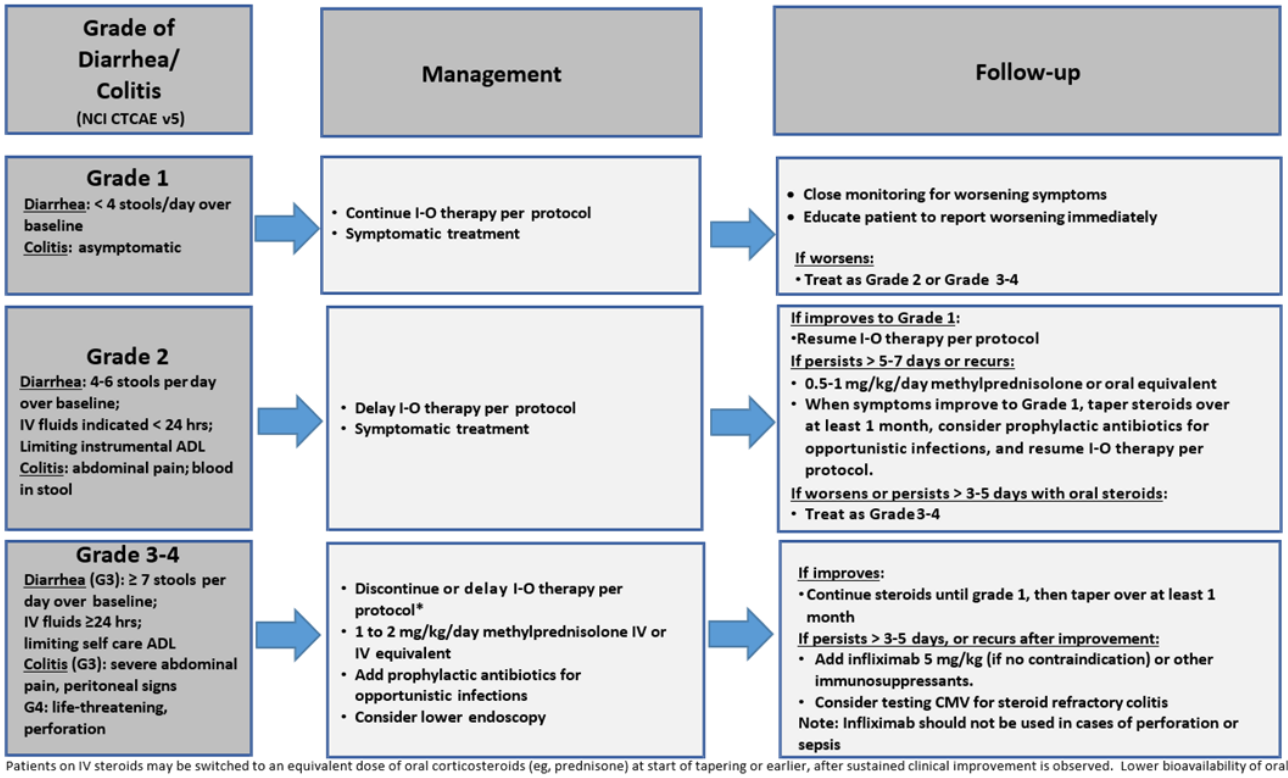
The CYP3A4 inducers and strong CYP3A4 inhibitors in Table 10–8 were identified using the Bayer-World Health Organization's Drug Dictionary (WHO-DD) and Bayer drug groupings for CYP3A4 inducers and CYP3A4 inhibitors.

10.9 Appendix 9: Guidance for Management of Immune-Related Adverse Events

The following AE management algorithms apply criteria from NCI-CTCAE v5

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 (eg, prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

* Discontinue for Grade 4 diarrhea or colitis. For Grade 3 diarrhea or colitis, Nivolumab can be delayed and can be resumed when symptoms improve to Grade 1.

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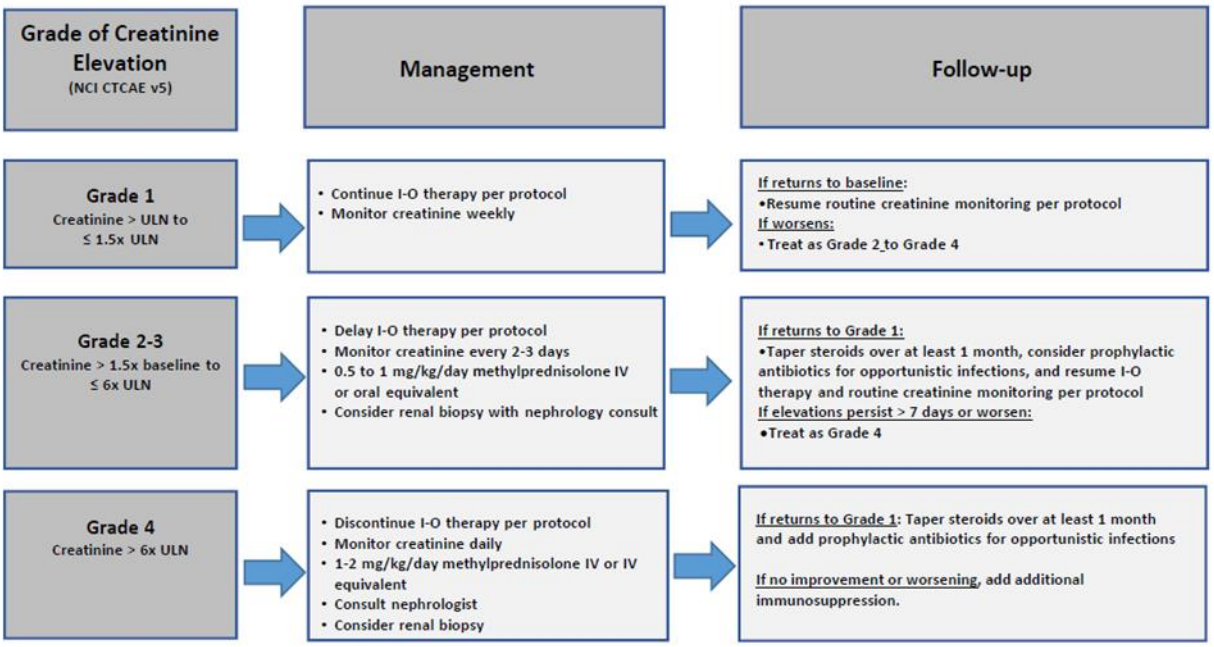
Renal Adverse Event Management Algorithm

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

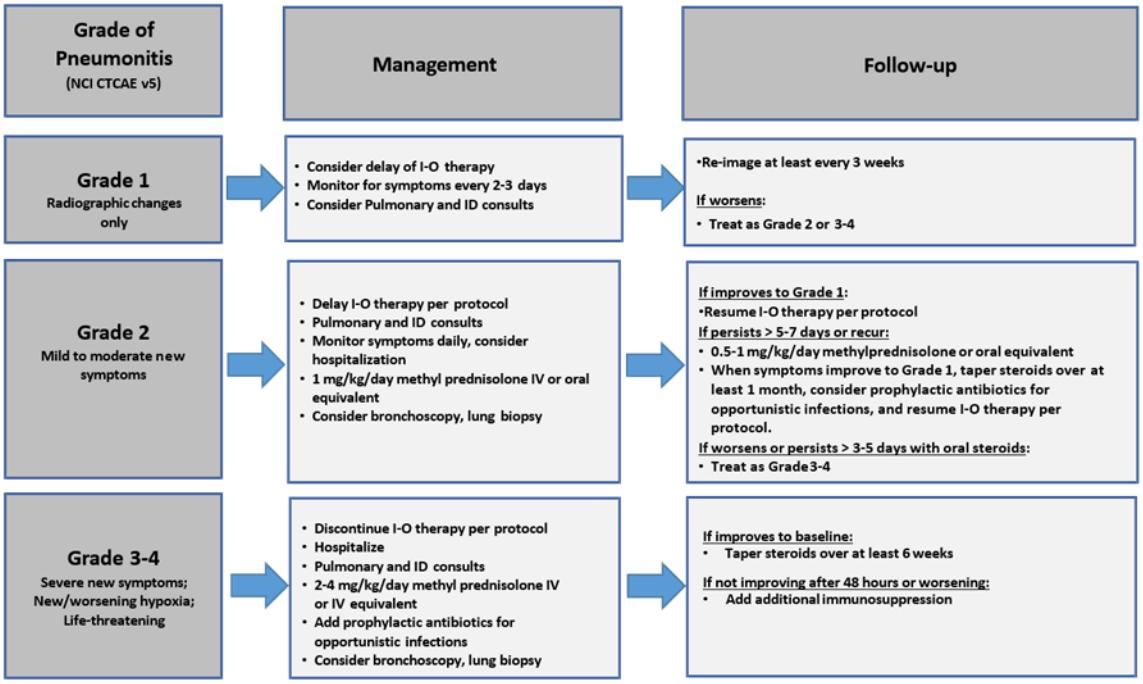


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

28-Sep-2020

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.

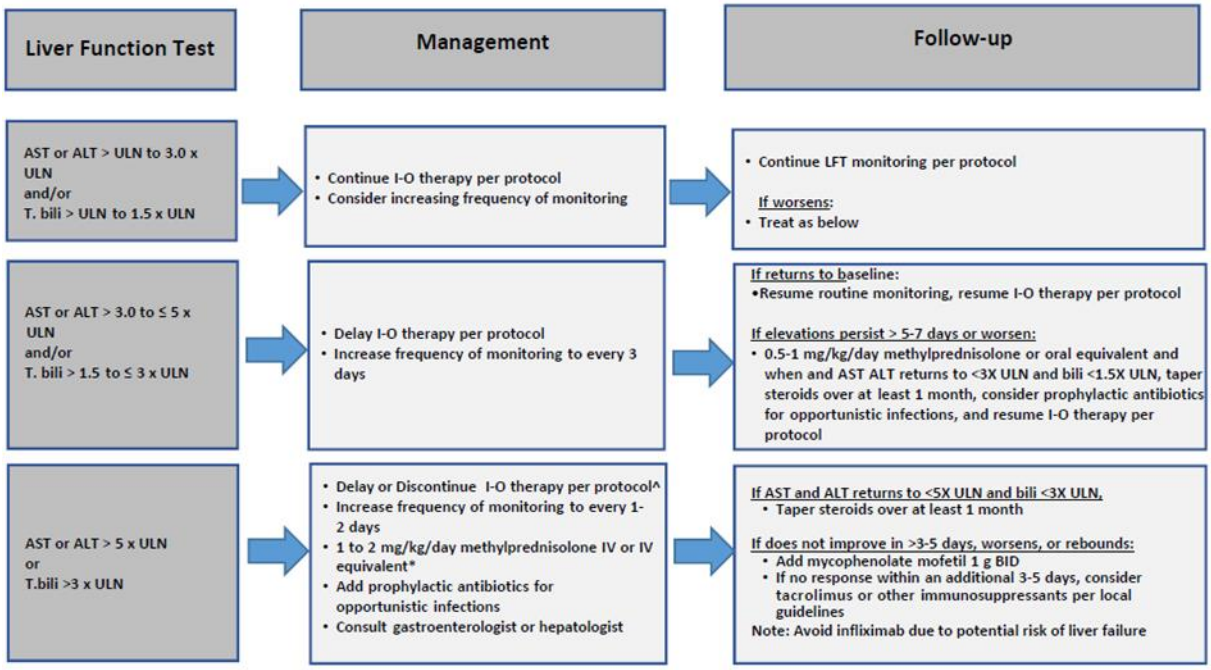


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

28-Sep-2020

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, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.
^ Please refer to protocol dose delay and discontinue criteria for specific details.
*The recommended starting dose for AST or ALT > 20 x ULN or bilirubin >10 x ULN is 2 mg/kg/day methylprednisolone IV.

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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.

Endocrinopathy	Management	Follow-up
Asymptomatic TSH abnormality or Hyperglycemia requiring no medical intervention	• Continue I-O therapy per protocol • If TSH < 0.5 x LLN, or TSH > 2 x ULN, or consistently out of range in 2 subsequent measurements: o include fT4 at subsequent cycles as clinically indicated; o consider endocrinology consult	• Monitor TSH as per protocol • Monitor blood sugar • If symptomatic or blood sugar requiring initiation of treatment or change in management, manage as below
Symptomatic endocrinopathy or hyperglycemia requiring initiation of treatment or change in daily management or work up	• Evaluate endocrine function; consider endocrinology consult • Consider pituitary scan Symptomatic with abnormal lab/pituitary scan: • Delay I-O therapy per protocol • 1-2 mg/kg/day methylprednisolone IV or PO equivalent for hypophysitis • Initiate appropriate hormone/medical therapy No abnormal lab/pituitary MRI scan but symptoms persist: • Continue IO therapy. Repeat labs in 1-3 weeks /MRI in 1 month Hyperglycemia: Screen for Diabetic Ketoacidosis (DKA). If negative, continue IO and treat diabetes. If DKA hold IO, admit, manage DKA. Steroids not recommended for DKA/hyperglycemia	If improves (with or without hormone replacement): • Taper steroids over at least 1 month and consider prophylactic antibiotics for opportunistic infections • Resume I-O therapy per protocol • Patients with adrenal insufficiency may need to continue steroids with mineralocorticoid component
Suspicion of adrenal crisis (eg, severe dehydration, hypotension, shock out of proportion to current illness)	• Delay or discontinue I-O therapy per protocol • Rule out sepsis • Stress dose of IV steroids with mineralocorticoid activity • IV fluids • Consult endocrinologist	• Patients with adrenal insufficiency may need to continue steroids with mineralocorticoid component • If adrenal crisis resolves and patient is adequately controlled with physiologic hormone replacement, patient can resume IO therapy per protocol.

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

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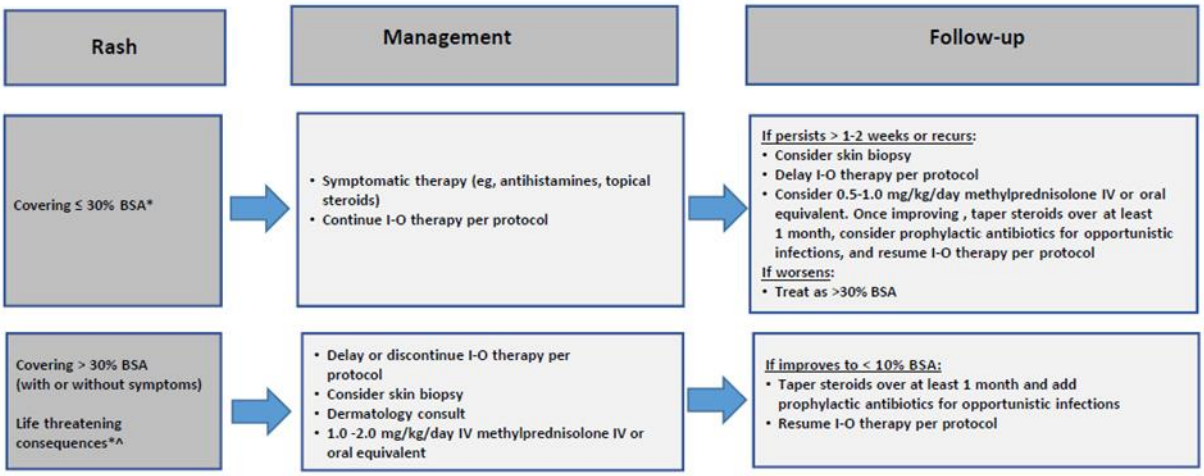
Skin Adverse Event Management Algorithm

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, after 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 v5 for term-specific grading criteria.

^If Steven-Johnson Syndrome (SJS),toxic epidermal necrosis (TEN), Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) is suspected, withhold I-O therapy and refer patient for specialized care for assessment and treatment. If SJS, TEN, or DRESS is diagnosed, permanently discontinue I-O therapy.

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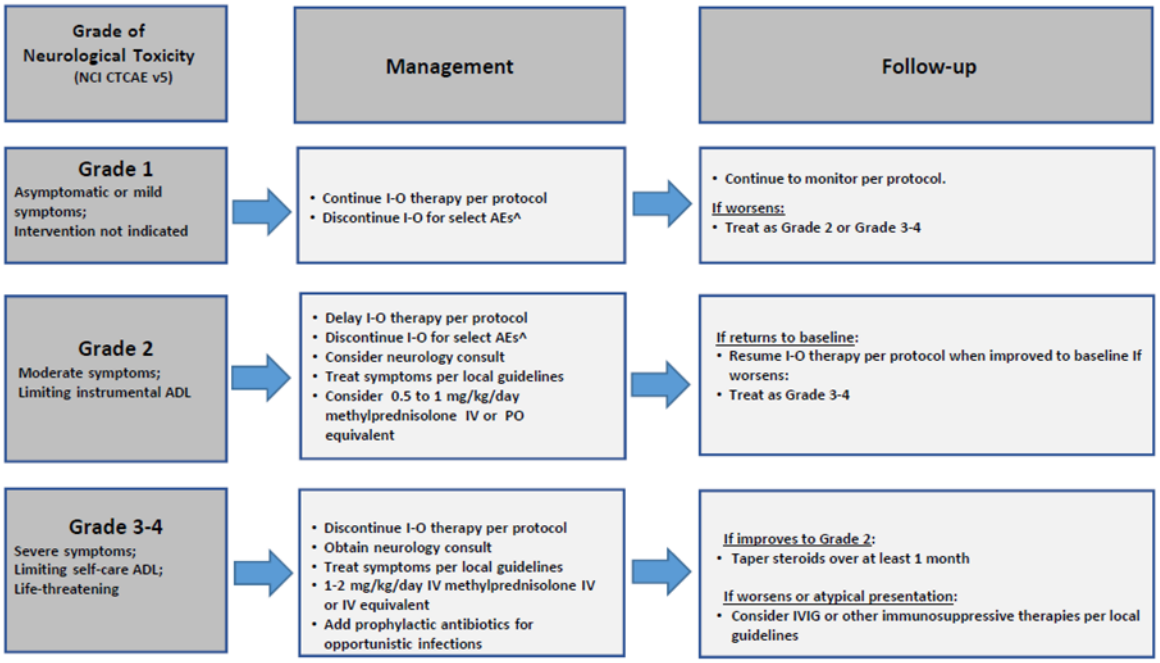
Neurological Adverse Event Management Algorithm

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 (eg. prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

^Discontinue for any grade myasthenia gravis, Guillain-Barre syndrome, treatment-related myelitis, or encephalitis.

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Myocarditis Adverse Event Management Algorithm

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

Myocarditis	Management	Follow-up

Symptoms with mild to moderate activity or exertion	• Delay I-O therapy; hospitalization with cardiac monitoring
	• Urgent cardiology consultation for evaluation and management
	  ○ Troponin and BNP
	  ○ ECG ± continuous cardiac monitoring
	  ○ Echocardiogram
	  ○ Cardiac MRI
	• Prompt initiation of 2 mg/kg/day methylprednisolone IV or equivalent
		• If worsens, intensify treatment according to grade
		• Upon recovery, taper steroids over at least 1 month with close monitoring of troponin and BNP. as well as for new symptoms
		• Repeat cardiac MRI for post treatment assessment and cardiology follow-up
		• Retreatment may be considered after recovery and completion of steroid taper

Severe with symptoms at rest or with minimal activity or exertion; intervention indicated
 	
Life-threatening consequences; urgent intervention indicated (e.g., continuous IV therapy or mechanical hemodynamic support)
	• Permanently discontinue I-O therapy
	• Hospitalize to intensive cardiac monitoring
	• Cardiac evaluation to include:
	  ○ Troponin and B-type natriuretic peptide monitoring
	  ○ ECG ± continuous cardiac monitoring
	  ○ Echocardiogram
	  ○ Cardiac MRI
	  ○ Myocardial biopsy if feasible
	• Immediate initiation of 2 mg/kg/day methylprednisolone IV or 1 g IV bolus
	• Consider adding a second immunosuppressive agent
	Additionally, for life threatening myocarditis:
	• Hospitalize/transfer to institution with expertise in intensive cardiac monitoring
	• Consider anti-thymocyte globulin as second agent given its immediate effect
		• If no improvement, consider additional immunosuppression
		• Upon recovery, taper steroids over at least 1 month with close monitoring of troponin and BNP as well as for new symptoms
		• Repeat cardiac MRI for post treatment assessments and cardiology follow-up

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.
Prophylactic antibiotics should be considered in the setting of ongoing immunosuppression.

28-Sep-2020

10.10 Appendix 10: Abbreviations

Table 10–9 Abbreviations

AA	Anaplastic astrocytoma
ADA	Anti-drug-antibodies
ADL	Activities of Daily Living
AE	Adverse event
AIDS	Acquired human immunodeficiency virus
AJCC	American Joint Committee on Cancer
ALT	Alanine aminotransferase
ALP	Alkaline phosphatase
ANC	Absolute neutrophil count
Ang1	Angiopoietin 1
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration time curve
BP	Blood pressure
BRAF	Proto-oncogene BRAF, type B of RAF
BCRP	Breast cancer resistance protein
BDM	Bi-dimensional measurements
BTC	Biliary tract carcinoma
BTIP	Brain tumor imaging protocol
BUN	Blood urea nitrogen
C	Cycle
CCA	Cholangiocarcinoma
CCL	cc-chemokine ligand
CCR	cc-chemokine receptor
ChT	Chemotherapy
CI	Confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CNS	Central nervous system
CR	Complete response
CRC	Colorectal cancer
CRF	Case report form
CSF1R	Colony-stimulating factor 1 receptor
CT	Computed tomography
CTCAE	Common terminology criteria for adverse events
ctDNA	Circulating tumor DNA
CTLA-4	Cytotoxic T-lymphocyte-associated protein 4
CXCL10	C-X-C motif chemokine ligand 10
CXCR3	CXC-motif-chemokine receptor 3
CYP	Cytochrome P450
D / (d)	Day(s)
DCR	Disease control rate
DLT	Dose limiting toxicity
DMC	Data monitoring committee
dMMR	Mismatch repair deficient
DNA	Deoxyribonucleic acid
DOR	Duration of response

DPD	Hydroxy ethylene diphosphonate
DWI	Diffusion-weighted imaging
EBV	Epstein-Barr virus
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture
eGFR	Estimated glomerular filtration rate
EoI	End of infusion
EoT	End of treatment
ESCC	Esophageal Squamous Cell Carcinoma
FAS	Full analysis set
FDA	Food and Drug Administration
FGFR	Fibroblast growth factor receptor
FPFV	First patient first visit
FSH	Follicle stimulating hormone
FT3	Free triiodothyronine
FT4	Free thyroxine
FU	Follow-up
G	Grade
GBC	Gallbladder cancers
GBM	Glioblastoma multiforme
GC	Gastric cancer
GCP	Good clinical practice
G-CSF	Granulocyte colony stimulating factor
GGT	Gamma-glutamyl transferase
GIST	Gastrointestinal stroma tumor
Hb	Hemoglobin
HbsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
hCG	Human chorionic gonadotropin
HCV	Hepatitis C virus
HDP	2,3-dicarboxypropane-1,1-diphosphonate
Hep B/C	Hepatitis B/C
Hg	Mercury
HFSR	Hand foot skin reaction
HIV	Human immunodeficiency virus
HMDP	Hydroxy methylene diphosphonate
HNSCC	Head and neck squamous-cell carcinoma
HPV	Human papilloma virus
hr	Hour(s)
HR	Hazard ratio
HRT	Hormonal replacement therapy
IB	Investigators brochure
ICF	Informed consent form
ICH	International Conference on Harmonization
ICI	Immune checkpoint inhibitor
IDH	Isocitrate dehydrogenase

IDO-1	Indoleamine 2, 3-dioxygenase 1
IEC	Independent ethics committees
IgG	Immunoglobulin
IMAE	Immune-mediated adverse event
IMP	Investigational medicinal product
IMS	Immunogenicity analysis set
INR	International normalized ratio
IO	Immunoncology
iRANO	immune response assessment in neuro-oncology
IRB	Institutional review board
iRECIST	Response evaluation criteria in solid tumors for trials testing immunotherapeutics
IV / i.v.	Intravenous
IxRS	Interactive voice/web response system
KIT	Stem cell factor receptor
LD	Last dose
LDH	Lactic dehydrogenase
LPLV	Last patient last visit
mAB	Monoclonal antibody
mCRC	Metastatic colorectal cancer
MDP	Methylene diphosphonate
MDSC	Myeloid-derived suppressor cells
MGMT	O^6-methylguanine DNA methyltransferase
MKI	Multi kinase inhibitor
MMR	Measles, mumps, rubella
MR	Minor response
MRI	Magnetic resonance imaging
MSI-H	Microsatellite instable-high
MSS	Microsatellite stable
MTD	Maximal tolerated dose
NA	Not applicable
NAB	Neutralizing antibodies
NCI	National Cancer Institute
NIMP	Non-investigational medicinal product
NLNT	New lesions – non target
NLT	New lesions - target
n-PKS	Nivolumab PK analysis set
NSCLC	Non-small cell lung cancer
NTRK	Tropomyosine receptor kinase
NYHA	New York Heart Association
ORR	Overall response rate
OS	Overall survival
PD	Progressive disease
PD-1	Programmed cell death protein 1
PDAC	Pancreatic ductal adenocarcinoma
PDGFR	Platelet-derived growth factor receptor
PD-L1/2	Programmed cell death protein 1 ligand 1/2
PFS	Progression free survival
PID	Participant identification number

PI/ICF	Participant information/informed consent form
PK	Pharmacokinetics
PKS	Pharmacokinetics analysis set
pMMR	Proficient mismatch repair
PO	Per oral (route of administration)
PR	Partial Response
PR-interval	PR-interval in ECG
PS	Performance status
PsP	Pseudoprogression
PsR	Pseudoresponse
PT	Prothrombin time
PT-INR	Prothrombin time – international normalized ratio
Q2/4W	Every two/four weeks
QD / q.d.	Quaque die (once daily)
QRS	QRS interval in ECG
QT	QT interval in ECG
QTcF	QT interval corrected for heart rate F
RAF-1	rapidly accelerated fibrosarcoma 1
RANKL	Nuclear factor kappa-B ligand
RANO	Response assessment in neuro-oncology
RBC	Red blood cell count
RCC	Renal cell cancer
RD	Recurrent disease
RECIST	Response evaluation criteria in solid tumors
RET	Rearranged during transfection
R/M	Recurrent / metastatic
RNA	Ribonucleic acid
ROS	Roll over study
r-PKS	Regorafenib PK analysis set
RT	Radiation therapy
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SAS	SAS Institute, Cary, North Carolina, USA
SCLC	Small Cell Lung Cancer
SD	Stable disease
SGOT	Serum glutamic-oxaloacetic transaminase
SGPT	Serum glutamic-pyruvic transaminase
SoA	Schedule of Activities
SOC	Standard of care
SUSAR	Suspected unexpected serious adverse reactions
TAM	Tumor associated macrophage
TEAE	Treatment-emergent adverse event
T_{eff}	Effector T cell(s)
TIE-2	Tyrosine kinase with immunoglobulin and epidermal growth factor homology domain 2
TMB	Tumor mutational burden
TMZ	Temozolomide
T_{reg}	Regulatory T cell(s)

TSH	Thyroid stimulating hormone
UC	Urothelial carcinoma
UGT1	UDP-glucuronosyltransferase 1-1
ULN	Upper limit of normal
UPD	Unconfirmed progressive disease
US	United States
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor
WBC	White blood cell count
WHO	World Health Organization
WHO-DD	World Health Organization's Drug Dictionary
WOCBP	Woman of childbearing potential

Table 10–10 Terms and Definitions

Fluoropyrimidine	comprises 5-fluorouracil and capecitabine
RAVE	Clinical data recording and management software

10.11 Appendix 11: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

Amendment 1 (27 JAN 2021)

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.

Overall Rationale for the Amendment

The protocol amendment 01 was triggered by an amendment to nivolumab IB version 19, that includes updates to the management guidance for immune-mediated adverse events related to nivolumab and to male contraception guidance.

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities	Table 1-2 Schedule of activities Updated mention of footnotes on tumor assessment (CT/MRI) visits Footnote e – updated to point out which AEs are collected Table 1-3 Schedule of Biomarker Blood Sampling Updated footnote	Schedule of Activities updated to more clearly define the timing of the CT/MRIs and the collection of AEs during follow-up. Footnote removed as it does not apply to study population.
4.1.3 Active FU	Added sentence on AE documentation after start of new anti-cancer treatment	Wording was updated so only related AEs are collected during the follow-up period once new anti-cancer treatment is started.
4.4 End of Study Definition	Additional wording on trial stop added.	To clarify options in case the trial is stopped.
5.1 Inclusion Criteria Cohort 1 (HNSCC, IO naïve)	Inclusion criteria number 102 edited.	Additional inclusion criteria for stage 2 participants to clarify previous therapies allowed.
5.1 Inclusion Criteria Cohort 3 (ESCC)	Inclusion criteria number 302 edited.	Additional inclusion criteria for stage 2 participants to clarify previous therapies allowed.

Section # and Name	Description of Change	Brief Rationale
5.1 Inclusion Criteria For all cohorts	Inclusion criteria 9: Updated guidance on contraception after study intervention regarding nivolumab	Updated guidance regarding male contraception based on updated nivolumab IB.
5.2 Exclusion Criteria For all cohorts	Exclusion criteria 1: Updated definition Exclusion criteria 12: Definition of poorly controlled hypertension updated to 'above **140**/90 mmHg'	To clearly specify that participants that have known NTRK **fusions** are excluded. Updated according to most recent guidelines and recommendations.
6 Study Intervention	Definition of light meal added	Additional text inserted to further define light meal.
6.5.3 Prohibited Prior and Concomitant Therapies	Strong UGT1A9 inhibitors included as prohibited therapy.	Updated to remain consistent with current regorafenib label.
6.6.1 Toxicity Management	Table 6-3 Dose Modification/ Dose Interruption Guide for Regorafenib-Related Toxicities Table 6-5 Regorafenib Dose Modification Guidance: Non-Immune Toxicities: Hypertension	Tables updated as per HA request.
6.6.2 Toxicity Management 6.6.2.1	Note referring to CTCAE v5 deleted.	Nivolumab toxicity management guidelines were updated to reflect incorporation of CTCAE v5 as well as changes consistent with updated nivolumab immune-mediated AE management algorithms. Guidance in section 10.9 was updated accordingly.

Section # and Name	Description of Change	Brief Rationale
	Table 6-7 updated Reference to Nivolumab management algorithm added	Recommended dose modification for nivolumab was updated according to the newest management algorithms for studies, under CTCAE v5. Section edited to be consistent with newest Nivolumab management algorithm.
6.6.2.2 Management of Immune-Mediated AEs	Definition of immune-mediated AE added	Make description clearer and more precise for the reader.
7.1 Discontinuation of Study Intervention	Section Withdrawal from active FU edited.	Wording updated to further clarify when patients must be withdrawn from active FU.
8 Study Assessments and Procedures	Sentence added on trial-continuity issues.	To specify possible measures in the event of a significant trial-continuity issue (e.g. caused by a pandemic).
8.1 Efficacy Assessments	Use of oral contrasts	Specification that oral contrast agents are required unless inconsistent with local regulations.
10.1.1 Regulatory and Ethical Considerations	Section edited regarding amendments.	Section updated to clarify that substantial amendments to the protocol require regulatory authority approval before implementation.
10.2 Appendix 2	Wording updated Updated Table 10-1 Protocol-Required Safety Laboratory Assessments	Wording updated to clarify which assessments are performed in the local laboratory. Table footnote updated: Amylase and lipase will be part of safety blood test conducted in each treatment cycle. GGT will be assessed if clinically indicated.

Section # and Name	Description of Change	Brief Rationale
10.6 Appendix 6 10.6.3 RANO	Definitions added and table updated.	Section was updated to improve readability and clarify on RANO criteria definitions.
10.9 Appendix 9	Update of AE management algorithms	AE management algorithms were all updated and apply criteria from NCI-CTCAE v5. Tables were exchanged accordingly.
Throughout	Minor editorial and clerical errors and document formatting revisions	Minor, therefore have not been summarized

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

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